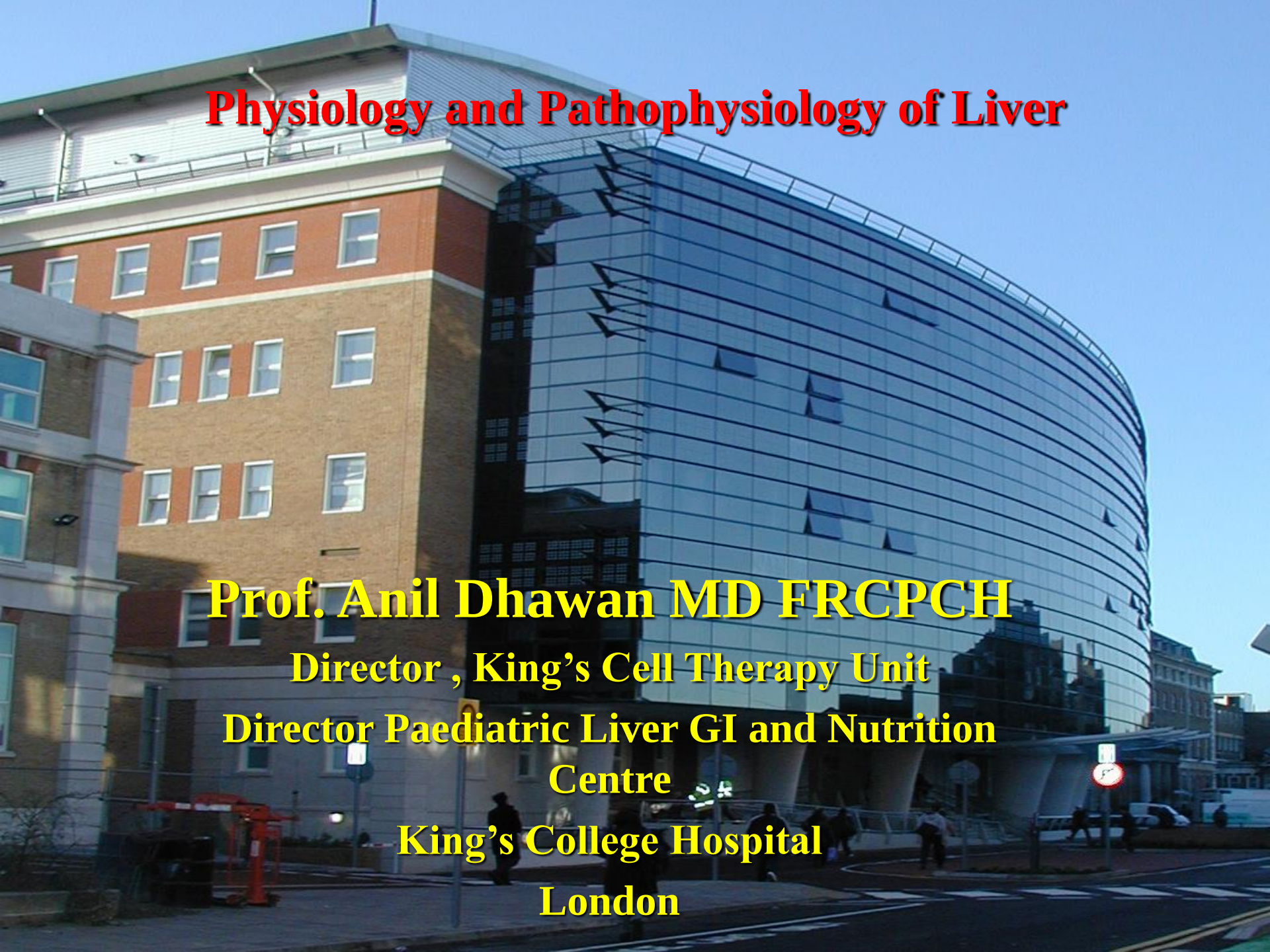
Physiology and Pathophysiology of Liver



Prof. Anil Dhawan MD FRCPCH

Director , King's Cell Therapy Unit

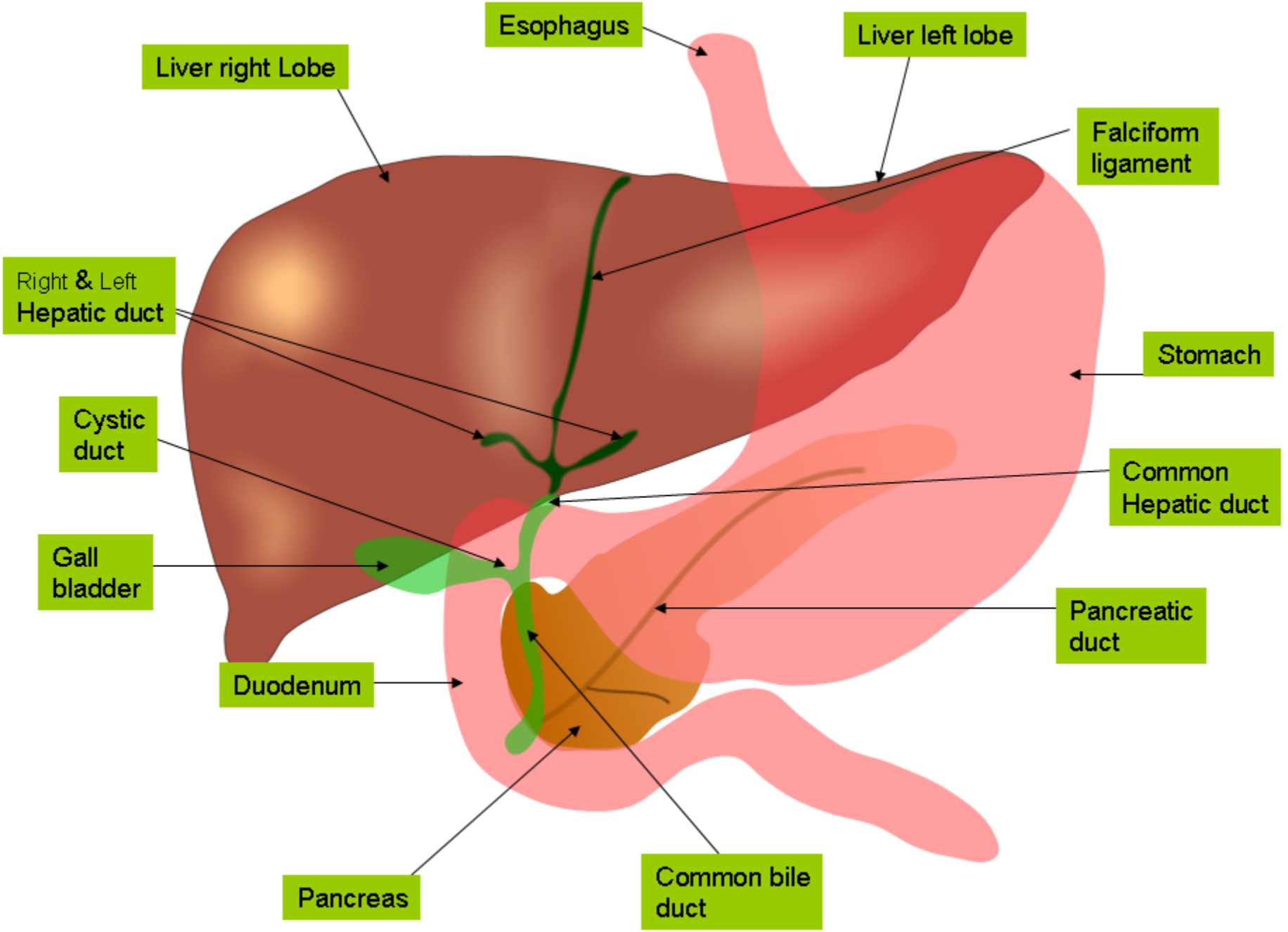
Director Paediatric Liver GI and Nutrition Centre

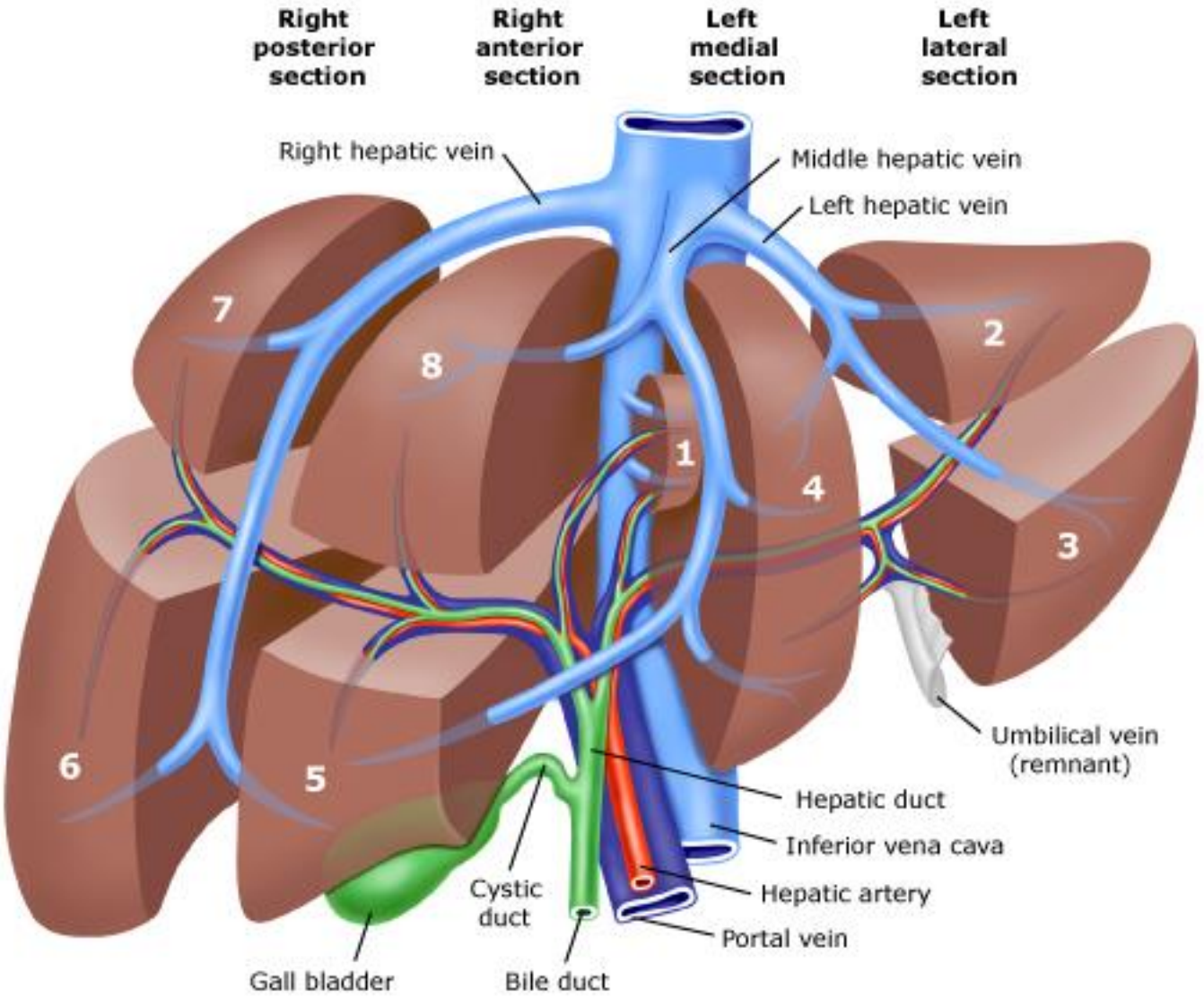
King's College Hospital

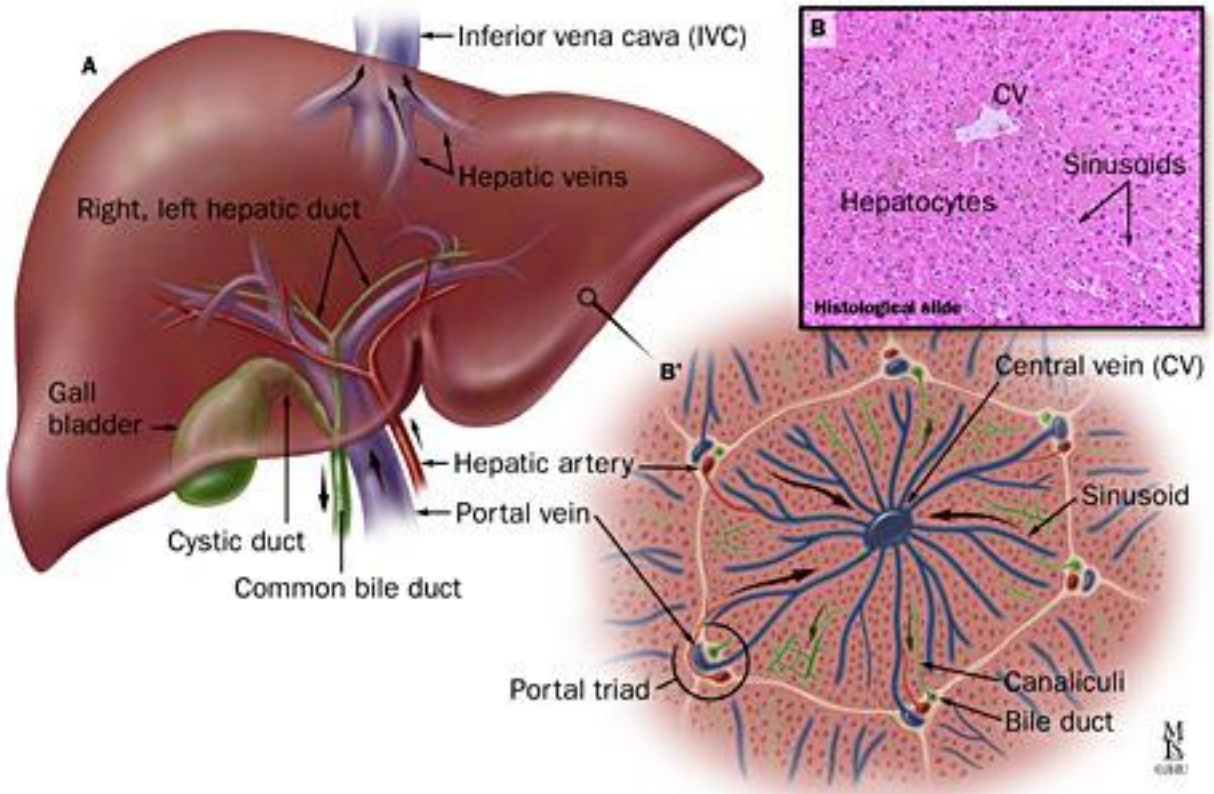
London

Remit of the talk

- Applied anatomy
- Synthetic functions
- Detoxification functions
- Common pathophysiology states in liver disease
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Ascites
  - Encephalopathy
  - Portal hypertension


Esophagus
Liver left lobe
Liver right Lobe
Falciform ligament
Right & Left Hepatic duct
Stomach
Cystic duct
Common Hepatic duct
Gall bladder
Pancreatic duct
Duodenum
Pancreas
Common bile duct


Right posterior section
Right anterior section
Left medial section
Left lateral section
Right hepatic vein
Middle hepatic vein
Left hepatic vein
7
8
2
1
4
3
6
5
Umbilical vein (remnant)
Hepatic duct
Inferior vena cava
Hepatic artery
Portal vein
Cystic duct
Gall bladder
Bile duct


A
Inferior vena cava (IVC)
Hepatic veins
Right, left hepatic duct
Gall bladder
Hepatic artery
Portal vein
Cystic duct
Common bile duct
B
CV
Sinusoids
Hepatocytes
Histological slide
B'
Central vein (CV)
Sinusoid
Portal triad
Canaliculi
Bile duct

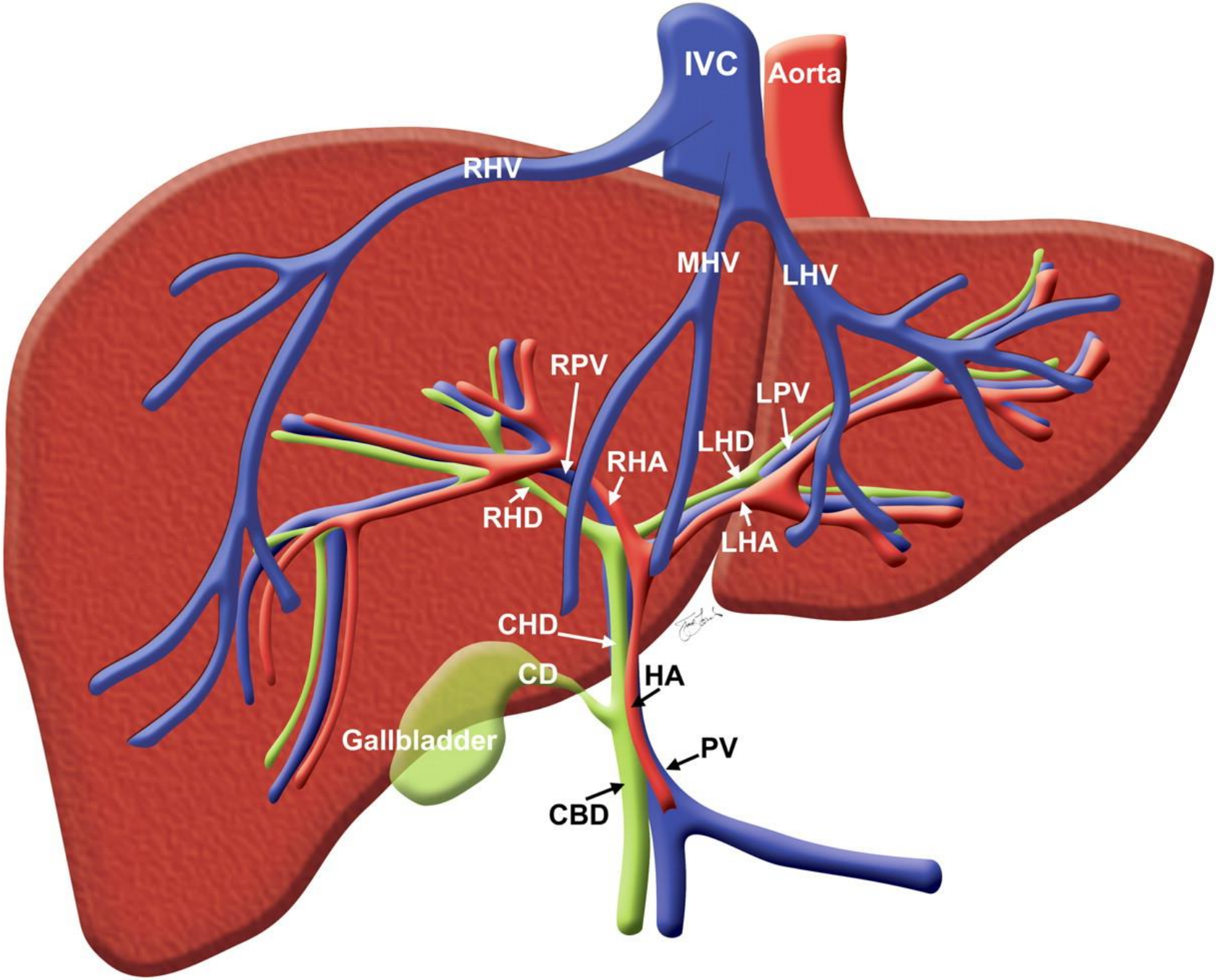
Hepatic Blood Flow

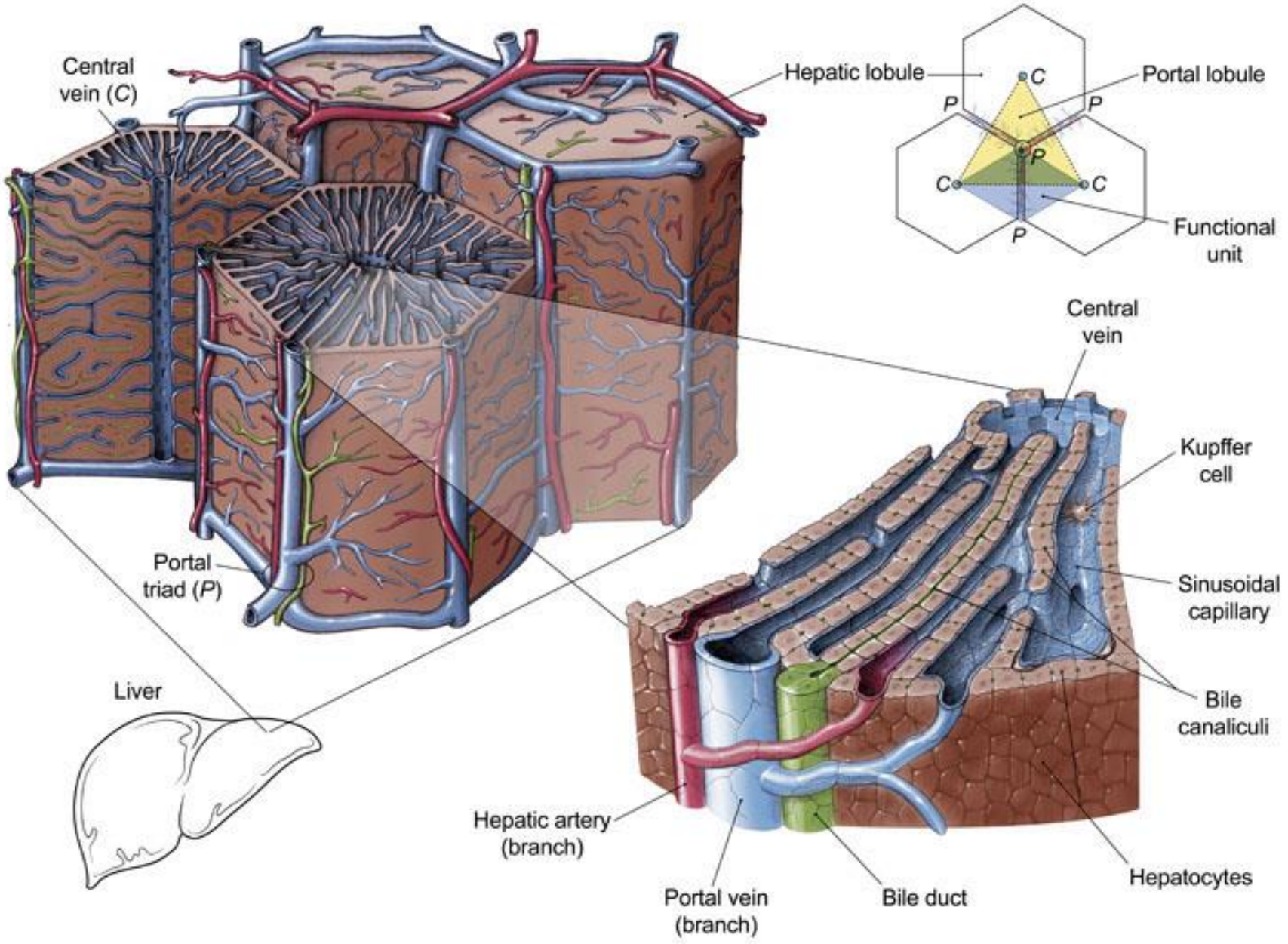
Dual blood supply

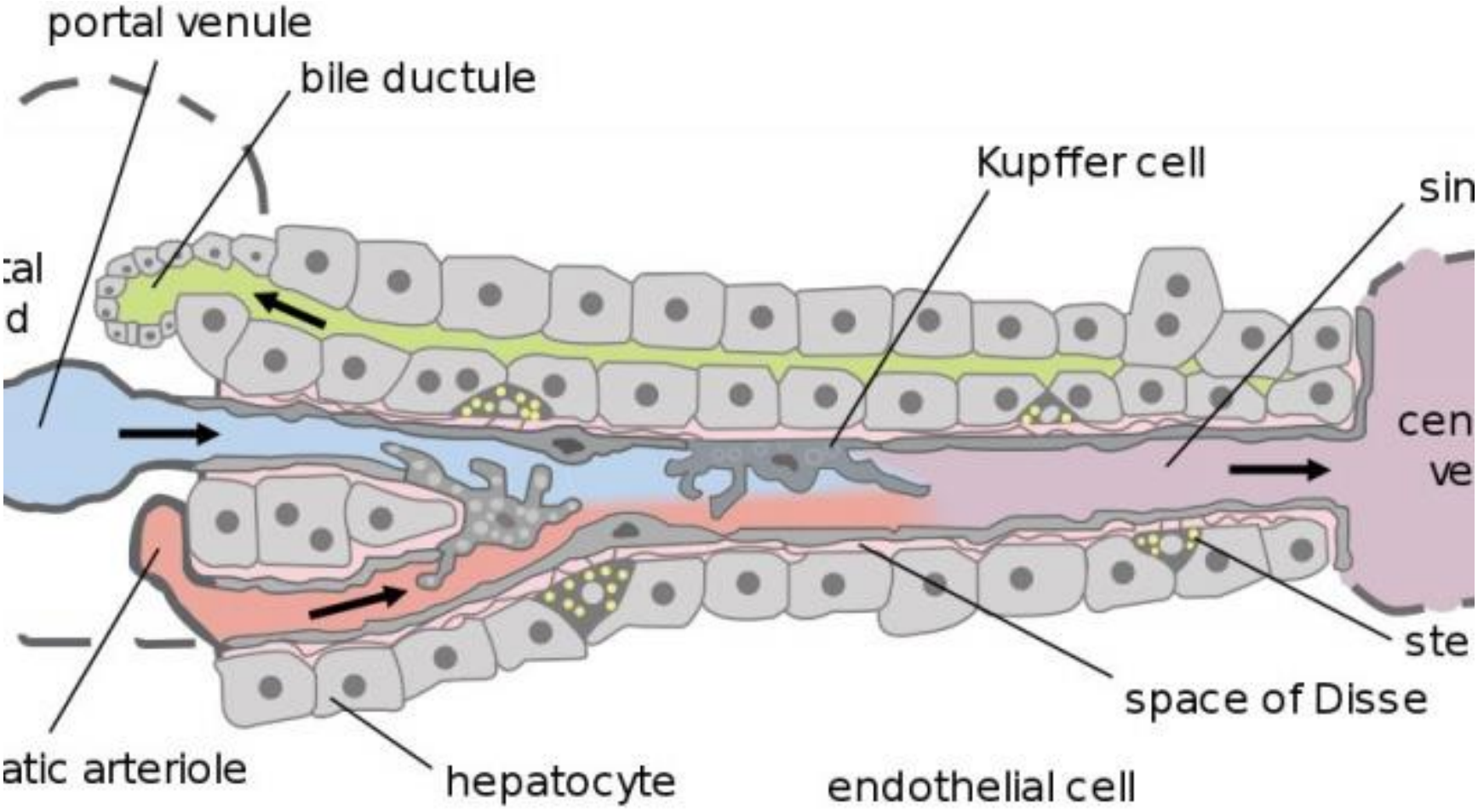
- Hepatic Artery (40%)
- Portal vein (60%)

Outflow

- Three Hepatic Veins

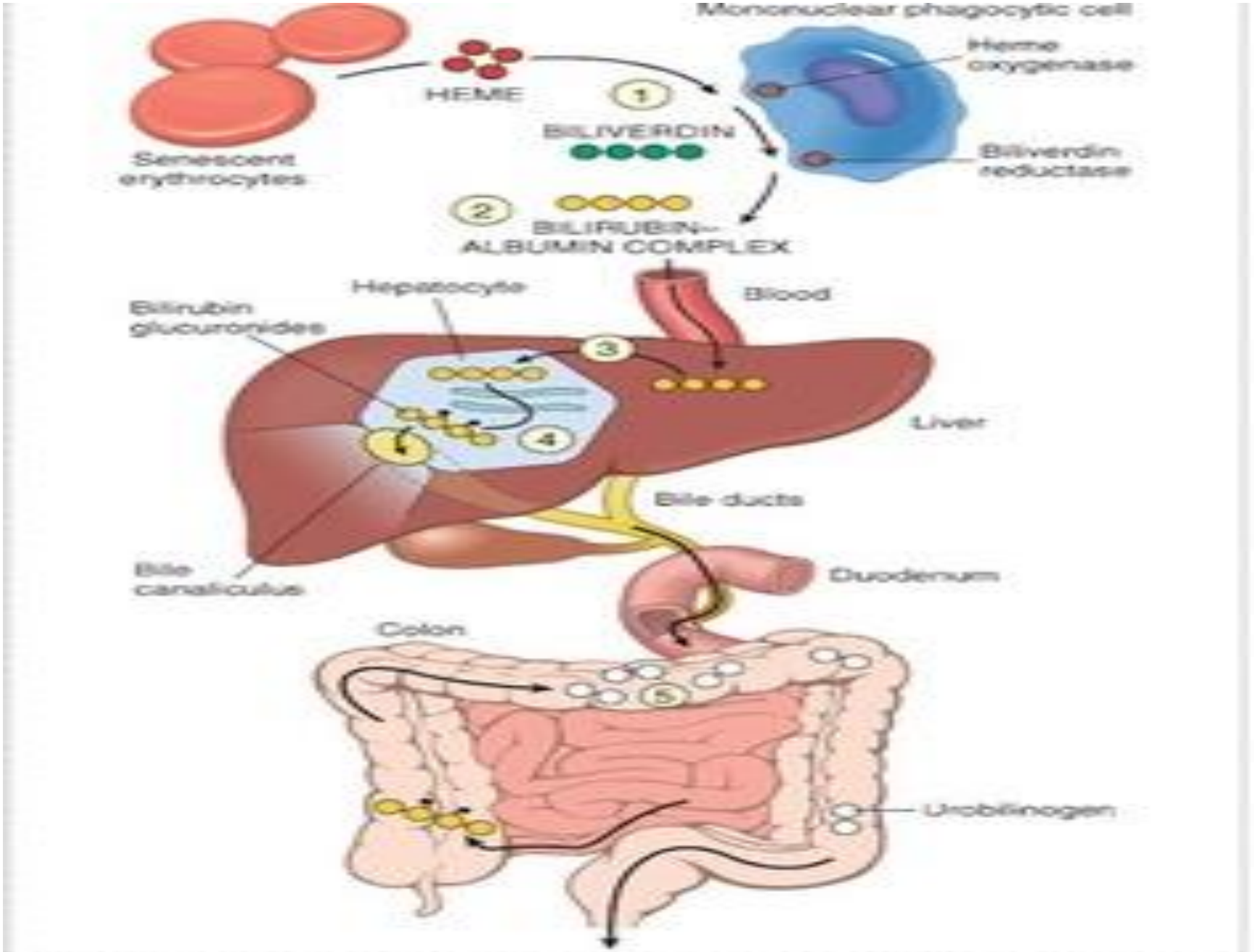

IVC
Aorta
RHV
MHV
LHV
RPV
LPV
LHD
RHA
RHD
LHA
CHD
CD
HA
Gallbladder
PV
CBD


Central vein (C)
Hepatic lobule
Portal lobule
C
P
P
P
C
C
P
Functional unit
Central vein
Kupffer cell
Portal triad (P)
Sinusoidal capillary
Liver
Bile canaliculi
Hepatic artery (branch)
Hepatocytes
Portal vein (branch)
Bile duct

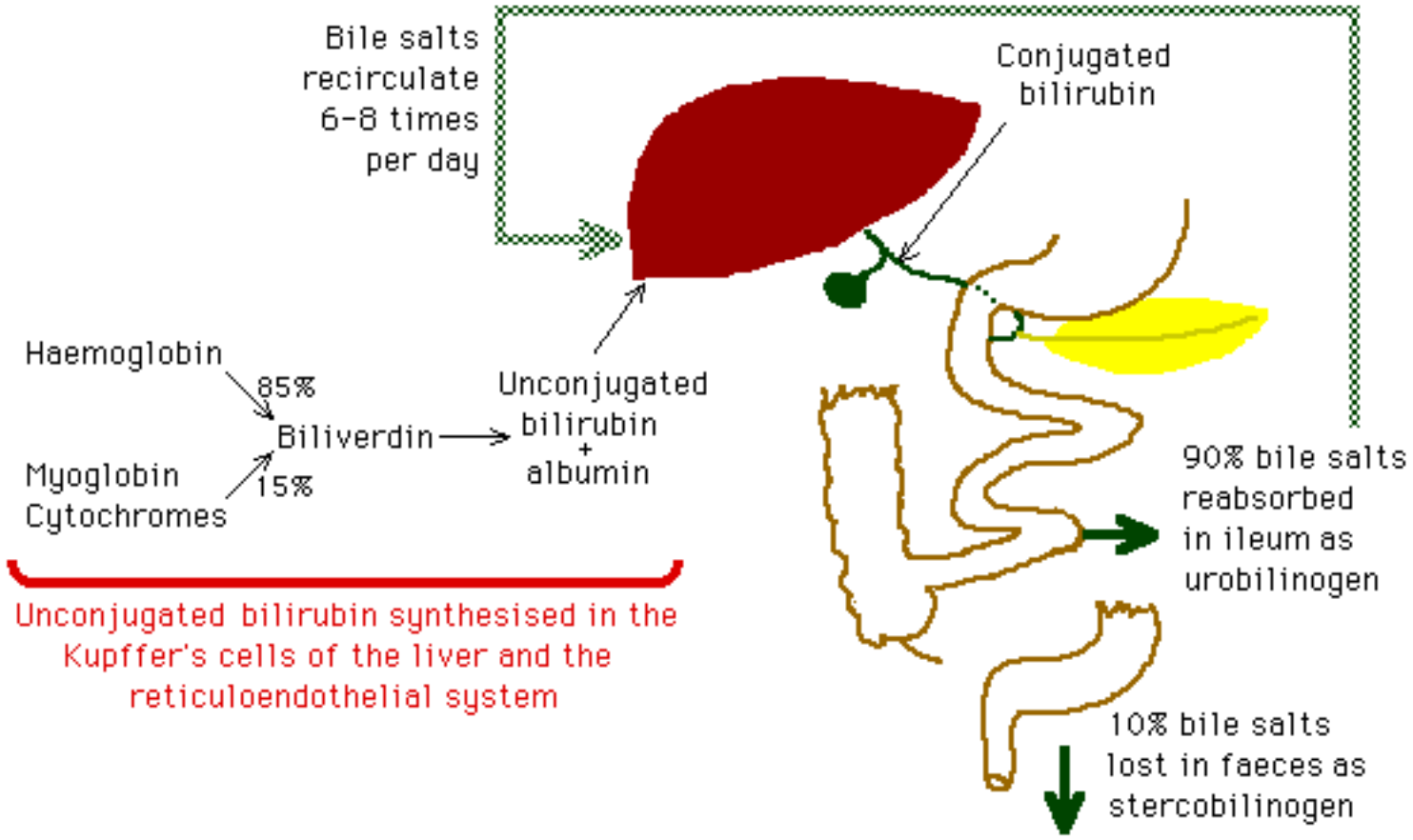

portal venule
bile ductule
Kupffer cell
sin
cen
ve
ste
space of Disse
atic arteriole
hepatocyte
endothelial cell

Formation of bile

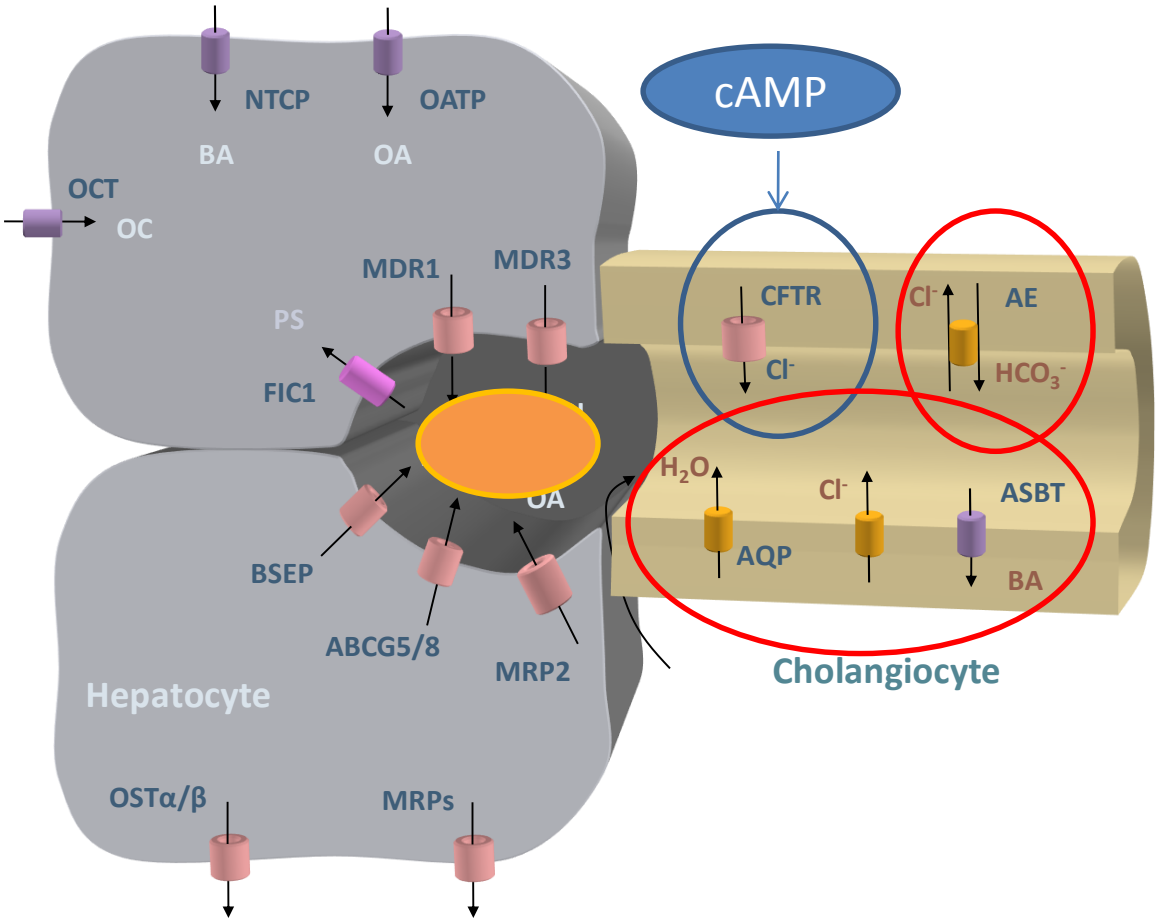
Central function of liver



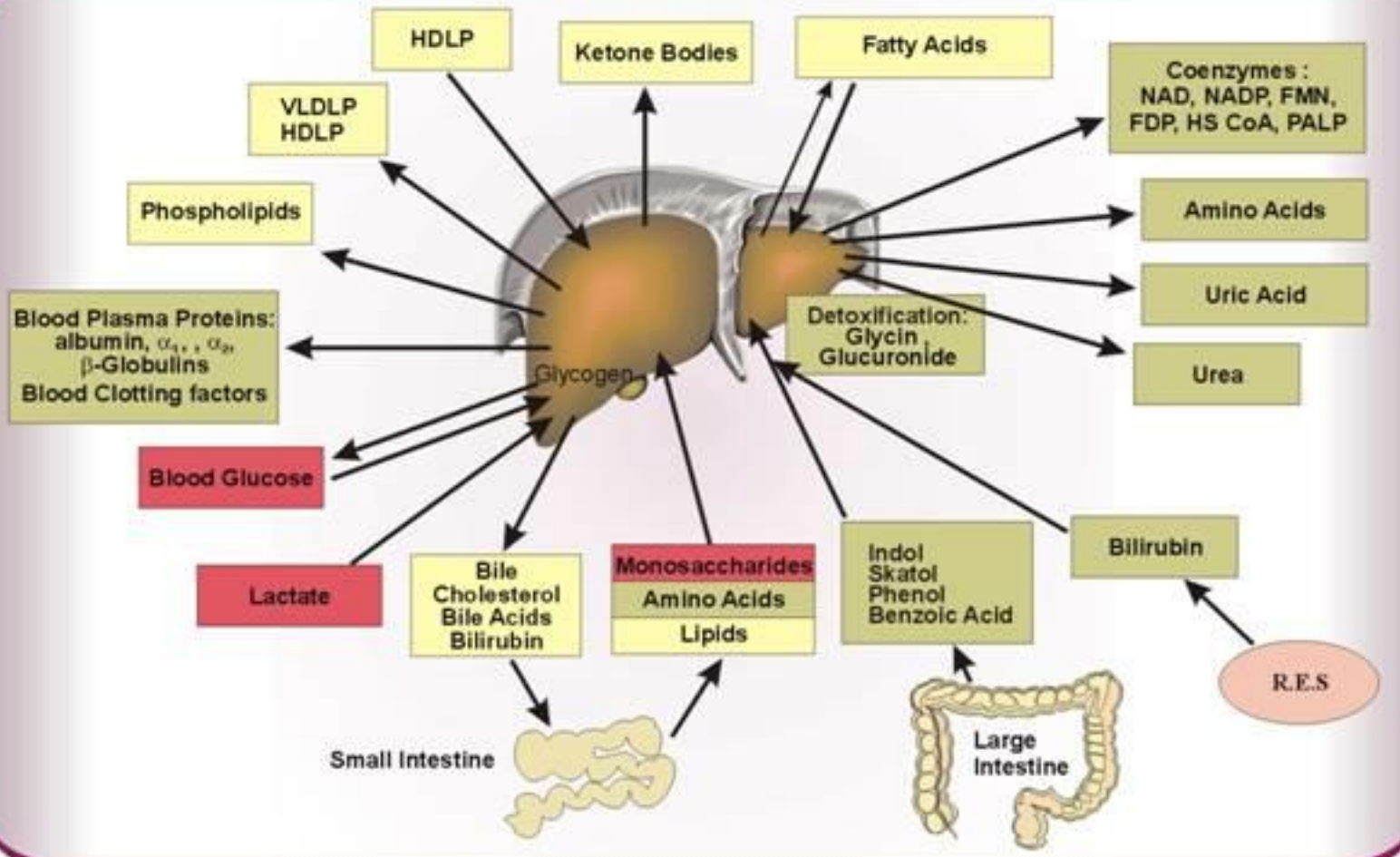
The synthesis and enterohepatic circulation of bile salts

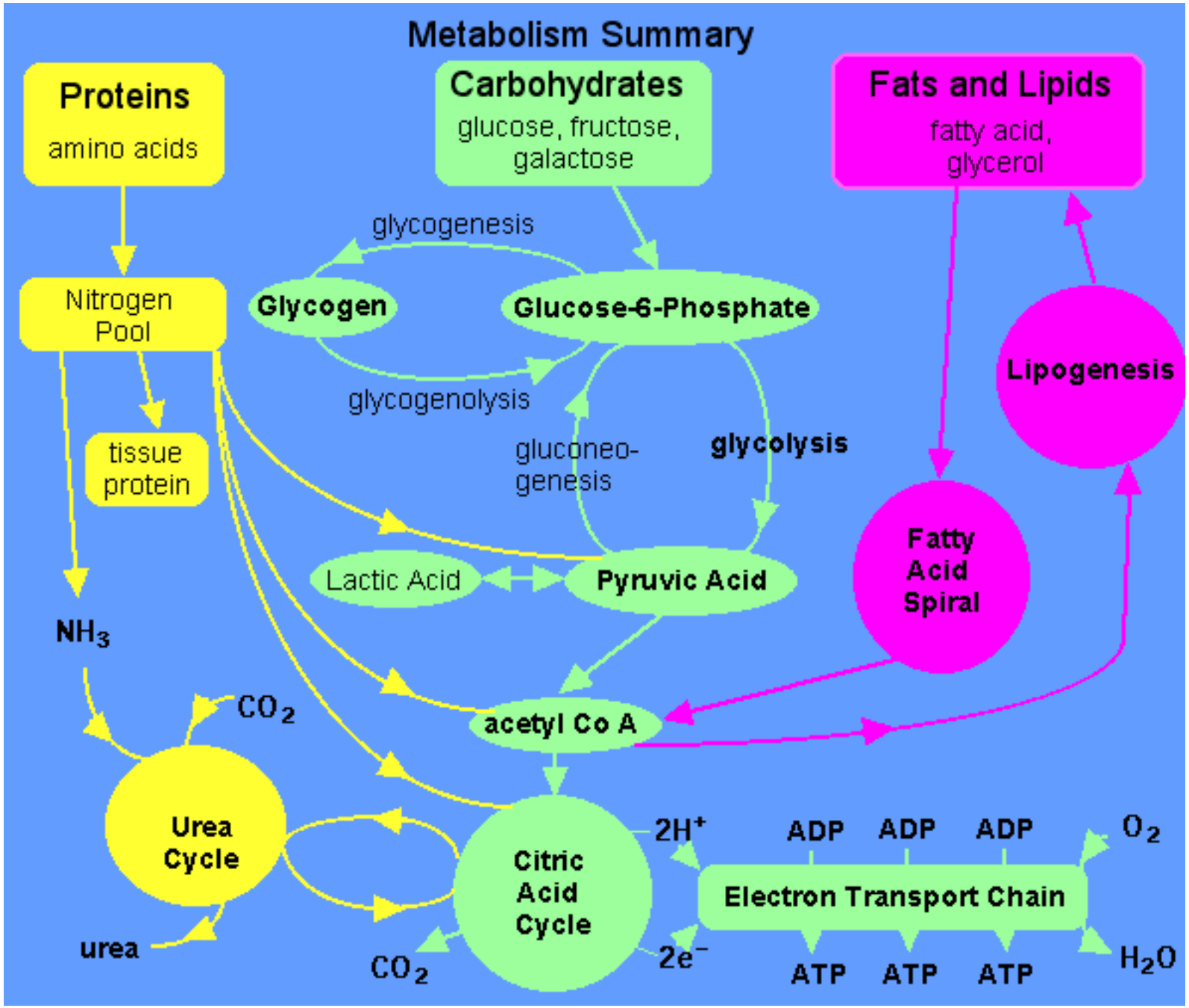


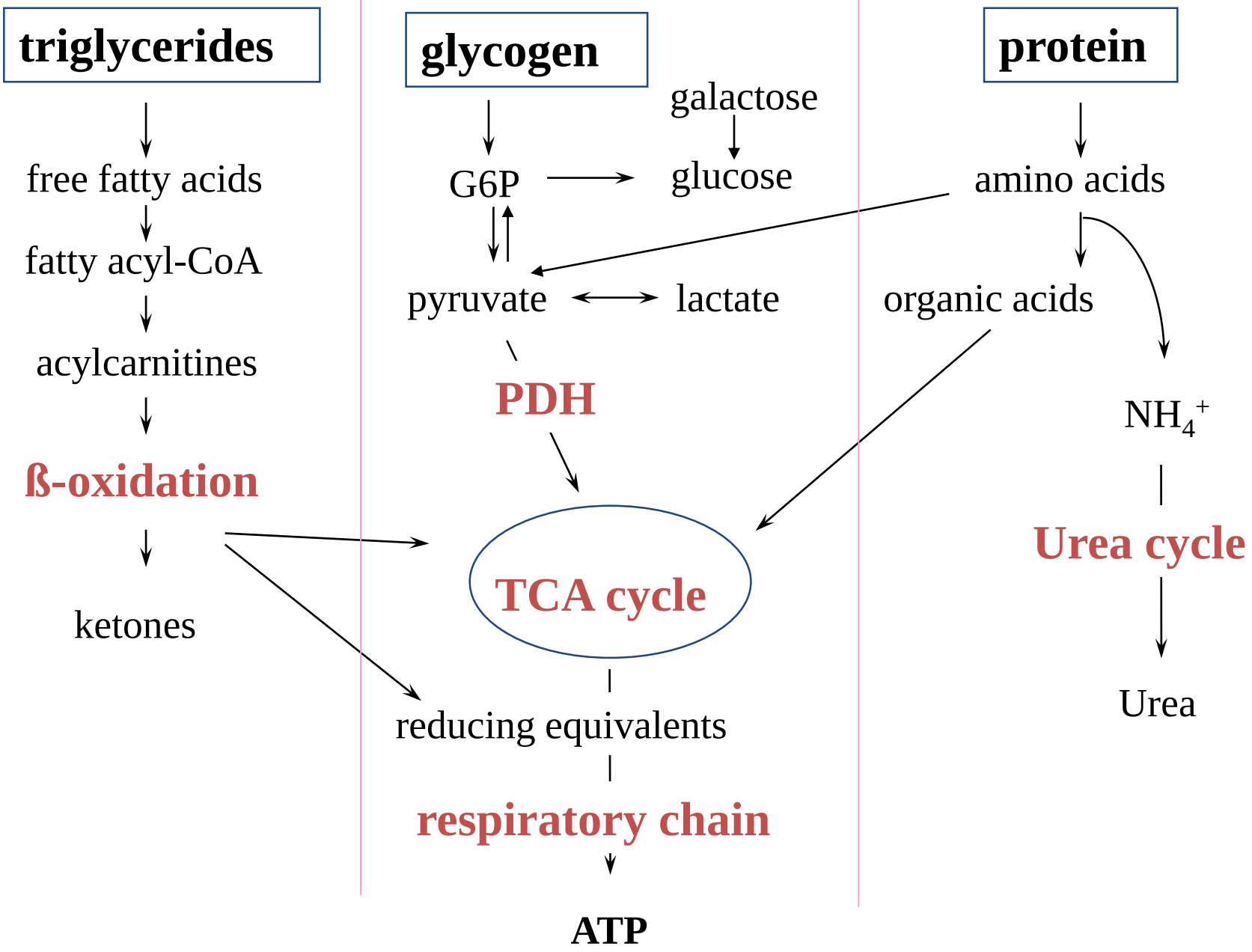
Focal biliary cirrhosis



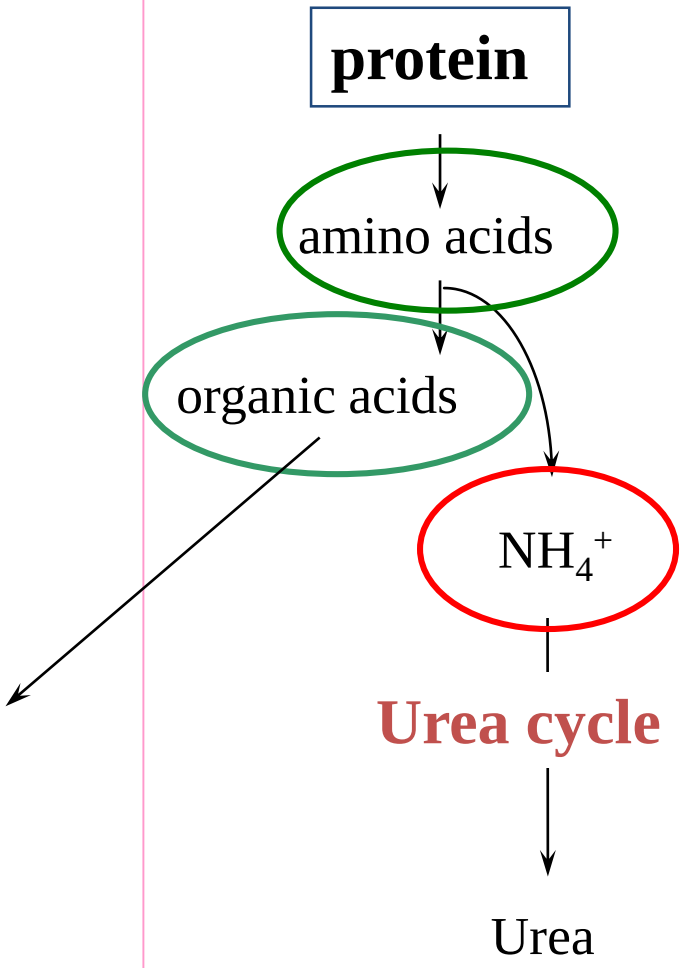
Role of Liver in Metabolism




Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e−
ATP ATP ATP
H2O


triglycerides
glycogen
protein
galactose
free fatty acids
G6P
glucose
amino acids
fatty acyl-CoA
pyruvate
lactate
organic acids
acylcarnitines
PDH
NH_4^+
ß-oxidation
TCA cycle
Urea cycle
ketones
reducing equivalents
Urea
respiratory chain
ATP

- aminoacidopathies
- organic acidemia
- urea cycle disorders



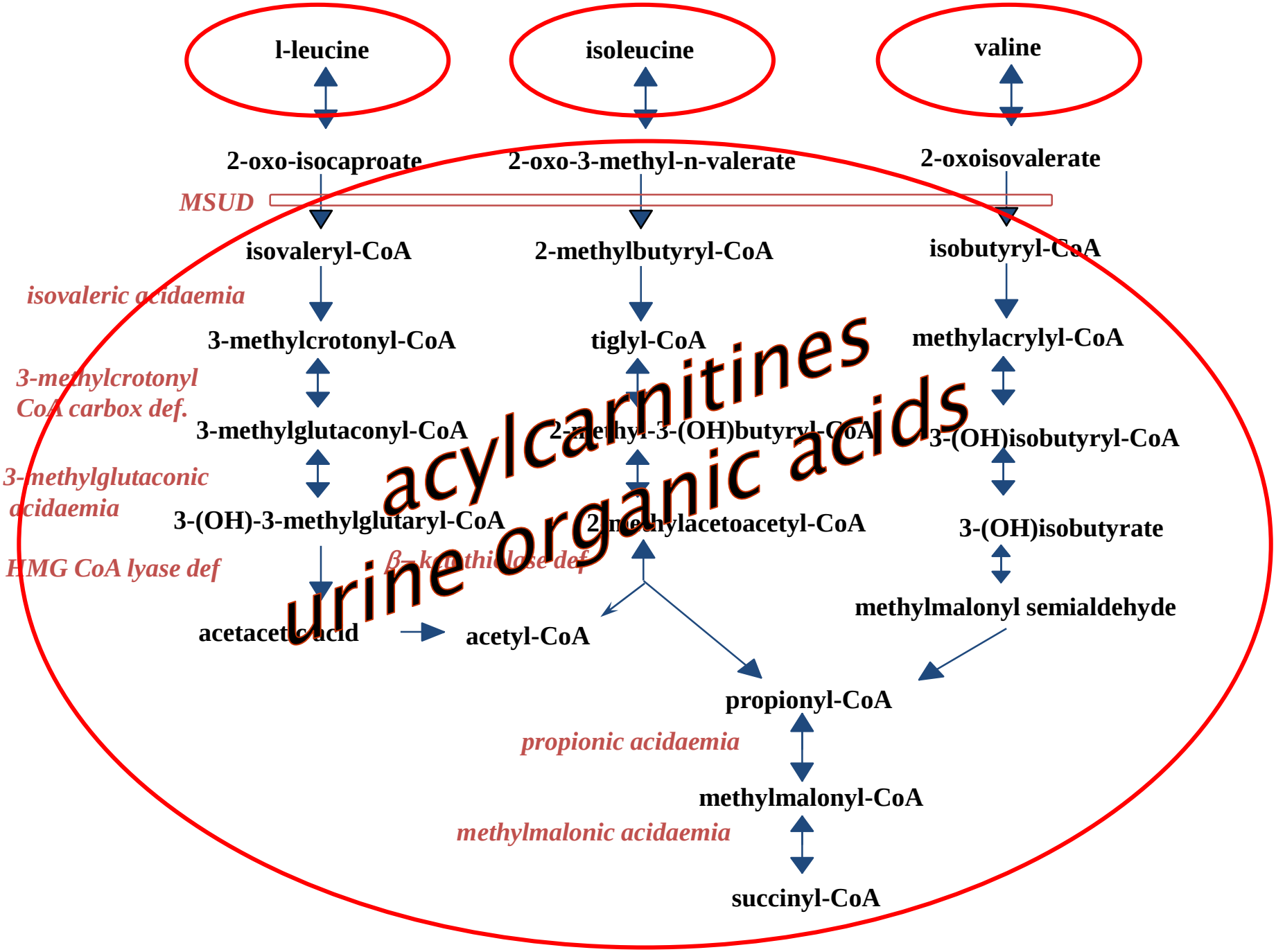
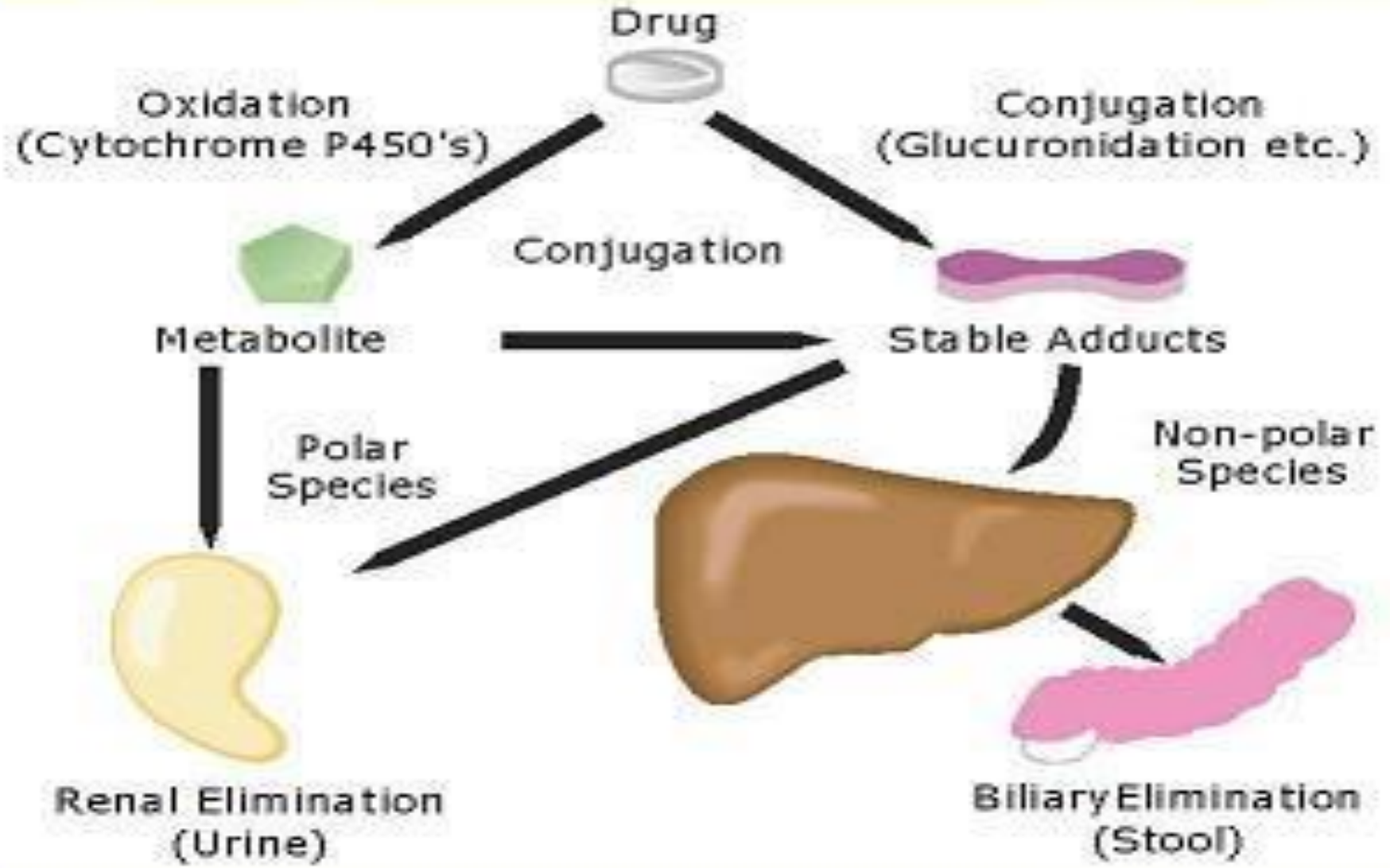
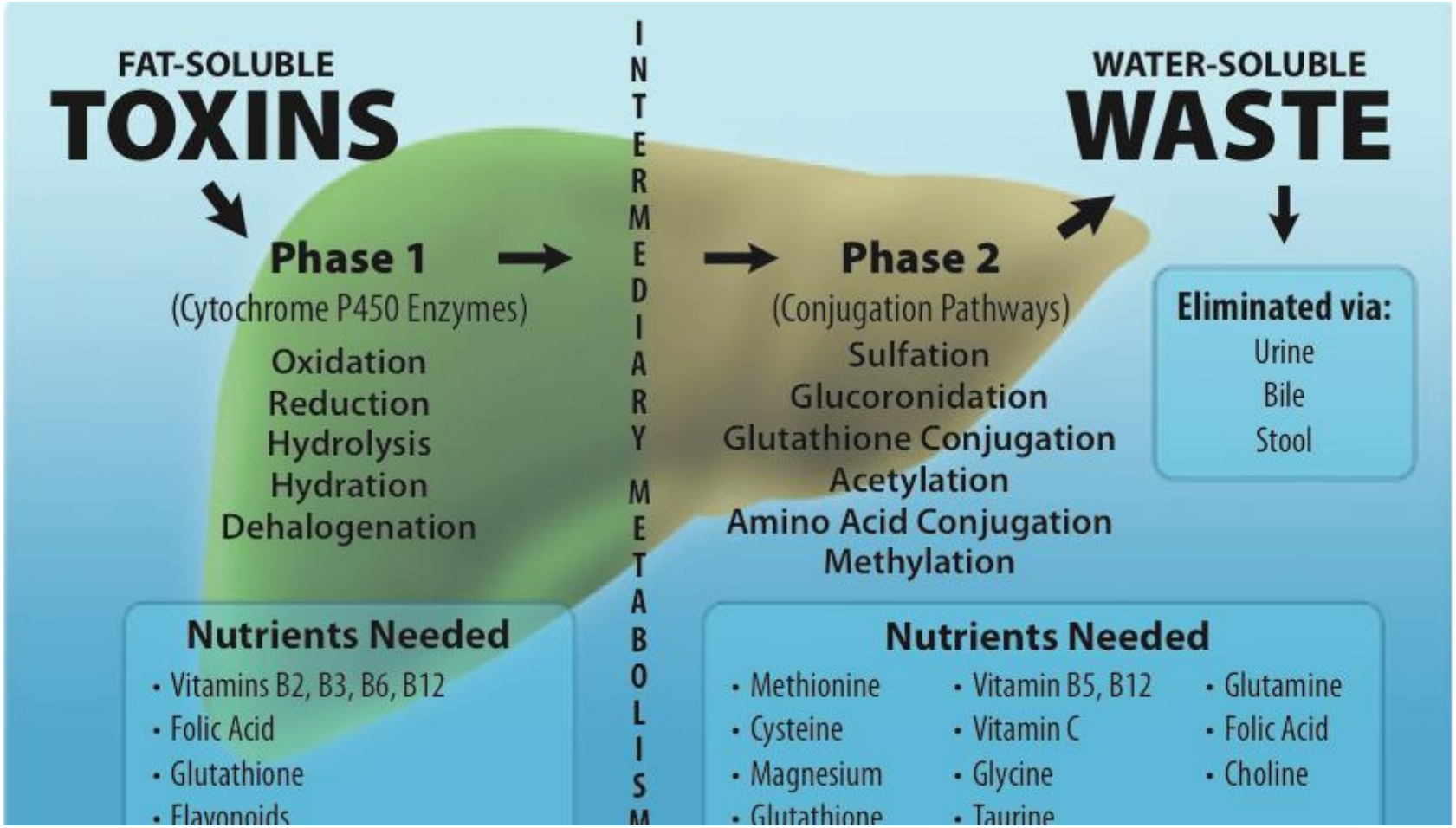
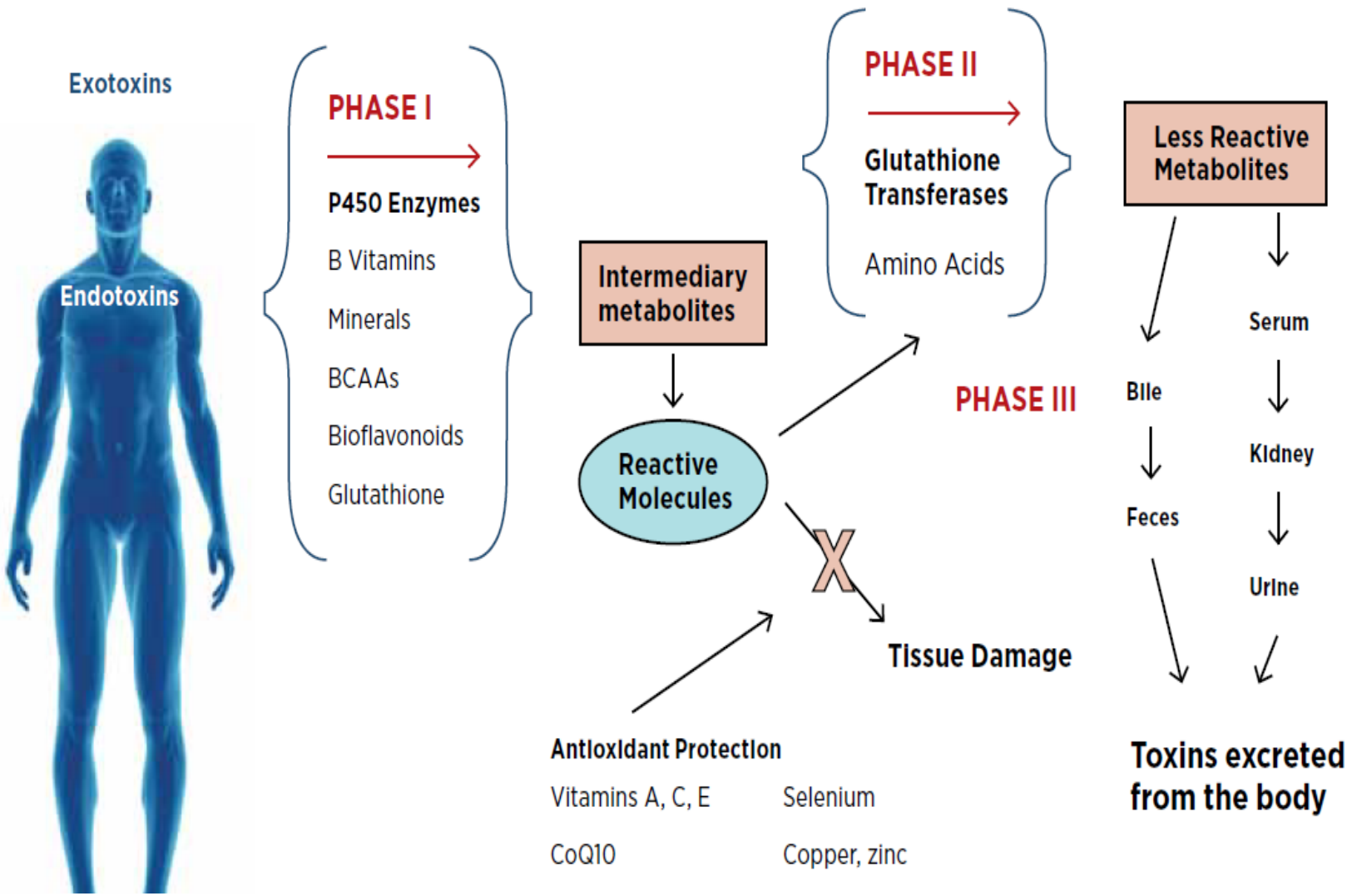
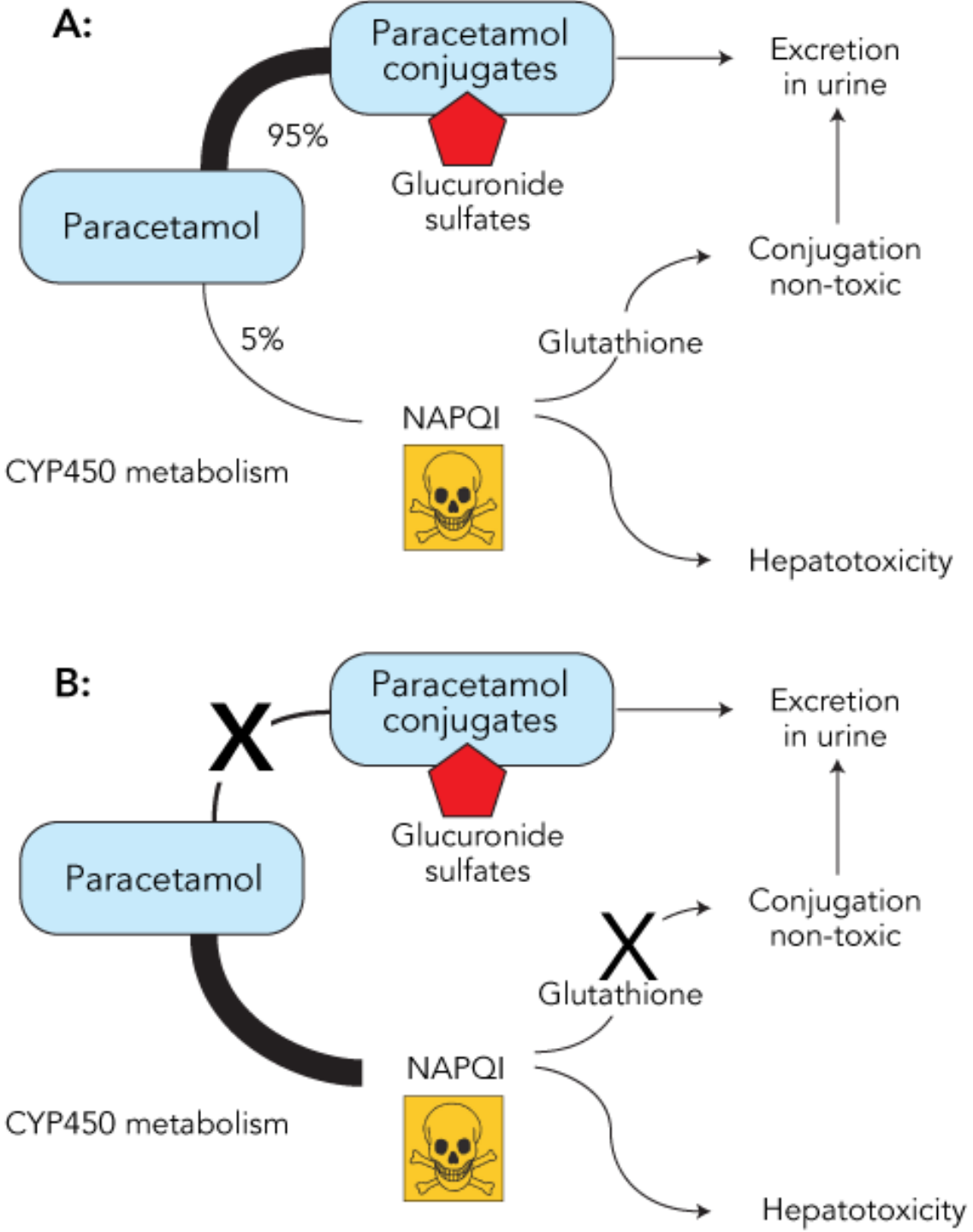

l-leucine
isoleucine
valine
2-oxo-isocaproate
2-oxo-3-methyl-n-valerate
2-oxoisovalerate
MSUD
isovaleryl-CoA
2-methylbutyryl-CoA
isobutyryl-CoA
isovaleric acidaemia
3-methylcrotonyl-CoA
tiglyl-CoA
methylacrylyl-CoA
3-methylcrotonyl CoA carbox def.
3-methylglutaconyl-CoA
2-methyl-3-(OH)butyryl-CoA
3-(OH)isobutyryl-CoA
3-methylglutaconic acidaemia
3-(OH)-3-methylglutaryl-CoA
2-methylacetoacetyl-CoA
3-(OH)isobutyrate
HMG CoA lyase def
β-ketothiolase def
methylmalonyl semialdehyde
acetoacetic acid
acetyl-CoA
propionyl-CoA
propionic acidaemia
methylmalonyl-CoA
methylmalonic acidaemia
succinyl-CoA
acylcarnitines
urine organic acids

Figure No. 1: DRUG METABOLISM PATHWAYS

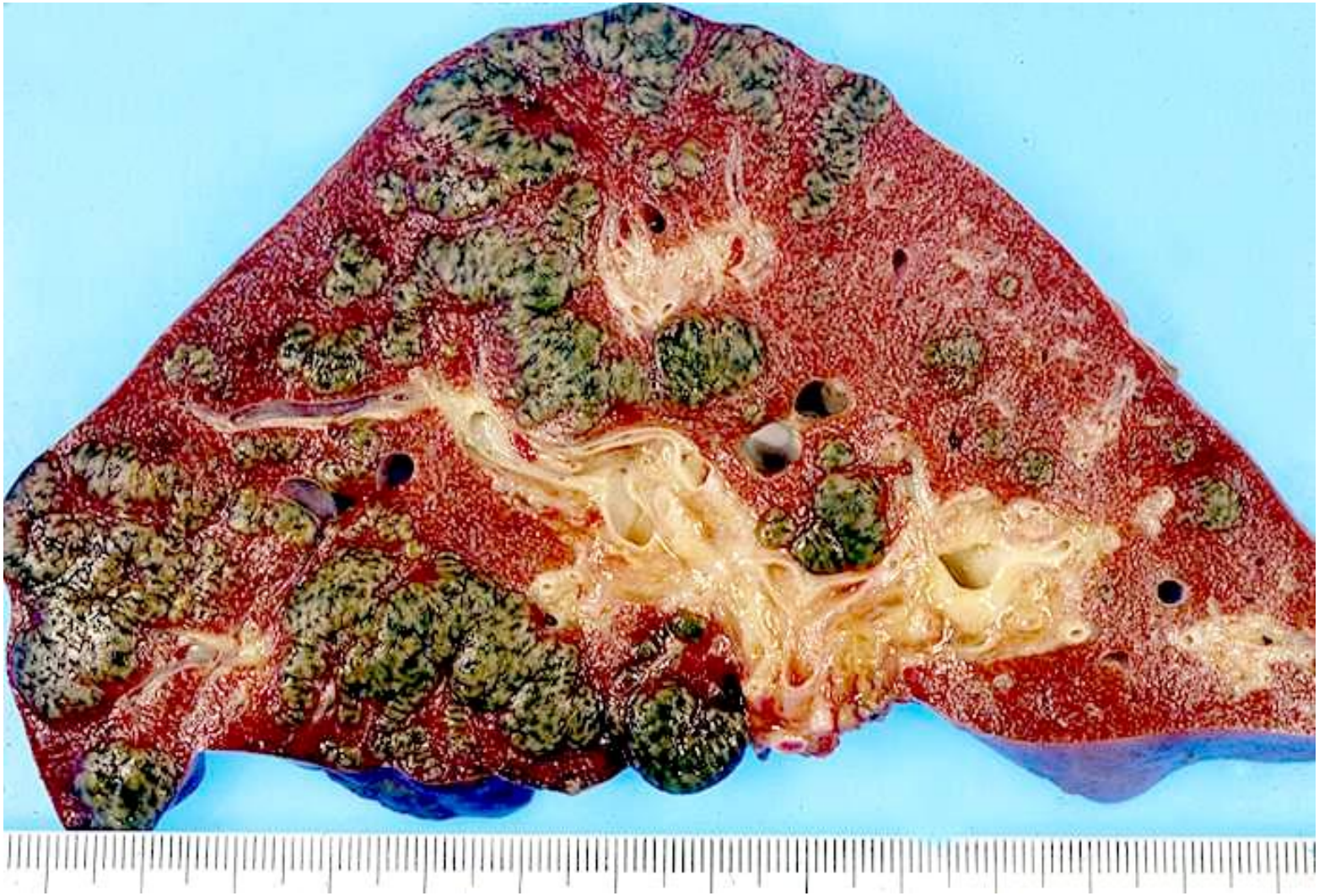


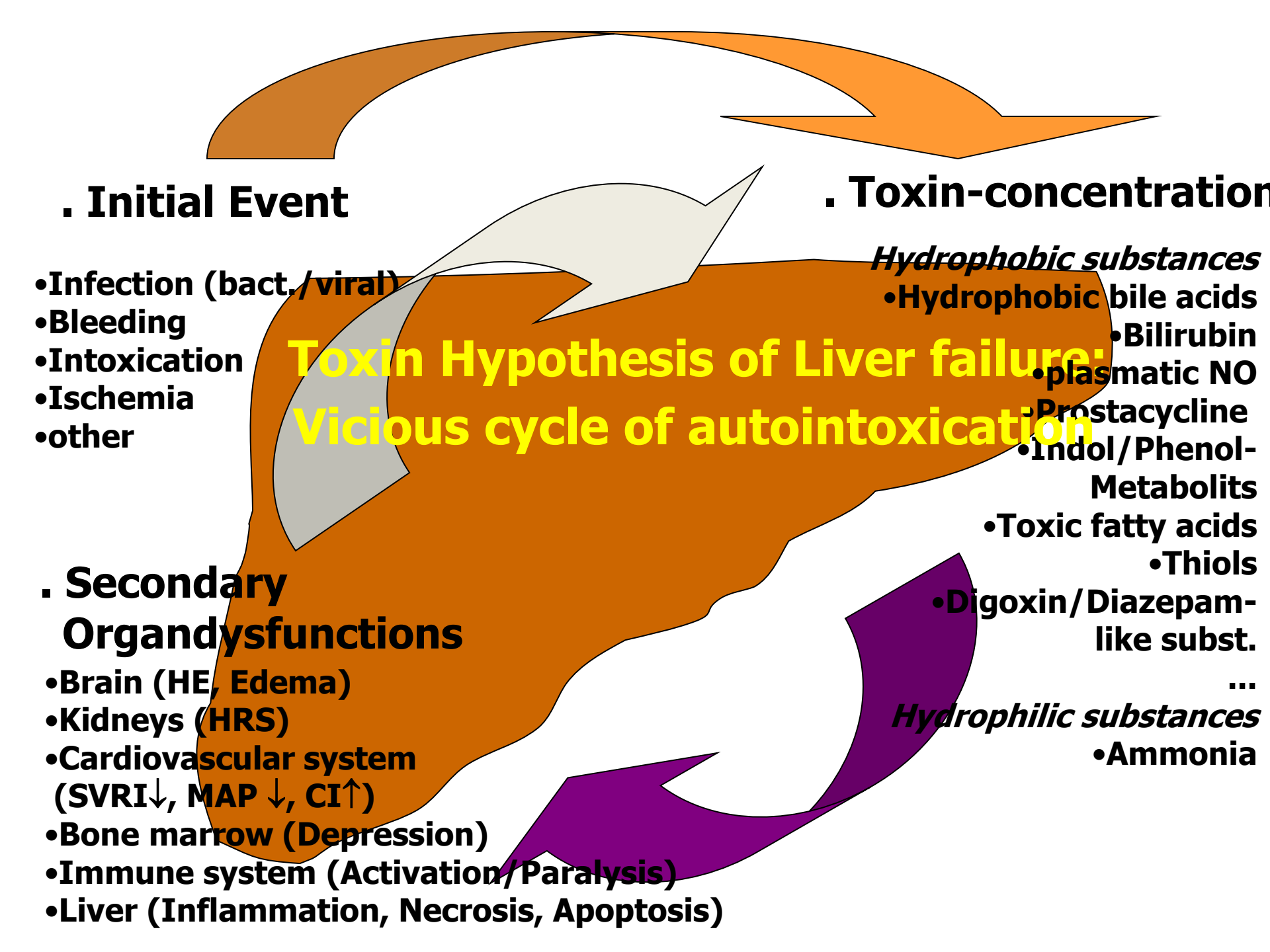

FAT-SOLUBLE
TOXINS
Phase 1
(Cytochrome P450 Enzymes)
Oxidation
Reduction
Hydrolysis
Hydration
Dehalogenation
INTERMEDIARY METABOLISM
Phase 2
(Conjugation Pathways)
Sulfation
Glucoronidation
Glutathione Conjugation
Acetylation
Amino Acid Conjugation
Methylation
WATER-SOLUBLE
WASTE
Eliminated via:
Urine
Bile
Stool
Nutrients Needed
• Vitamins B2, B3, B6, B12
• Folic Acid
• Glutathione
• Flavonoids
Nutrients Needed
• Methionine
• Cysteine
• Magnesium
• Glutathione
• Vitamin B5, B12
• Vitamin C
• Glycine
• Taurine
• Glutamine
• Folic Acid
• Choline


Exotoxins
Endotoxins
PHASE I
P450 Enzymes
B Vitamins
Minerals
BCAAs
Bioflavonoids
Glutathione
Intermediary metabolites
Reactive Molecules
PHASE II
Glutathione Transferases
Amino Acids
PHASE III
Less Reactive Metabolites
Bile
Feces
Serum
Kidney
Urine
Tissue Damage
Antioxidant Protection
Vitamins A, C, E
CoQ10
Selenium
Copper, zinc
Toxins excreted from the body

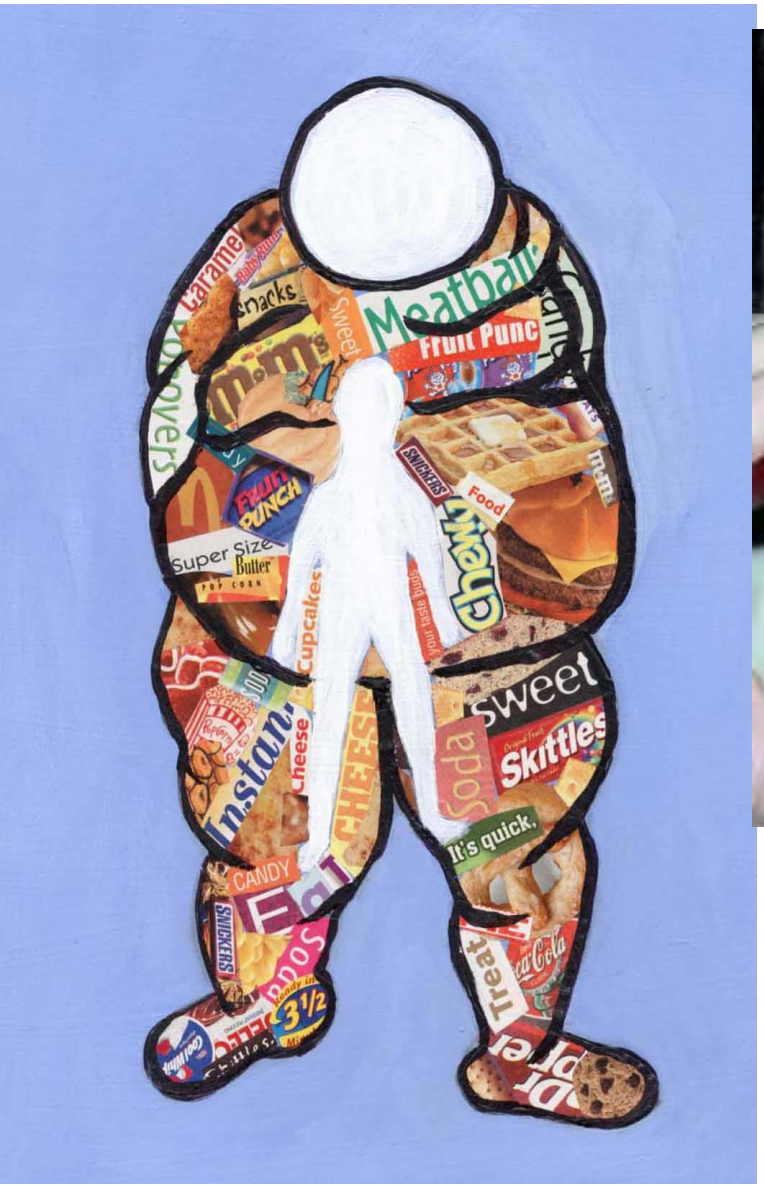

A:
Paracetamol conjugates
Excretion in urine
95%
Glucuronide sulfates
Paracetamol
Conjugation non-toxic
5%
Glutathione
NAPQI
CYP450 metabolism
Hepatotoxicity
B:
Paracetamol conjugates
Excretion in urine
Glucuronide sulfates
Paracetamol
Conjugation non-toxic
Glutathione
NAPQI
CYP450 metabolism
Hepatotoxicity

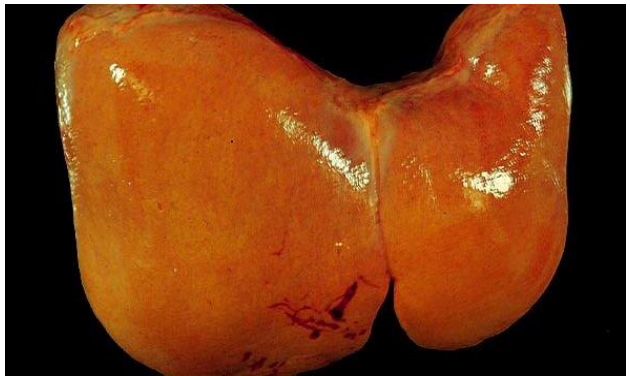
Detoxification Functions of Liver

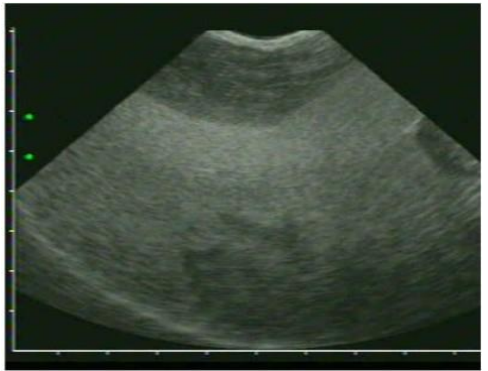



. Initial Event
•Infection (bact./viral)
•Bleeding
•Intoxication
•Ischemia
•other
. Toxin-concentration
Hydrophobic substances
•Hydrophobic bile acids
•Bilirubin
•plasmatic NO
•Prostacycline
•Indol/Phenol-Metabolits
•Toxic fatty acids
•Thiols
•Digoxin/Diazepam-like subst.
...
Hydrophilic substances
•Ammonia
Toxin Hypothesis of Liver failure:
Vicious cycle of autointoxication
. Secondary Organdysfunctions
•Brain (HE, Edema)
•Kidneys (HRS)
•Cardiovascular system (SVRI↓, MAP ↓, CI↑)
•Bone marrow (Depression)
•Immune system (Activation/Paralysis)
•Liver (Inflammation, Necrosis, Apoptosis)

NAFLD In Children

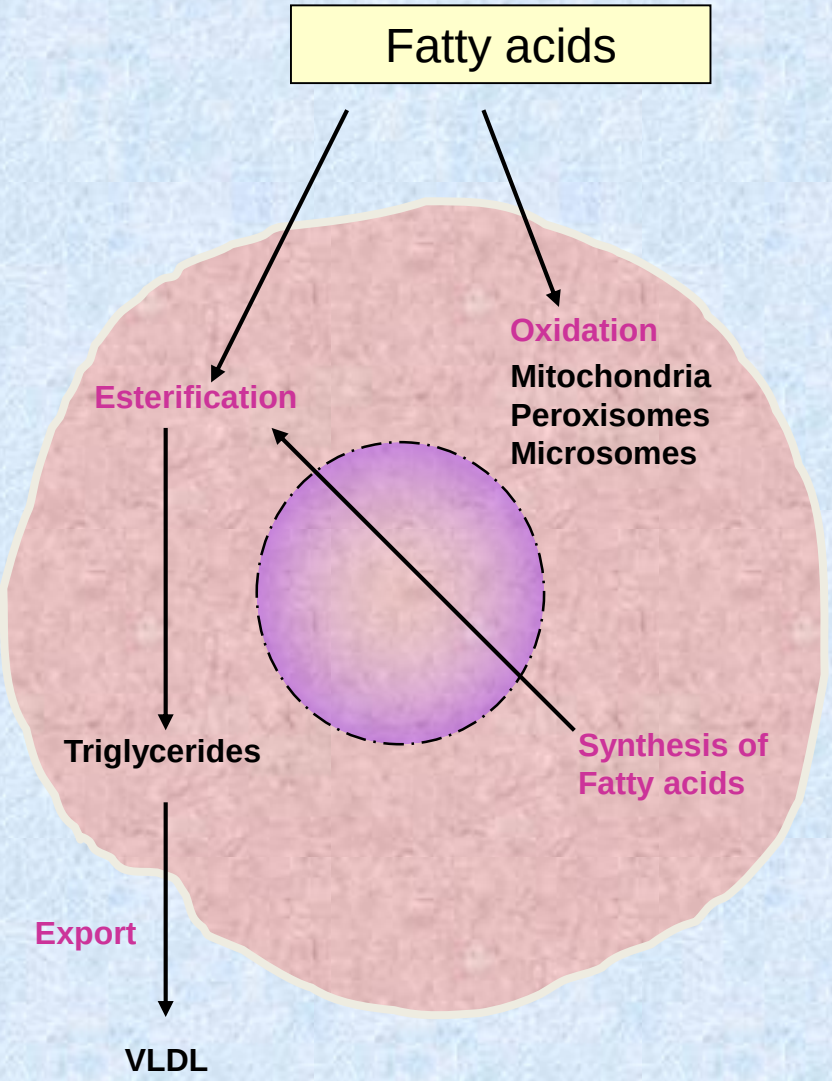


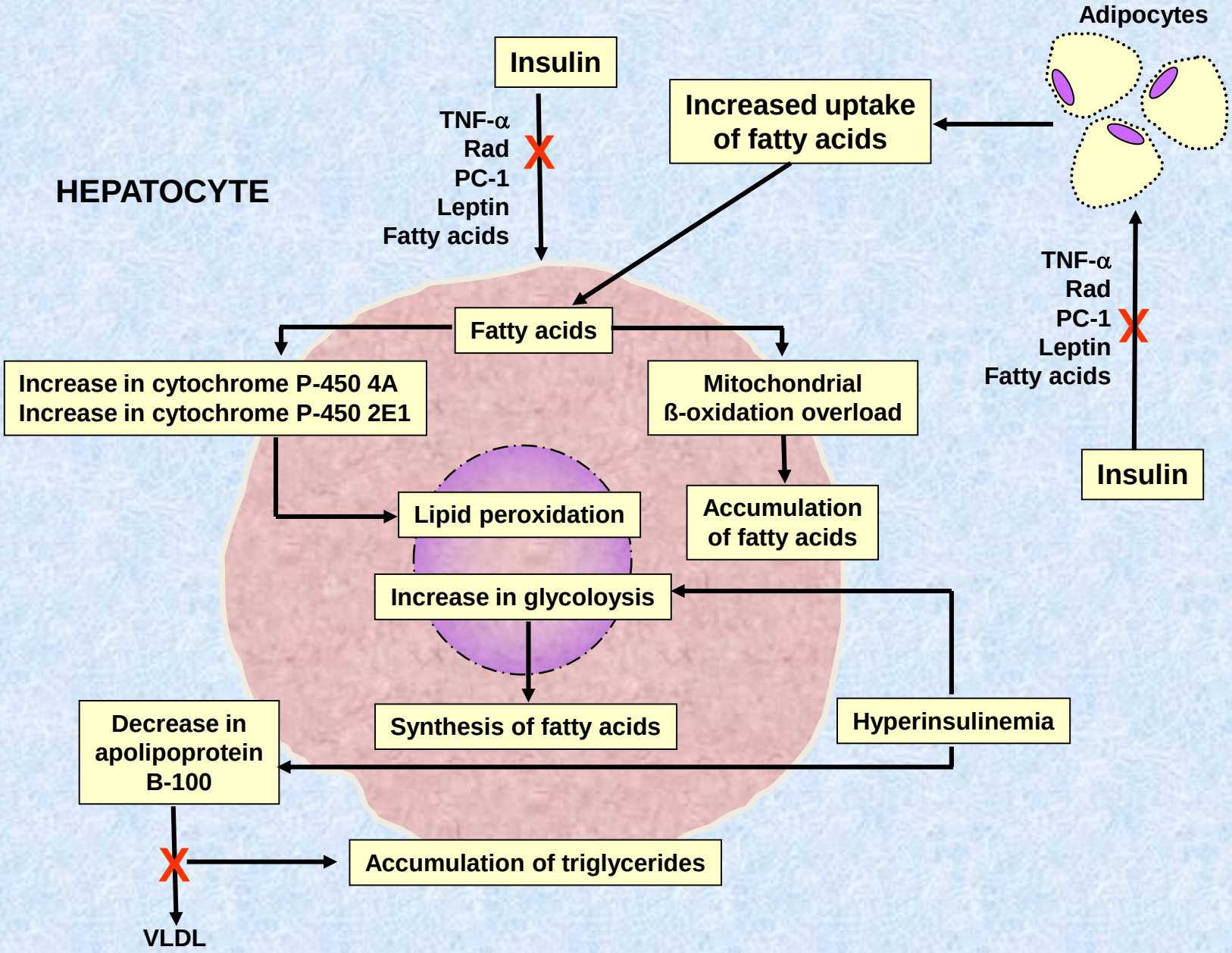


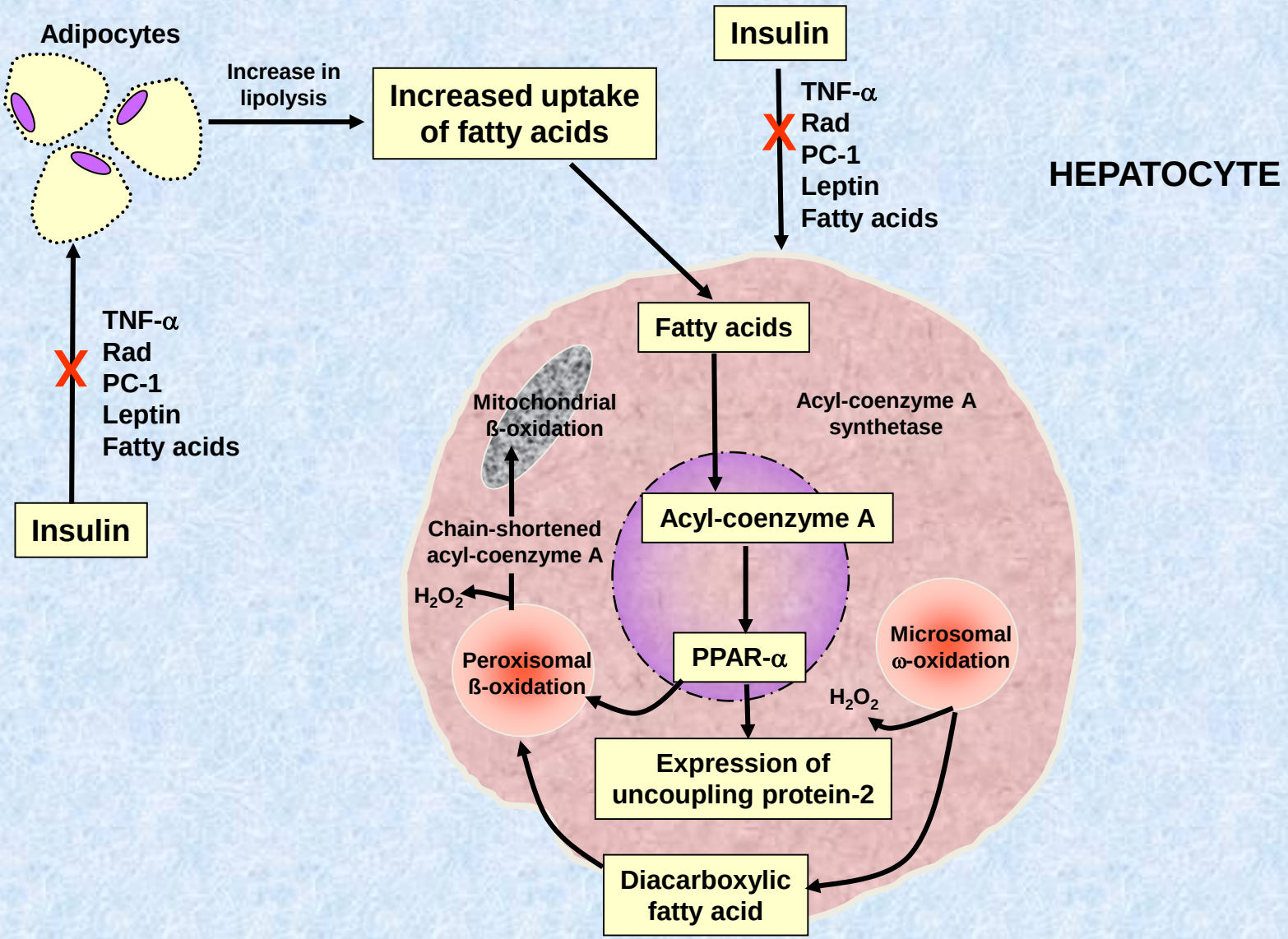


Pathogenesis of NAFLD

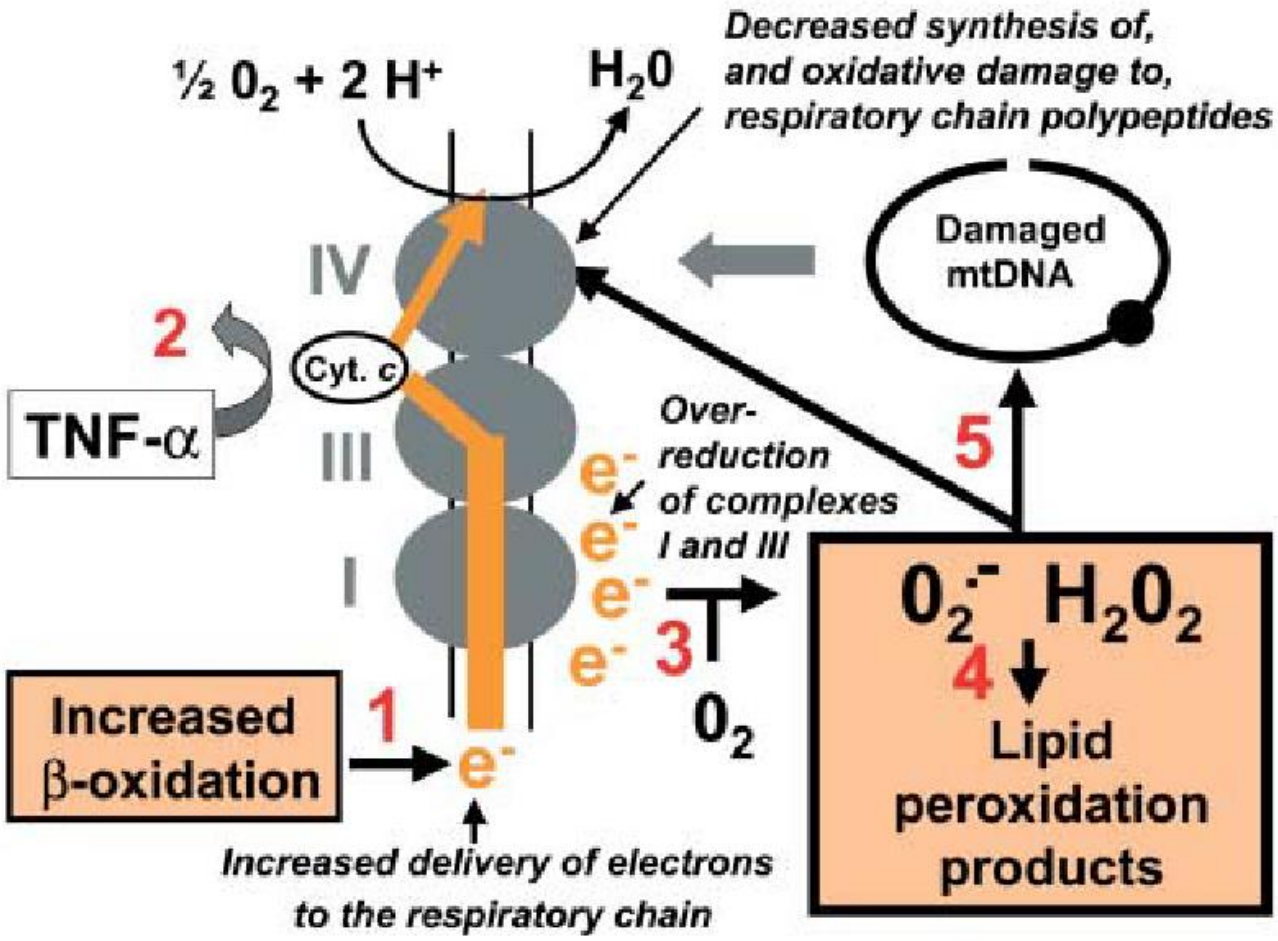
HEPATOCYTE


Fatty acids
Oxidation
Mitochondria
Peroxisomes
Microsomes
Esterification
Triglycerides
Synthesis of
Fatty acids
Export
VLDL


Adipocytes
Insulin
TNF-α
Rad
PC-1
Leptin
Fatty acids
Increased uptake of fatty acids
HEPATOCYTE
TNF-α
Rad
PC-1
Leptin
Fatty acids
Fatty acids
Increase in cytochrome P-450 4A
Increase in cytochrome P-450 2E1
Mitochondrial ß-oxidation overload
Insulin
Lipid peroxidation
Accumulation of fatty acids
Increase in glycoloysis
Synthesis of fatty acids
Hyperinsulinemia
Decrease in apolipoprotein B-100
Accumulation of triglycerides
VLDL

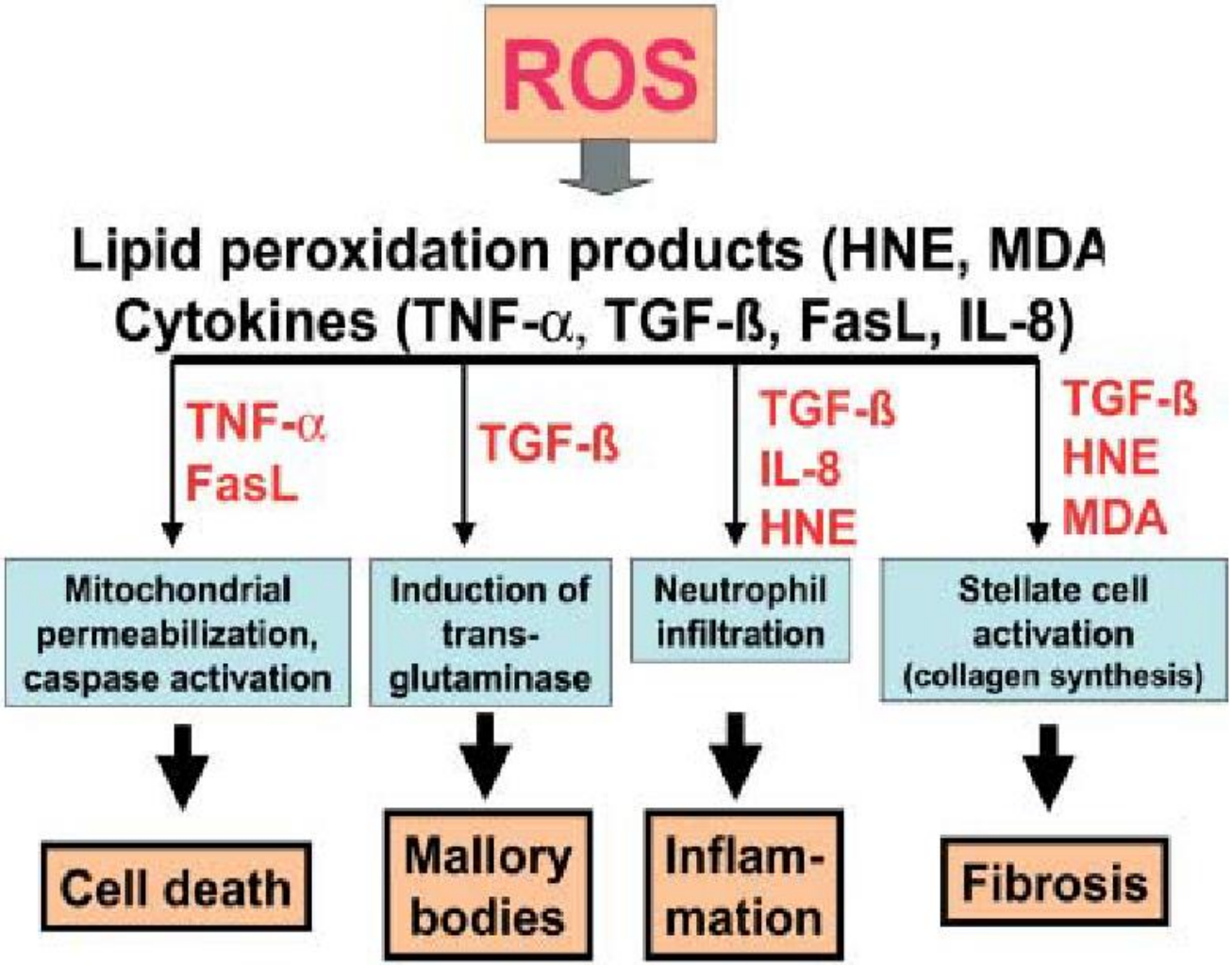

Adipocytes
Increase in lipolysis
Increased uptake of fatty acids
Insulin
TNF-α
Rad
PC-1
Leptin
Fatty acids
HEPATOCYTE
TNF-α
Rad
PC-1
Leptin
Fatty acids
Insulin
Fatty acids
Mitochondrial ß-oxidation
Acyl-coenzyme A synthetase
Acyl-coenzyme A
Chain-shortened acyl-coenzyme A
H_2O_2
Peroxisomal ß-oxidation
PPAR-α
Microsomal ω-oxidation
H_2O_2
Expression of uncoupling protein-2
Diacarboxylic fatty acid

Pathogenesis of NAFLD



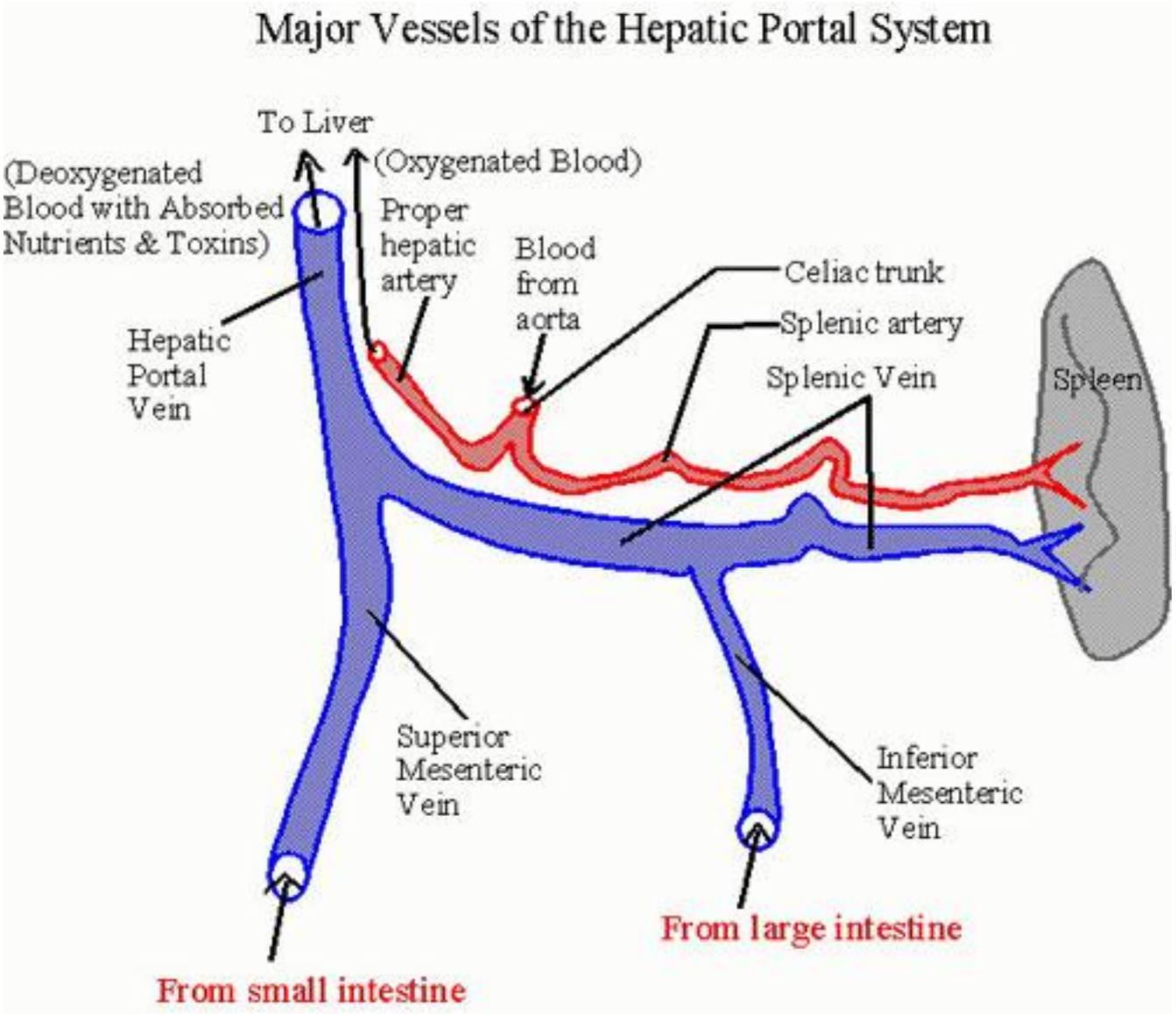
Pathogenesis of NAFLD

ROS to Steatohepatitis

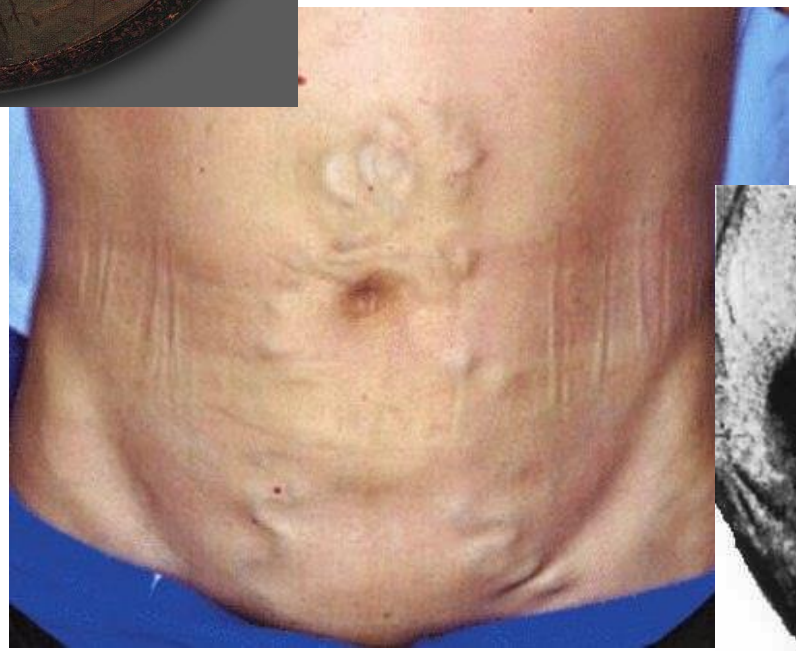


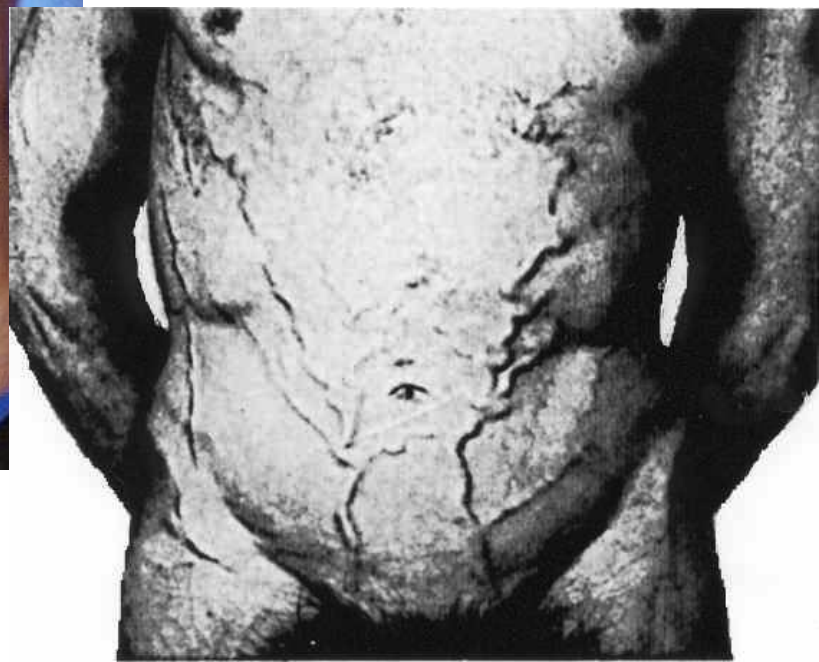
Vascular Pathologies

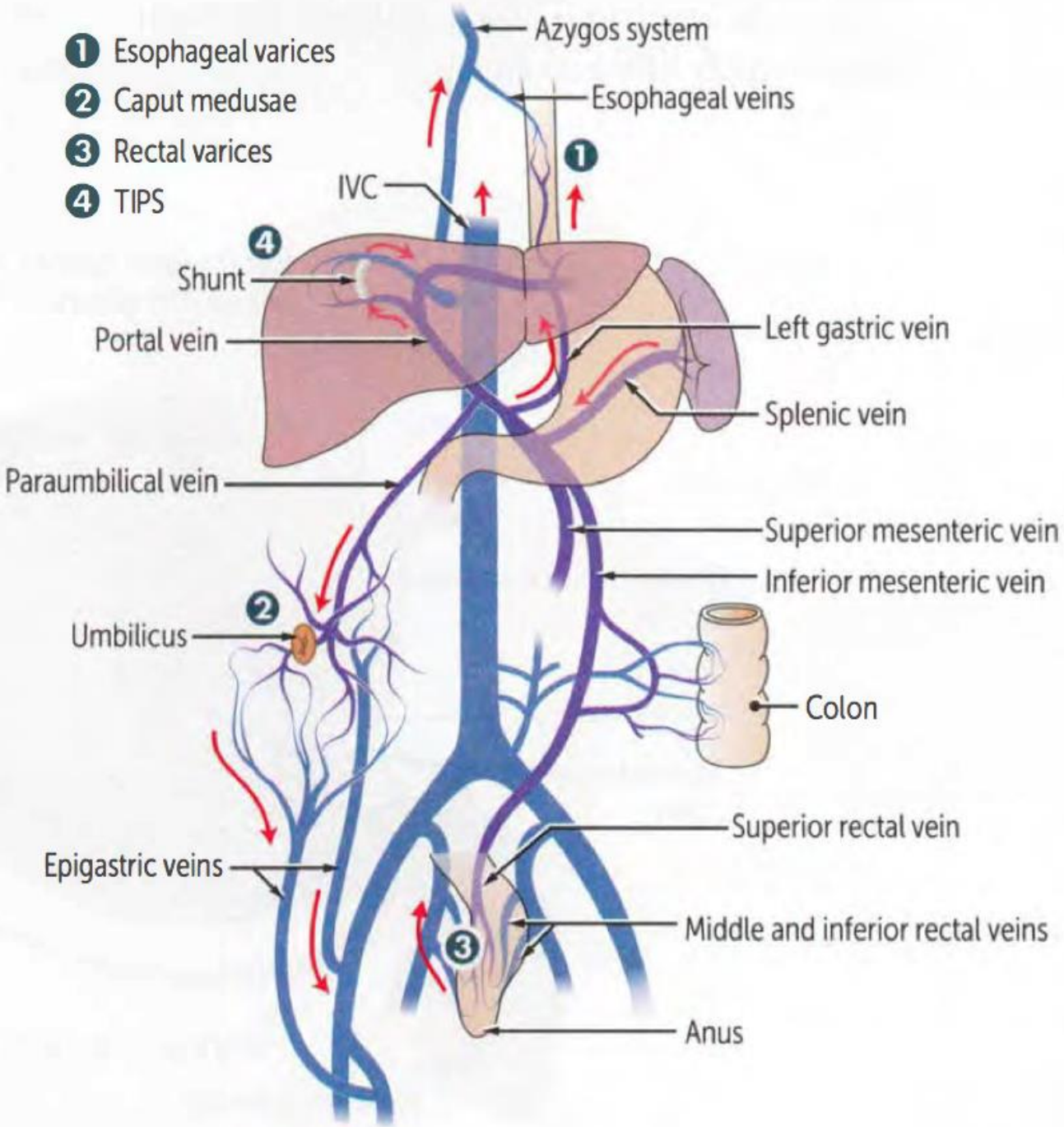
- Portal inflow
  - EHPVO
  - Portal Vein Sclerosis
- Hepatic artery pathologies
  - Rare , hepatic artery problems more seen after LTx
- Hepatic venous outflow
  - Budd Chiari Syndrome
  - Sinusoidal obstruction syndrome

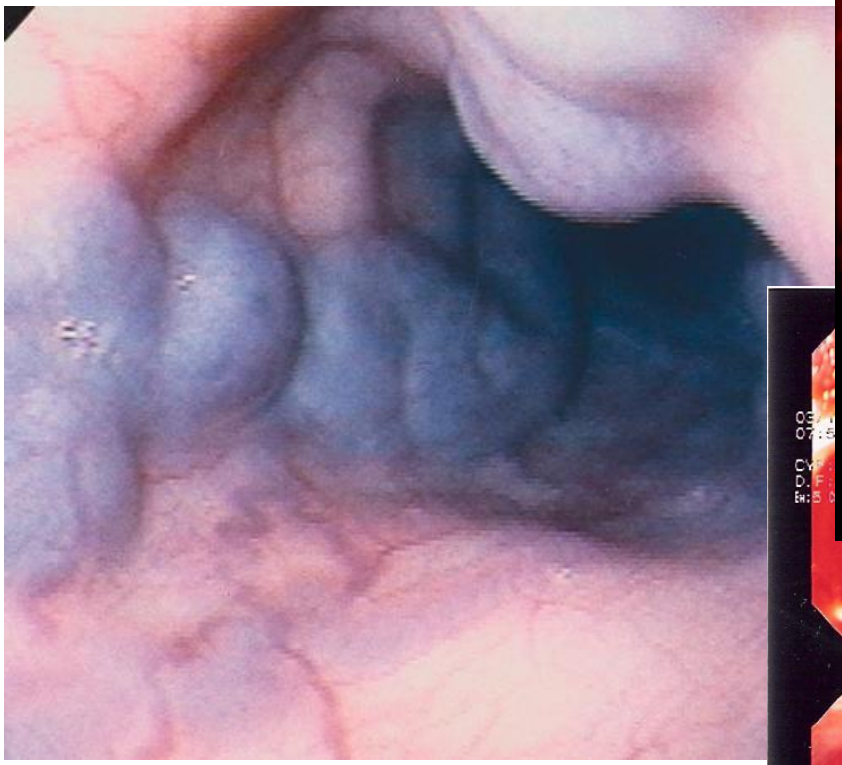

Major Vessels of the Hepatic Portal System
To Liver
(Deoxygenated Blood with Absorbed Nutrients & Toxins)
(Oxygenated Blood)
Proper hepatic artery
Blood from aorta
Celiac trunk
Splenic artery
Splenic Vein
Spleen
Hepatic Portal Vein
Superior Mesenteric Vein
Inferior Mesenteric Vein
From large intestine
From small intestine

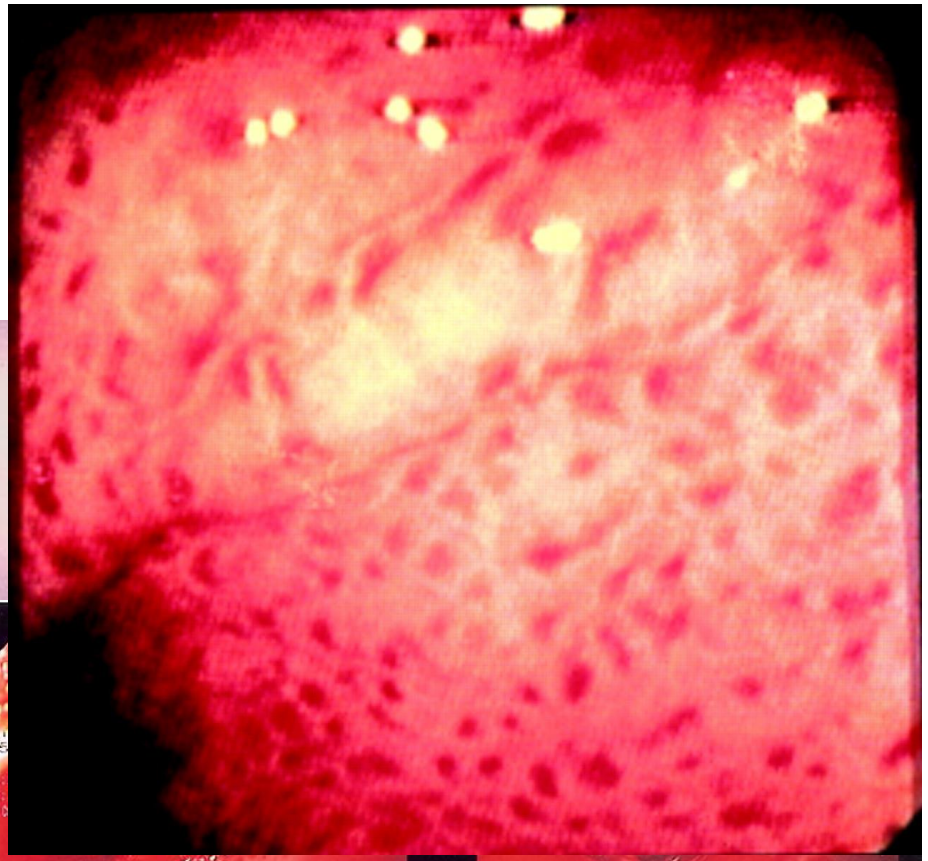
Medussa Head venous pattern

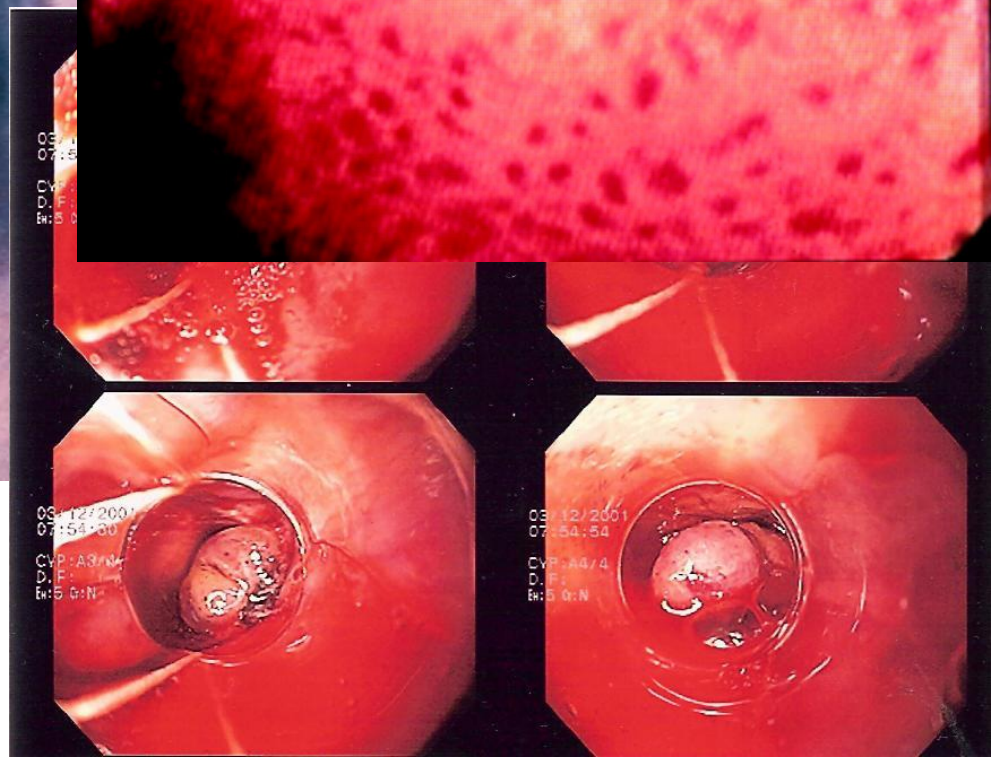





1 Esophageal varices
2 Caput medusae
3 Rectal varices
4 TIPS
Azygos system
Esophageal veins
IVC
Shunt
Portal vein
Left gastric vein
Splenic vein
Paraumbilical vein
Superior mesenteric vein
Inferior mesenteric vein
Umbilicus
Colon
Superior rectal vein
Epigastric veins
Middle and inferior rectal veins
Anus






03/12/2001
07:54:54
CVP:A4/4
D.F:
EM:5 G:N

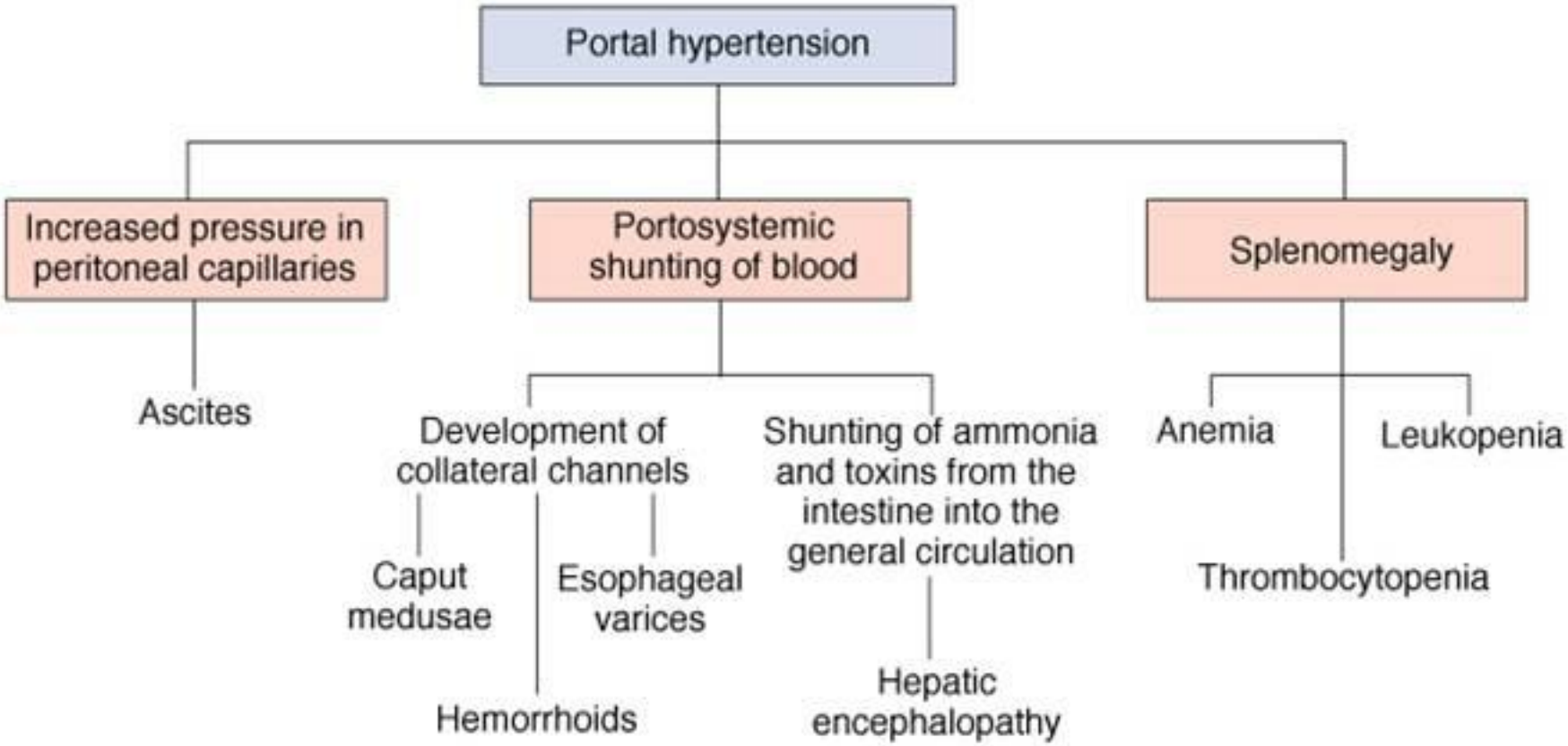
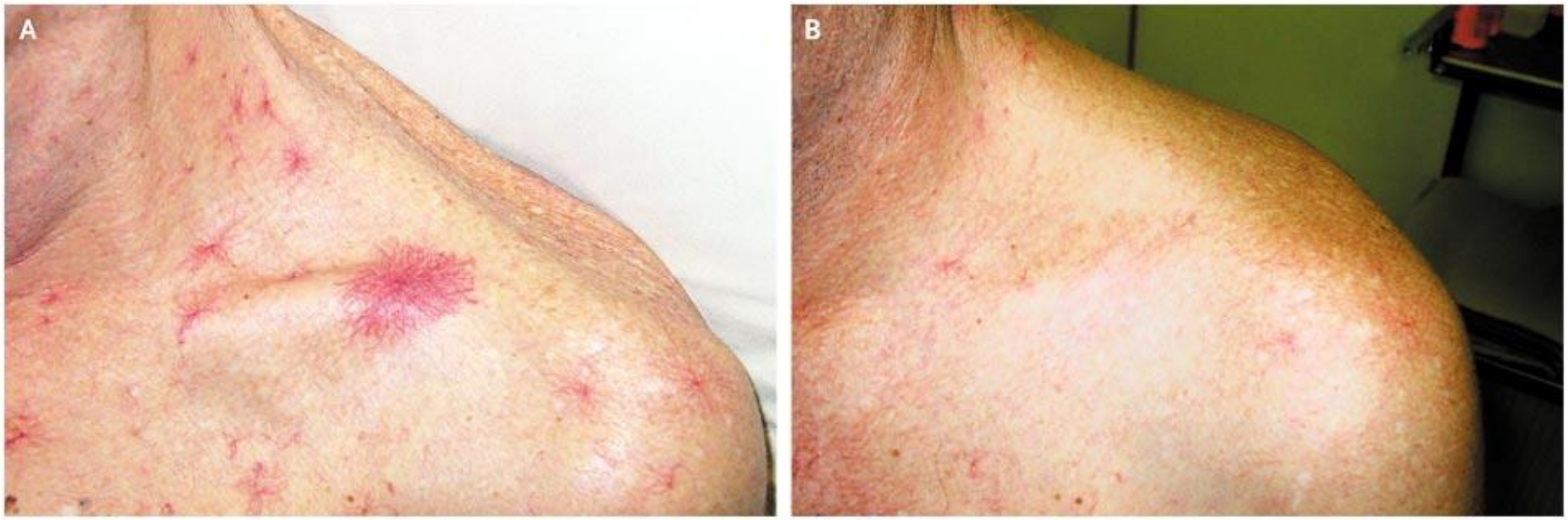


Figure 40-13 Mechanisms of disturbed liver function related to portal hypertension.

Spider Naevi



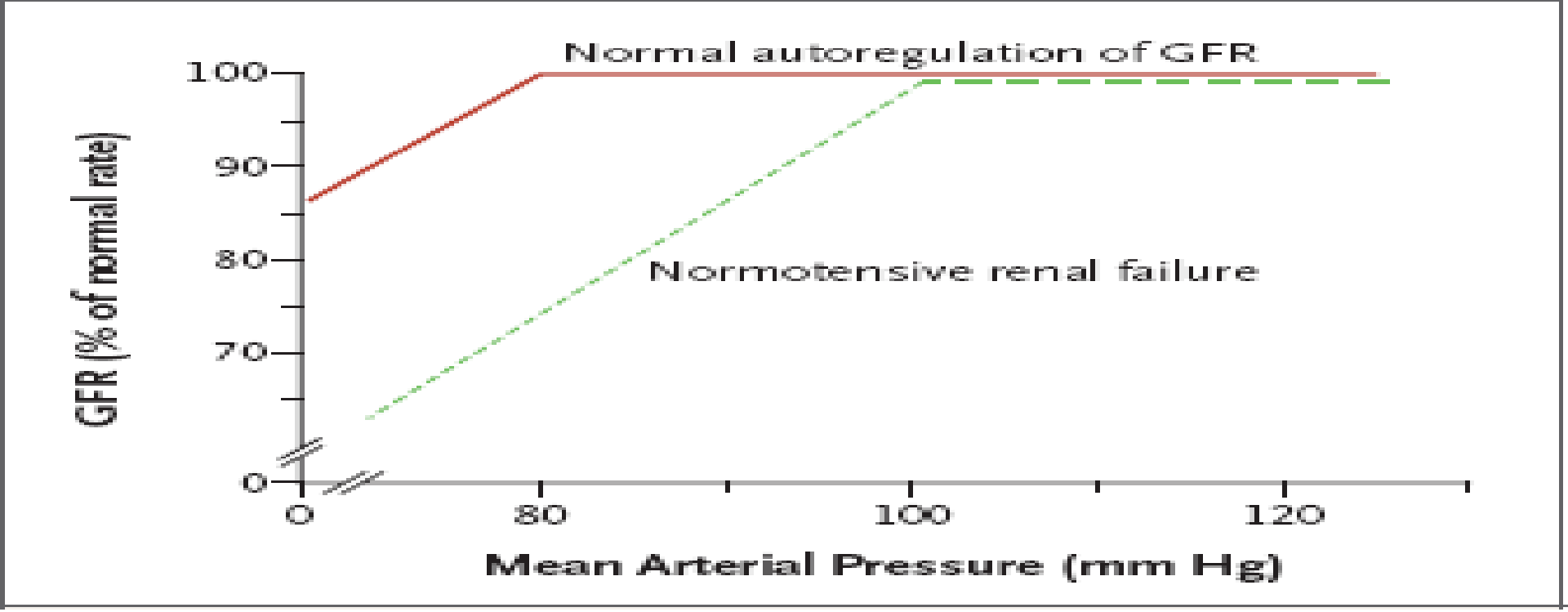
Renal Involvement In Liver Disease

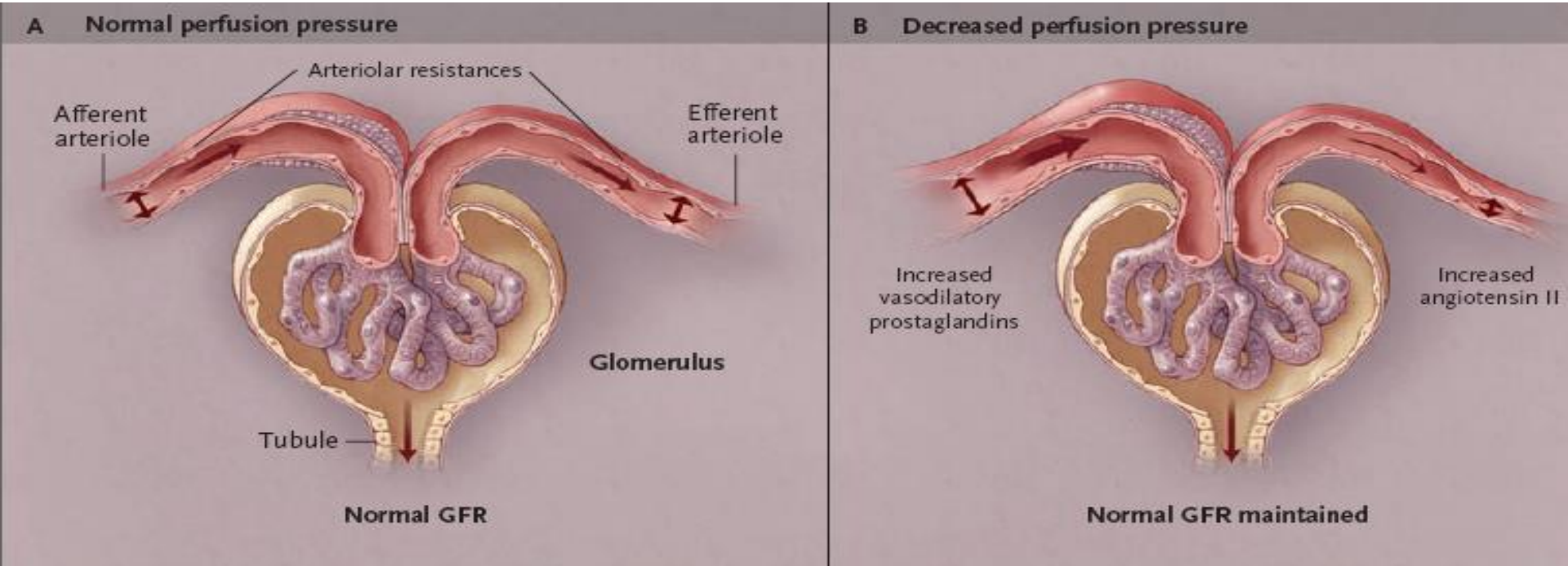
Pathogenesis of Acute Kidney Injury

Arterial vasodilatation (''VASOPLEGIA'')

Decreased SVR High Cardiac Output

Renal Auto-regulation becomes Pressure Dependent - Intra-renal Vasoconstriction

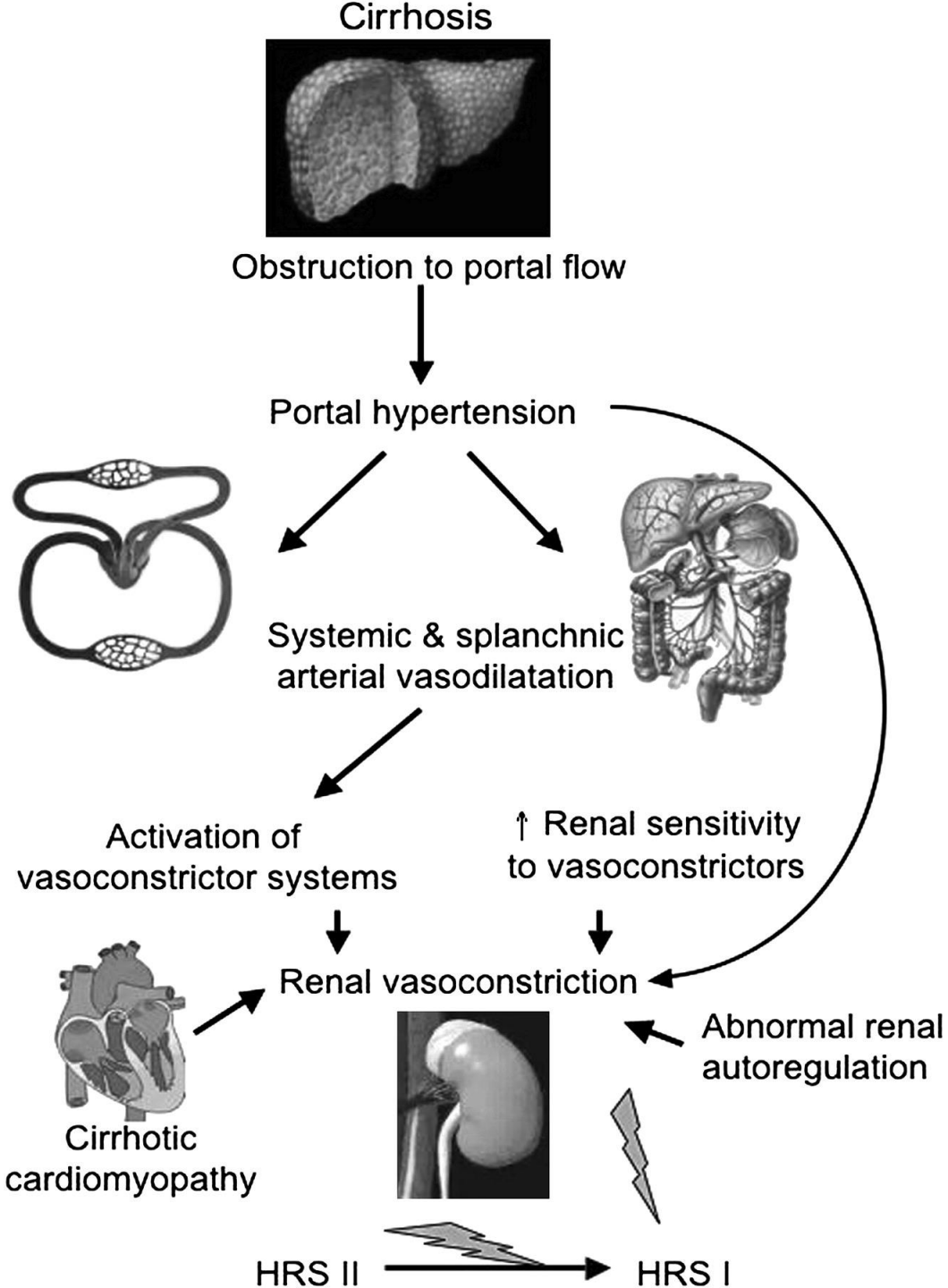

Normal autoregulation of GFR
Normotensive renal failure
GFR (% of normal rate)
100
90
80
70
0
0
80
100
120
Mean Arterial Pressure (mm Hg)


A Normal perfusion pressure
Arteriolar resistances
Afferent arteriole
Efferent arteriole
Glomerulus
Tubule
Normal GFR
B Decreased perfusion pressure
Increased vasodilatory prostaglandins
Increased angiotensin II
Normal GFR maintained

Aetiology of renal involvement in LD

- Multifactorial
- Hypovolaemia induced pre-renal AKI
- Acute tubular necrosis due to profound hypovolemia and hypotension.
- Direct drug nephrotoxicity (paracetamol, NSAIDs) OR Drugs affecting both liver/kidney
- Hepatorenal syndrome
- Intra-abdominal hypertension (IAH) and development of ICS

HEPATO-RENAL SYNDROME


Cirrhosis
Obstruction to portal flow
Portal hypertension
Systemic & splanchnic arterial vasodilatation
Activation of vasoconstrictor systems
↑ Renal sensitivity to vasoconstrictors
Renal vasoconstriction
Abnormal renal autoregulation
Cirrhotic cardiomyopathy
HRS II
HRS I

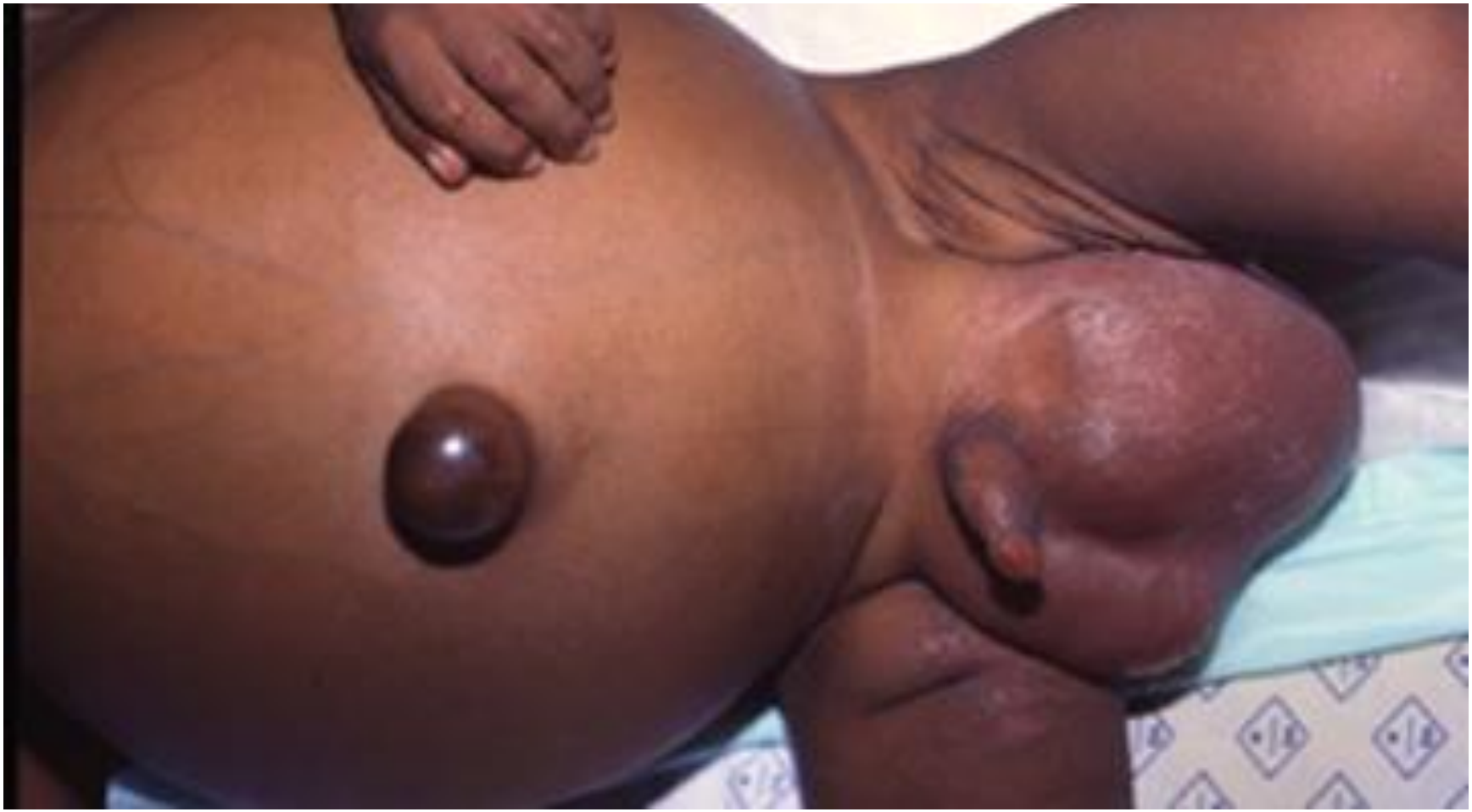
HRS - Diagnosis of exclusion

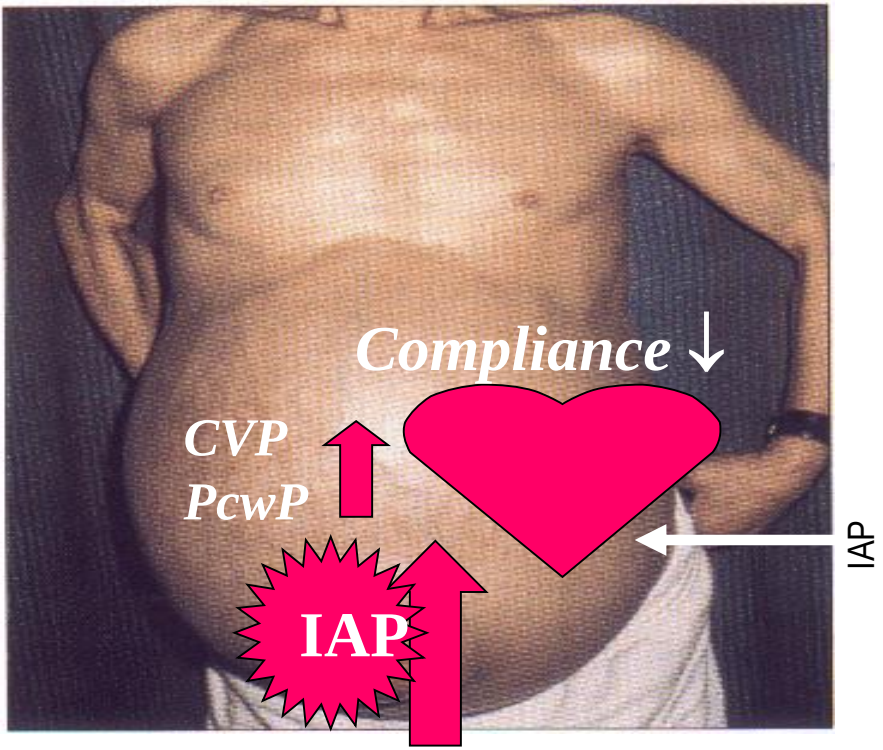
- Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure
- **The diagnosis of HRS is one of exclusion, so investigations should be performed to rule out other common causes of AKI.**

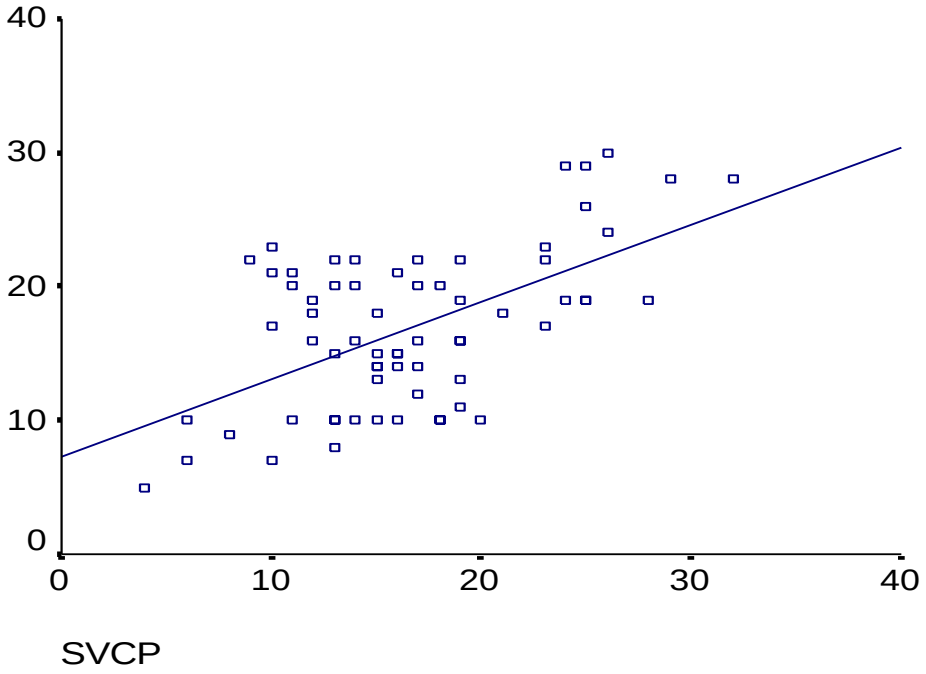
Characteristics of Type 1 and Type 2 Hepatorenal Syndrome

	Course	Precipitating Event	History of Diuretic-Resistant Ascites	Prognosis
Type -1 HRS	Precipitous doubling of serum creatinine in < 2 weeks	Present in > 50% of cases	May or may not be present	Without therapy-90-day survival of 10%
Type -2 HRS	Gradually progressive	Absent	Always Present	Median survival-6 months

Ascites



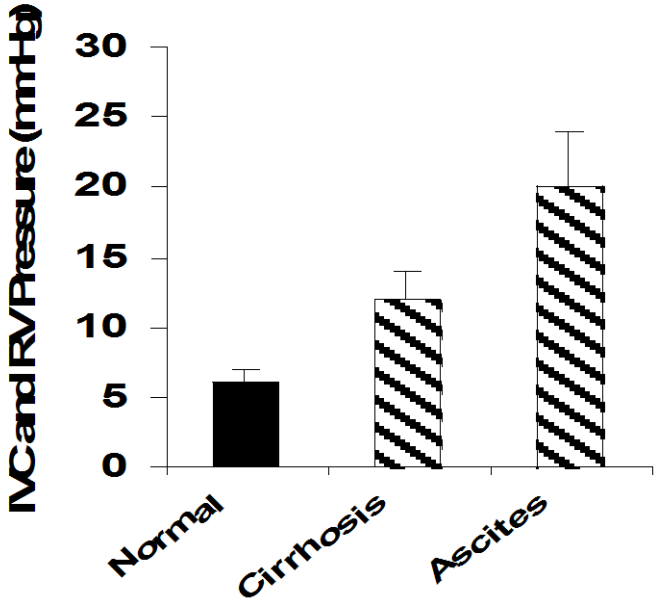




Intra-abdominal pressure

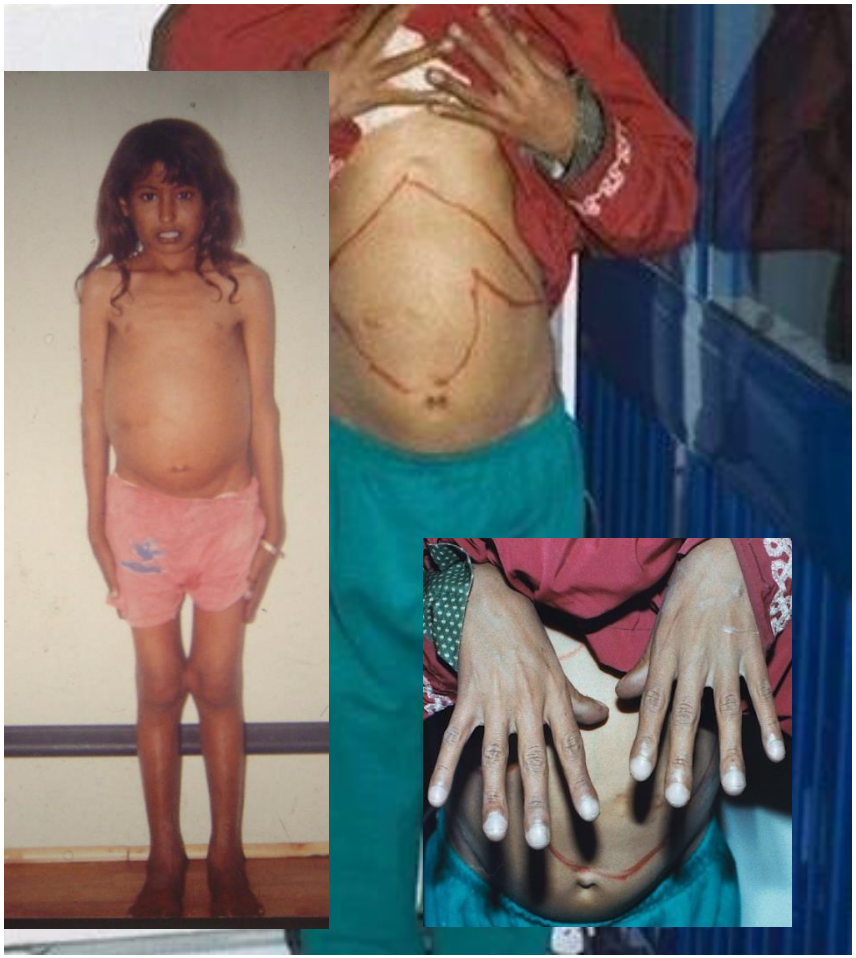
Sugrue et al Arch Surg 1999 134:1082
Malbrain CCM 2005;33:315

263 patients 40.7% increased IAP
Renal dysfunction:
32% with IAP elevated
14% with normal IAP
32% IAP > 12
40% IAP > 20



HEPATOPULMONARY SYNDROME

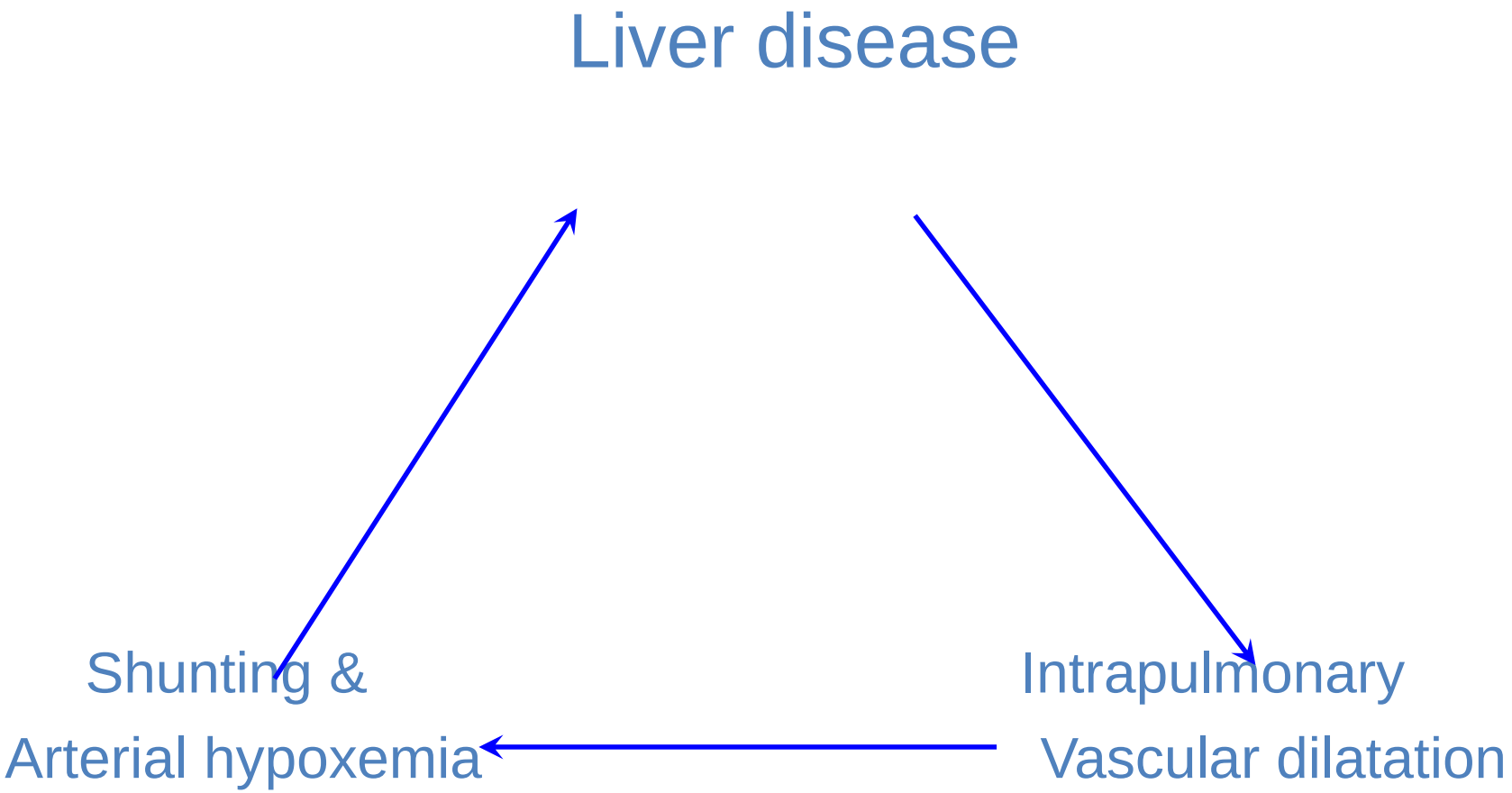
HPS and clubbing in CLD



Definition – HEPATOPULMONARY SYNDROME

Arterial Oxygenation Defect induced by intrapulmonary vascular dilatation(IPVD) associated with hepatic disease

Hepatopulmonary syndrome (HPS)

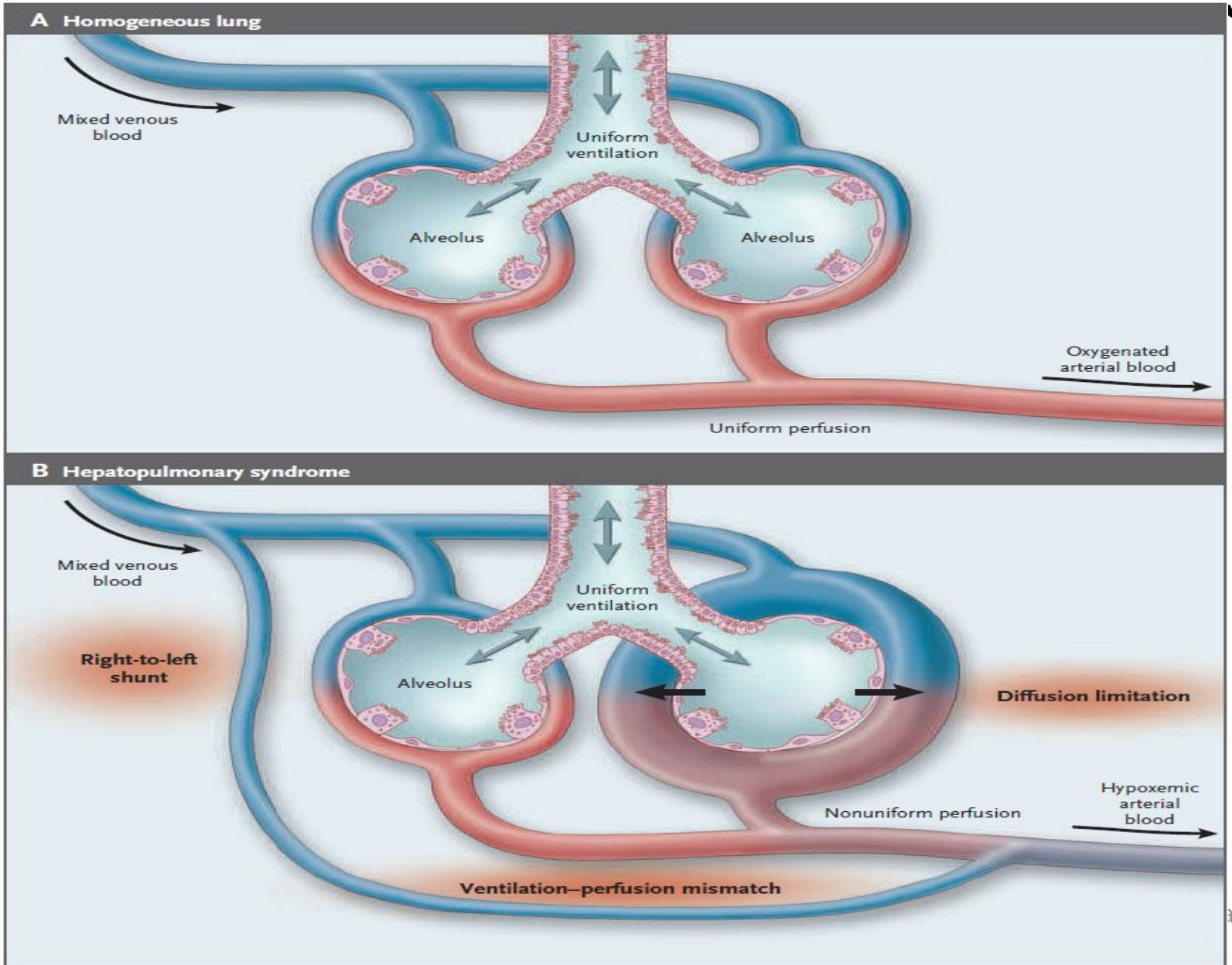


In absence of intrinsic cardiopulmonary disease

Pathogenesis

- Enhanced pulmonary production of nitric oxide
- Exhaled nitric oxide increased in HPS , normalise after transplant
- Nitric oxide synthesized by nitric oxide synthase – eNO and iNO
- eNO – pulmonary endothelial cells
- iNO – alveolar macrophages
- Endothelin 1 acts through ET-A (vascular smooth muscle)or ET-B receptors (pulmonary endothelium)
- ET-A causes vasoconstriction, ET-B causes vasodilatation

Mechanism of hypoxaemia in HPS



Clinical Features of HPS

- Non-specific
- Dyspnoea at rest/exertion
- Platypnoea/orthodeoxea – Arterial PaO2 decreases by 5% or more when the patient moves from a supine to an upright position -further ventilation-perfusion mismatch
- Spider nevi, digital clubbing, cyanosis
- Differential Diagnosis :

❑ Several pulmonary complications or pleural complications

❑ Porto-pulmonary hypertension (PPHTN)

CARDIOVASCULAR INVOLVEMENT IN ALF

Cardiovascular changes in ALF - Pathogenesis

- Multi-factorial
- Lesser intake, ongoing losses - hypovolaemia
- Severe SIRS and sepsis play a paramount role.
- Vasodilatation - due to loss of vascular tone leads to systemic hypotension, low effective arterial blood volume and high cardiac output
- Cytokine release from the failing liver appears to be partly responsible for the observed haemodynamic disturbances
- Subclinical myocardial injury

Implication

The associated cardiovascular collapse and organ hypo-perfusion may be central to the progression of multiple organ failure

Strategy

- Target hypovolaemia - fluids
- Target SIRS, infection - antibiotics
- Target vasodilatation – vasopressors- noradrenaline , vasopressin
- If myocardial depression - Inotropes
- Target Adrenal insufficiency
- **Optimise oxygen delivery**

Neurological Involvement In Liver Disease

Neurologic Support; Brain Swelling

Acute Hepatic Dysfunction

Neurotoxins; ↑ Ammonia

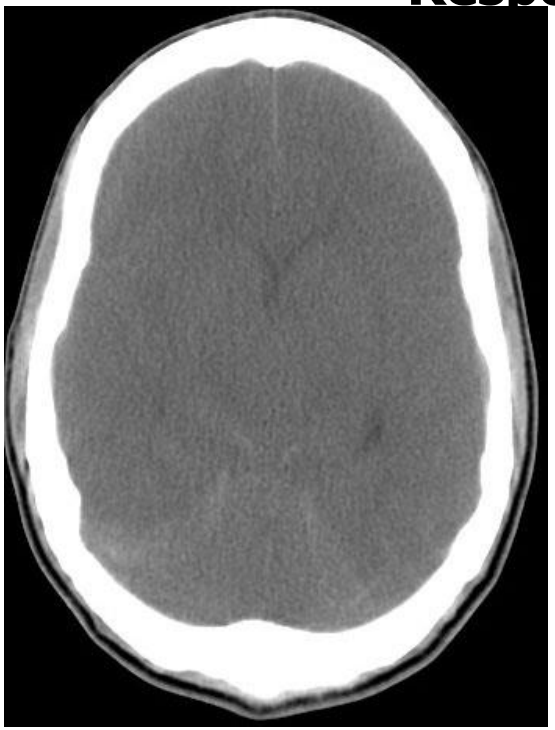
Astrocytic metabolism to glutamine

Increased intra-cellular osmotic load

Mitochondrial toxicity

Failure of energy metabolism

Neurotransmitter alterations



Systemic Inflammatory Response

Vascular function

Vasomotor dysfunction
Endothelial dysfunction

Alterations in BBB ?

Water/neurotoxin permeability

Mitochondrial toxicity

Failure of energy metabolism

Neurological involvement in ALF

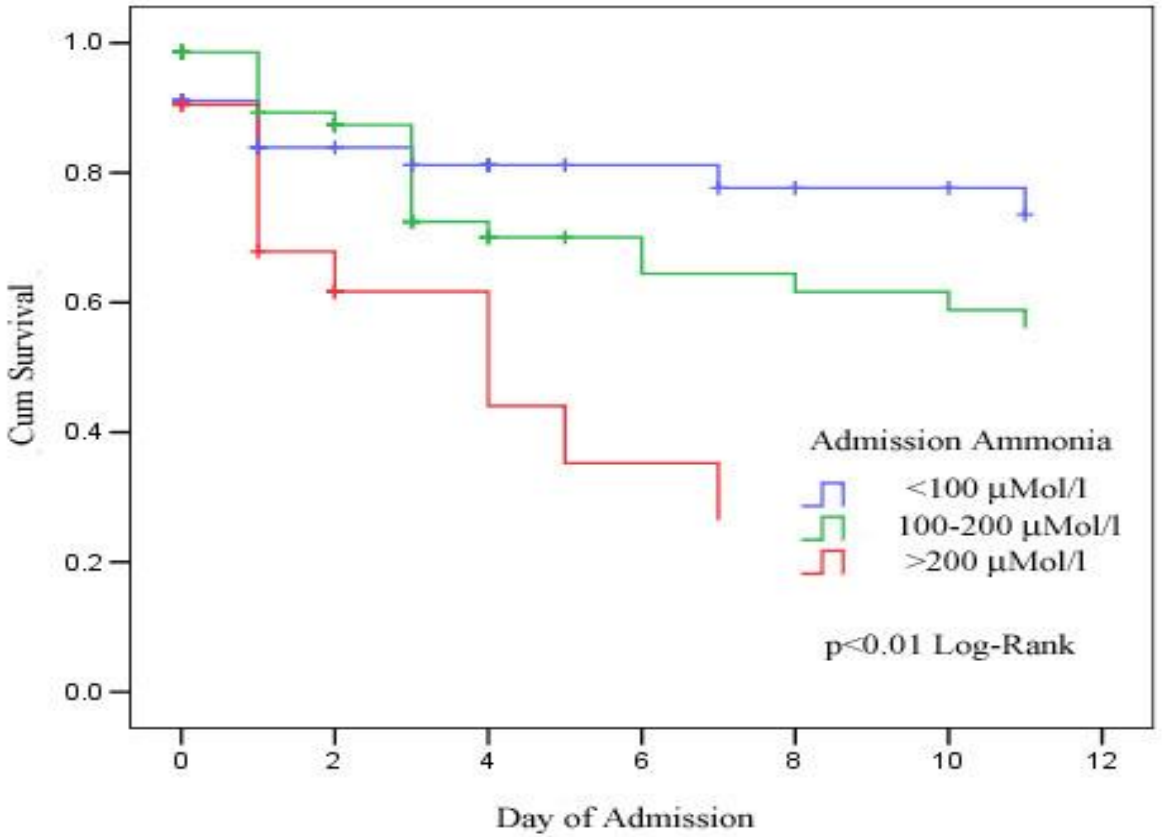
- Highly contentious in ALF
- Concept of Hyperaemia vs Ischaemia
- Risk factors for ICP ??
- Neuro-critical care monitoring –To Bolt or Not to bolt ???
- Role of non/minimally invasive monitoring ??
- Management uncertainties ??????

Who is at risk of raised ICP?

- 25-75% of ALF with Grade iii/iv encephalopathy
- Rapid onset
- High ammonia
- Younger age
- Inotropic support
- RRT

Neurologic Support; Arterial Ammonia and Risk of Cerebral Oedema

ALF Cases, n=165



BERNAL W, ET AL. *HEPATOLOGY* 2007; 46:1844-52

Why does raised ICP matter

- Compromises CPP
- Transtentorial herniation
- 2nd commonest cause of death in ALF
- Does measuring it help?

Summary

Presentation of cirrhosis/portal hypertension.

Conclusions

Understanding of applied anatomy and physiology is essential to understand the complications and natural history of liver disease