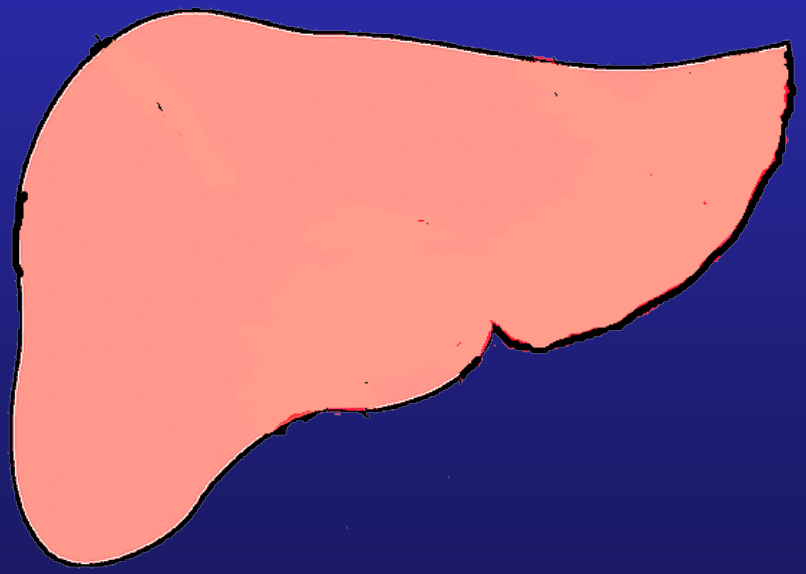
PATOPHYSIOLOGY OF THE LIVER



Institute of Pathological Physiology

Martin Vokurka
mvoku@lf1.cuni.cz

2010/2011

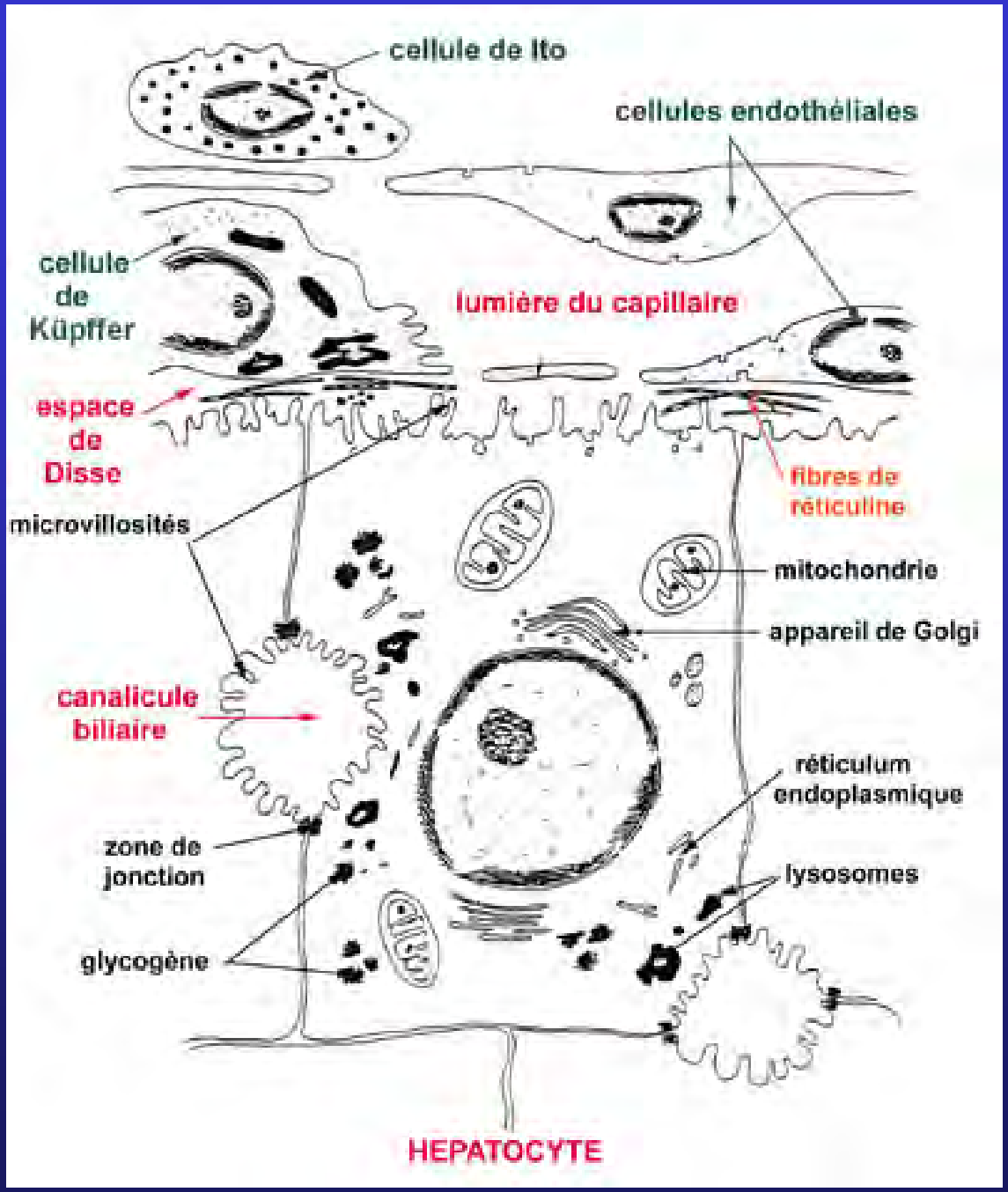
LIVER CELLS

- ***hepatocytes***
- ***reticuloendothelial cells***

Kupffer cells

endothelia

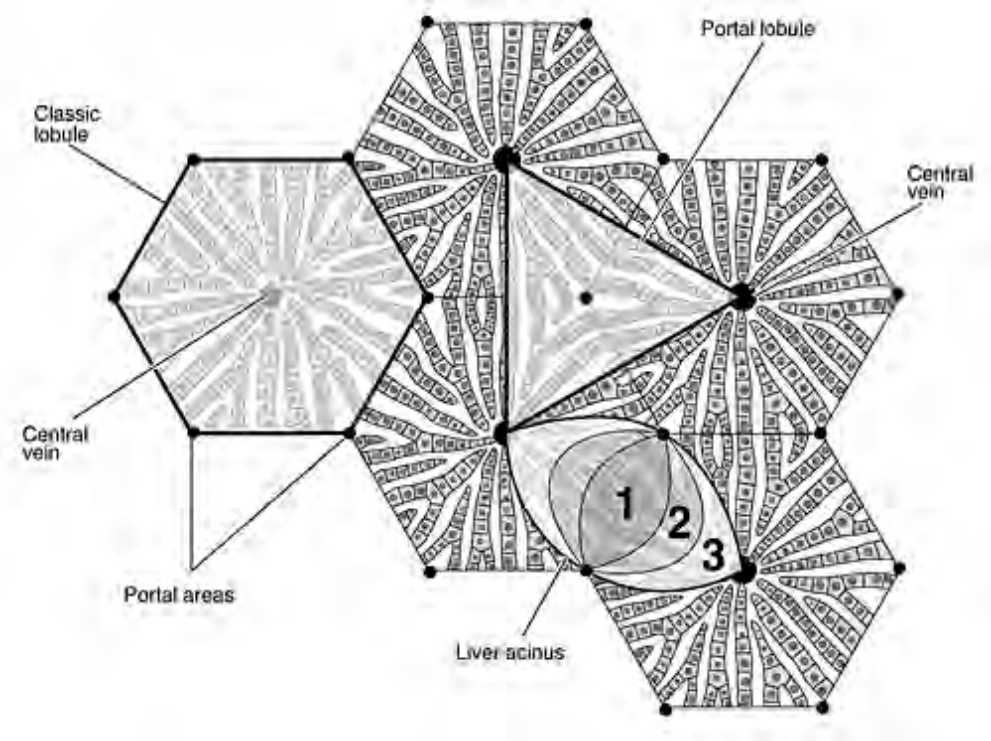
- ***hepatic stellate cells*** (HSC), Ito cell, lipocytes


cellule de Ito
cellules endothéliales
cellule de Küpffer
lumière du capillaire
espace de Disse
fibres de réticuline
microvillosités
mitochondrie
appareil de Golgi
canalicule biliaire
réticulum endoplasmique
zone de jonction
lysosomes
glycogène
HEPATOCYTE

Hepatocytes – polarized cells

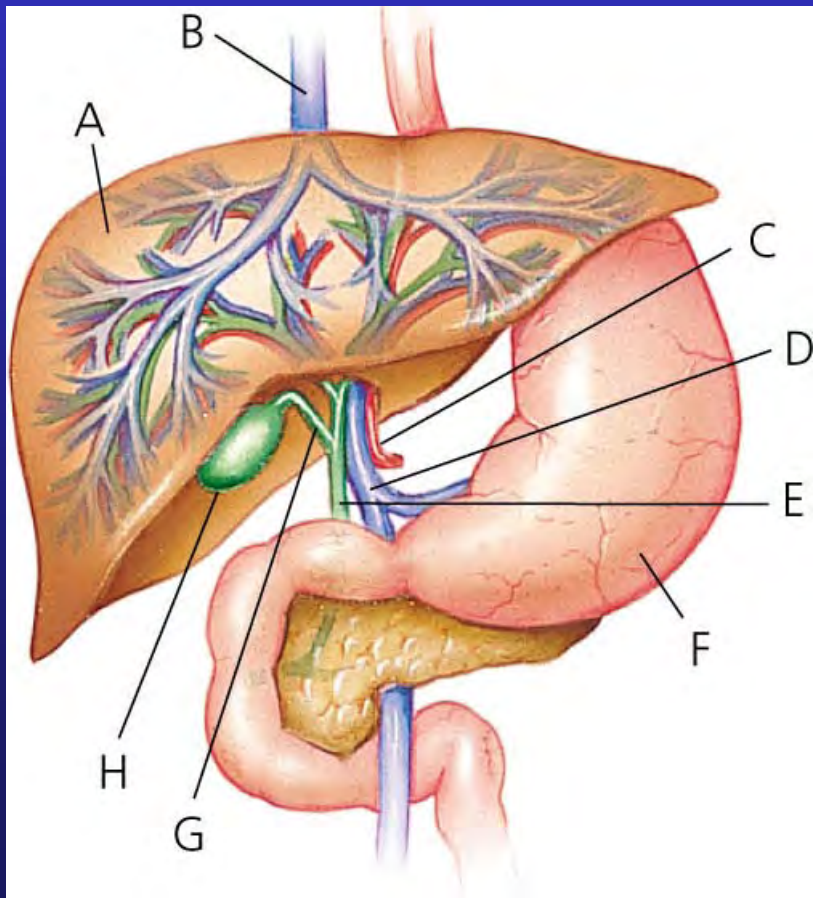
- basolateral membrane (surface) – sinusoids, bloodstream
- apical (canalicular) membrane – bile canaliculus

Liver structure



Blood flow

* *portal vein*
* *hepatic artery*
* *capillary fenestrations*
* *low resistence*



Conditions for normal liver functioning

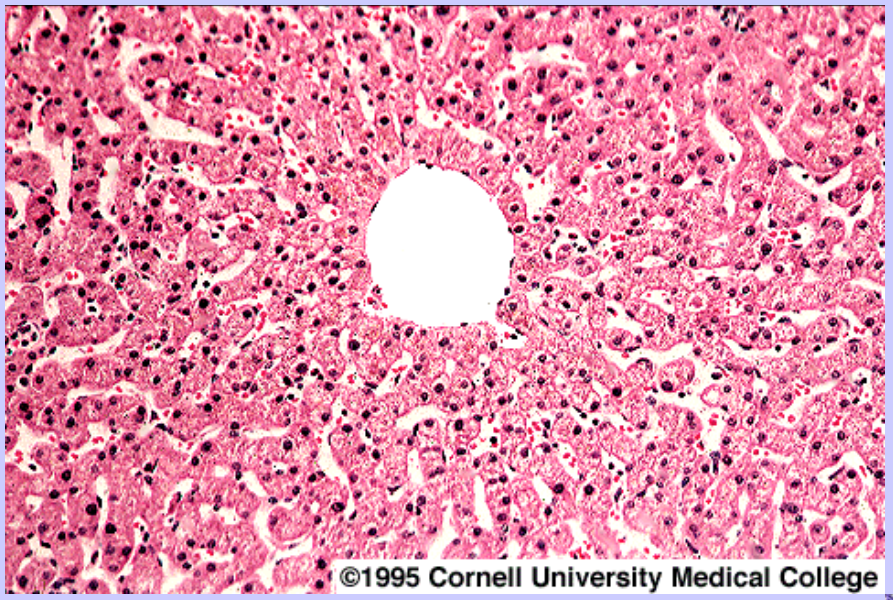
- sufficient amount of hepatocytes
- appropriate blood flow through liver: sufficient contact of cells with blood

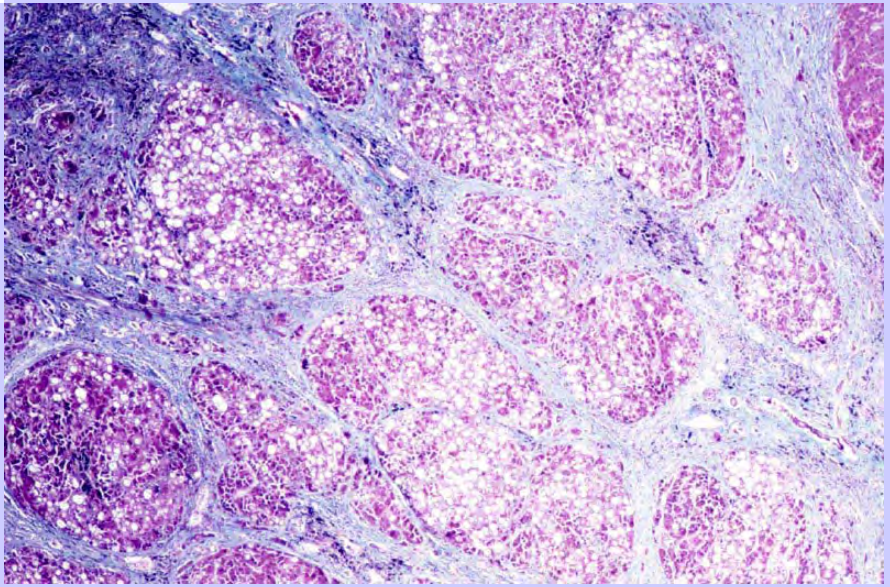
* Functional liver reserve

* Capacity for regeneration

Damage of the liver

- disturbance of hepatocytes
- death of hepatocytes
- loss of liver parenchyme
- activation of other liver cells
- change of liver structure
- liver blood flow disturbances

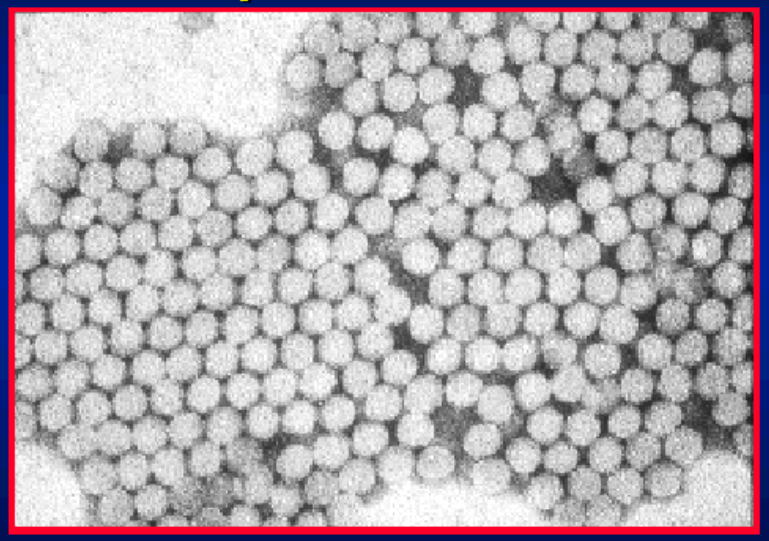

©1995 Cornell University Medical College



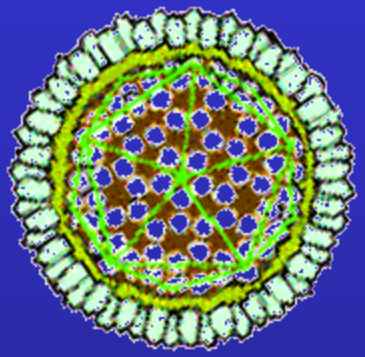
Principle causes of liver damage

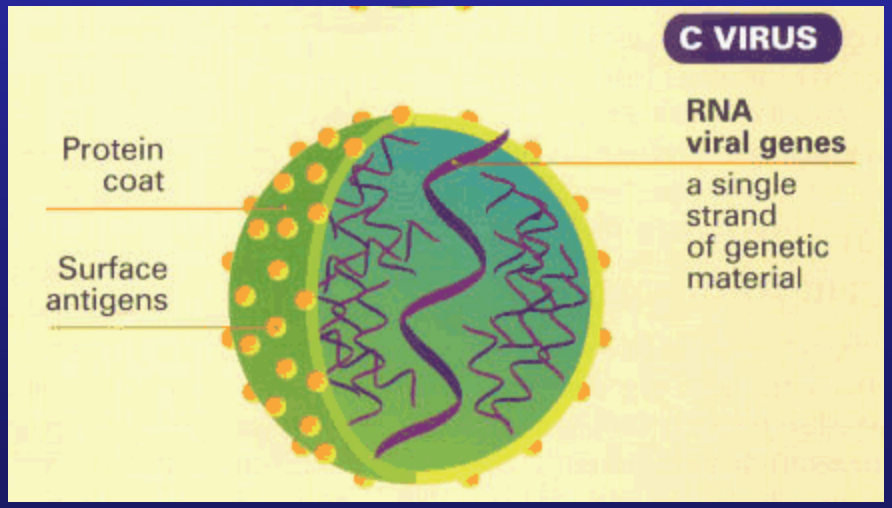
- viruses
- alcohol
- circulatory disturbances
- metabolic diseases
- hepatotoxic substances incl. drugs
- tumors
- systemic diseases

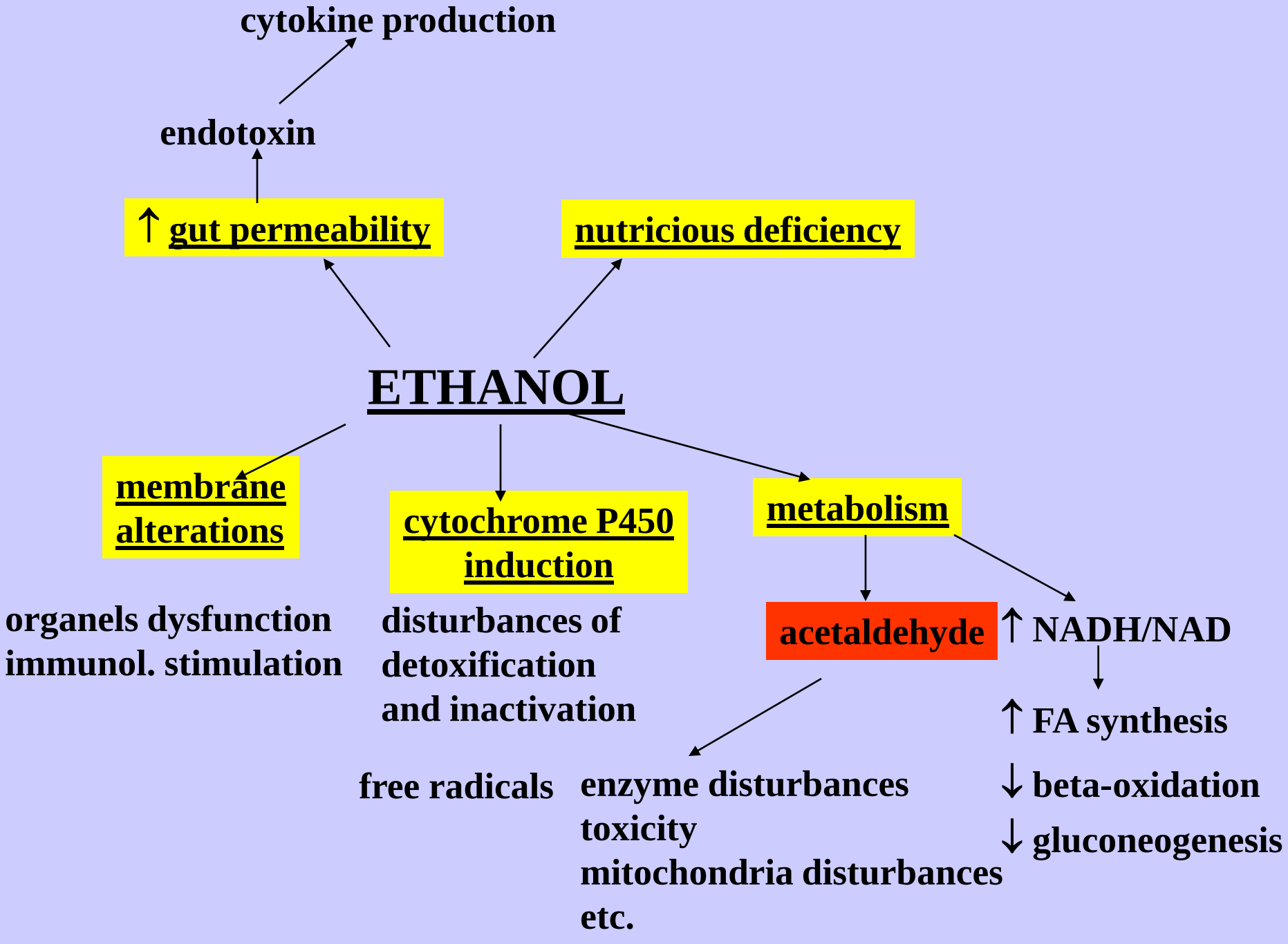
Hepatitis A Virus



HBV

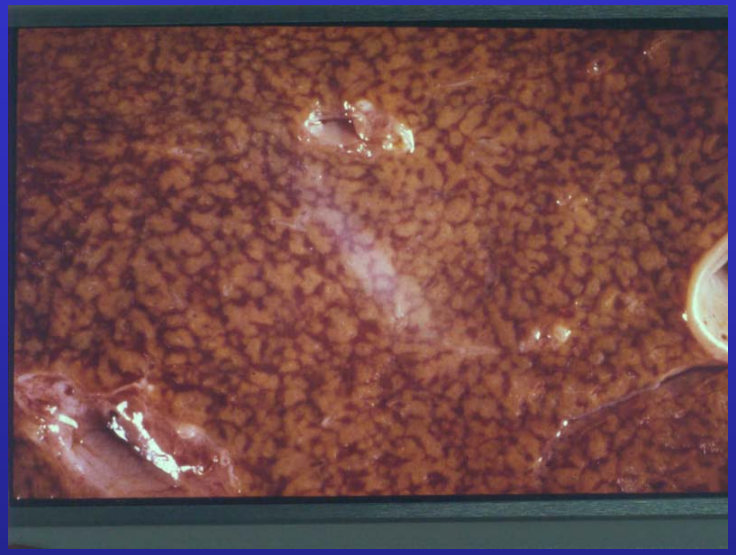





cytokine production
endotoxin
↑ gut permeability
nutricious deficiency
ETHANOL
membrane alterations
cytochrome P450 induction
metabolism
organels dysfunction
immunol. stimulation
disturbances of detoxification and inactivation
acetaldehyde
↑ NADH/NAD
↑ FA synthesis
↓ beta-oxidation
↓ gluconeogenesis
free radicals
enzyme disturbances
toxicity
mitochondria disturbances
etc.

Circulatory disturbances

* blood congestion
right heart failure –
nutmeg liver



* hypoperfusion, e.g. due to shock

Metabolic diseases

- hemochromatosis
- porphyria
- Wilson’s disease
- glykogenosis
- thesaurosis

Wilson's disease

(hepatolenticular degeneration)

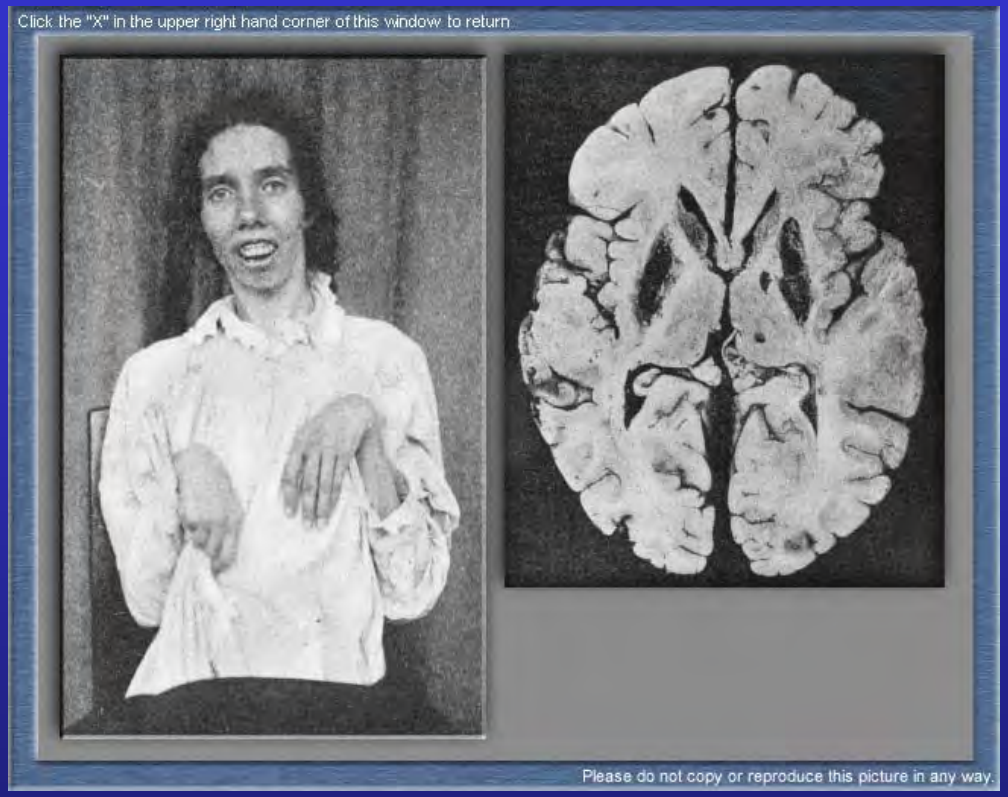
AR inherited disorder (1:30 000) of *copper* metabolism

impairment of normal excretion of hepatic copper

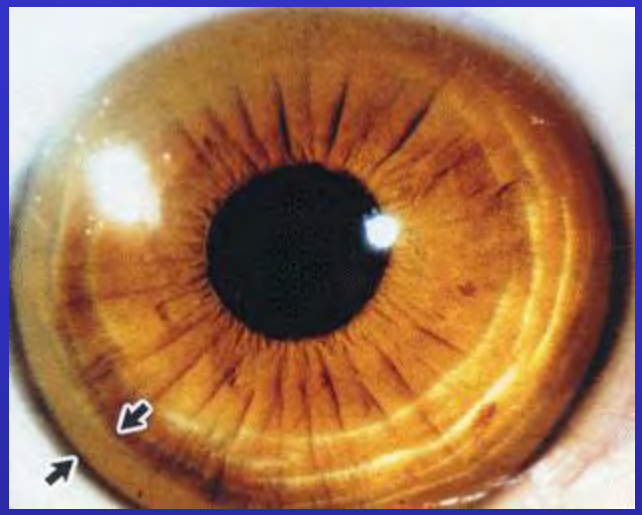
toxic accumulation of the metal in liver, brain and other organs

low serum ceruloplasmin concentration

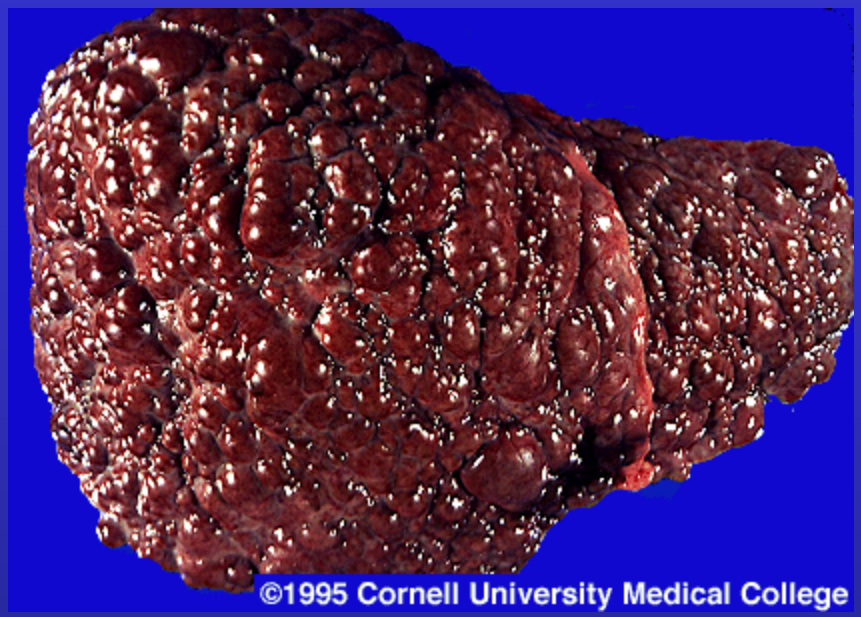
Neuropsychiatric damage



The entire March 1912 issue of Brain was devoted to S. A. Kinnier **Wilson's description of familial hepatolenticular degeneration**. On the left is one of Wilson's original patients, demonstrating the characteristic posture of the arms and hands and fixed facial features with involuntary mouth opening. On the right is the cut brain of one of Wilson's patients, showing bilateral degeneration of the lenticular nuclei.



Kayser-Fleischer ring



Hepatic disturbances

- acute hepatitis
- fulminant hepatitis
- chronic active hepatitis
- cirrhosis

ATP7B gene (13th chromosome)
P type, copper-transporting *ATPase*
more than 40 mutant forms have been identified

Hemochromatosis

- disorder of iron storage
- mostly AR inherited disease
  (almost 0,3% incidence with incomplete penetration)
  inappropriate increase in intestinal iron absorption
- deposition of excessive amount of iron in parenchymal cells with tissue damage

Porphyria

inherited or acquired disorder of specific enzymes in the heme biosynthetic pathway with accumulation of porphyrins of their precursors

some of them – mainly PCT (*porphyria cutanea tarda*) – represent higher risk of cirrhosis and even hepatocellular carcinoma

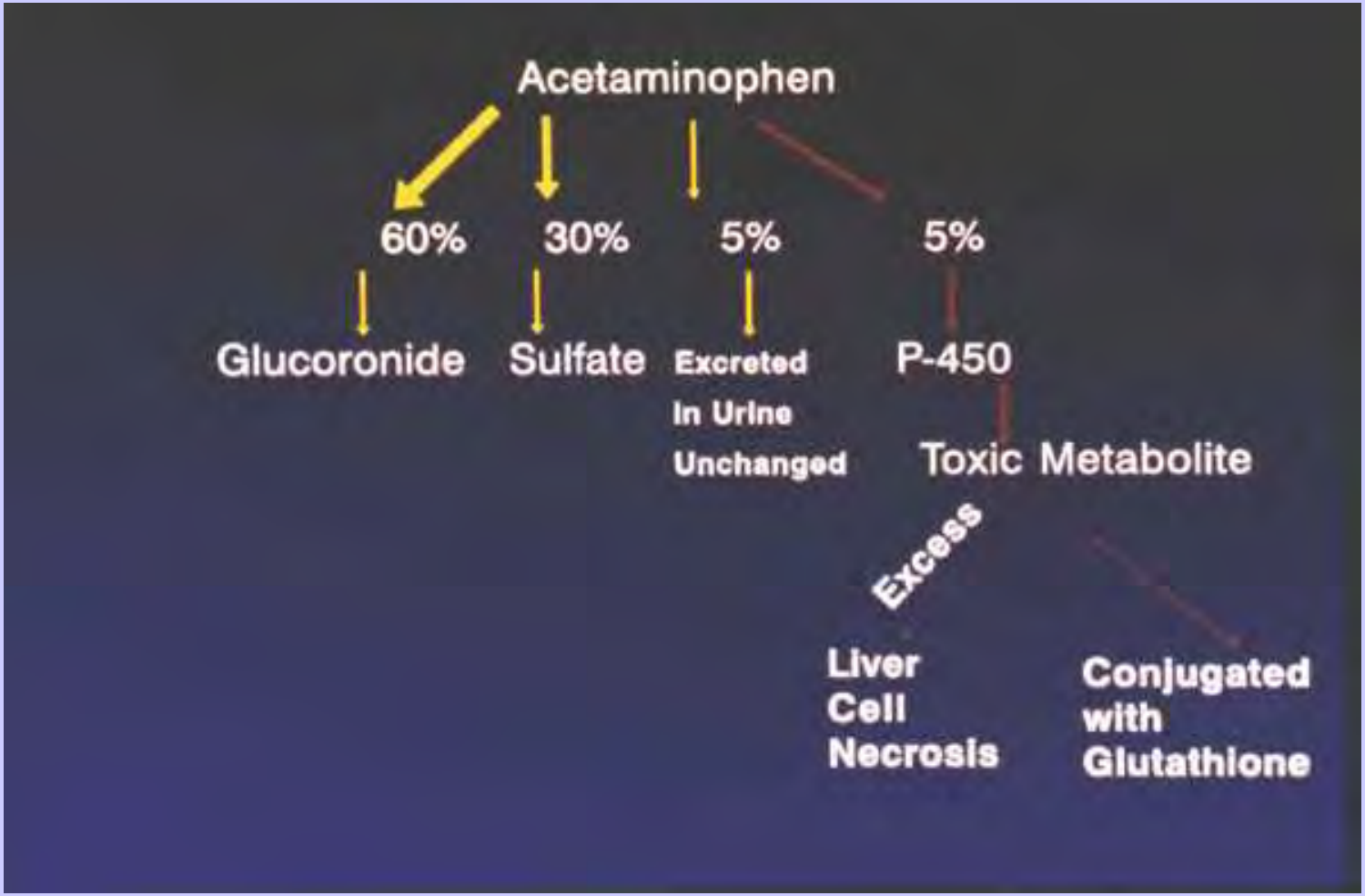
Chemicals, toxins, drugs

* tetrachlormethan and other solvants

* faloidin

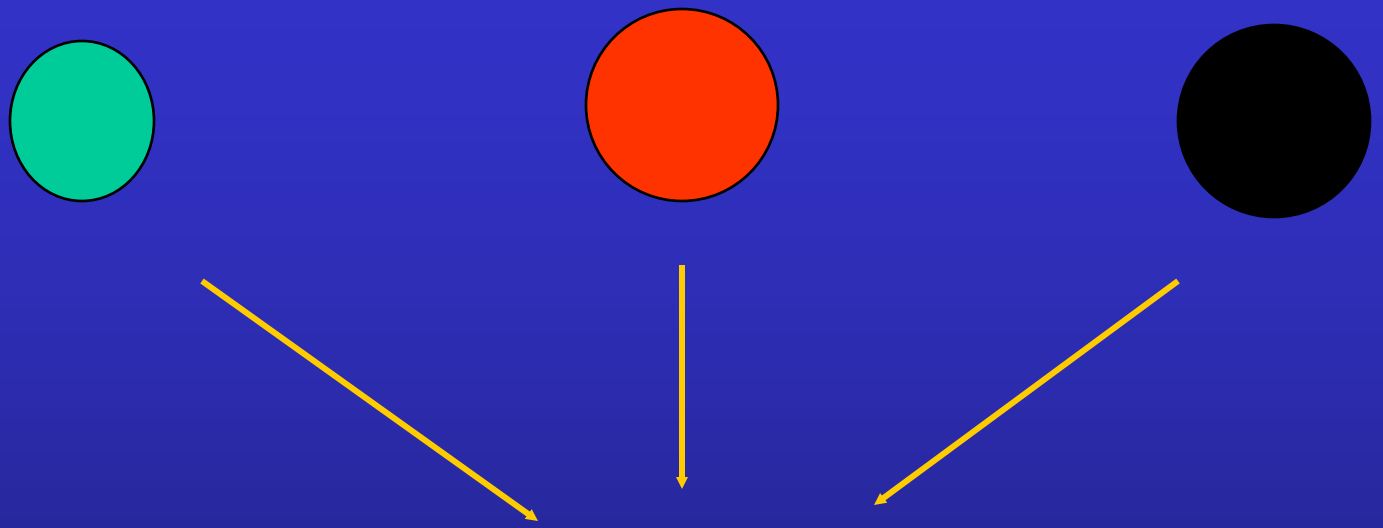
* PARACETAMOL = ACETAMINOFEN

* *many others… !!!*


Acetaminophen
60%
30%
5%
5%
Glucoronide
Sulfate
Excreted
In Urine
Unchanged
P-450
Toxic Metabolite
Excess
Liver
Cell
Necrosis
Conjugated
with
Glutathione

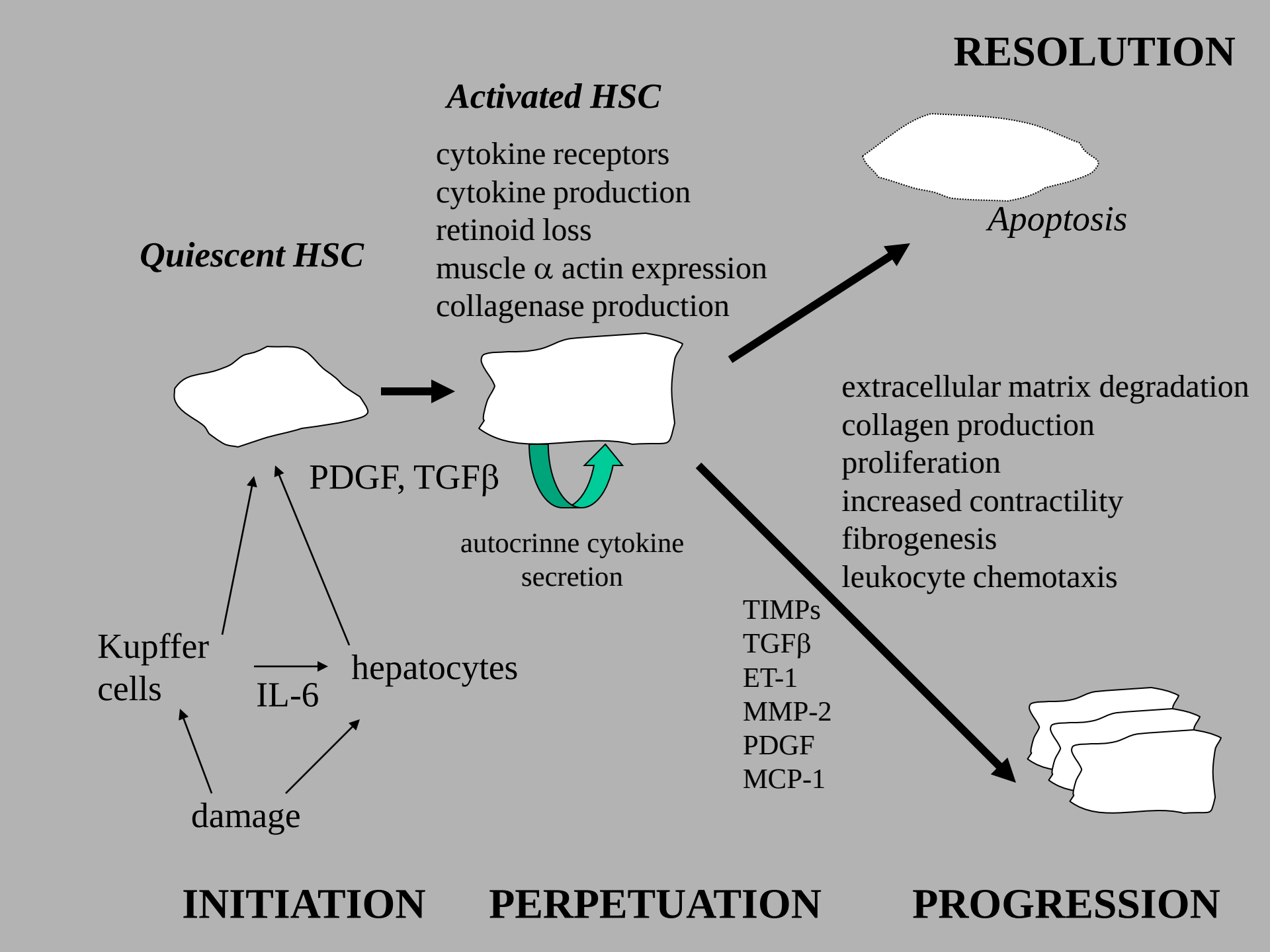
Liver reaction to damage

damaging factors



liver reaction

liver disease


RESOLUTION
Activated HSC
cytokine receptors
cytokine production
retinoid loss
muscle α actin expression
collagenase production
Apoptosis
Quiescent HSC
extracellular matrix degradation
collagen production
proliferation
increased contractility
fibrogenesis
leukocyte chemotaxis
PDGF, TGFβ
autocrinne cytokine secretion
TIMPs
TGFβ
ET-1
MMP-2
PDGF
MCP-1
Kupffer cells
IL-6
hepatocytes
damage
INITIATION
PERPETUATION
PROGRESSION

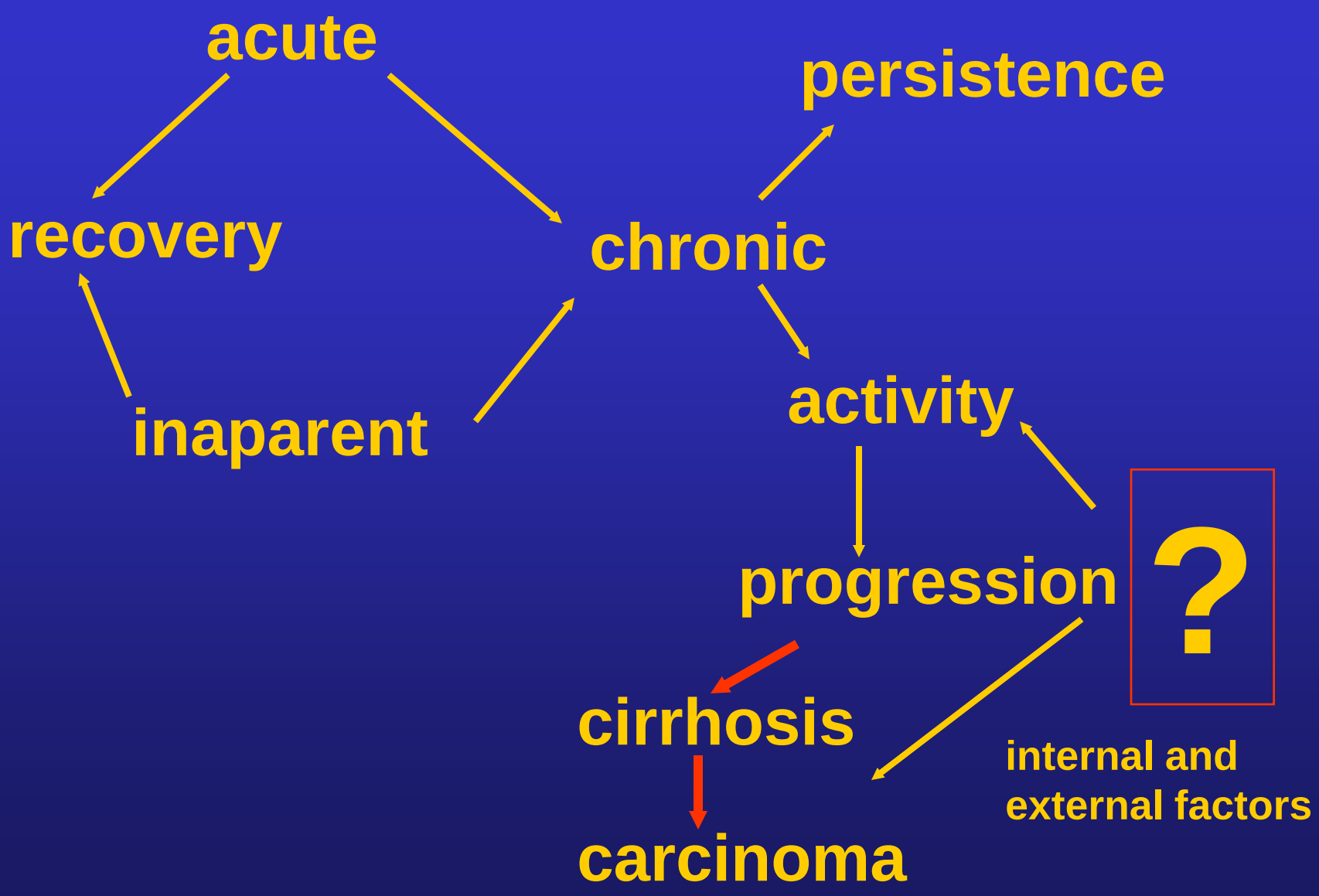
Hepatitis

Etiology

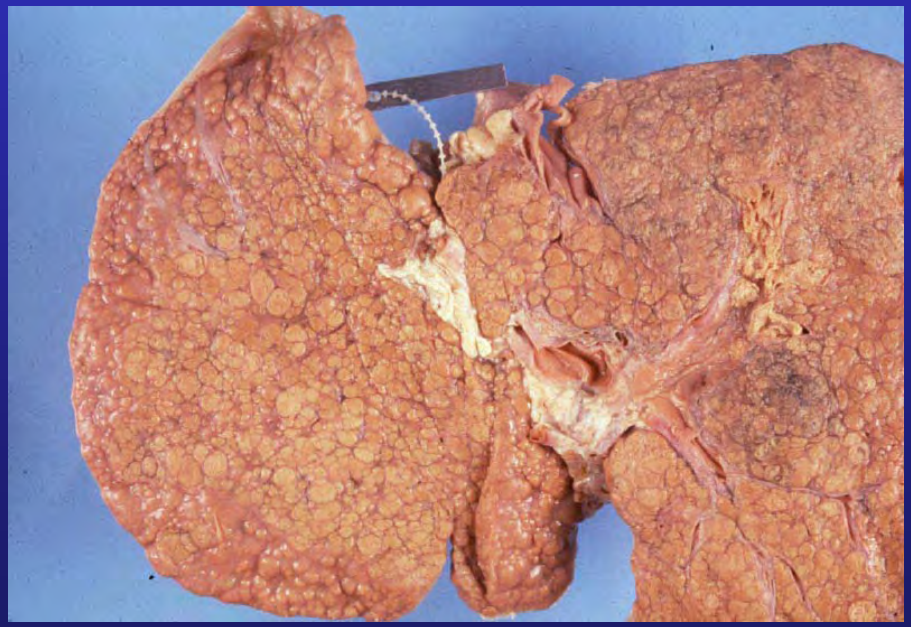
* viruses - clascical (A,B,C,D,E…)
* other viruses and bacteria (e.g. CMV, Leptospira)
* alcoholic hepatitis

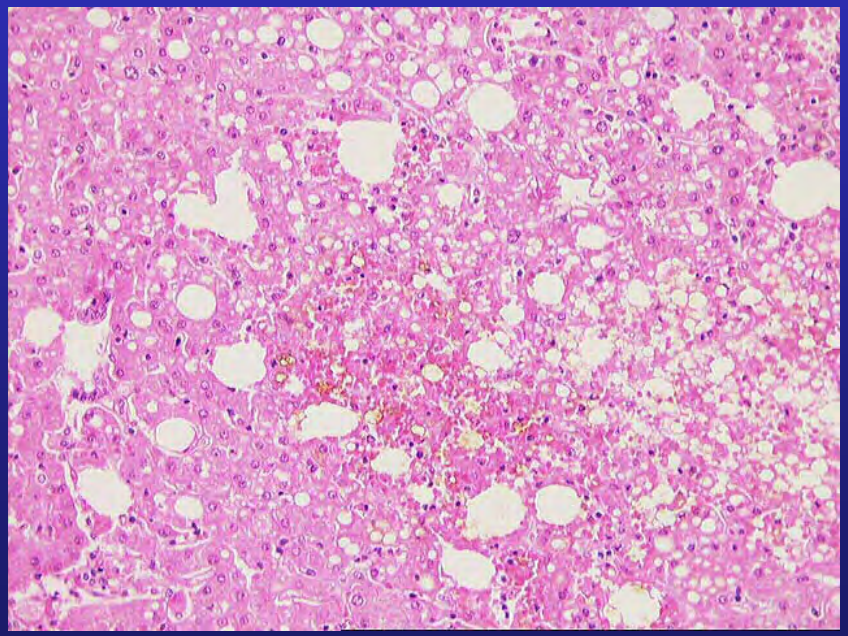
Clinical forms

* *acute* (ev. fulminant)
* *chronic* (B, mainly C)
- persistent (CPH)
- active (CAH) – progression


acute
persistence
recovery
chronic
activity
inaparent
progression
?
cirrhosis
internal and
external factors
carcinoma

Liver steatosis, steatohepatitis





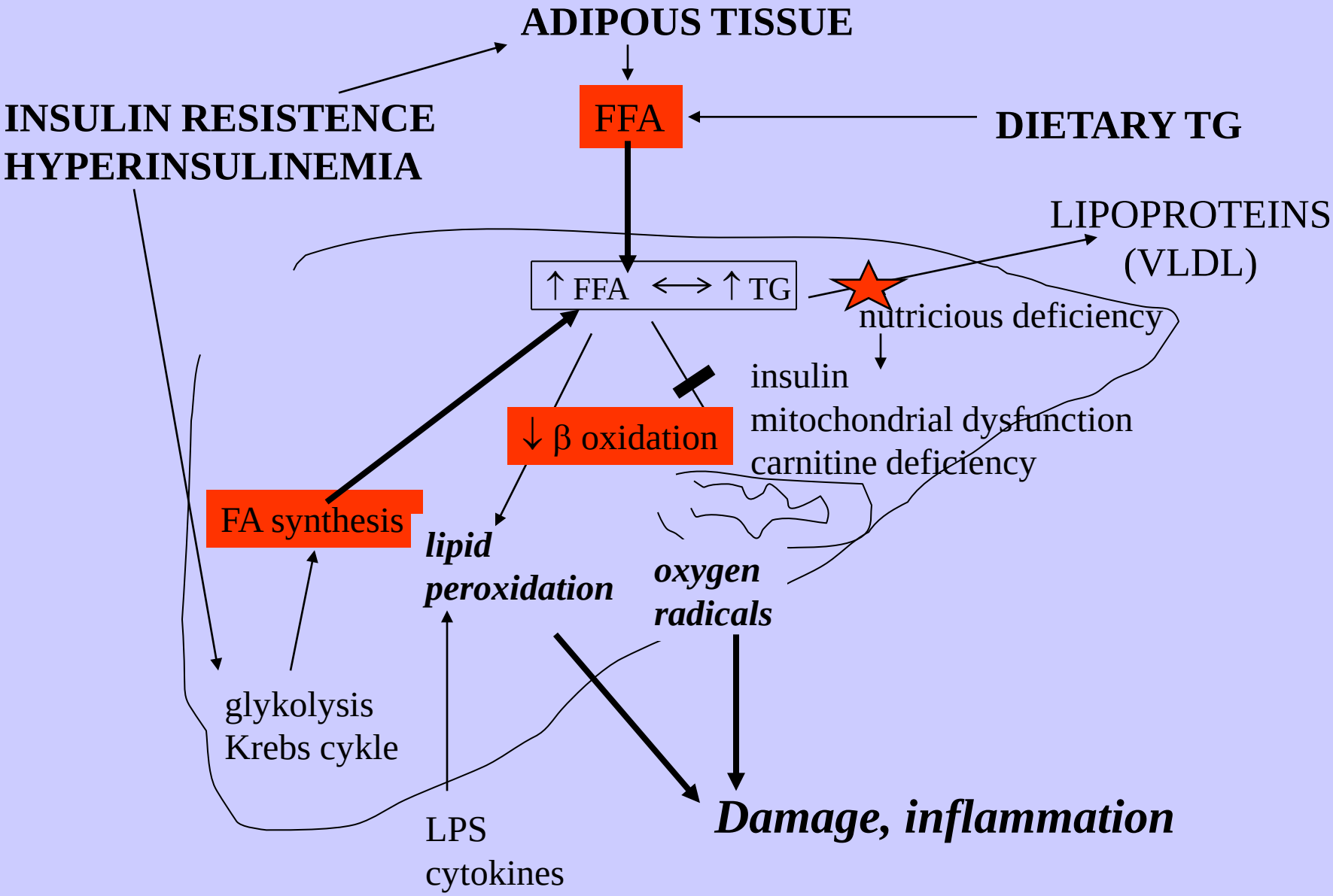
Etiopathogenesis

Alcoholic

* energy
* metabolic changes
* cytochrome induction
* increased TNFα production

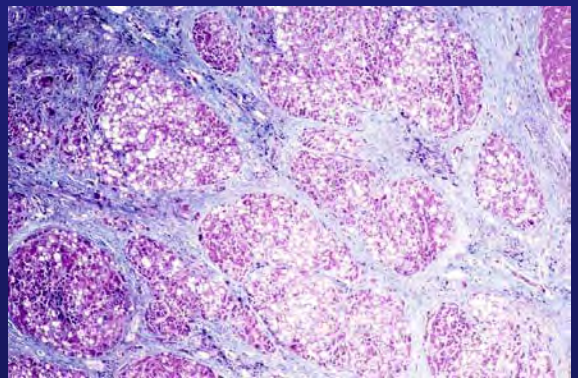
Nonalcoholic steatohepatitis (NASH)

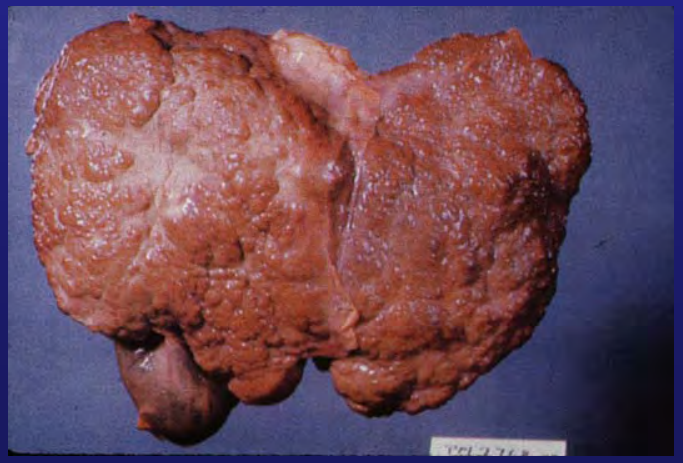
* insulin resistence, obesity, DM 2, hyperlipoproteinemia
* malnutrice, profound weight loss
* toxic substances, drugs


ADIPOUS TISSUE
INSULIN RESISTENCE
HYPERINSULINEMIA
FFA
DIETARY TG
LIPOPROTEINS
(VLDL)
↑ FFA ⟷ ↑ TG
nutricious deficiency
insulin
mitochondrial dysfunction
carnitine deficiency
↓ β oxidation
FA synthesis
lipid
peroxidation
oxygen
radicals
glykolysis
Krebs cykle
LPS
cytokines
Damage, inflammation

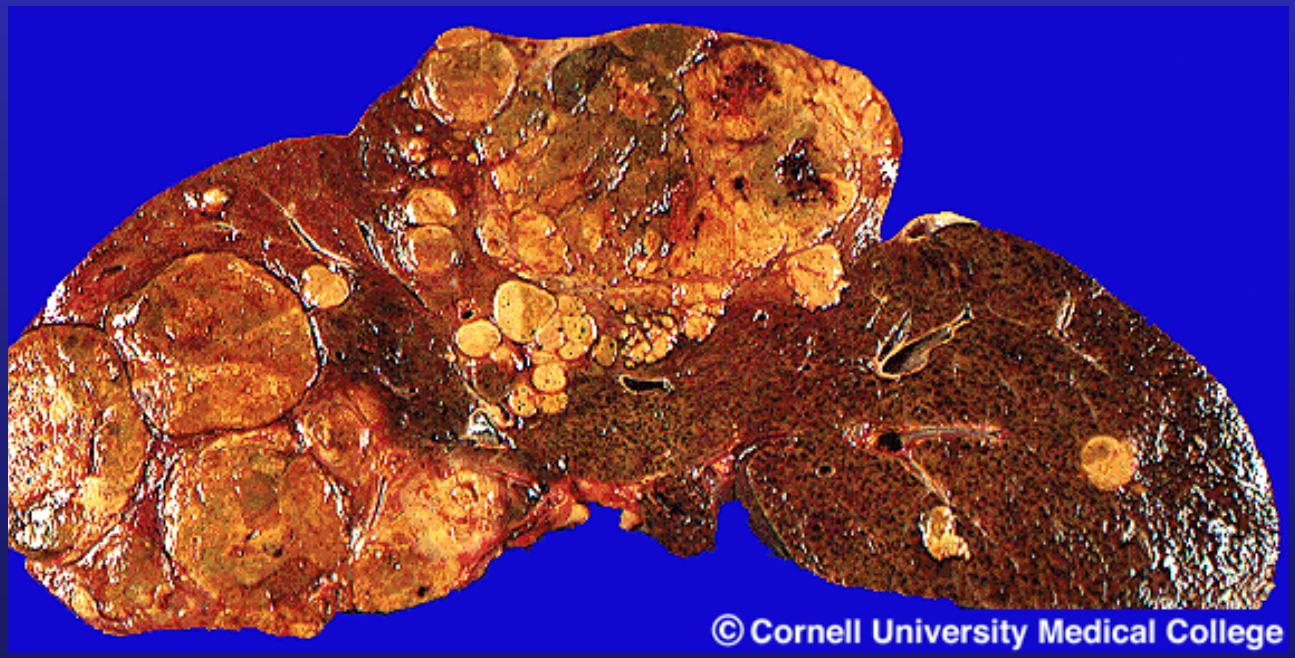
Liver cirrhosis

* hepatic injury
* fibrosis
* nodular regeneration
* irreversible distortion of normal liver architecture
* blood flow disturbances
* loss of parenchyma





Hepatocellular carcinoma (HCC)



* mainly occurs in cirrhosis

* etiology is largely common with cirrhosis
- viruses (HBV and HCV!)
- alcohol a toxins (e.g. aflatoxins, mycotoxins)
- hemochromatosis, porphyria
- combination

* studies on molecular level

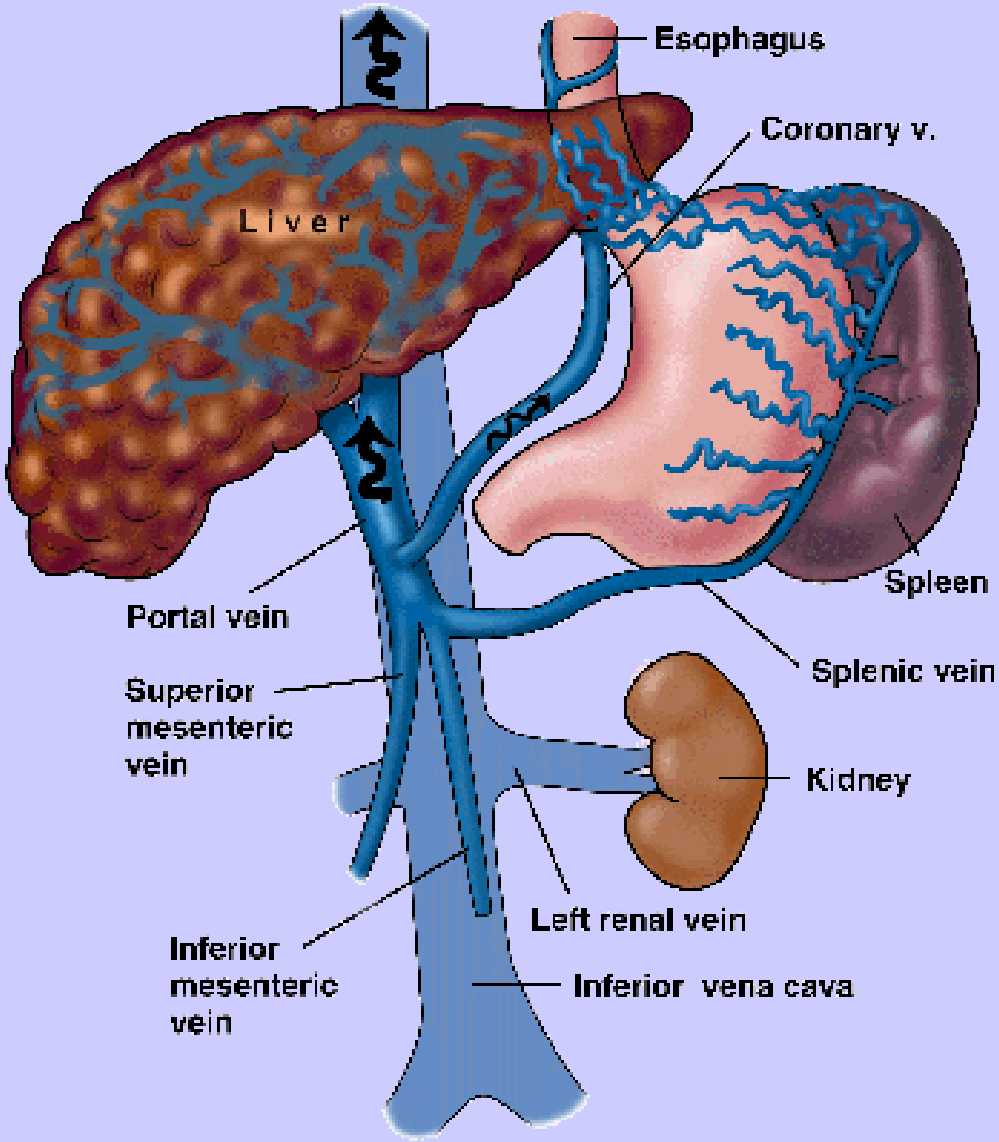
Clinical features of liver diseases

1) progressive hepatocellular dysfunction and *loss of hepatocytes*

2) disturbances of blood flow through liver

- *portal hypertension*

Portal hypertension



Types:

* prehepatic
* (intra)hepatic
* posthepatic

Intrahepatic PH:

* presinusoidal
* sinusoidal
* postsinusoidal

$$P = Q \times R$$

pressure

flow

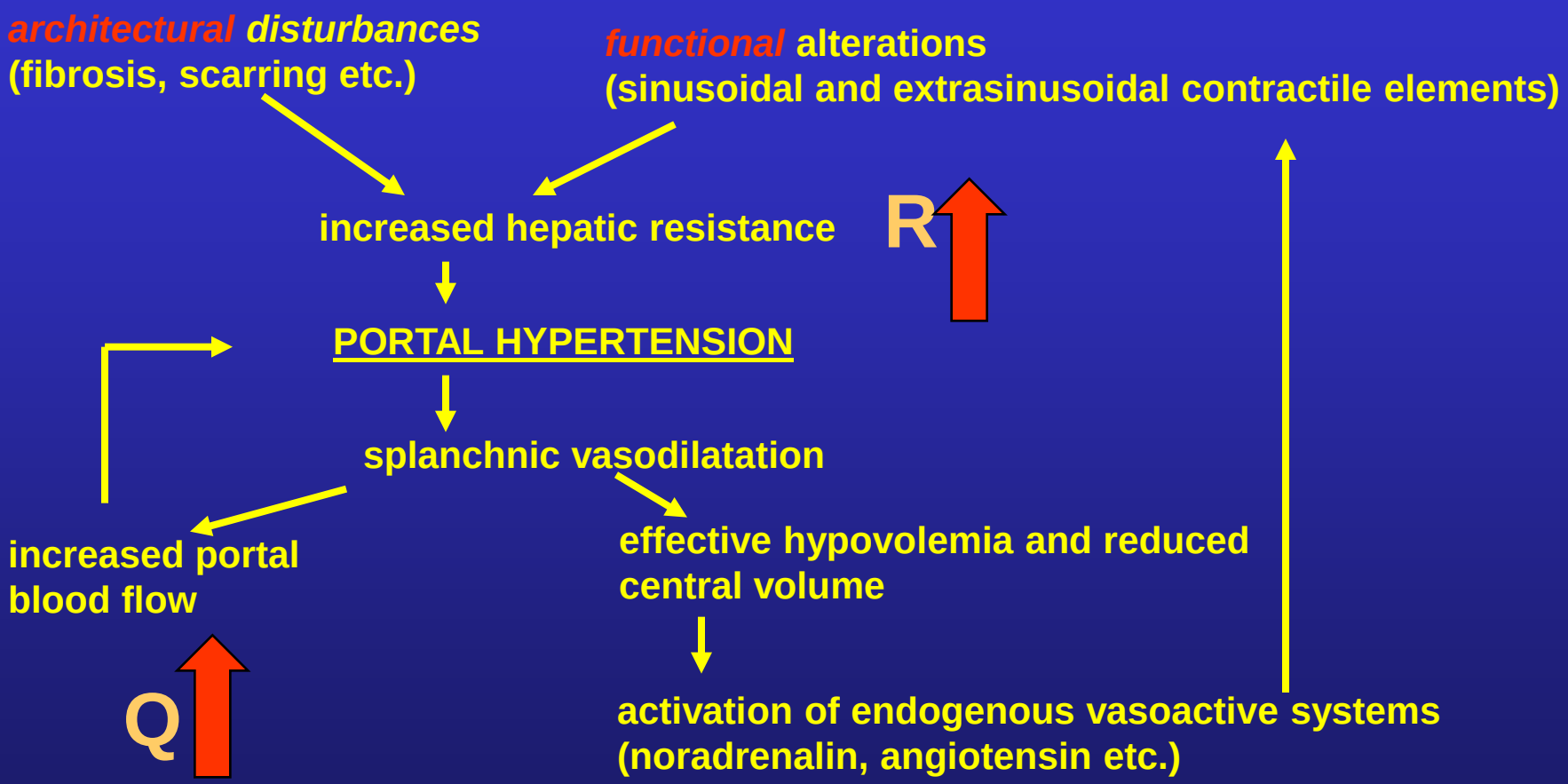
resistance

Mechanisms:

a) **increased flow** through portal region caused by vasodilation and by hyperkinetic circulation

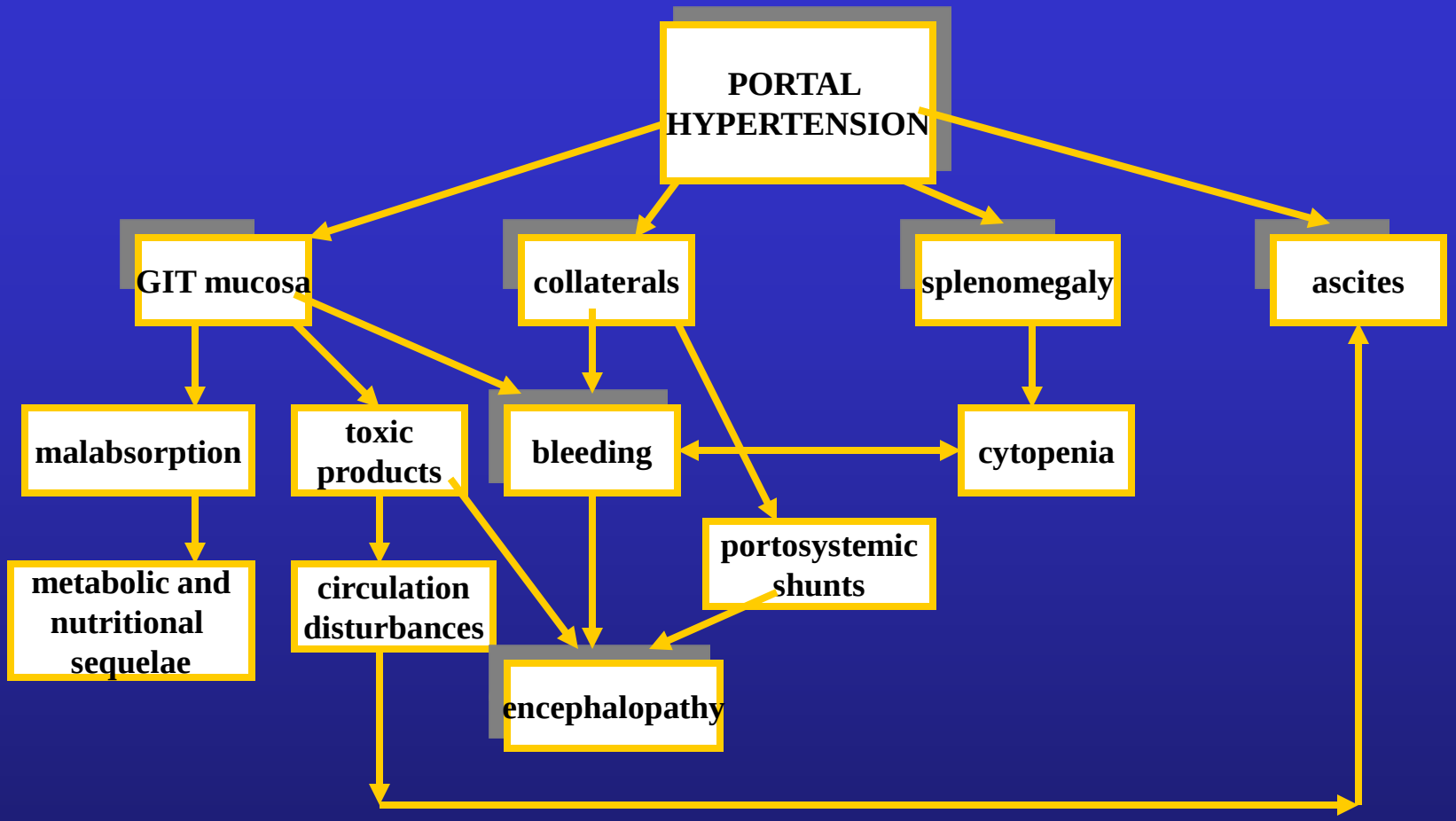
b) **increased resistence** in liver circulation

- ***mechanical*** due to structural changes and fibrosis in liver
- ***functional*** (endothelial dysfunction, HSC activation, elevated production of vasoconstrictory endothelin, decreased production of vasodilatory nitric oxid – NO)


architectural disturbances
(fibrosis, scarring etc.)
functional alterations
(sinusoidal and extrasinusoidal contractile elements)
increased hepatic resistance
R
PORTAL HYPERTENSION
splanchnic vasodilatation
increased portal
blood flow
Q
effective hypovolemia and reduced
central volume
activation of endogenous vasoactive systems
(noradrenalin, angiotensin etc.)

Consequences and main clinical manifestations of portal hypertension

* portocaval (portal-to-systemic) shunting
* blood stagnation in abdomen organs
* gastointestinal bleeding
* hepatic (portosystemic) encefalopathy (PSE)
* ascites
* splenomegaly
* circulatory disturbances
* hepatorenal syndrome
* spontaneous bacterial peritonitis


PORTAL HYPERTENSION
GIT mucosa
collaterals
splenomegaly
ascites
malabsorption
toxic products
bleeding
cytopenia
portosystemic shunts
metabolic and nutritional sequelae
circulation disturbances
encephalopathy

Enlargment of blood vessels that anastomose with the portal vein – *varices*

*** bleeding**

*** *blood shunting* directly to systmic circulation**

- nutrients
- gastrointestinal hormones
- drugs
- toxic substances exogenous and gut-derived

Disturbances of hemostasis

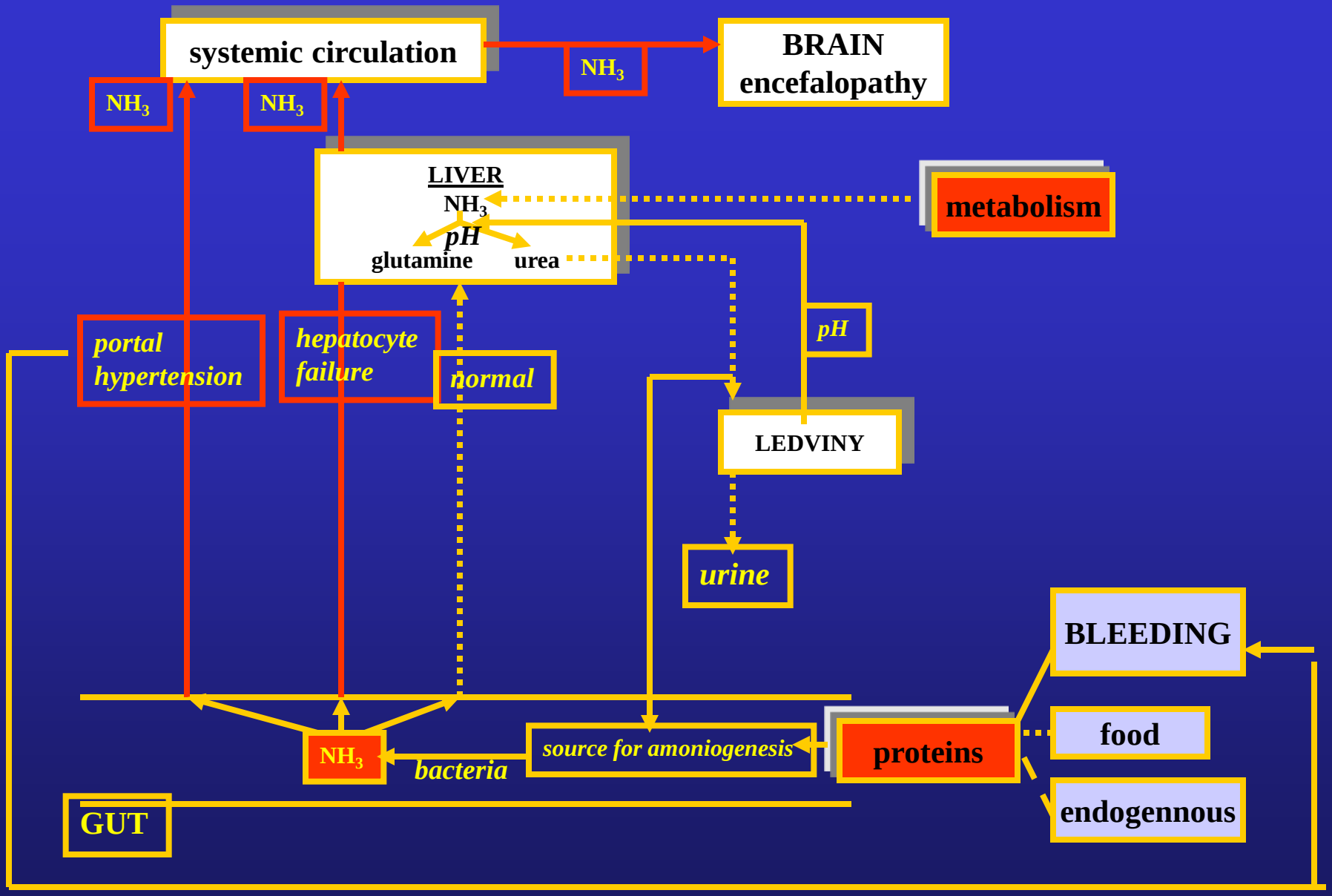
- **coagulopathy**
  synthesis of coagulation factors
- **thrombocytopenia**
  splenomegaly…
- **decreased clearance of activated factors**

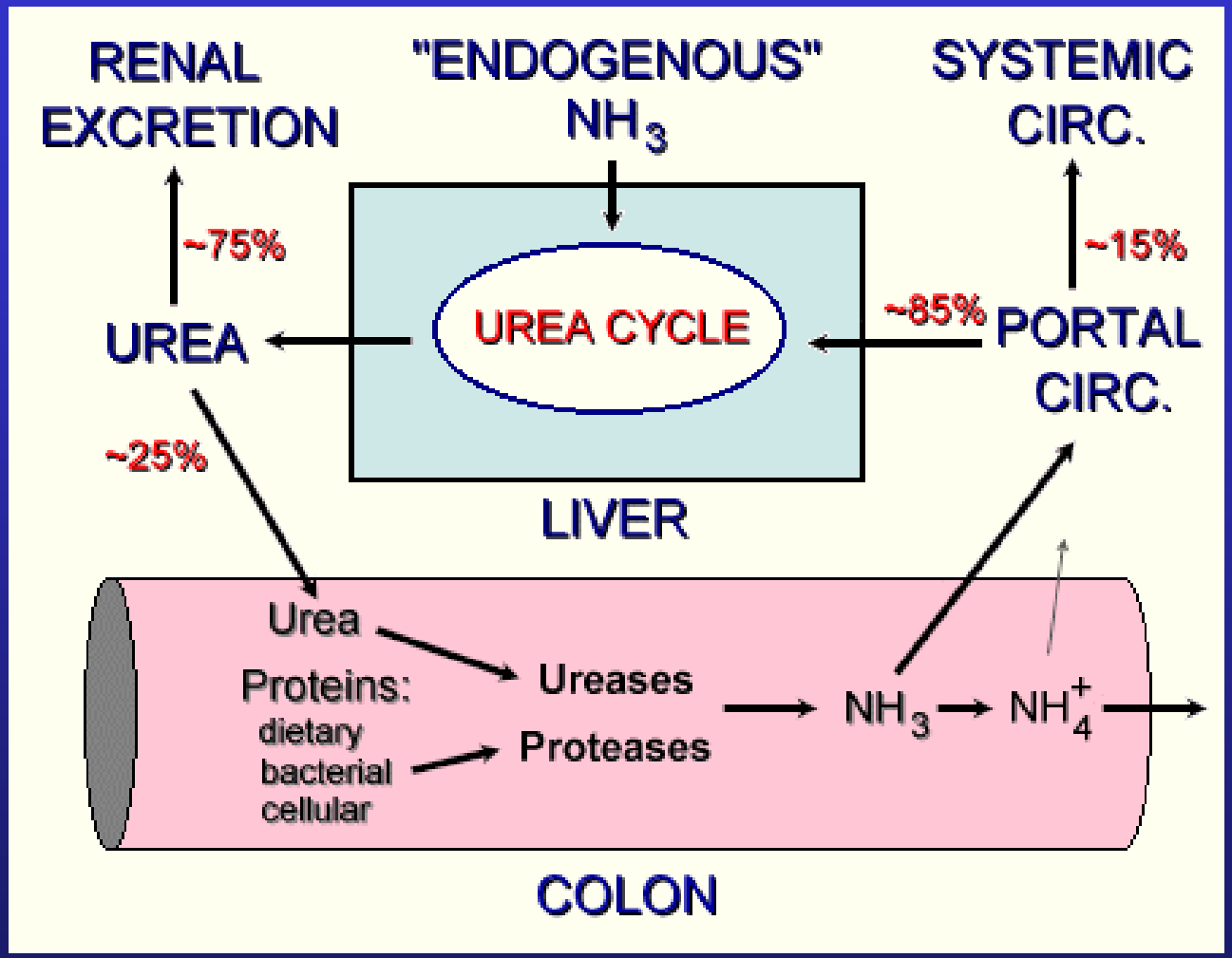
Hepatic encephalopathy

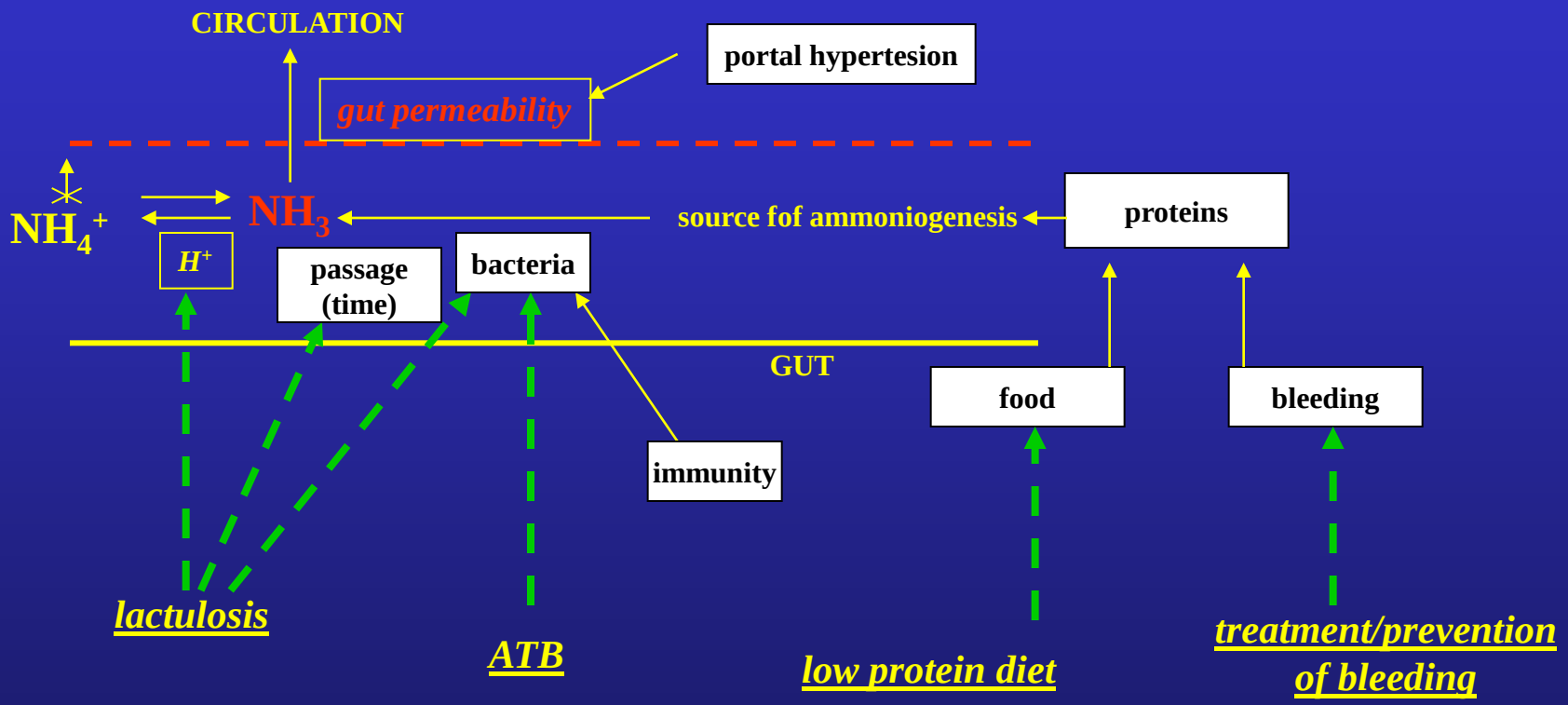
- acute LF
- portosystemic encephalopathy

Pathogenesis has not been completely elucidated yet, the role of several factors is supposed

- ***ammonia*** and other gut-derived substances
- disturbances in ***blood-brain barrier (BBB) permeability*** (cytokines – TNF-α, NO…)
- disturbances in ***neurotransmission*** (↑GABA, ↓glutamate, ↑endogenous benzodiazepins, neurosteroids)
- false neurotransmiters (e.g. octopamin)
- increase of benzodiazepin receptors (peripheral type) in astrocytes
- changes in aminoacid spectrum (↑aromatic, ↓branched)
- osmotic changes and brain edema in hepatic encefalopathy during acute LF
- role of proinflammatory cytokines (IL-1, IL-6, TNF-α) on blood-brain barrier permeability and on endothel in brain vessels (e.g. induction of NO production with changes in brain circulation)
- other: deposits of manganese in gl. pallidus, phenol, short-chain fatty acids...


systemic circulation
NH3
BRAIN
encefalopathy
NH3
NH3
LIVER
NH3
pH
glutamine
urea
metabolism
portal
hypertension
hepatocyte
failure
normal
pH
LEDVINY
urine
BLEEDING
food
endogennous
proteins
source for amoniogenesis
NH3
bacteria
GUT


RENAL EXCRETION
"ENDOGENOUS" NH_3
SYSTEMIC CIRC.
~75%
~15%
UREA
UREA CYCLE
~85%
PORTAL CIRC.
~25%
LIVER
Urea
Proteins:
dietary
bacterial
cellular
Ureases
Proteases
NH_3
NH_4^+
COLON


CIRCULATION
portal hypertesion
gut permeability
NH_4^+
NH_3
source of ammoniogenesis
proteins
H^+
passage (time)
bacteria
GUT
food
bleeding
immunity
lactulosis
ATB
low protein diet
treatment/prevention of bleeding

food proteins

tyrosin

fenylalanin

DOPA

normal synthesis in the nervous tissue

decarboxylation in the gut

dopamin

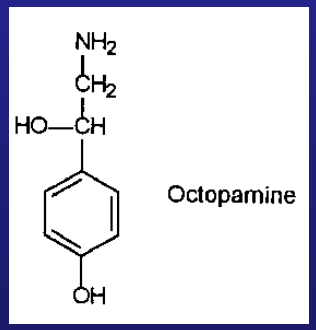
tyramin

noradrenalin

octopamin

β-fenyletanolamin

false



Octopamine

neurotransmitters of sympathic nerves

DISTURBANCE OF BRAIN FUNCTION/METABOLISMS

Precipitating factors:

- bleeding,
- proteins,
- constipation,
- renal failure with blood urea increase (source for ammonia generation in gut),
- drugs,
- electrolyte imbalance,
- infection, surgery etc.

CIRCULATORY DISTURBANCES

PORTAL HYPERTENSION

↓

SPLANCHNIC VASODILATATION (NO etc.)

↓

SYSTEMIC UNDERFILLING

↓

VASOCONSTRICTION
IN OTHER ORGANS,
MAINLY IN THE KIDNEYS

↓

FLUID RETENTION

CIRCULATORY CHANGES – SYSTEMIC CIRCULATION

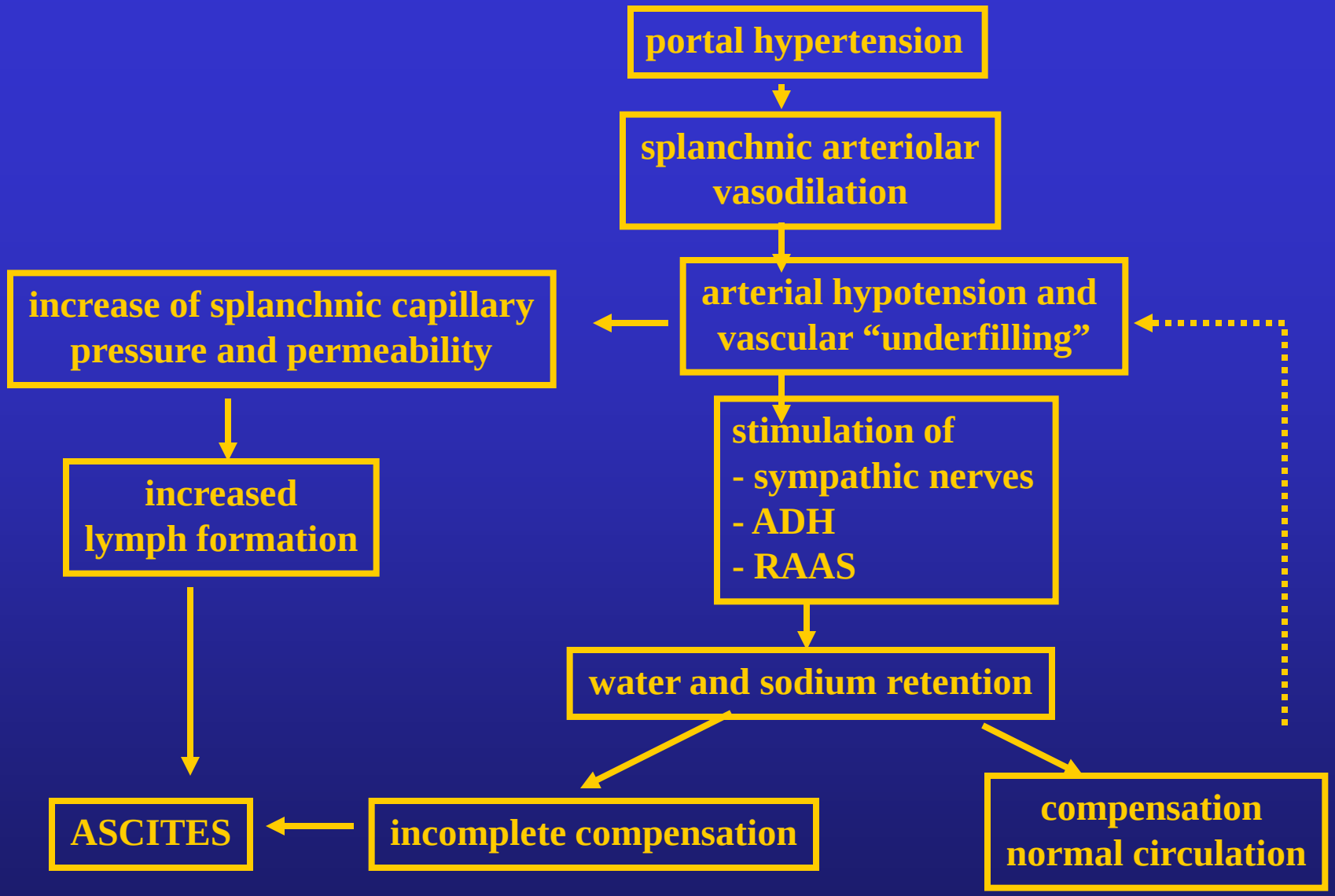
DECREASE OF SYSTEMIC RESISTANCE

INCREASE OF CARDIAC OUTPUT

HYPOTENSION

TACHYCARDIA

HYPERKINETIC CIRCULATION

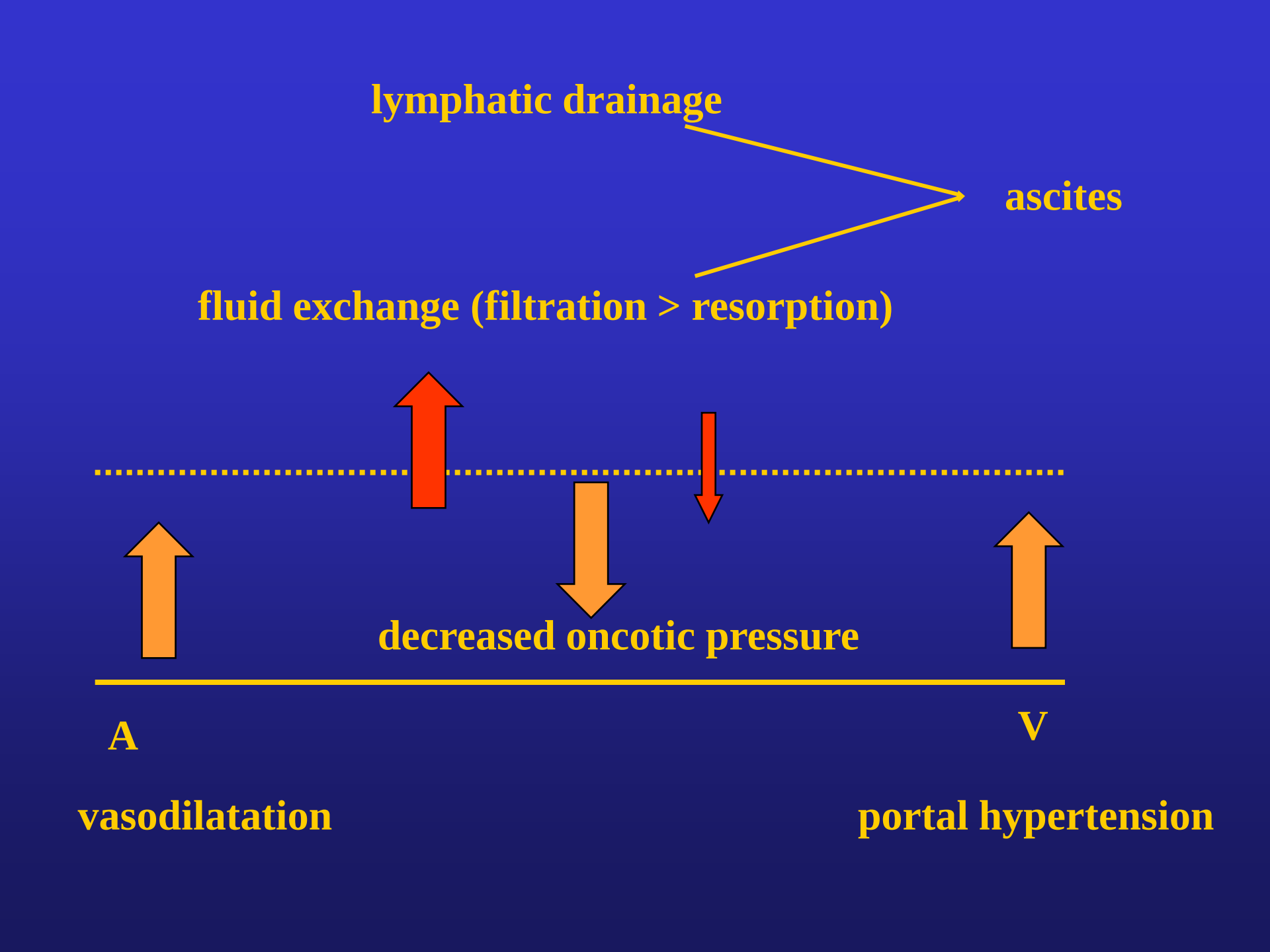

portal hypertension
splanchnic arteriolar vasodilation
arterial hypotension and vascular "underfilling"
increase of splanchnic capillary pressure and permeability
increased lymph formation
stimulation of
- sympathic nerves
- ADH
- RAAS
water and sodium retention
ASCITES
incomplete compensation
compensation normal circulation

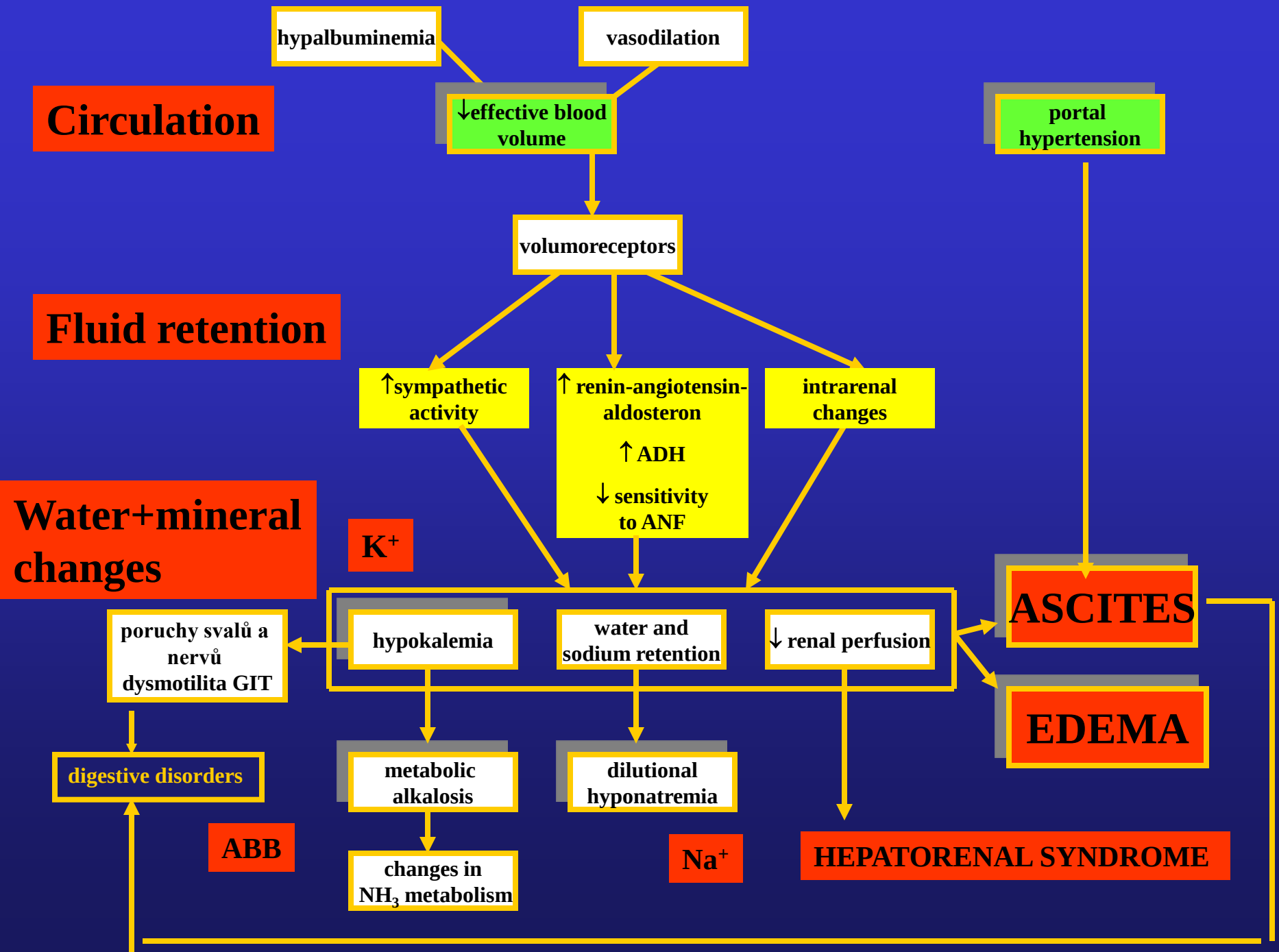
ASCITES

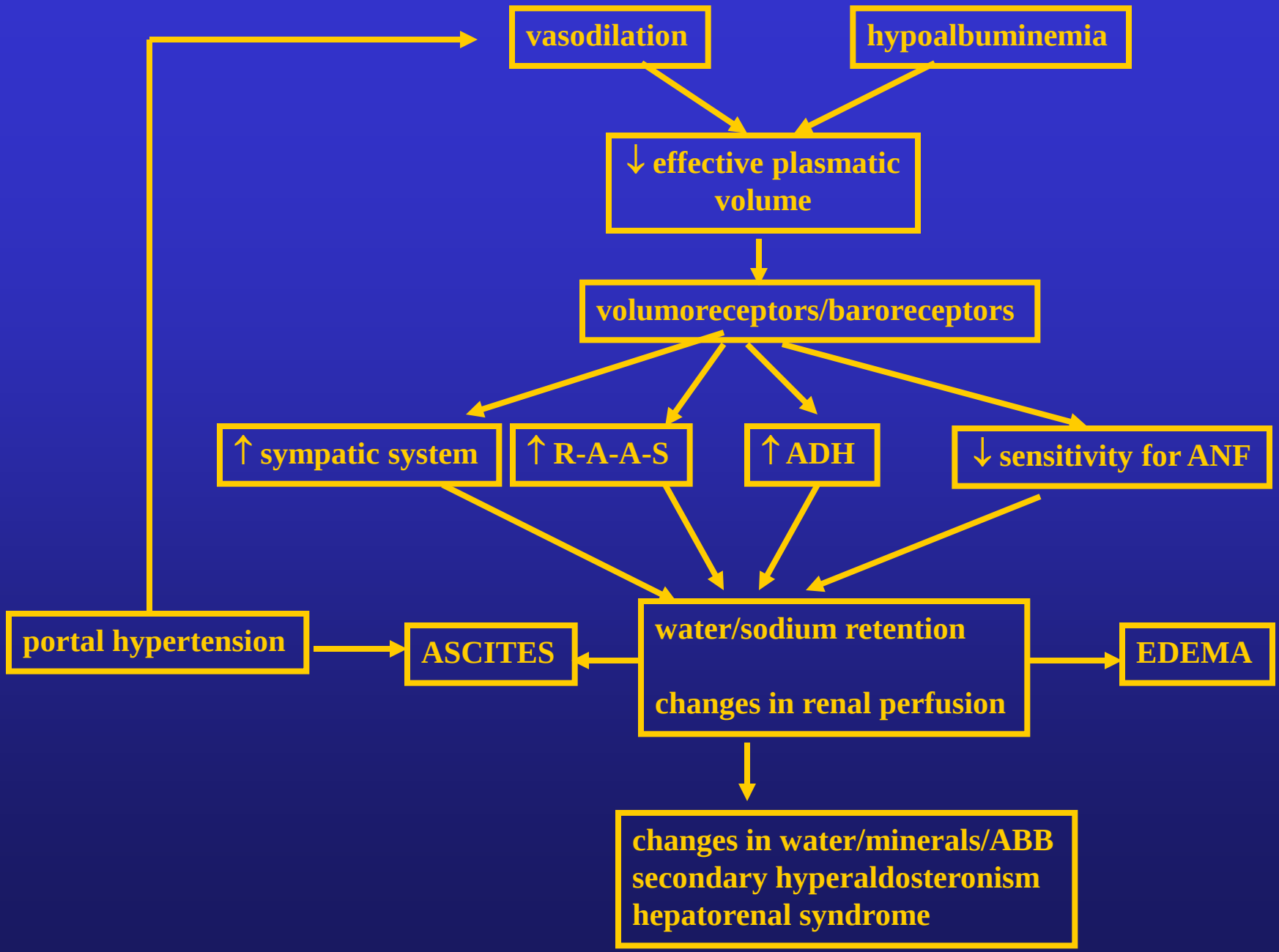
Mechanisms of origin:

a) portal hypertension
b) hypoalbuminemia
c) circulatory changes (vasodilation, hyperkinetic circulation)
d) water and sodium retention – key role of the *kidney* in ascites formation
e) lymphatic vessels disorders

These mechanisms are responsible also for edema (except for portal hypertension).


lymphatic drainage
ascites
fluid exchange (filtration > resorption)
decreased oncotic pressure
A
V
vasodilatation
portal hypertension


hypalbuminemia
vasodilation
Circulation
↓effective blood volume
portal hypertension
volumoreceptors
Fluid retention
↑sympathetic activity
↑ renin-angiotensin-aldosteron
↑ ADH
↓ sensitivity to ANF
intrarenal changes
Water+mineral changes
K+
ASCITES
poruchy svalů a nervů dysmotilita GIT
hypokalemia
water and sodium retention
↓ renal perfusion
EDEMA
digestive disorders
metabolic alkalosis
dilutional hyponatremia
ABB
changes in NH3 metabolism
Na+
HEPATORENAL SYNDROME


vasodilation
hypoalbuminemia
↓ effective plasmatic volume
volumoreceptors/baroreceptors
↑ sympatic system
↑ R-A-A-S
↑ ADH
↓ sensitivity for ANF
portal hypertension
ASCITES
water/sodium retention
changes in renal perfusion
EDEMA
changes in water/minerals/ABB
secondary hyperaldosteronism
hepatorenal syndrome

Sequelae of ascites:

a) increase in body weight (might be another complication in general bad status)
b) diaphragm elevation (decreased lung vital capacity)
c) negative impact on GIT
d) mechanical influencing abdomen wall, hernias etc.

HEPATORENAL SYNDROME (HRS)

portal hypertension

↓

splanchnic vasodilatation

increased production of splanch. VD substances

↓

severe arterial underfilling

BP decrease

↓

stimulation of vasoconstrictive mechanisms → **vasoconstriction in the brain and the limbs**

↓

vasoconstriction in the kidneys

renal vasoconstrictors prevail over renal vasodilatatory mechanisms (mainly prostaglandines)

↓

HRS

HEPATORENAL SYNDROME (HRS)

Renal failure in patients with advanced (chronic) liver disease, the histological appearance of the kidneys is normal, they can be transplanted

The hallmark of HRS is *vasoconstriction* in the renal circulation due to *sympathic system* and *RAAs* activation. Endothelins a leukotriens might be also involved.

The vasoconstrictor systems are activated as a response to vasodilation induced
by e.g. NO, which persists in splanchnic regions while in the kidneys leads to vasoconstriction .

Protective action on kidney perfusion have *prostaglandins* (caution with many drugs !)

HEPATORENAL SYNDROME (HRS)

- oligoanuria

- increase of serum creatinine and urea

- decrease of GF below 20 ml/min

- tubular functions are preserved

- worsening response on diuretic therapy

- sodium and water retention, edema, ascites, dilutional hyponatremia

Hepatorenal syndrome (HRS)

type I – rapid progression of renal functions with increase of serum creatinin

type II – slower onset

The syndrome is characterized by functional changes in kidney; the histology is normal

Gastrointestinal&digestion disorders

- ***Portal-hypertensive gastropathy*** (PHG): dilated vessels in the mucosa and submucosa in the absence of inflammation, leading to small or less frequently large erosions. No clinical manifestation but ***bleeding*** in cases with large erosions.
- ***Gastric acid*** secretory activity is reduced, whereas the gastric mucosal barrier is impaired.
- Gastric ***mucosal haemodynamics***: whether „overflow“ (i.e. active congestion) or „stasis“ (i.e. passive congestion) causes gastric mucosal hyperaemia is not known
- Disorders of ***bile secretion*** – malabsorption of fat + fat-soluble vitamins
- Impaired ***resorption***

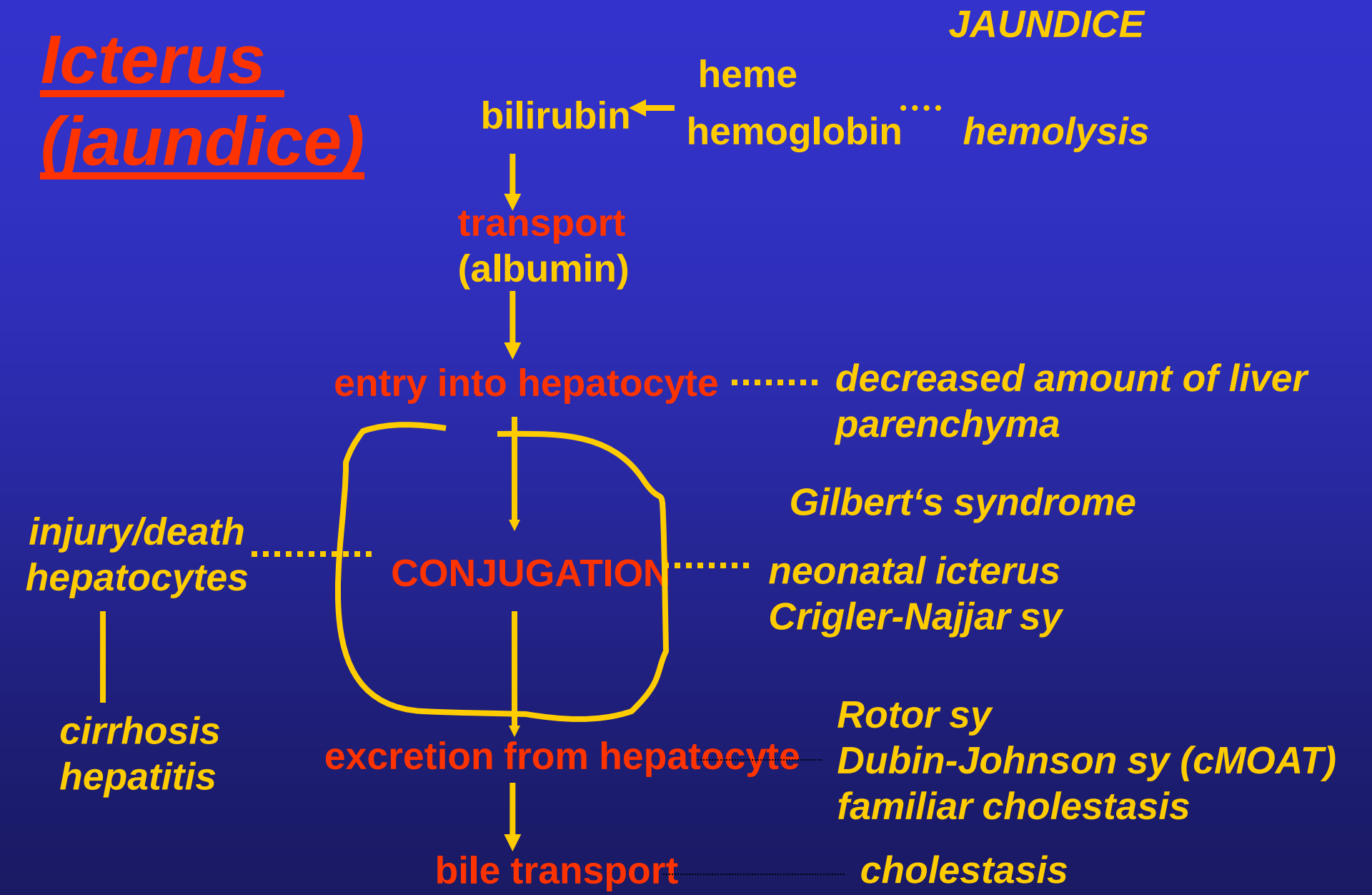
Hormonal disturbances

Altered hormone clearance in liver – decreased removal of free steroid hormones from blood and their inactivation, decrease in inactivation of insulin/glucagon

Steroid hormones clearance is diminished – increased peripheral aromatization of androgens to estrogens: ***gynecomasty*** in man, testicular atrophy, sexual disturbances…

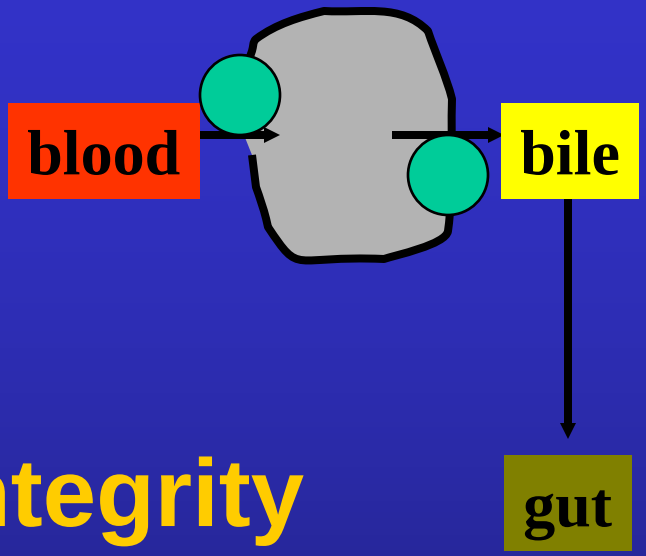
Decrease aldosterone metabolism contributes to the ***secondary hyperaldosteronism***

Icterus (jaundice)



Cholestasis

Bile production and secretion



Liver

* transport mechanisms
  in hepatocytes
* structural hepatocyte integrity
* energy

Bile flow

* intrahepatic biliary ducts
* extrahepatic biliary ducts

Principle bile components

* water
* bile salts
* phospholipides
* cholesterol and other steroids
* minerals
* endogenous substances
* exogennous substances incl. drugs, toxins etc.

Important - *fluidity*

Hepatocyte and transporters

* hepatocyte damage incl. energetic metabolism
* inborn defects of transporters
* competition between various substances during transport
* change in gene expression of transporters

Hereditary disorders

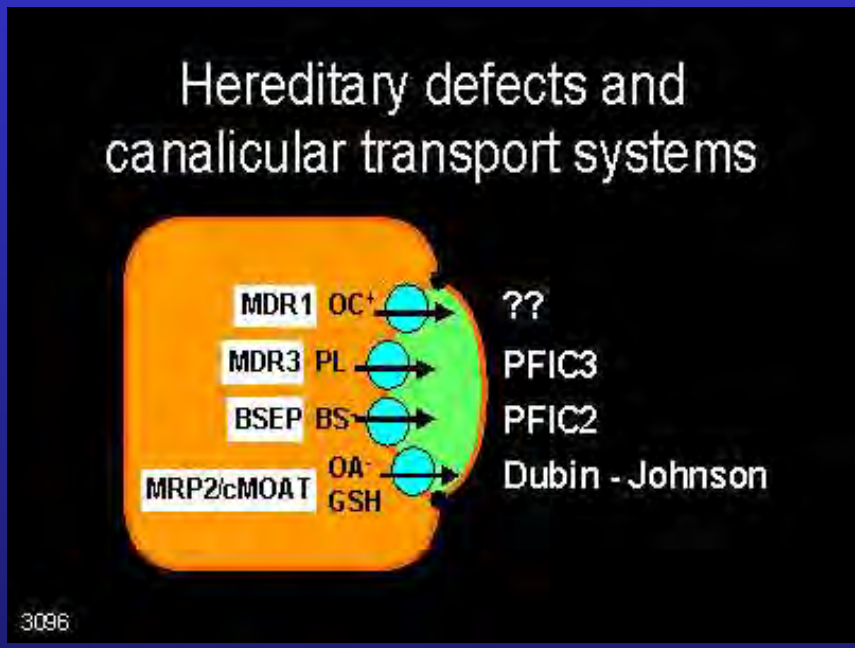
**** progressive familiar intrahepatic cholestasis (PFIC)***

- type 1 - MDR3

- type 2 - BSEP

**** Dubin-Johnson syndrome***

- cMOAT

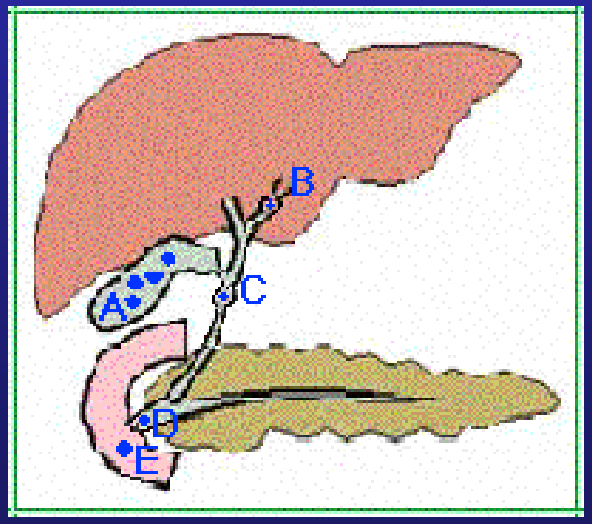


Canalicular disorders

* *cholangitis* incl. autoimmunity
* granulomas
* ischemia
* cystic fibrosis
* tumors …

Extrahepatic disorders

* cholelithiasis (stones)
* tumors



Consequences

* bile stagnation in the
* lack of bile in the intestine

Damage to hepatocytes and liver

- ***bile acids***

*** detergent action, membrane damage**
*** lipase activation**
*** vasoactive action**
*** interference with metabolism, transduction**
*** incorporation into membranes, covalent binding to proteins**
*** apoptosis**
*** immunomodulatory functions**

- ***bilirubin***

mitochondrial uncoupling
jaundice (icterus)

- ***leukotriens***

hemodynamic effects
inflammation

- ***copper***

lipid peroxidation

- ***cholesterol***

change in membrane fluidity

Sequelae:

biliar cirrhosis

Lack of bile in the intestine

* lipid digestion disturbed
* malabsorption, incl. fat-soluble vitamins (hypovitaminosis)
- calcium, bones (D)
- coagulopathy (K)
- damage to epithelium, vision disturbances etc. (A)
* acholic stools

Clinical manifestation

* jaundice
* pruritus (bile acids, endorfins)
* pain (extrahepatic biliary obstruction)
* sequelae of disturbances of digestion

Gilbert's syndrome

non-conjugated familiar hyperbilirubinemia

incidence: several % in population, mainly men

jaundice can manifest during stress, fasting and can simulate hepatitis

genetic changes in promotor sequence of gene for *UDP-glucuronyltransferase*.
decrease in gene expression

increase in repetitive sequences TA in TATAA region of promotor, which decreases binding of transcription factors

The End

(+ supplement)

Cytokine action

influence regeneration × apoptosis
fibroproduction
origine: inflammation, endotoxin
source: parenchymatous and nonparenchymatous cells
autocrinne and paracrinne secretion

Intestinal changed permeability and action of endotoxin

long time influence of alcohol
portal hypertension
endotoxin penetrates to portal blood and stimulates macrophages to production of cytokines, NO, oxygen radicals

Basolateral membrane

* sodium-potassium ATPase
* potassium channel
* sodium dependent transport (proton, bicarbonate)
* *NTCP* – sodium-taurocholate cotransporter (primary carrier for conjugated bile-salt uptake from portal blood)
* *OATP1,2* – (sodium independent) organic-anion transporter (multispecific carrier: bile salts, org. anions, bilirubin, estrogens …)

Canalicular (apical) membrane

* *MDR1* – multidrug-resistance-1 P-glycoprotein
  (ATP depend. excretion of large org. cations, toxins, xenobiotics)
* *MDR3* – multidrug-resistance-1 P-glycoprotein
  (phospholipide transport)
* *BSEP* – bile-salt export pump
  (ATP-depend. bile salt transport into bile, stimulation of bile flow)
* *MRP2/cMOAT* – canalicular multispecific organic-anion transporter
  (ATP-depend. transport of organic anions incl. bilirubin diglucuronide)

Principle functions of the normal liver

* *energy metabolism and substrate interconversion*
* *protein synthetic functions: plasma proteins incl. albumin and coagulation factors*
* *solubilization, transport, storage*
* *protective and clearance functions, detoxification, inactivation*

Mechanisms of virus liver damage

* direct - cell necrosis (HAV)

* indirect, mediated by immune mechanisms, apoptosis, Fas system

Mechanisms of liver damage

Cell damage

Cell death

necrosis
apoptosis

the way of cell death druh may depend on intensity of stimulus and of status of liver cells (ATP, antioxidative mechanisms etc.)

Provoking mechanisms

Oxidative stress
- *intracellular* in hepatocyte: 2-5% oxygen
oxidative mechanisms in mitochondria
detoxification reactions (cytochrom P450)
increased due to TNFα, ischemia/reperfusion
etc.
- *intercellular* - activated phagocytes, leukocytes
nitric oxide

Viruses
Toxins

Cytokines (e. g. TNFα)

final outcome depends on cell status:
depletion of antioxidants (e.g. by alcohol) leads to cell *death*, meanwhile with their abundance the cytokine action might be *proliferative*

Fibroproduction

key role: non-parenchymatous cells
autocrinne and paracrinne stimulation

HSC
15 % of cells in liver
Disse space
retinoid storage
heterogenous group of cells, embryon. from neural crest

activation – proliferation / fibroproduction / contractility

Initiation
from damaged hepatocytes, endothelial cells, Kupffer cells,
change in extracellular matrix
production of oxygen radicals

Perpetuation
production of various cytokines and enzymes
dividing of HSC, contractility, collagen production, change in extracellular matrix,
chemotaxis of HSC and leukocytes, loss of retinoids

Resolution
is the *deactivation* possible ? – IL-10
apoptosis

Sodium&Water Balance, Acid-Base Balance

Mechanisms:

a) hypoalbuminemia
b) circulation changes (vasodilatation of systemic and splanchnic vascular bed, hyperkinetic circulation, development of vasoconstriction in kidneys)
c) secondary hyperaldosteronism

- water retention

decreased capacity of patients in excreting water

ADH, diminished production of prostaglandins in kidney, decreased delivery of filtrate to distal parts of nephron and collecting tubules

- sodium retention

- „undefilling“ hypothesis – low renal perfusion due to diminished effective intravascular volume (hypoalbuminemia, systemic and portal circulatory changes with *vasodilation* and hyperkinetic circulation), developing *vasoconstriction in renal circulation* and then funtional fluid and sodium retention due to activation of the system *renin-angiotensin-aldosteron* (secondary hyperaldosteronism) and *ADH*, activation of *sympathetic nerves* etc.
- „overflow“ hypothesis: primary is increased soidum resorption (probably both in proximal and distal tubules)

Hyponatremia (dilutional) is very often observed together with general increased amount of sodium in body. Hyponatremia reflects the water retention.

- hypokalemia

- metabolic alkalosis (metabolic acidosis develops in terminal phases), in connection with hypokalemia (hyperaldosteronism); depletion of kalium, protons enter the cells, intracellulary is acidosis (!)

Protein metabolism

decreased syntesis of albumin (normally 12 g/day, about 20 days half-life), coagulation factors, transport proteins
oxidative deamination and transamination of amino acids

Urea cycle

Synthesis of urea from *ammonia* in periportal hepatocytes; requires energy (ATP); key enzyme – carbamylphosphate synthetase

Synthesis of urea is connected with *regulation of acid-base balance*

Alkalemia increases the activity of carbamylphosphate synthetase, the synthesis of urea is increased, synthesis of glutamine is decreased; in kidneys NH_3 (the substrate for urea synthesis) is resorbed + proton

Acidemia inhibits urea synthesis, ammonia is rather transformed in perivenous hepatocytes to glutamine which is transported to kidneys (NH_4^+ is excreted to urine)

Carbohydrate metabolism

Liver plays role of „***glucostat***“ (glykogen storage, glukoneogenesis, target organ of acting and inactivation of hormons)

chronic LF – cirrhosis: often ***insulin resistence or diabetes***

terminal phase or acute severe LF – ***hypoglycemia***