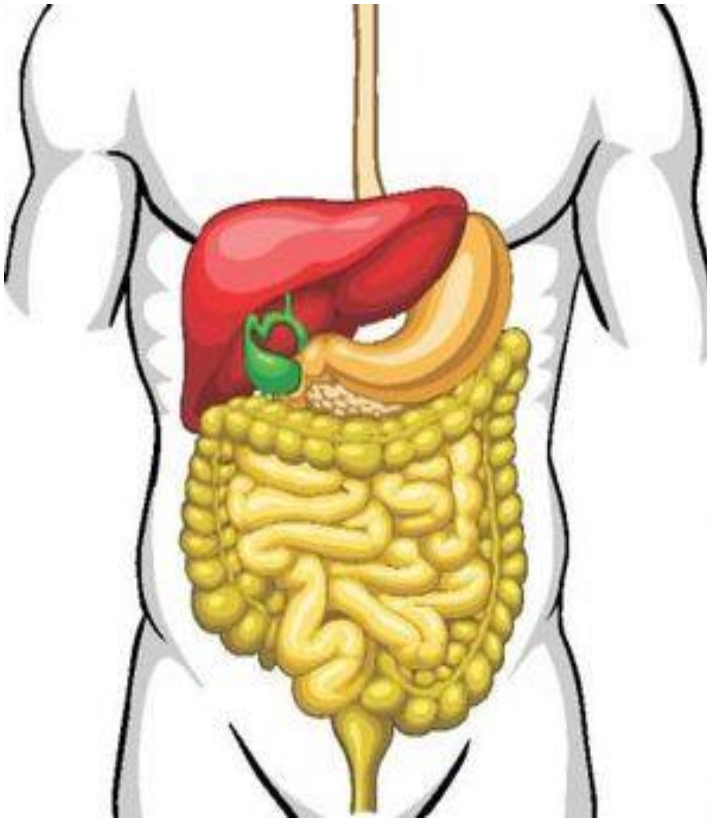
Patho physiology of liver disease



Major hepatic functions

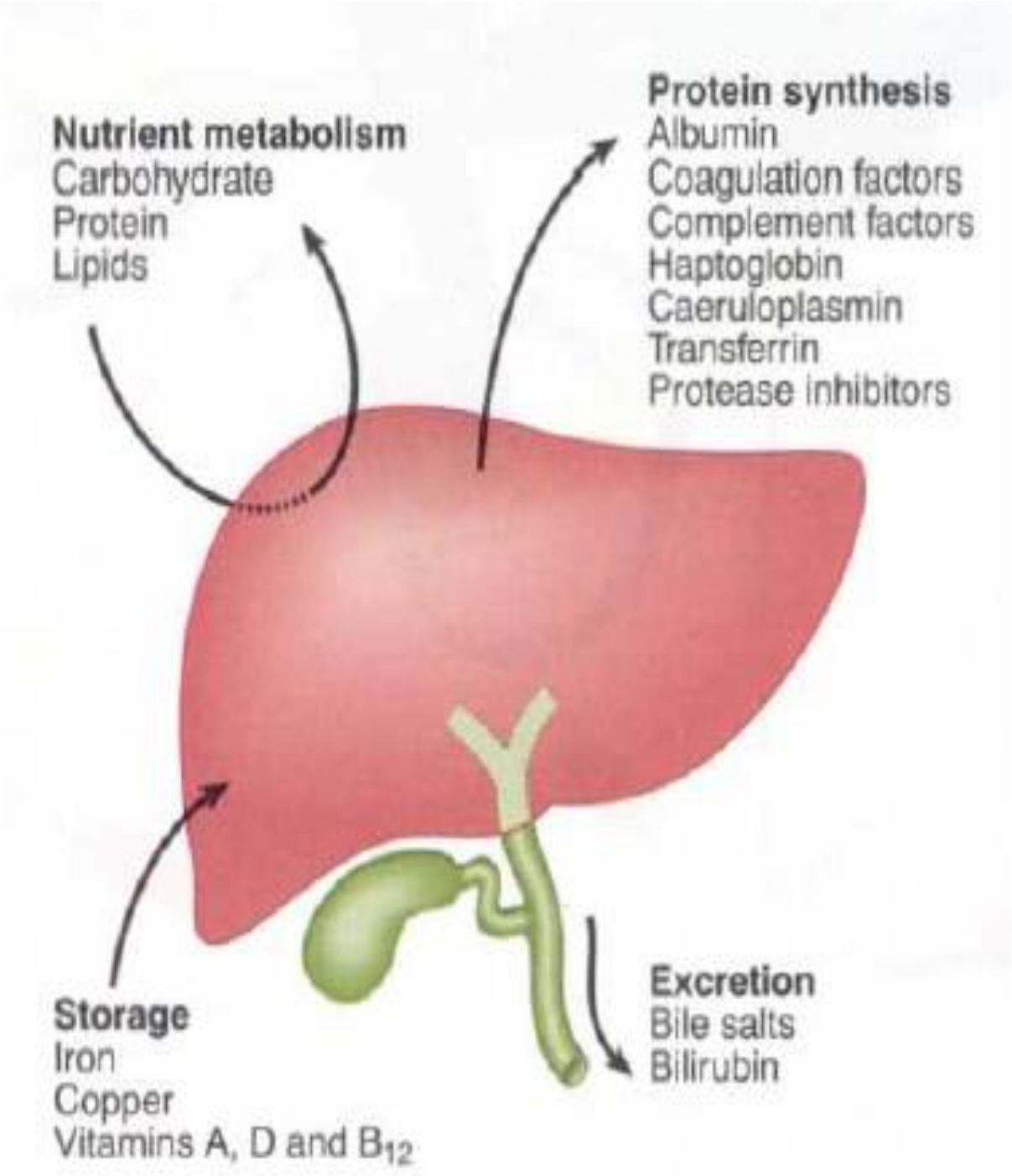
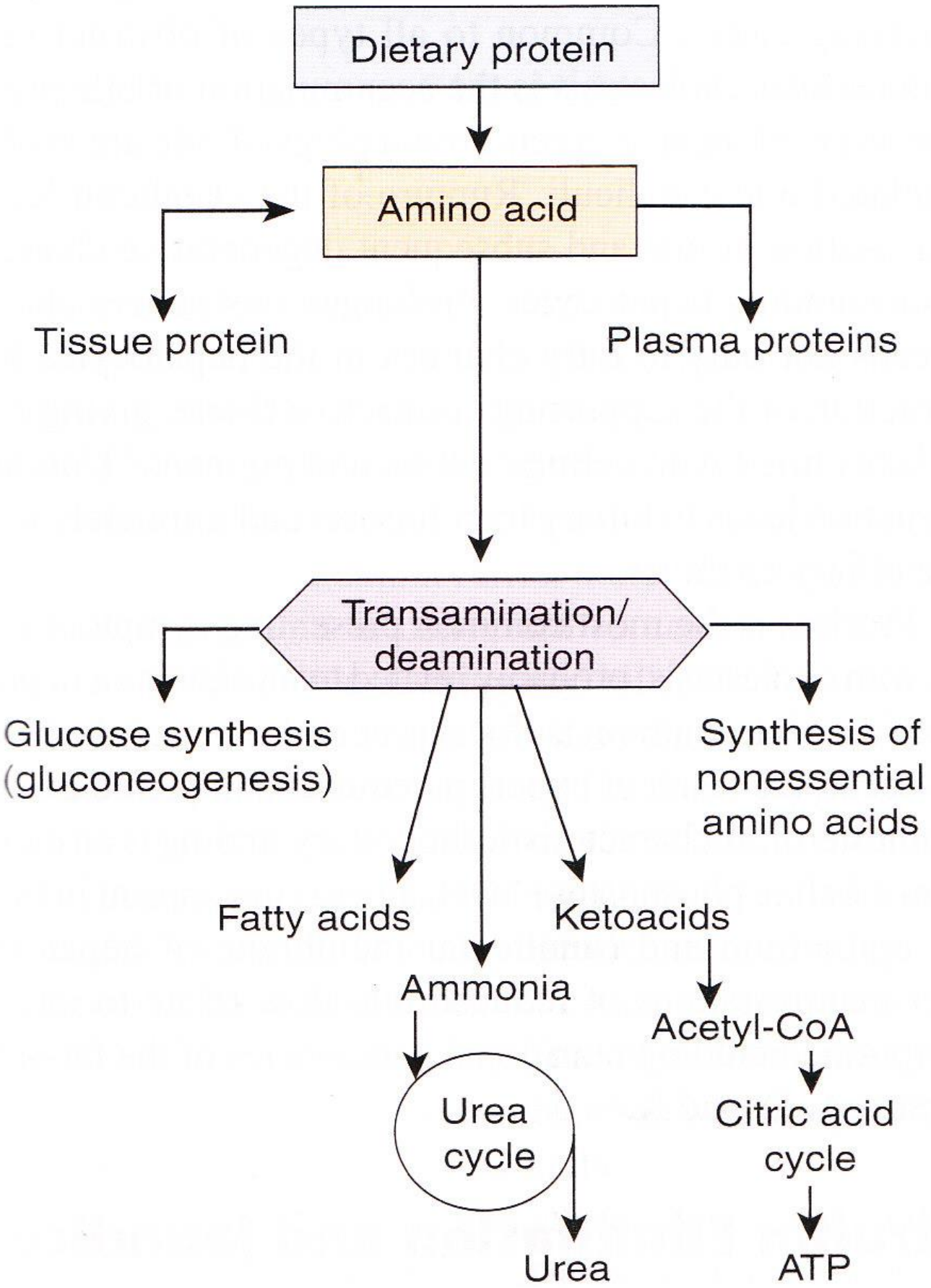


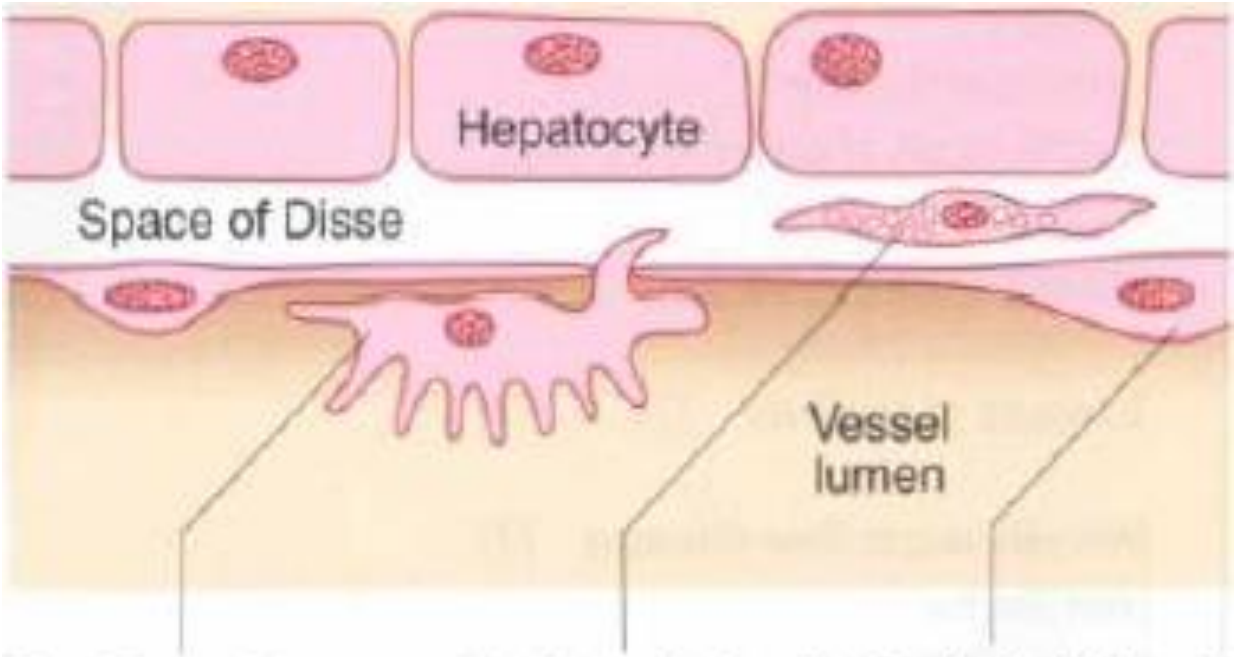
TABLE 38-1 Functions of the Liver and Manifestations of Altered Function

FUNCTION	MANIFESTATIONS OF ALTERED FUNCTION
Production of bile salts	Malabsorption of fat and fat-soluble vitamins
Elimination of bilirubin	Elevation in serum bilirubin and jaundice
Metabolism of steroid hormones	
Sex hormones	Disturbances in gonadal function, including gynecomastia in the male
Glucocorticoids	Signs of increased cortisol levels (*i.e.*, Cushing syndrome)
Aldosterone	Signs of hyperaldosteronism (*e.g.*, sodium retention and hypokalemia)
Metabolism of drugs	Decreased drug metabolism
	Decreased plasma binding of drugs owing to a decrease in albumin production
Carbohydrate metabolism	Hypoglycemia may develop when glycogenolysis and gluconeogenesis are impaired
Stores glycogen and synthesizes glucose from amino acids, lactic acid, and glycerol	Abnormal glucose tolerance curve may occur because of impaired uptake and release of glucose by the liver
Fat metabolism	
Formation of lipoproteins	Impaired synthesis of lipoproteins
Conversion of carbohydrates and proteins to fat	
Synthesis, recycling, and elimination of cholesterol	Altered cholesterol levels
Formation of ketones from fatty acid	
Protein metabolism	
Deamination of proteins	
Formation of urea from ammonia	Elevated blood ammonia levels
Synthesis of plasma proteins	Decreased levels of plasma proteins, particularly albumin, which contributes to edema formation
Synthesis of clotting factors (fibrinogen, prothrombin, factors V, VII, IX, X)	Bleeding tendency
Storage of minerals and vitamins	Signs of deficiency of fat-soluble and other vitamins that are stored in the liver
Filtration of blood and removal of bacteria and particulate matter by Kupffer cells	Increased exposure of the body to colonic bacteria and other foreign matter

Metabolic Functions of the Liver

- Carbohydrate Metabolism
- Protein synthesis and Conversion of Ammonia to Urea
- Lipid Metabolism


Dietary protein
Amino acid
Tissue protein
Plasma proteins
Transamination/
deamination
Glucose synthesis
(gluconeogenesis)
Synthesis of
nonessential
amino acids
Fatty acids
Ketoacids
Ammonia
Acetyl-CoA
Urea
cycle
Citric acid
cycle
Urea
ATP



Kupffer cell

Lipoprotein uptake and metabolism

IgG complex removal

Clearance of bacteria, viruses and erythrocytes

Lipopolysaccharide binding and removal

Cytokine production

Stellate (Ito) cell

Uptake and storage of vitamin A

Synthesis of extracellular matrix

Synthesis and release of collagenase and metalloproteinase inhibitors

Cytokine synthesis and release

Endothelial cell

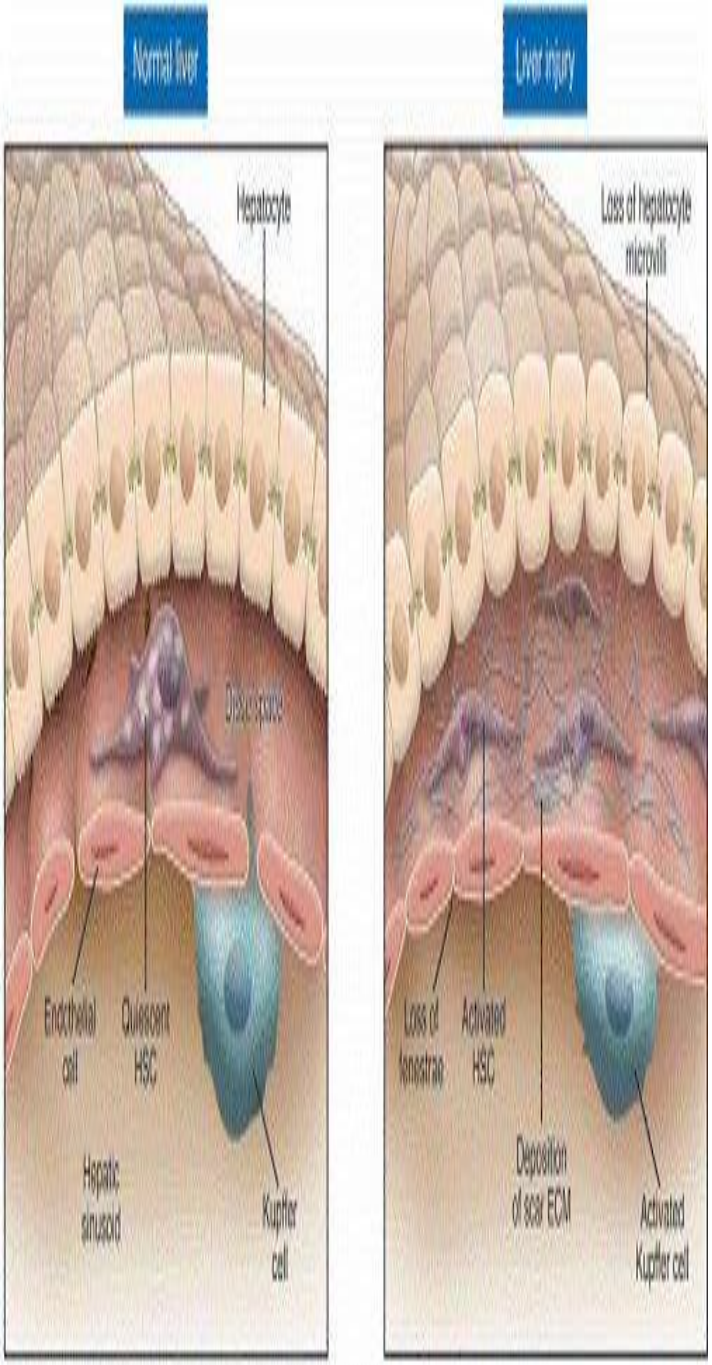
Hyaluronan uptake

Lipoprotein binding and uptake

IgG complexes

Cytokine production

Defects in Amino Acid Metabolism



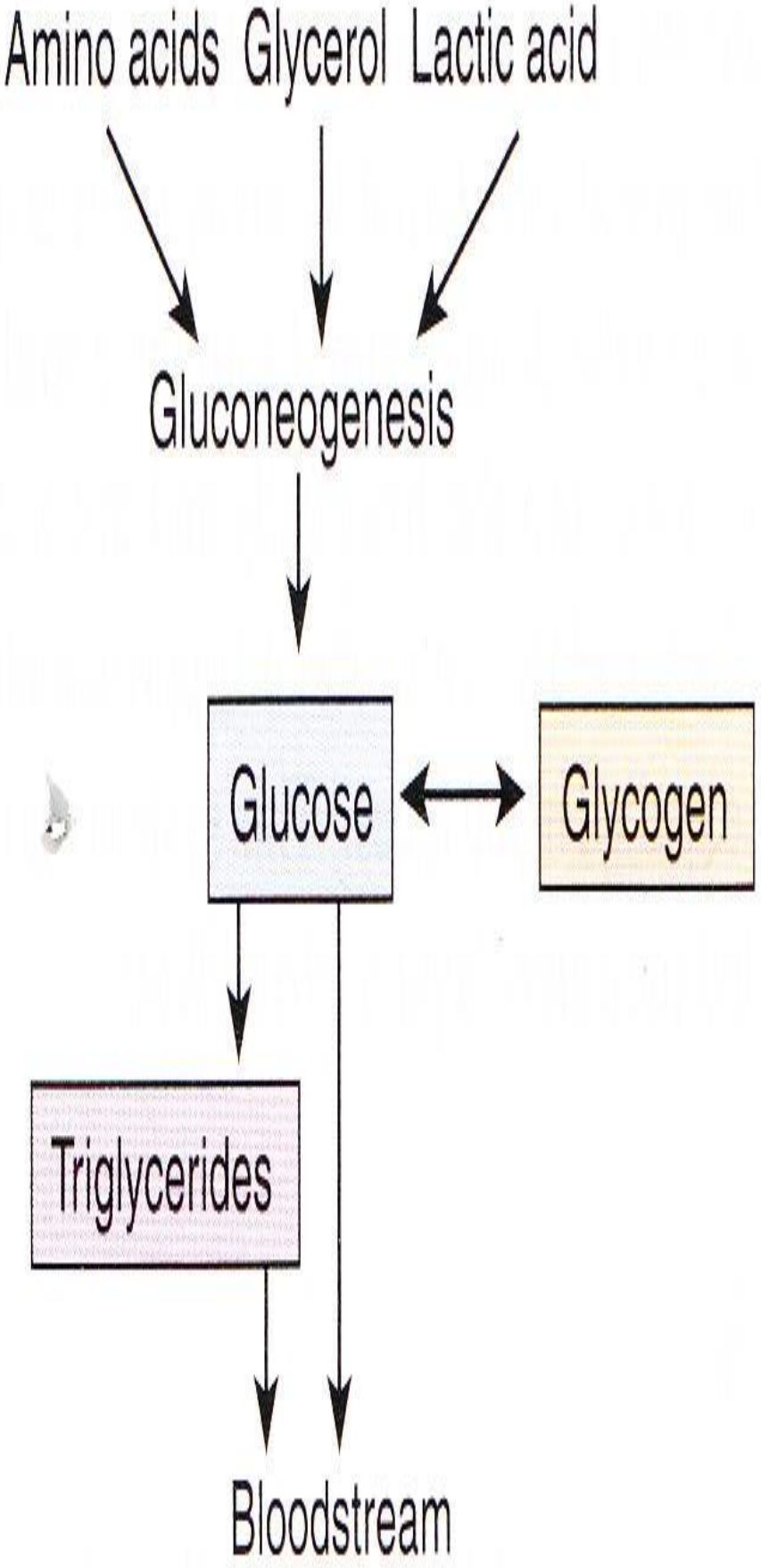
- Oxydative deamination
- Transamination
- Diminution of the blood urea nitrogen level
- Increase in the amount of circulating ammonia
- Hepatic coma

Ketoacid

- It can be modified and cycled through the Krebs cycle, producing **ATP;**
- It can be converted into **glycogen, fatty acids**, or **transaminated;**
- It can be transaminated, converting it to **another kind of keto**

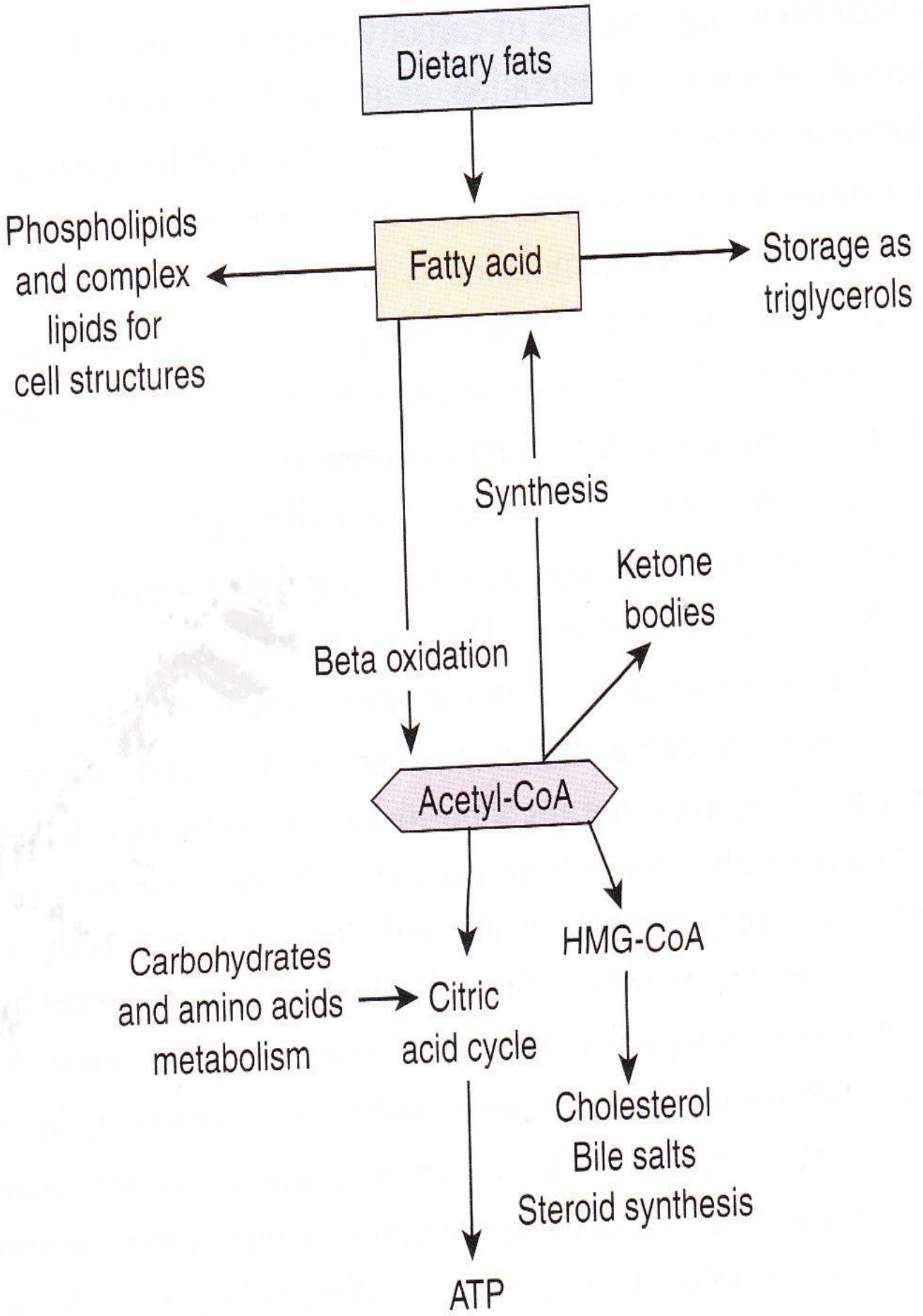
Impaired Production of Clotting Factors

- Fibrinogen, **prothrombin,** Factors 5, 7, 10
- Coagulation defects


Amino acids Glycerol Lactic acid
Gluconeogenesis
Glucose
Glycogen
Triglycerides
Bloodstream

Defects in Carbohydrate Metabolism

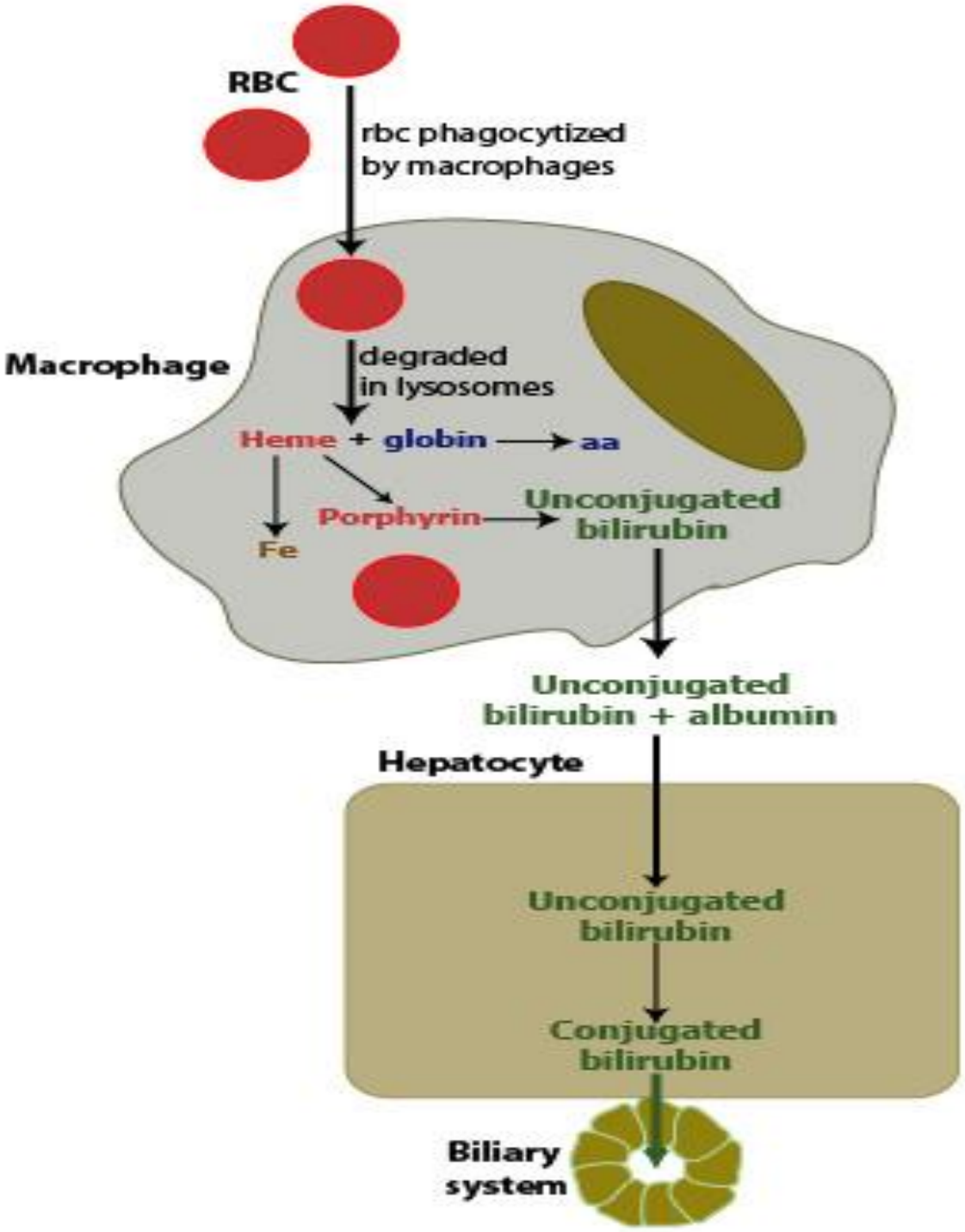
- Glucose tolerance like in diabetus mellitus
- Hyperglycemia
- Hepatic diabetes


Dietary fats
Fatty acid
Phospholipids and complex lipids for cell structures
Storage as triglycerols
Synthesis
Ketone bodies
Beta oxidation
Acetyl-CoA
HMG-CoA
Carbohydrates and amino acids metabolism
Citric acid cycle
Cholesterol
Bile salts
Steroid synthesis
ATP

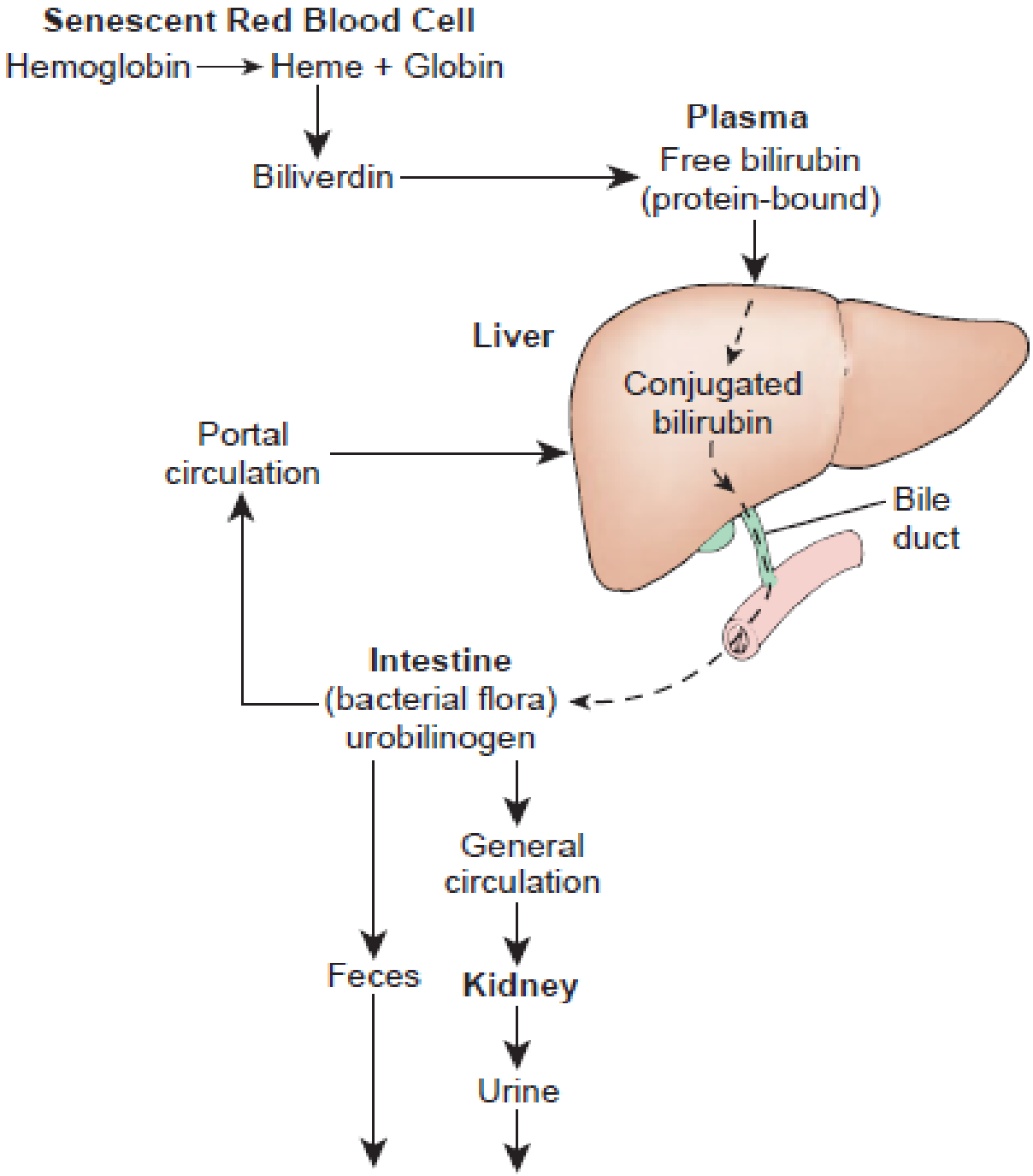
Defects in Lipid Metabolism

- Deposition of triglycerides – ”fatty liver”
- Diminution in the rate of synthesis of cholesterol

Bile production and cholestasis



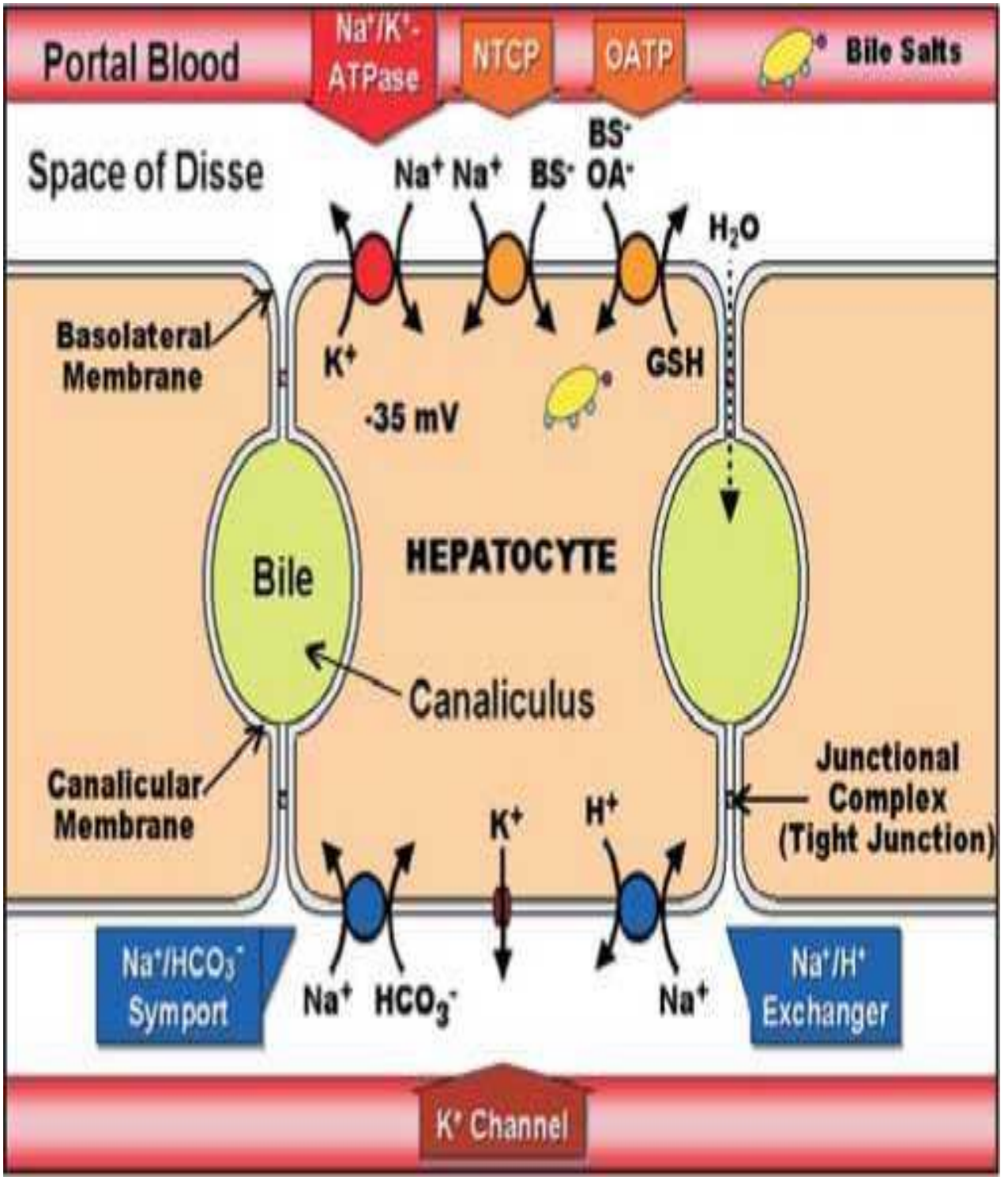
Bilirubin formation, circulation, and elimination



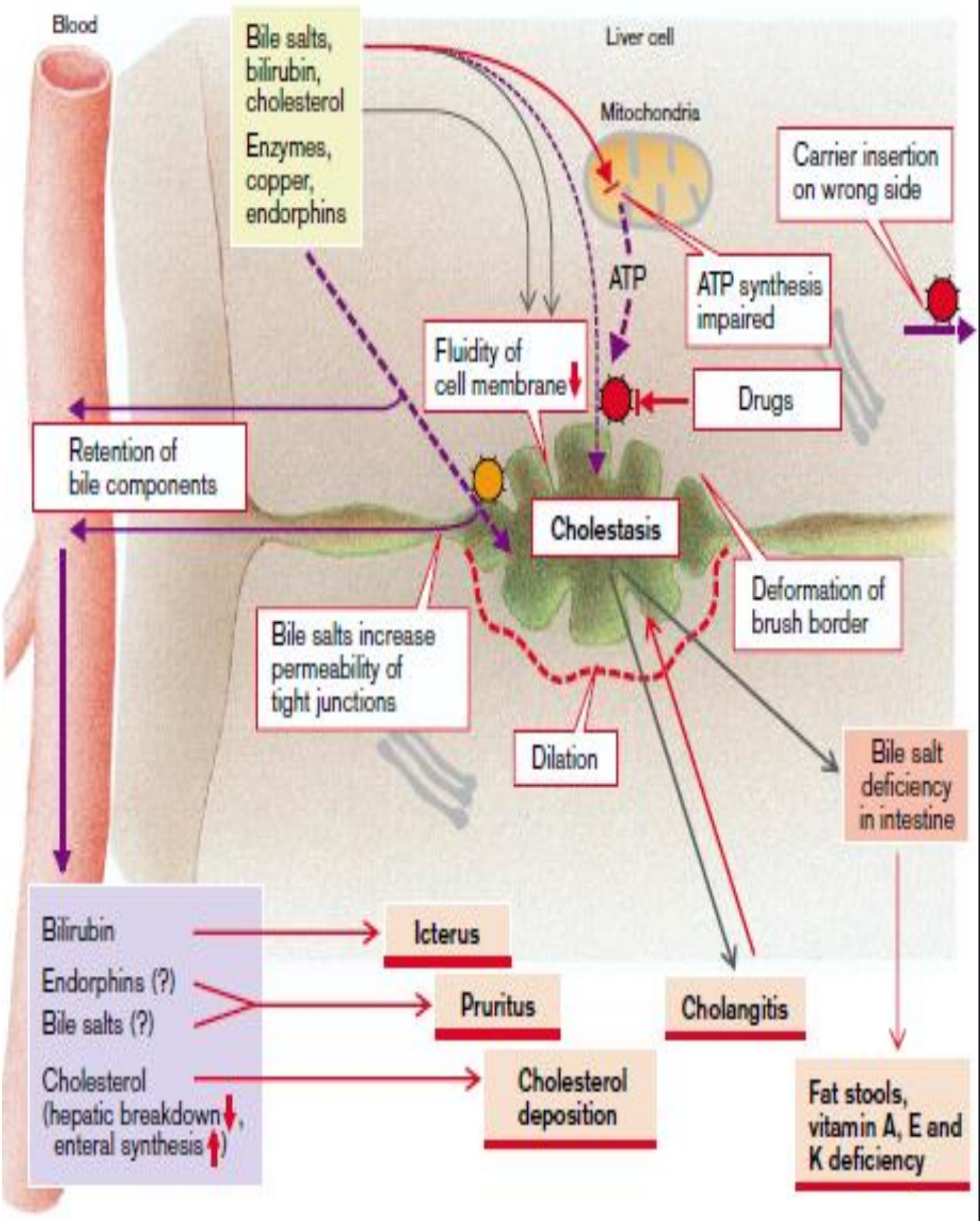
Cholestasis

- **1. Intrahepatic disorders**
- Cystic fibrosis
- Granulomatosis
- Drug side effects (allopurinol, sulfonamides)
- High estrogen concentration (pregnancy, contraceptive pill)
- **2. Extrahepatic bile duct occlusion**

Cholestasis



B. Mechanisms and Consequences of Cholestasis



Causes of Jaundice

Prehepatic (Excessive Red Blood Cell Destruction)

Hemolytic blood transfusion reaction
Hereditary disorders of the red blood cell
- Sickle cell anemia
- Thalassemia
- Spherocytosis

Acquired hemolytic disorders
Hemolytic disease of the newborn
Autoimmune hemolytic anemias

Intrahepatic

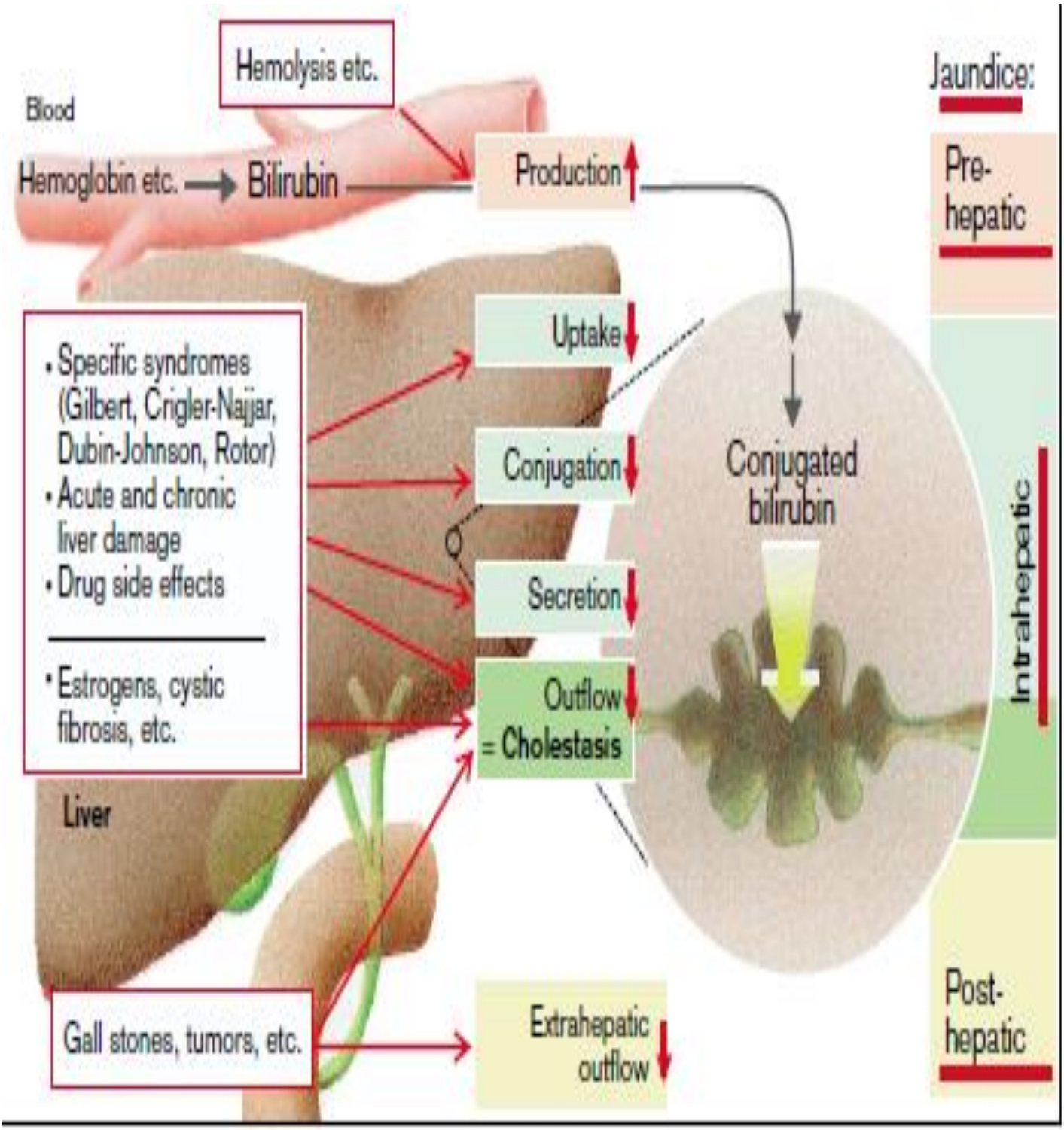
Decreased bilirubin uptake by the liver
Decreased conjugation of bilirubin
Hepatocellular liver damage
- Hepatitis
- Cirrhosis
- Cancer of the liver

Drug-induced cholestasis

Posthepatic (Obstruction of Bile Flow)

Structural disorders of the bile duct
Cholelithiasis
Congenital atresia of the extrahepatic bile ducts
Bile duct obstruction caused by tumors

Types of jaundice



General features of hepatic diseases

- 1. metabolic
- 2. toxic
- 3. microbial
- 4. circulatory
- 5. neoplastic insults
- **Major primary diseases**
- viral hepatitis
- alcoholic liver disease
- nonalcoholic fatty liver disease (NAFLD)
- hepatocellular carcinoma (HCC)

General features of hepatic diseases

- **Secondary diseases:**
- cardiac failure
- disseminated cancer
- extrahepatic infections

PATTERNS OF HEPATIC INJURY

- Hepatocyte degeneration and intracellular accumulations
- Hepatocyte necrosis and apoptosis
- Inflammation
- Regeneration
- Fibrosis

- **Clinically:**
- hepatic failure
- cirrhosis
- portal hypertension
- jaundice
- cholestasis

Hepatic failure

The destruction of overall hepatic function

2000 cases per year US

80-90% of HF

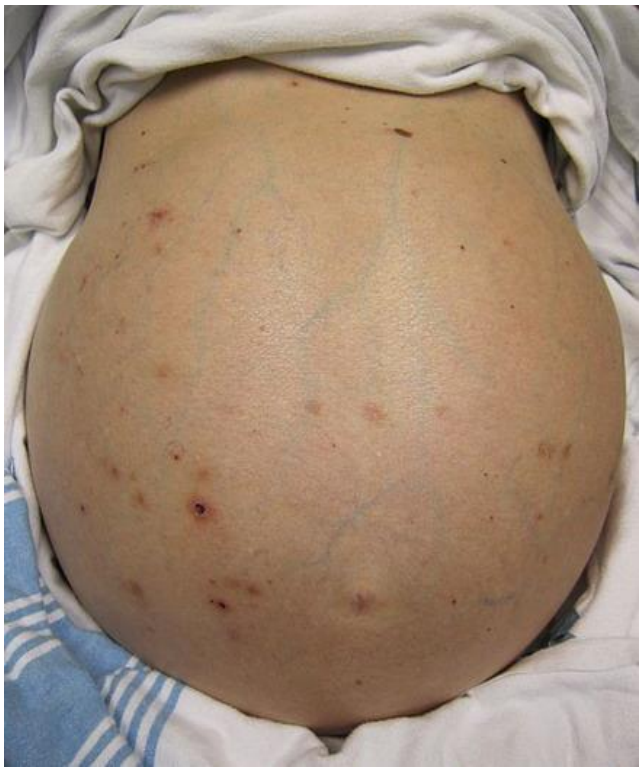
Mortality is 80%

Alterations that cause LF:

- Acute liver failure (fulminant LF)
- Chronic liver disease
- Hepatic dysfunction without overt necrosis

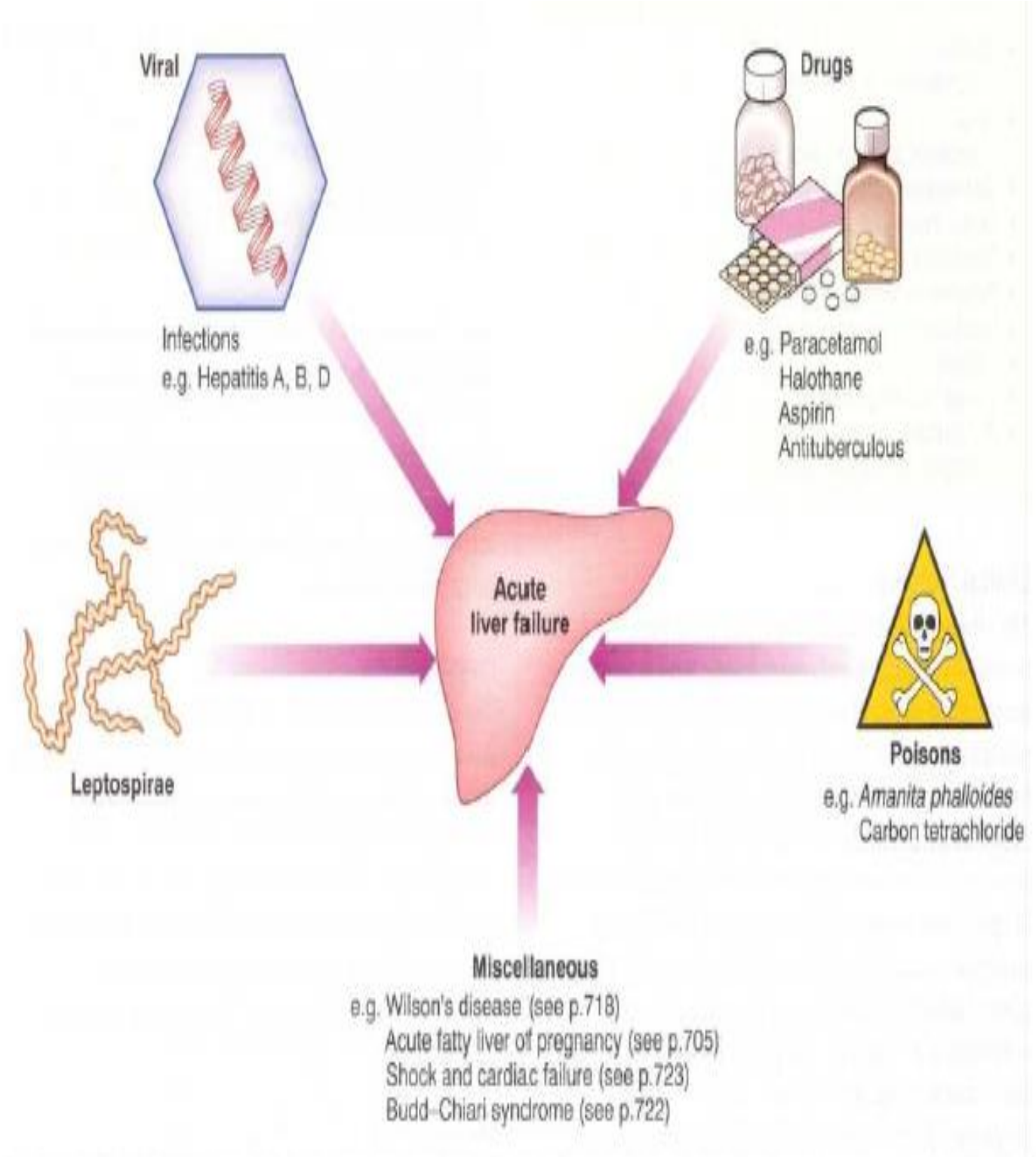
Hepatic failure

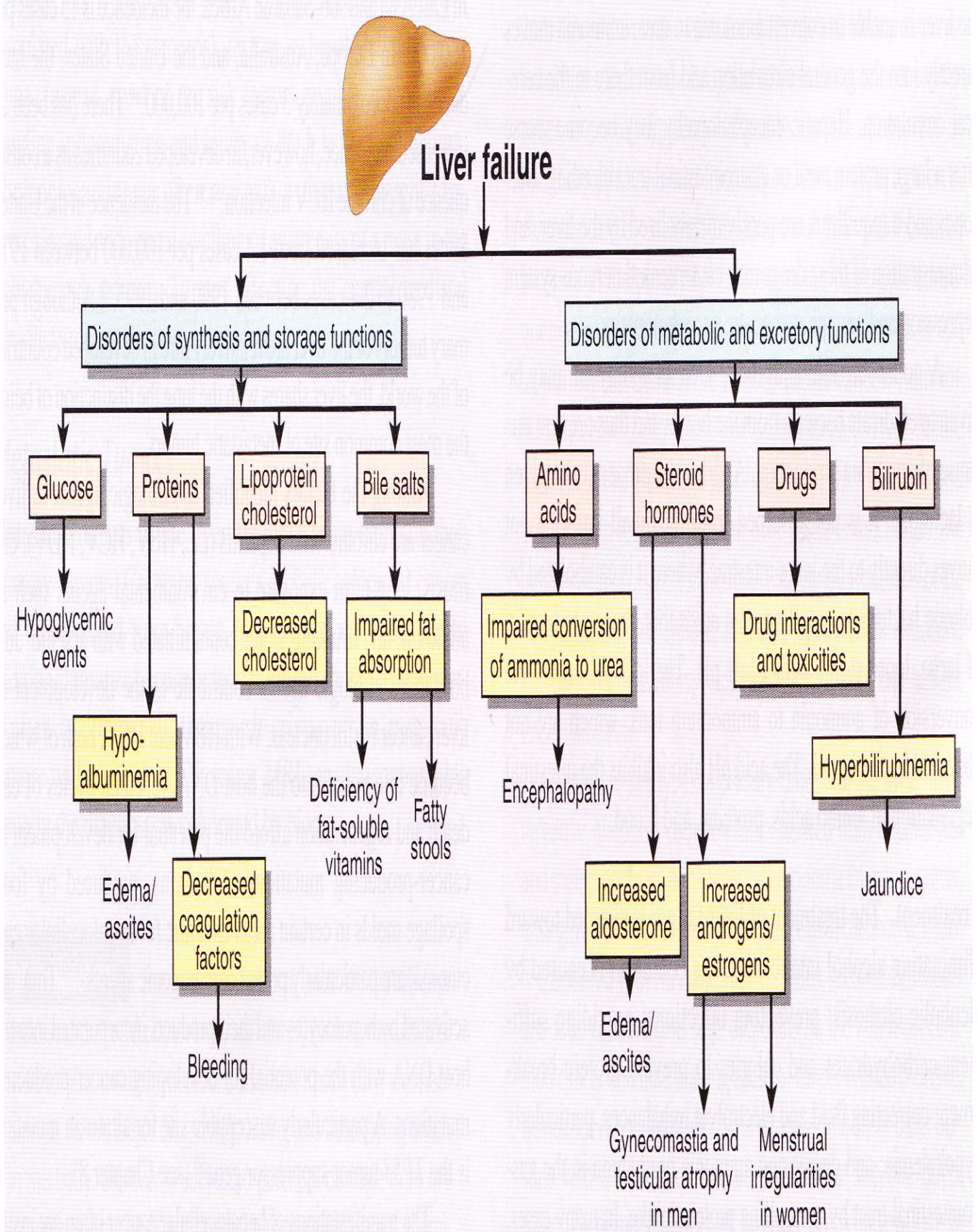
- Sudden and massive liver destruction
- Alcoholic cirrhosis
- End stage of progressive chronic damage



- Hematologic disorders
- Endocrine disorders
- Skin Disorders
- Hepatorenal Syndrome
- Hepatic Encephalopathy
- Hepatopulmonary syndrome

Causes of acute (fulminant) hepatic failure

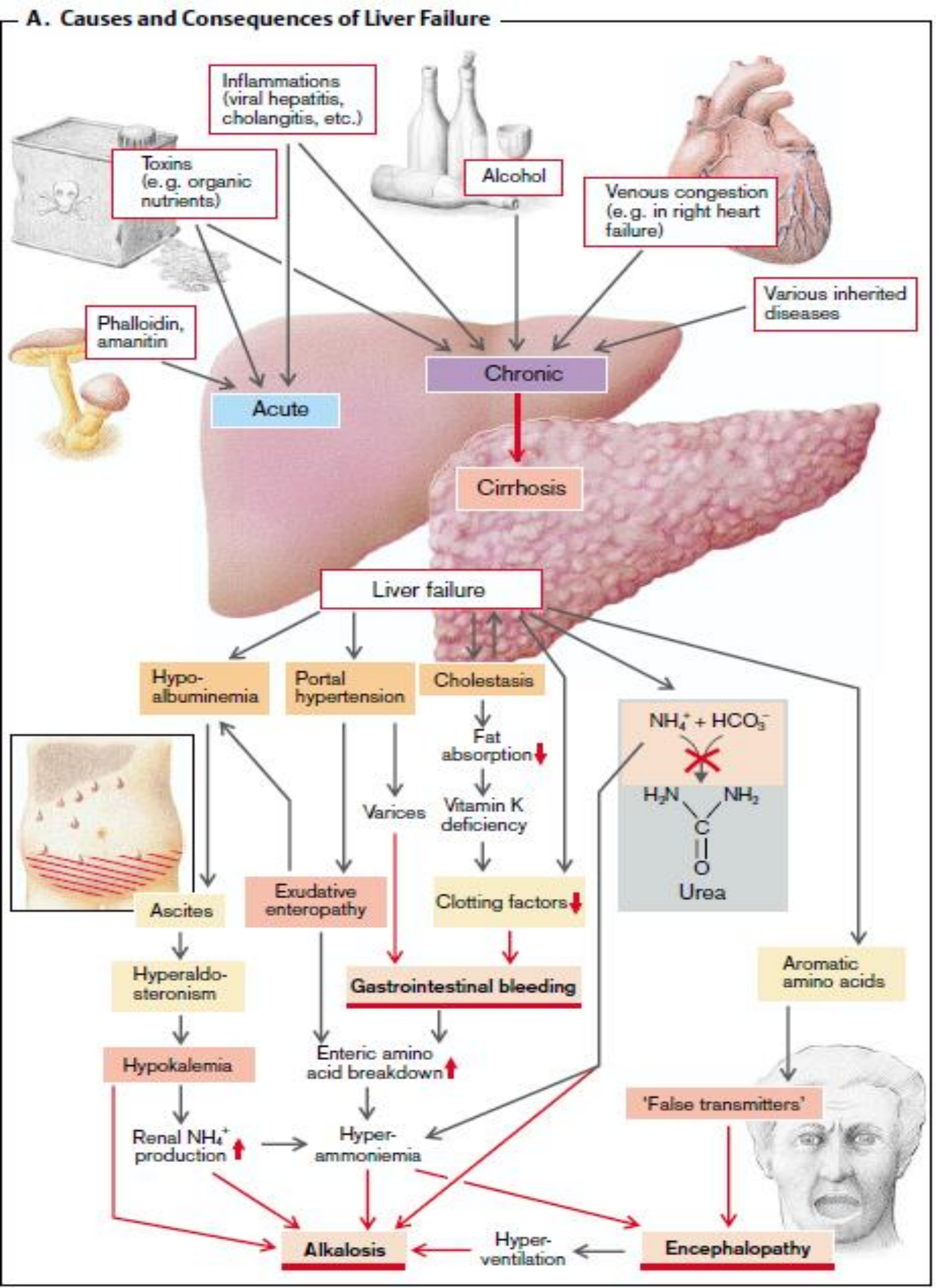



Liver failure
Disorders of synthesis and storage functions
Disorders of metabolic and excretory functions
Glucose
Proteins
Lipoprotein cholesterol
Bile salts
Amino acids
Steroid hormones
Drugs
Bilirubin
Hypoglycemic events
Hypo-albuminemia
Edema/ ascites
Decreased coagulation factors
Bleeding
Decreased cholesterol
Impaired fat absorption
Deficiency of fat-soluble vitamins
Fatty stools
Impaired conversion of ammonia to urea
Encephalopathy
Drug interactions and toxicities
Hyperbilirubinemia
Jaundice
Increased aldosterone
Edema/ ascites
Increased androgens/ estrogens
Gynecomastia and testicular atrophy in men
Menstrual irregularities in women

Hepatic failure

- Jaundice
- Hypoalbuminemia
- Hyperammonemia
- Fetor hepaticus
- Portosystemic shunting
- Palmar erythema
- Spider angiomas
- Hypogonadism
- Gynecomastia

A. Causes and Consequences of Liver Failure



Hematologic Disorders

- Anemia (blood loss, excessive red blood cells destruction, impaired formation of red blood cells)
- Thrombocytopenia (splenomegaly)
- Coagulation defects (decline of factors 5, 7, 9, 10, prothrombin, fibrinogen)
- Mal absorbtion of the fat-soluble vitamin K
- Leucopenia

Endocrine Disorders

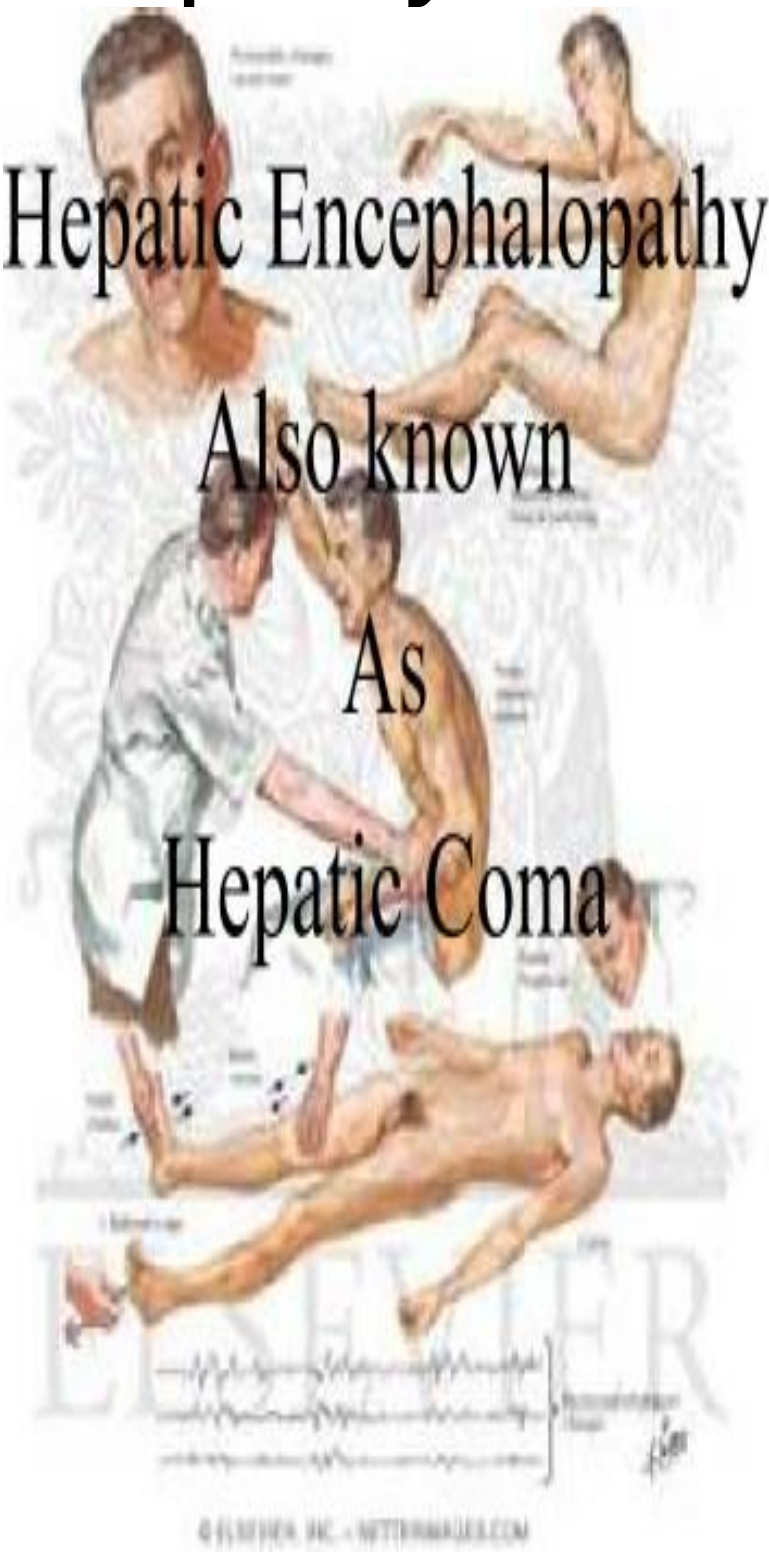
- Disturbances in gonadal sex hormone function
- Menstrual irregularities , loss of libido, sterility
- Testes atrophy, loss of libido, impotence, gynecomastia
- Salt and water retention

Skin disorders

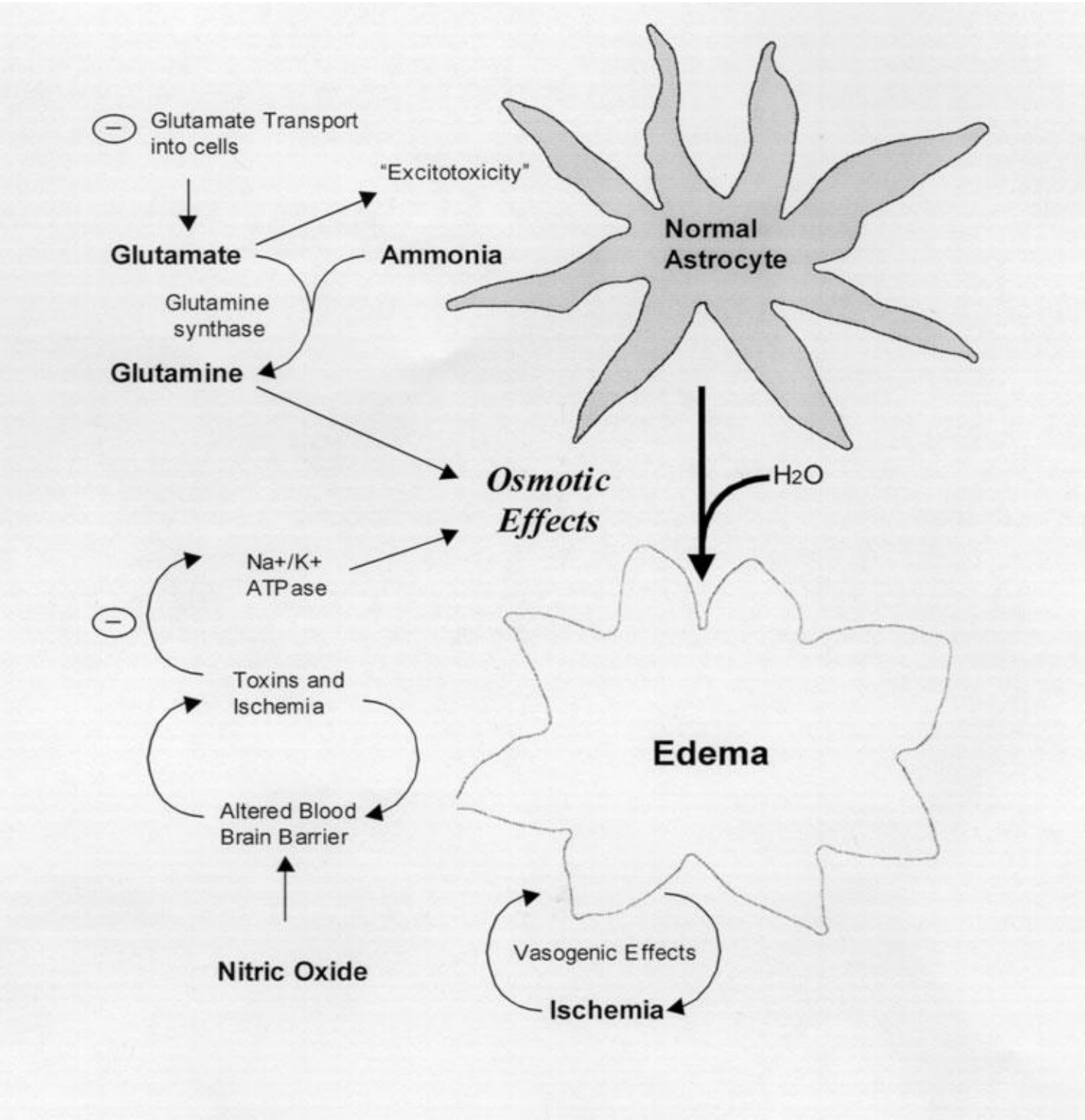
- Vascular spiders
- Telangiectases
- Spiders angiomas
- Spider nervi
- Palmar erythema
- Clubbing of the fingers (cirrhosis)
- Jaundice

Hepatic encephalopathy

- **Lack of mental alertness to confusion, coma, and convulsions**
- **Flapping tremor called asterixis**
- **Euphoria**
- **Irritability**
- **Anxiety**

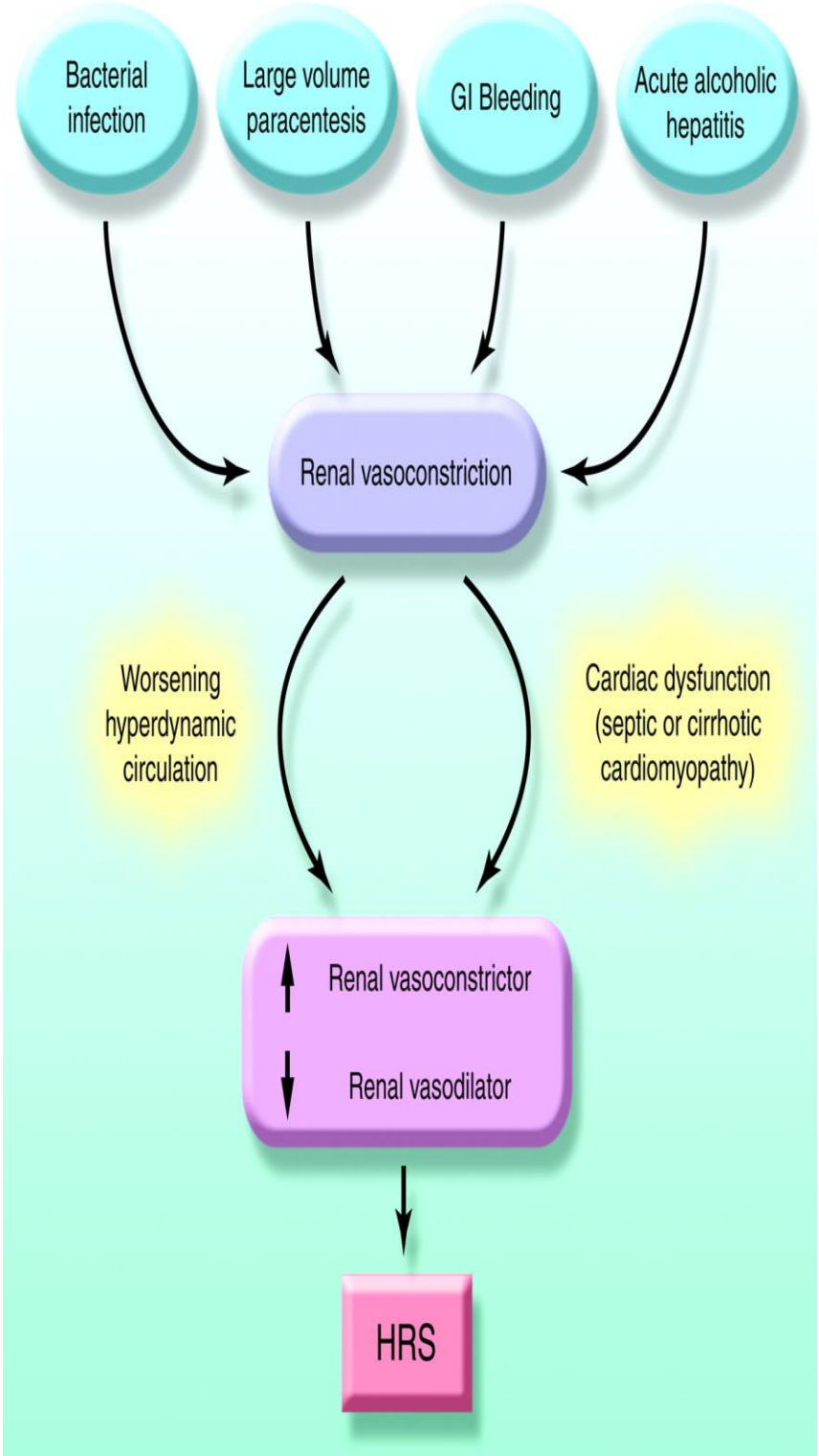


Hepatic encephalopathy



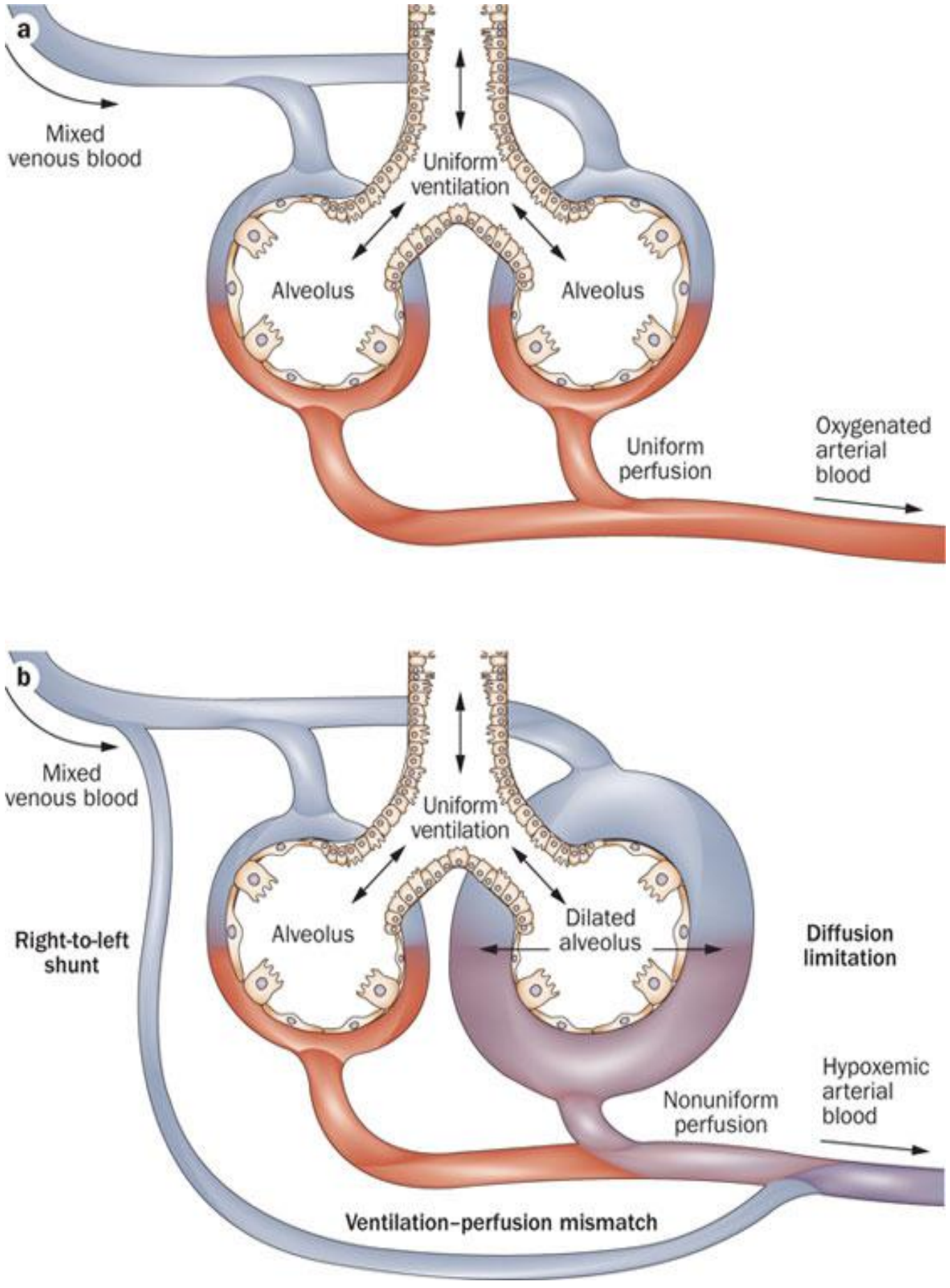
Hepatorenal Syndrome

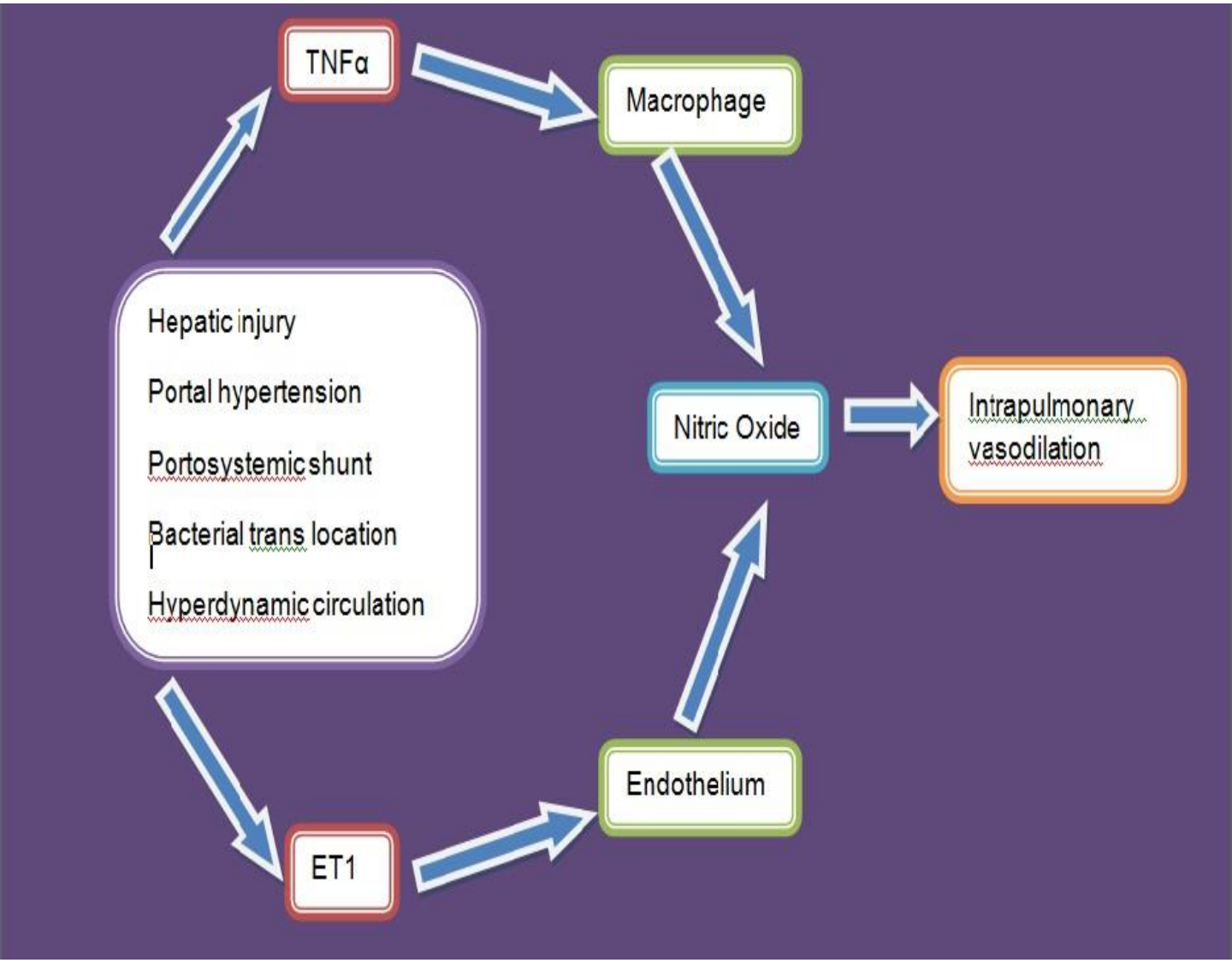
- **Azotemia**
- **Increased serum creatinine levels**
- **Oliguria**
- **Hepatic encephalopathy**
- **Coma**

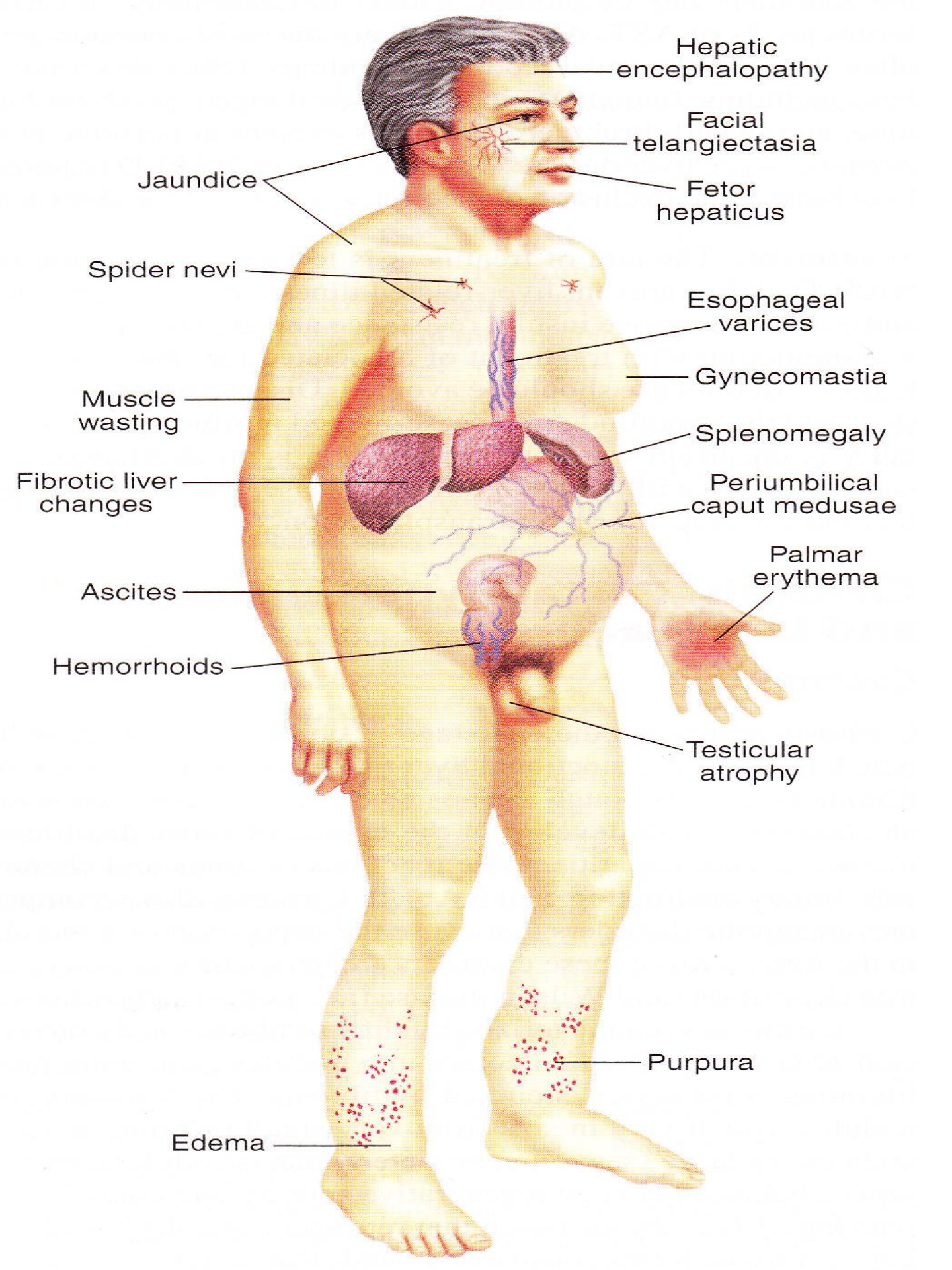


Hepatopulmonary syndrome (HPS)

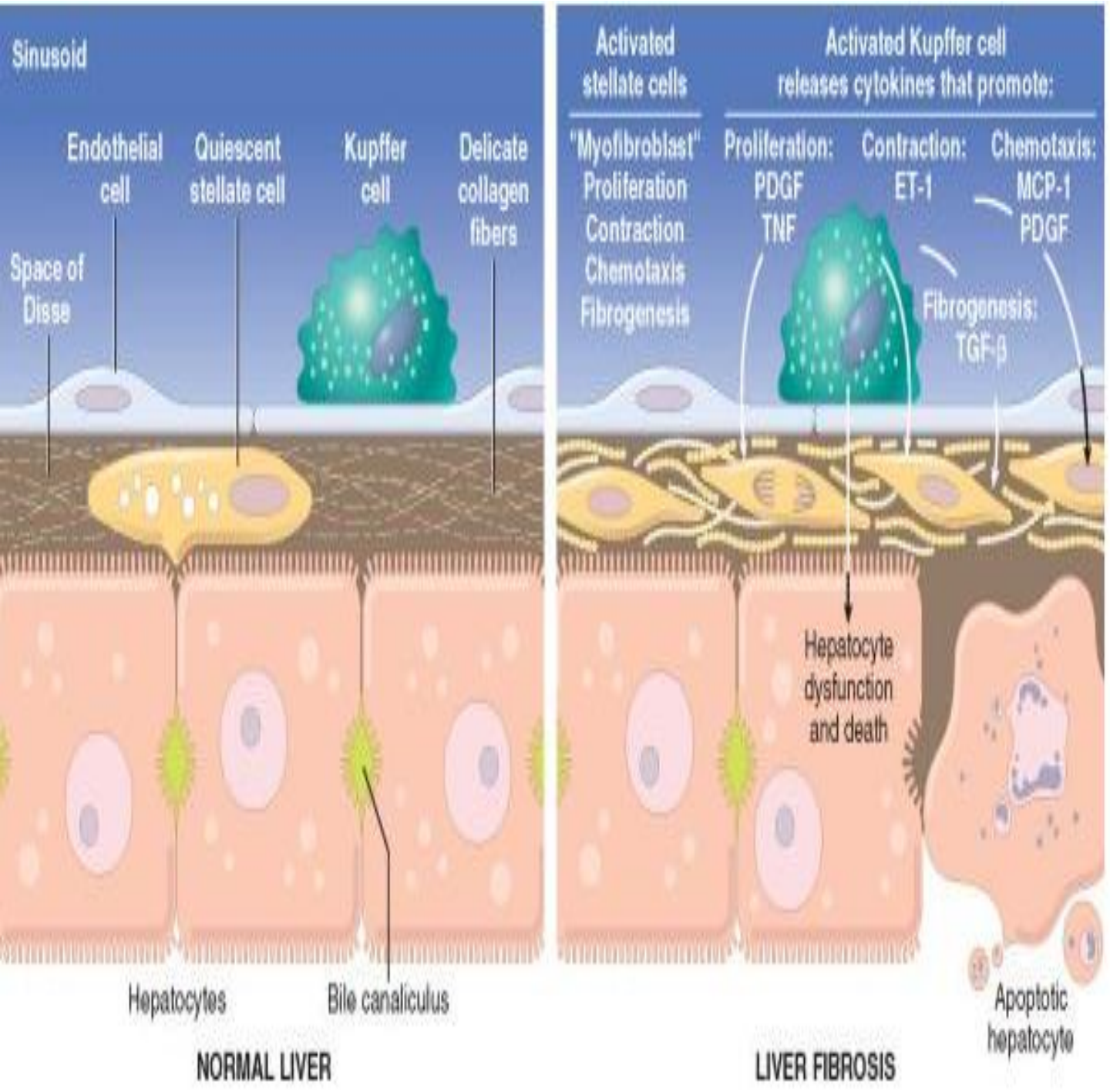
- Chronic liver disease
- Hypoxemia
- Intra-pulmonary vascular dilations


a
Mixed
venous blood
Uniform
ventilation
Alveolus
Alveolus
Uniform
perfusion
Oxygenated
arterial
blood
b
Mixed
venous blood
Uniform
ventilation
Alveolus
Dilated
alveolus
Right-to-left
shunt
Diffusion
limitation
Hypoxemic
arterial
blood
Nonuniform
perfusion
Ventilation–perfusion mismatch

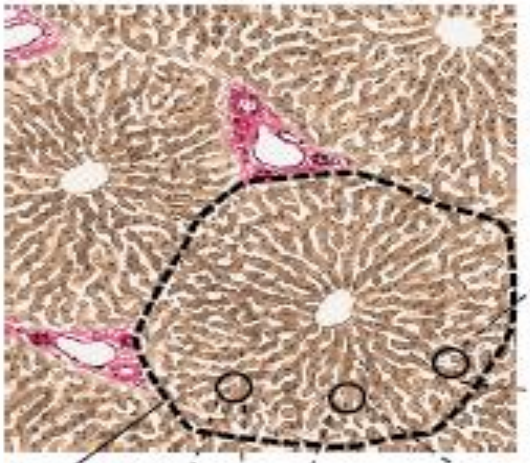

TNFα
Macrophage
Hepatic injury
Portal hypertension
Portosystemic shunt
Bacterial trans location
Hyperdynamic circulation
Nitric Oxide
Intrapulmonary vasodilation
Endothelium
ET1


Hepatic encephalopathy
Facial telangiectasia
Jaundice
Fetor hepaticus
Spider nevi
Esophageal varices
Gynecomastia
Muscle wasting
Splenomegaly
Fibrotic liver changes
Periumbilical caput medusae
Palmar erythema
Ascites
Hemorrhoids
Testicular atrophy
Purpura
Edema

Cirrhosis


Sinusoid
Endothelial cell
Quiescent stellate cell
Kupffer cell
Delicate collagen fibers
Space of Disse
Hepatocytes
Bile canaliculus
NORMAL LIVER
Activated stellate cells
"Myofibroblast"
Proliferation
Contraction
Chemotaxis
Fibrogenesis
Activated Kupffer cell releases cytokines that promote:
Proliferation: PDGF TNF
Contraction: ET-1
Chemotaxis: MCP-1 PDGF
Fibrogenesis: TGF-β
Hepatocyte dysfunction and death
Apoptotic hepatocyte
LIVER FIBROSIS

A. Fibrosis and Cirrhosis of the Liver



Liver lobule

Noxious factors (alcohol, viral hepatitis, etc.)

Necrosis

Hepatocyte

Matrix

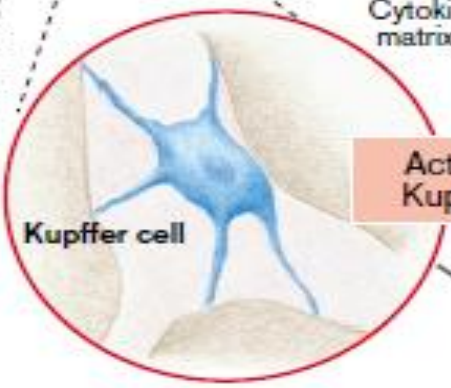
Enzyme leak

Cell debris

Cytokines and other matrix components

Chemotaxis of inflammatory cells

Activation of Kupffer cells



Kupffer cell

Granulocytes
Lymphocytes

Monocyte

Growth factors and cytokines

MCP-1 → Chemotaxis

Ito (fat) cell

Chemotaxis

TGFβ

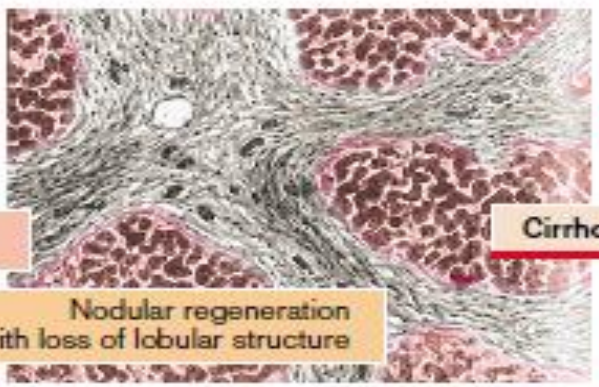
Myofibroblast

Macrophage

Extracellular matrix production ↑↑

Fibroblast proliferation

Collagen type I, III, IV ↑
Proteoglycans ↑
Matrix glycoproteins ↑



Fibrosis

Nodular regeneration with loss of lobular structure

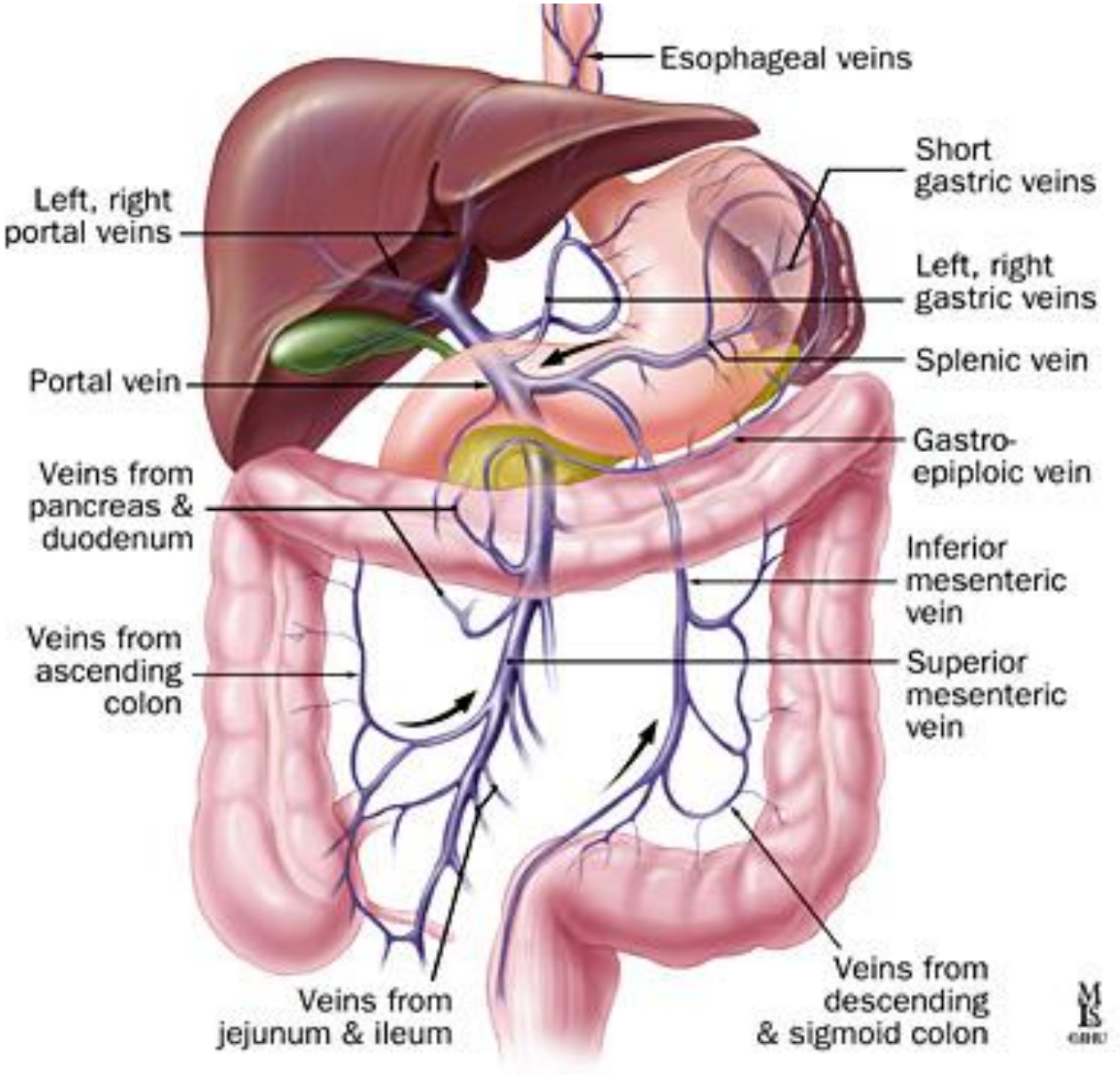
Cirrhosis

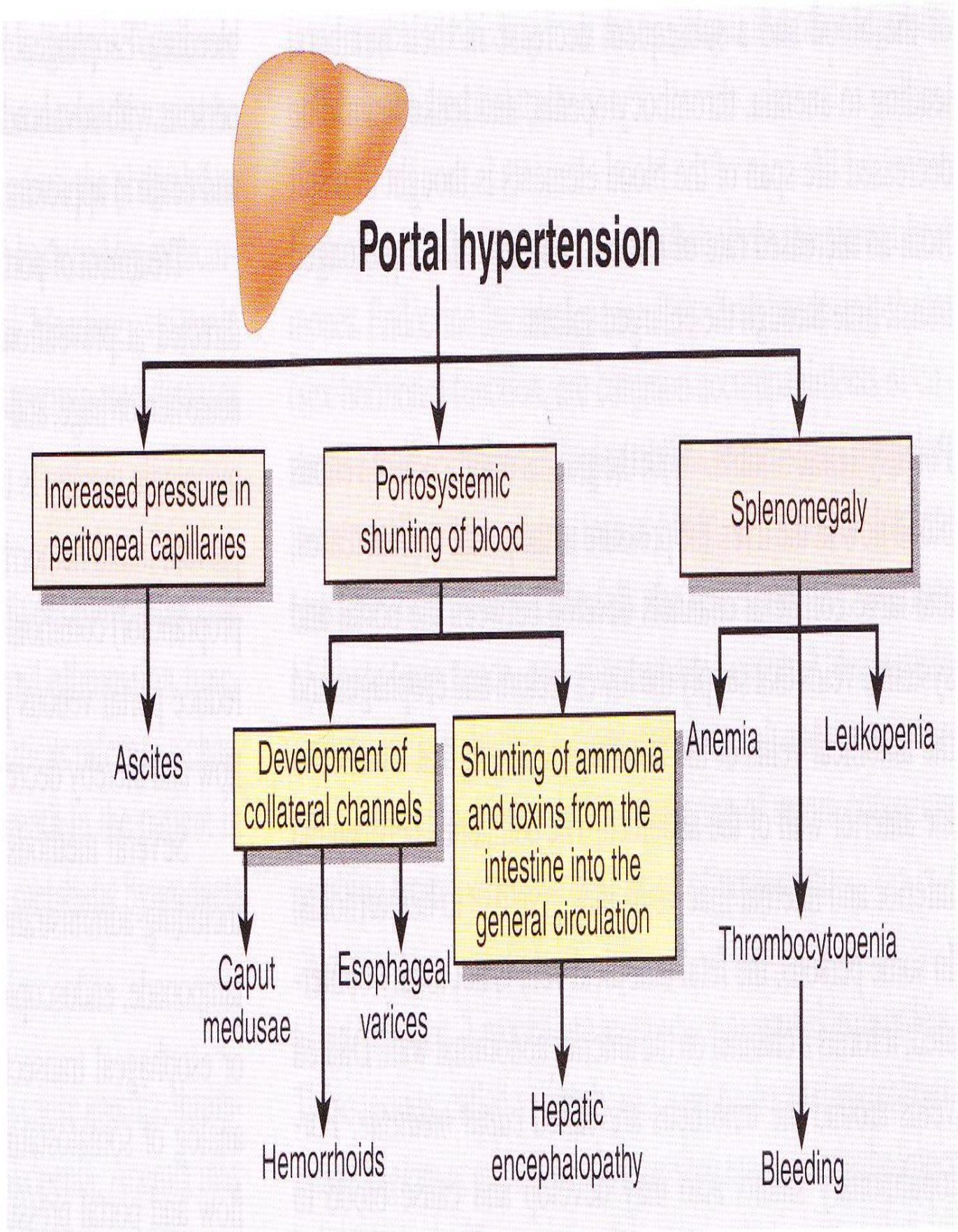
Cholestasis

Portal hypertension

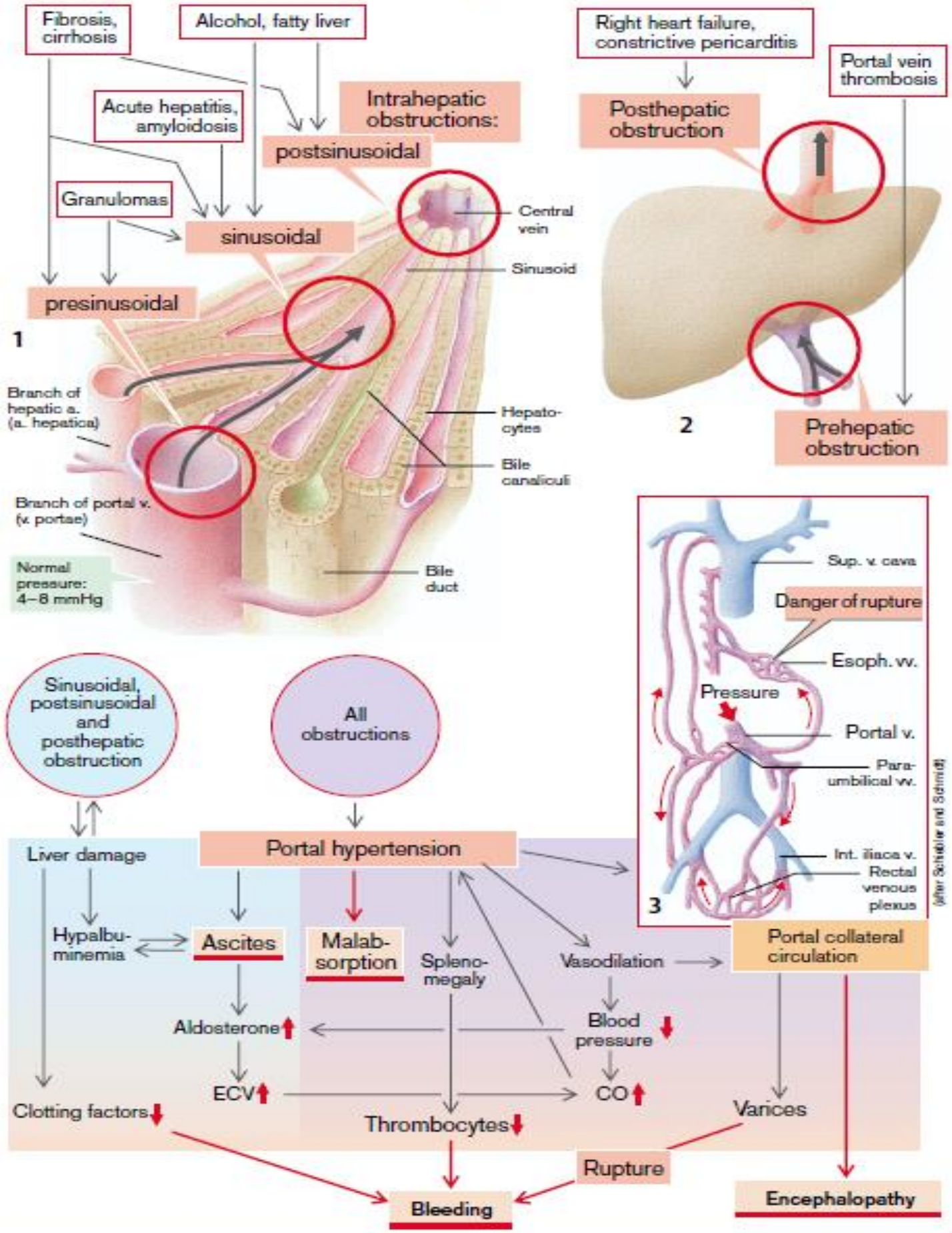
Metabolic failure

Increased resistance to flow in the portal venous system and sustained portal vein pressure above 12mm Hg




Portal hypertension
Increased pressure in peritoneal capillaries
Portosystemic shunting of blood
Splenomegaly
Ascites
Development of collateral channels
Shunting of ammonia and toxins from the intestine into the general circulation
Anemia
Leukopenia
Caput medusae
Esophageal varices
Thrombocytopenia
Hemorrhoids
Hepatic encephalopathy
Bleeding

A. Causes and Consequences of Portal Hypertension



Ascites

The fluid amount in the peritoneal cavity is increased

The mechanisms of ascites

- Increase in capillary pressure due to portal hypertension
- Obstruction of venous flow through the liver
- Salt and water retention by the kidney
- Decreased colloidal osmotic pressure due to impaired synthesis of albumin by the liver

Spontaneous bacterial peritonitis

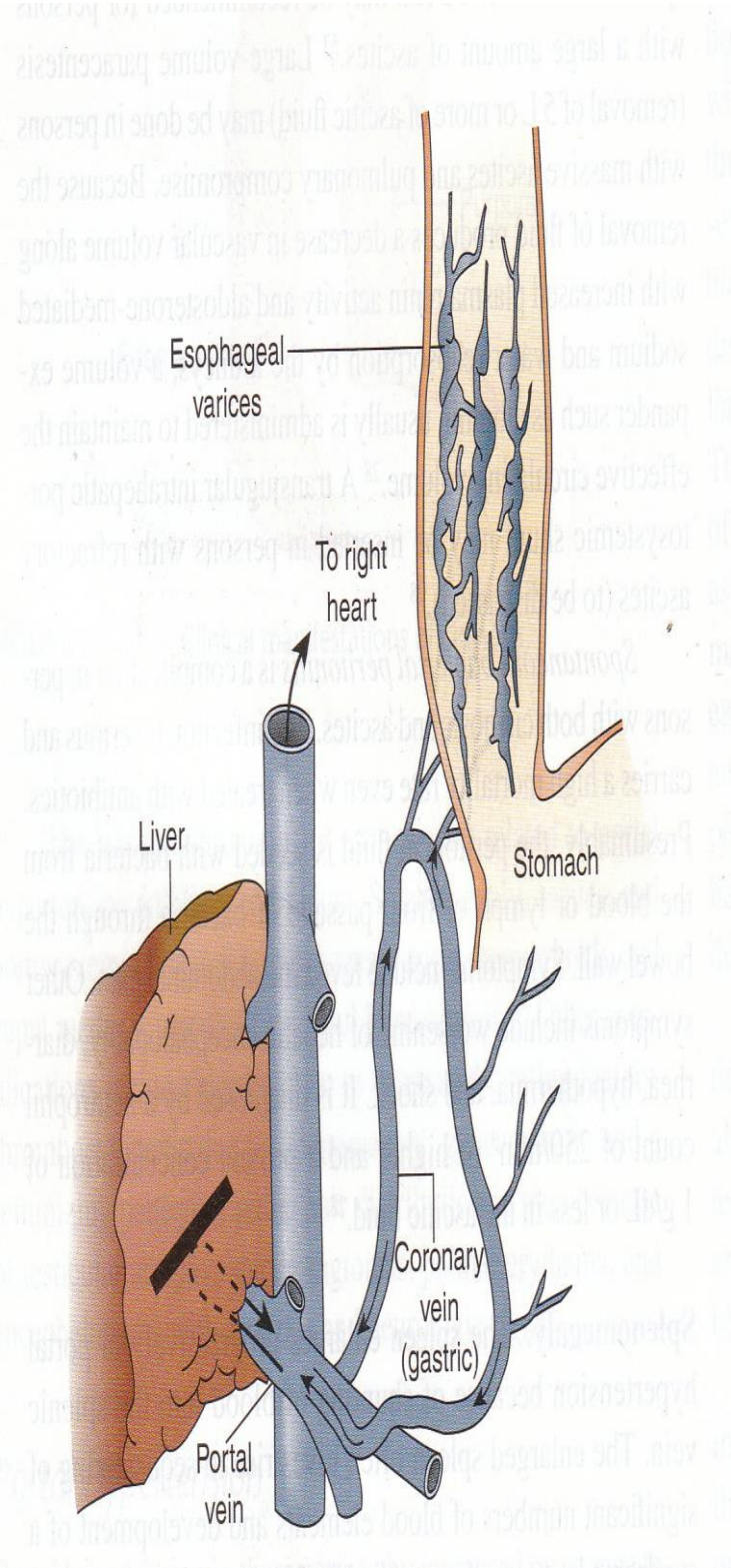
- Fever
- Abdominal pain
- Worsening of hepatic encephalopathy
- Diarrhea
- Hypothermia
- Shock

Spleno megaly

Hyper splenism-a decrease in the life span of all the formed elements of the blood and a subsequent decrease in their numbers, leading to anemia, thrombocytopenia, and leukopenia

Porto systemic Shunts

- Gradual obstruction of venous blood flow in the liver
- The pressure in the portal vein increases
- Large collateral channels develop between portal and systemic veins that supply the lower rectum and esophagus and the umbilical veins of the falciform ligament
-



Thank you for your atention