

# EXAMINATIONS IN GASTROENTEROLOGY

Liver and Pancreas

Jan Živný

Ústav patologické fyziologie

1. LF UK

[jzivny@LF1.cuni.cz](mailto:jzivny@LF1.cuni.cz)

# Outline

- Functional examination of the Liver
  - Basic liver “panel”
  - Other tests for liver diseases
- Functional examination the pancreas exocrine function

# **LIVER AND BILIARY SYSTEM**

# Liver Structure and Function

- 1–1.5 kg (1.5–2.5% of the lean body mass)
- Blood supply
  - hepatic artery - 20% oxygen-rich blood
  - portal vein - 80% nutrient-rich (toxin-rich) blood from the stomach, intestines, pancreas, and spleen
- Cell composition
  - hepatocytes (~60-70%)
  - Kupffer cells (reticuloendothelial system)
  - Stellate (Ito or fat-storing) cells
  - Endothelial cells and blood vessels
  - Bile ductular cells

# Structural organization of liver tissue

- Lobules
  - portal areas at the periphery and central veins in the center of each lobule

## Classical Hepatic Lobule

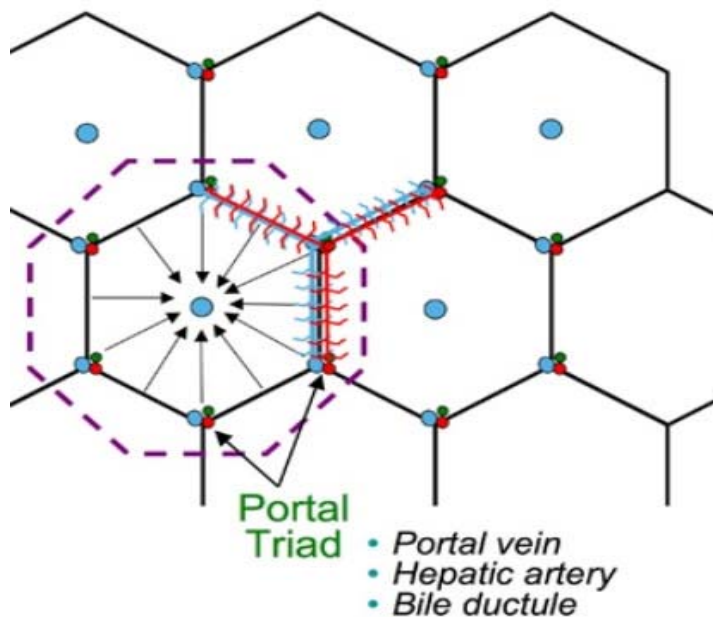
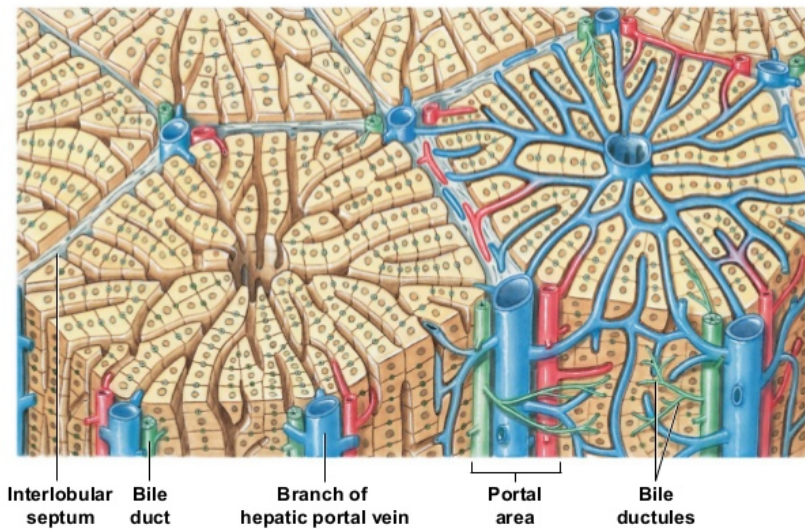


Figure 25.21a Liver Histology

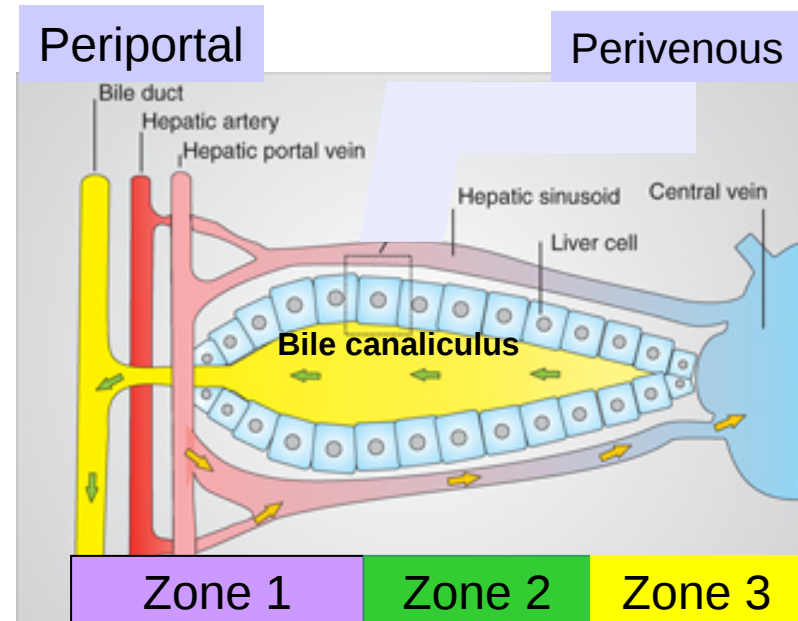
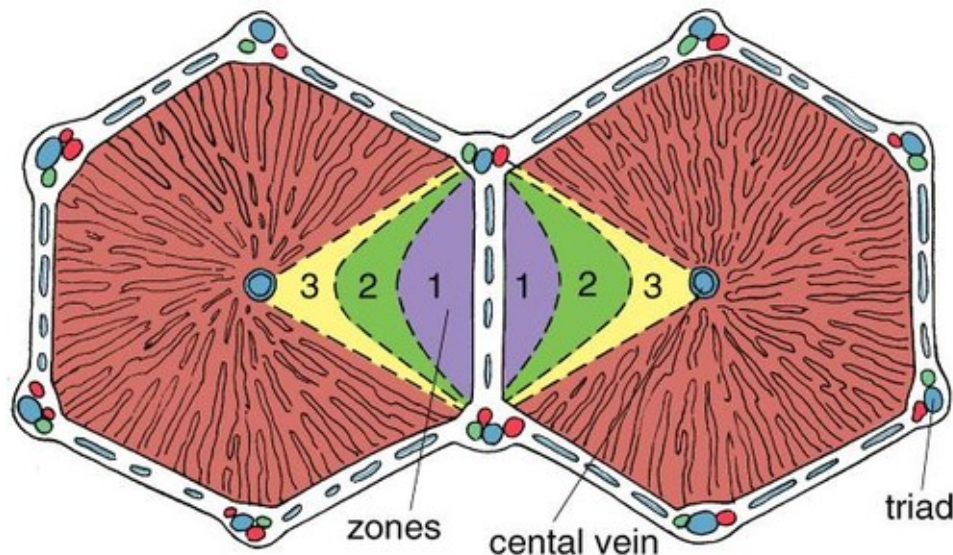


Diagrammatic view of lobular organization

# Functional organization of liver tissue

Acinus is a functional physiologic unit of the liver

- Acini
  - Hepatic arterial and portal venous blood entering the acinus from the portal areas (zone 1)
  - Intervening hepatocytes with sinusoids (zone 2)
  - Sinusoids entering the central hepatic vein (zone 3)



# Liver Diseases

- Many causes of liver disease
- Present clinically in a few distinct patterns
  - Hepatocellular
    - liver injury, inflammation, and necrosis
    - e.g. viral hepatitis, alcoholic liver disease
  - Cholestatic (obstructive)
    - inhibition of bile flow
    - e.g. gallstone, malignant obstruction, primary biliary cirrhosis, some drug-induced liver diseases
  - Mixed
    - e.g. cholestatic forms of viral hepatitis and many drug-induced liver diseases

# The most common causes of acute liver disease

- Viral hepatitis (particularly hepatitis A, B, and C)
- Drug-induced liver injury
- Cholangitis (infection caused by obstruction)
- Alcoholic liver disease

# The most common causes of chronic liver disease

- Chronic hepatitis C
- Alcoholic liver disease
- Nonalcoholic steatohepatitis
- Chronic hepatitis B
- Autoimmune hepatitis
- Sclerosing cholangitis
- Primary biliary cirrhosis
- Hemochromatosis
- Wilson's disease

# Laboratory Testing

- To distinguish hepatocellular versus cholestatic liver disease
- To decide whether the disease is acute or chronic
- To find whether cirrhosis and hepatic failure are present

# Goal of evaluation of liver function

- detect the presence of liver disease
- distinguish among different types of liver disorders
- gauge the extent of known liver damage
- follow the response to treatment

# BASIC LIVER PANEL

- Bilirubin (total and conjugated/direct)
- Aspartate aminotranspherase (AST)
- Alanine aminotranspherase (ALT)
- Alkaline phosphatase (ALP)
- Albumin
- Prothrombin time

# Pathological results of liver tests (serum/plasma)

- **Hepatocyte damage**
  - **Increased** aminotransferases (AST, ALT), bilirubin
- **Cholestasis**
  - **Increased** bilirubin, alkaline phosphatase, cholesterol
- **Decrease** of amount of functioning hepatic **tissue** (cirrhosis, liver failure)
  - **Decreased synthesis** of proteins (e.g. albumin, clotting factors)
- Porto-systemic **shunts**
  - **Decreased uptake** of substances from blood (e.g. increased ammonia)

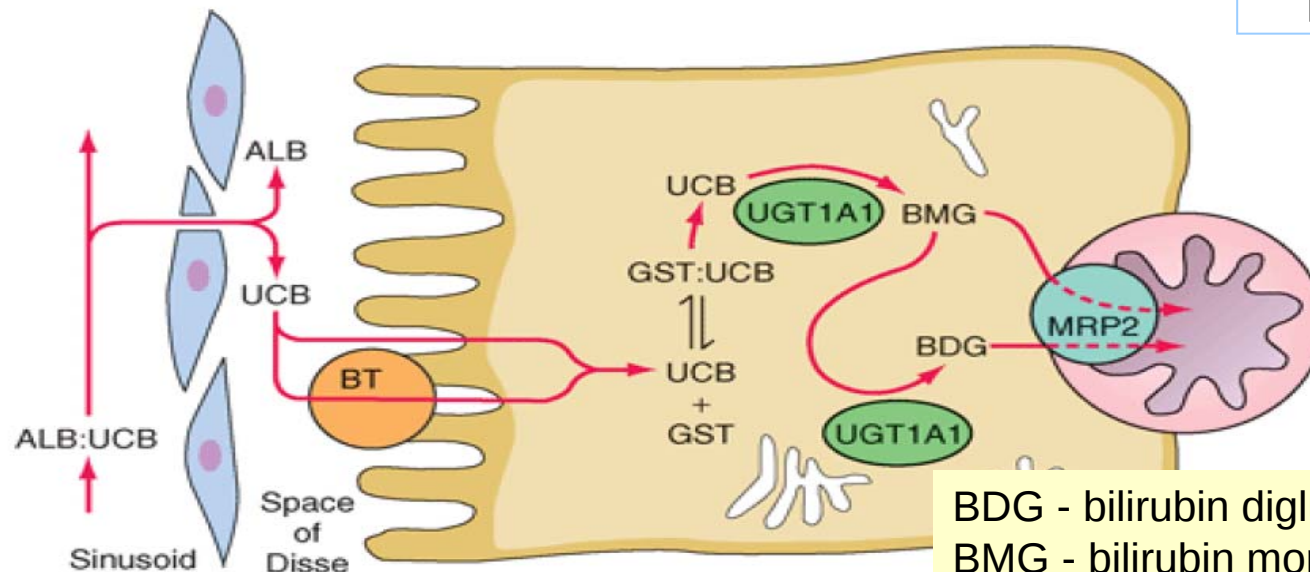
# **Liver Detoxification and Excretory Functions tests**

- Serum Bilirubin
- Urine Bilirubin
- Blood Ammonia

# Bilirubin

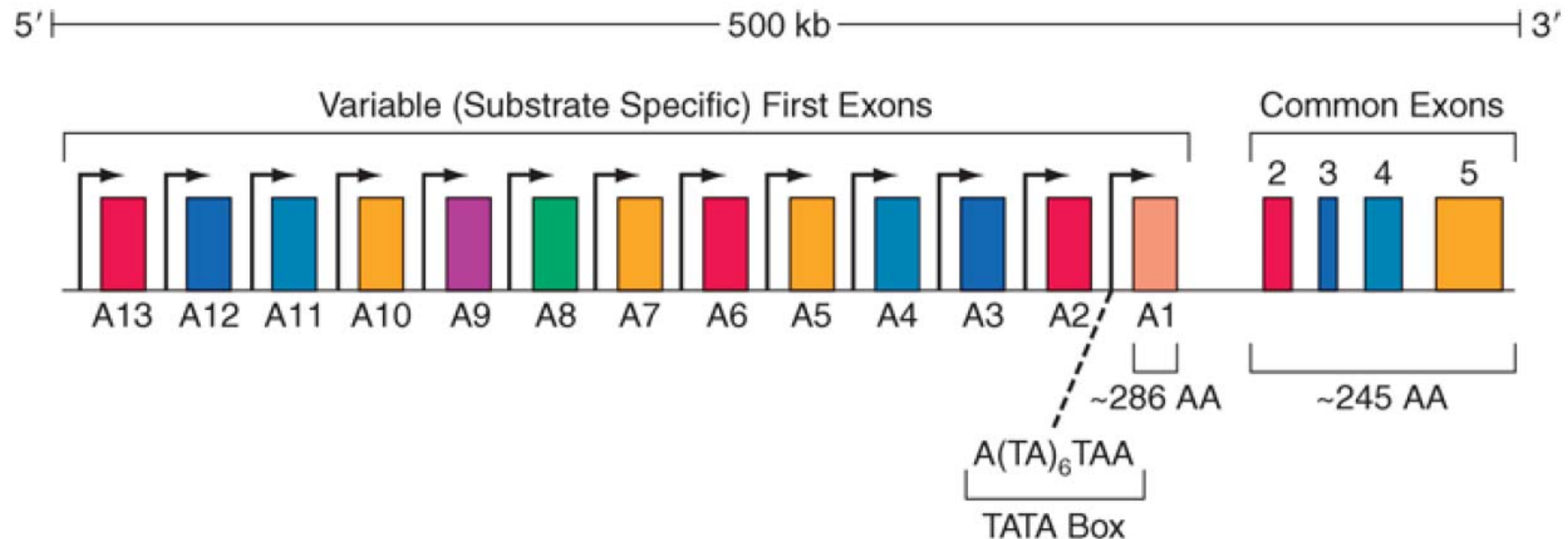
- Bilirubin, a breakdown product of the porphyrin ring of heme-containing proteins (70-90% from Hgb)

| TRANSPORT               |                                  |                                     | CONJUGATION                            | EXCRETION                                 |
|-------------------------|----------------------------------|-------------------------------------|----------------------------------------|-------------------------------------------|
| Albumin-bound bilirubin | facilitated and simple diffusion | bound to glutathione-S-transferases | bilirubin-UDP-glucuronosyl-transferase | multidrug resistance-associated protein 2 |



# UGT1 family of UDP-glucuronosyltransferases

- Exon A1 (substrate specific) and the four common exons (2-5) encode the physiologically critical enzyme bilirubin-UDP-glucuronosyltransferase (UGT1A1)
- Mutation in one of the first exons will affect only a single enzyme isoform
- Mutation in exons 2–5 will alter all isoforms encoded by the *UGT1* gene complex



# Serum bilirubin

(17-20  $\mu\text{mol/L}$ , 0.3 - 1.9 mg/dL)

- Found in the blood in two fractions
  - unconjugated (indirect)
    - insoluble in water and is bound to albumin in the blood
    - The rate-limiting step in bilirubin metabolism is not conjugation of bilirubin, but rather the transport of conjugated bilirubin into the bile canaliculi
  - conjugated (direct)
    - water soluble and can be excreted by the kidney
    - if <15% of the total bilirubin is considered to all be unconjugated
    - conjugated hyperbilirubinemia almost always implies liver or biliary tract disease

# Bilirubin in diseases

## Causes of hyperbilirubinemia

- UNCONJUGATED HYPERBILIRUBINEMIA
  - Increased bilirubin production (e.g. hemolysis, ineffective erythropoiesis)
  - Decreased hepatic uptake (e.g. Gilbert's syndrome)
  - Impaired conjugation (e.g. neonatal jaundice, Crigler-Najjar Syndrome )
- MIXED OR PREDOMINANTLY CONJUGATED HYPERBILIRUBINEMIA
  - Hepatic parenchymal disorders (e.g. acute hepatitis)
  - Obstructive disorders (e.g. bile duct stones)

**Viral hepatitis** - The higher the serum bilirubin, the greater the hepatocellular damage  
**Alcoholic hepatitis** – Serum bilirubin level correlates with outcome

# Urine Bilirubin

- Conjugated bilirubin (implies the presence of liver disease)
- Dipstick test give the same information as fractionation of the serum bilirubin (almost 100% accurate)
- In patients recovering from jaundice, the urine bilirubin clears prior to the serum bilirubin

# Blood Ammonia

- Ammonia is produced in the body during normal protein metabolism and by intestinal bacteria (esp. colon)
  - The liver convert ammonia to urea, which is excreted by the kidneys
  - Striated muscle also plays a role in detoxification of ammonia, which is combined with glutamic acid to form glutamine
- Poor correlation between the acute encephalopathy presence or severity and elevation of blood ammonia
- Poor correlation of the blood serum ammonia and hepatic function
- Useful for identifying occult liver disease in patients with mental status changes

# Hepatocyte damage and cholestasis tests

## **Serum Liver Enzymes**

- Enzymes that reflect damage to hepatocytes
- Enzymes that reflect cholestasis
- Enzyme tests that do not fit precisely into either pattern

# Enzymes that reflect damage to hepatocytes

## **The aminotransferases (transaminases)**

- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- Elevation ~ 100-fold of normal occur almost exclusively in disorders associated with extensive hepatocellular injury
  - viral hepatitis, ischemic liver injury, toxin- or drug-induced liver injury
- Elevation ~ 10-fold of normal are nonspecific (in any type of liver disorder)

# Aspartate-aminotransferase (AST)

- 0.5-0.65  $\mu\text{kat/L}$
- Heart, muscles, brain, kidneys, pancreas, lungs, leukocytes, and ***liver***
- Severe elevation – acute viral or toxic hepatitis
- Elevation – myocardial infarction, heart failure, muscle injury, CNS diseases, and other non-hepatic diseases; ***hepatocellular damage***
- Reliable marker with good monitoring value in liver diseases (decline to normal values are observed during regeneration)

# Alanine-aminotransferase (ALT)

- 0.55-0.65  $\mu\text{kat/L}$
- Primary in hepatocytes – more specific for liver diseases than AST

# Ratio AST / ALT

- The pattern of the aminotransferase elevation can be helpful diagnostically
- Typically  $AST/ALT \leq 1$
- $AST/ALT < 1$ 
  - chronic viral hepatitis and non-alcoholic fatty liver disease
- $AST/ALT > 1$ 
  - cirrhosis
- $AST/ALT > 2$  ( $>3$ )
  - alcoholic liver disease (alcohol-induced deficiency of pyridoxal phosphate - active B6 = cofactor for ALT)

# Enzymes that Reflect Cholestasis

## **Elevated in cholestasis**

- **Alkaline phosphatase**
- 5'-nucleotidase
- glutamyl transpeptidase (GGT)

# Alkaline phosphates (ALP, AP)

- liver, bone, placenta, and intestine
- 2.3-2.7  $\mu\text{kat/L}$
- found in or near the bile canalicular membrane of hepatocytes
- Severe elevation
  - **cholestasis** from **intrahepatic** (prim. biliarny cirrhosis) and **extrahepatic** causes (bile duct obstruction)
- mild elevation
  - hepatocellular damage (hepatitis, cirrhosis)
- isolated elevation
  - granulomatous or focal liver lesions (abscess, tumor)
  - nonhepatic tumors (bronchogenic ca, Hodgkin's lymph.)
  - Bone diseases (metastases, osteomalatia)
  - Pregnancy

# ALP

- **Elevations > 4-fold of normal**
  - cholestatic liver disorders
  - infiltrative liver diseases (cancer, amyloidosis)
  - bone conditions (e.g., Paget's disease).
- **Nonspecific elevation**
  - Patients over age 60 (1–1.5 times normal)
  - Individuals with blood types O and B can have an elevation of the serum alkaline phosphatase after eating a fatty meal (intestinal ALP)
  - Children and adolescents undergoing rapid bone growth (bone ALP)
  - Late in normal pregnancies (placental ALP)
- **Less than 3-fold elevation can be seen in almost any type of liver disease**

# Glutamyl transpeptidase (GGT)

- To test whether alkaline phosphatase elevations are due to liver disease
- Rarely elevated in conditions other than liver disease
- Located in the endoplasmic reticulum and in bile duct epithelial cells
- Less specific for cholestasis than are elevations of ALP or 5'-nucleotidase
- Identify patients with occult alcohol use (nonspecific)

# 5'-nucleotidase

- To test whether alkaline phosphatase elevations are due to liver disease
- Found in or near the bile canalicular membrane of hepatocytes (as is ALP)

# Tests that Measure Biosynthetic Function of the Liver

- Serum Albumin
- Serum Globulins
- Coagulation Factors
- The prothrombin time

Evaluation of the amount of functioning hepatic tissue  
(cirrhosis, liver failure)

# Serum Albumin

- synthesized exclusively by hepatocytes
- long half-life
  - 18–20 days (4% degraded / day)
  - is not a good indicator of acute or mild hepatic dysfunction
- Hypoalbuminemia usually reflects severe liver damage and decreased albumin synthesis
- Is not specific for liver disease

# Causes of hypoalbuminemia

- Chronic liver disease
- Protein malnutrition of any cause
- Protein-losing enteropathies
- Nephrotic syndrome
- Chronic infections (associated with prolonged increases in IL1 and/or TNF)
- Serum albumin should not be measured for screening without suspicion of liver disease
  - 12% of patients had abnormal test results (the finding was of clinical importance in only 0.4%)

# Serum Globulins

- Serum globulins are a group of proteins made up of immunoglobulins produced by B lymphocytes and globulins produced primarily in hepatocytes.
- Globulins are increased in chronic liver disease
  - Increased synthesis of antibodies (gut antigen stimulation)
- Helpful in the recognition of certain chronic liver diseases
  - autoimmune hepatitis - Diffuse polyclonal increases in IgG (>100% increase)
  - primary biliary cirrhosis (IgM levels)
  - alcoholic liver disease (IgA levels)

# Coagulation Factors

- Made exclusively in hepatocytes (exception F. VIII – endothelial cells)
- Serum half-lives ranging from 6 h for factor VII to 5 days for fibrinogen
- Best acute measure of hepatic synthetic function and helpful in both the diagnosis and assessing the prognosis of acute parenchymal liver disease

# Prothrombin time

- May be elevated in
  - hepatitis
  - cirrhosis
  - disorders that lead to vitamin K deficiency
    - obstructive jaundice
    - fat malabsorption
- Marked prolongation of the prothrombin time (>5 s above control) and not corrected by parenteral vitamin K administration, is a poor prognostic sign in acute viral hepatitis and other acute and chronic liver diseases.

# Shortcomings of liver tests

- Can be normal in patients with serious liver disease and abnormal in patients with diseases that do not affect the liver
- Rarely suggest a specific diagnosis
  - rather, they suggest a general category of liver disease (hepatocellular or cholestatic)
- Many tests do not measure liver function
  - they detect liver cell damage or interference with bile flow
  - e.g. aminotransferases or alkaline phosphatase

# Other laboratory tests

- Hepatitis serology to define the type of viral hepatitis
- Autoimmune markers

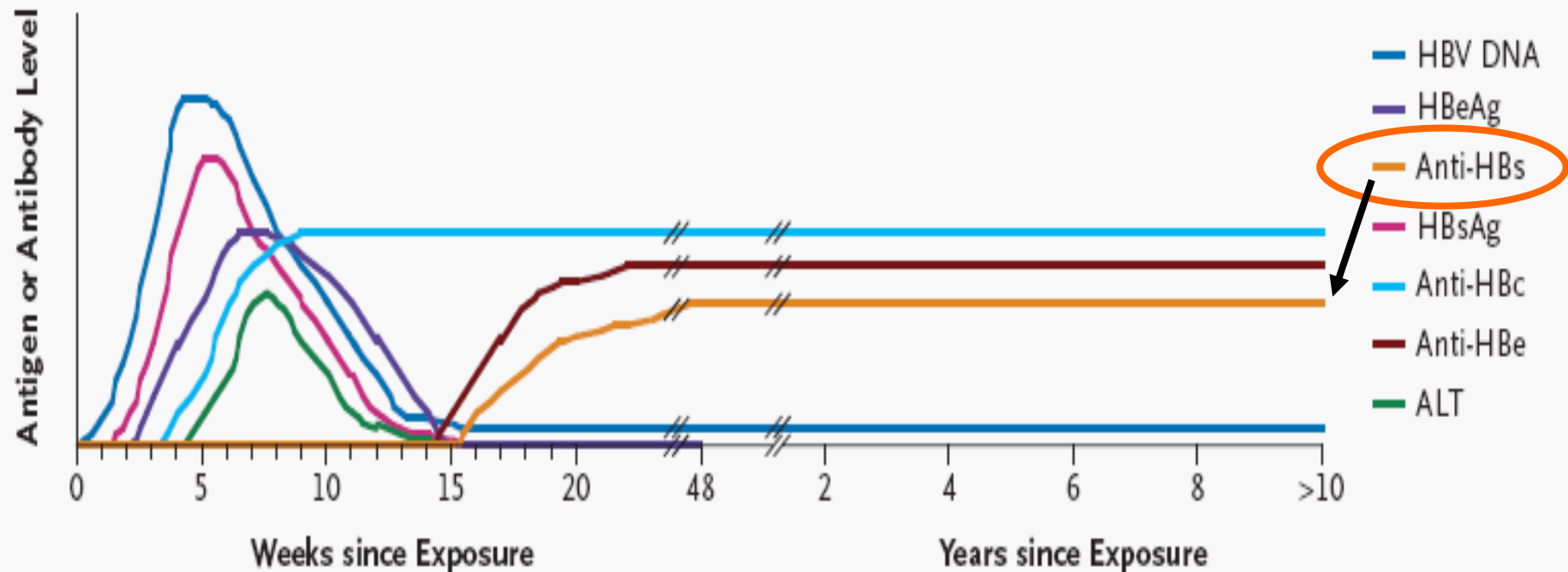
# HBV infection tests

## **Viral antigens = Ag**

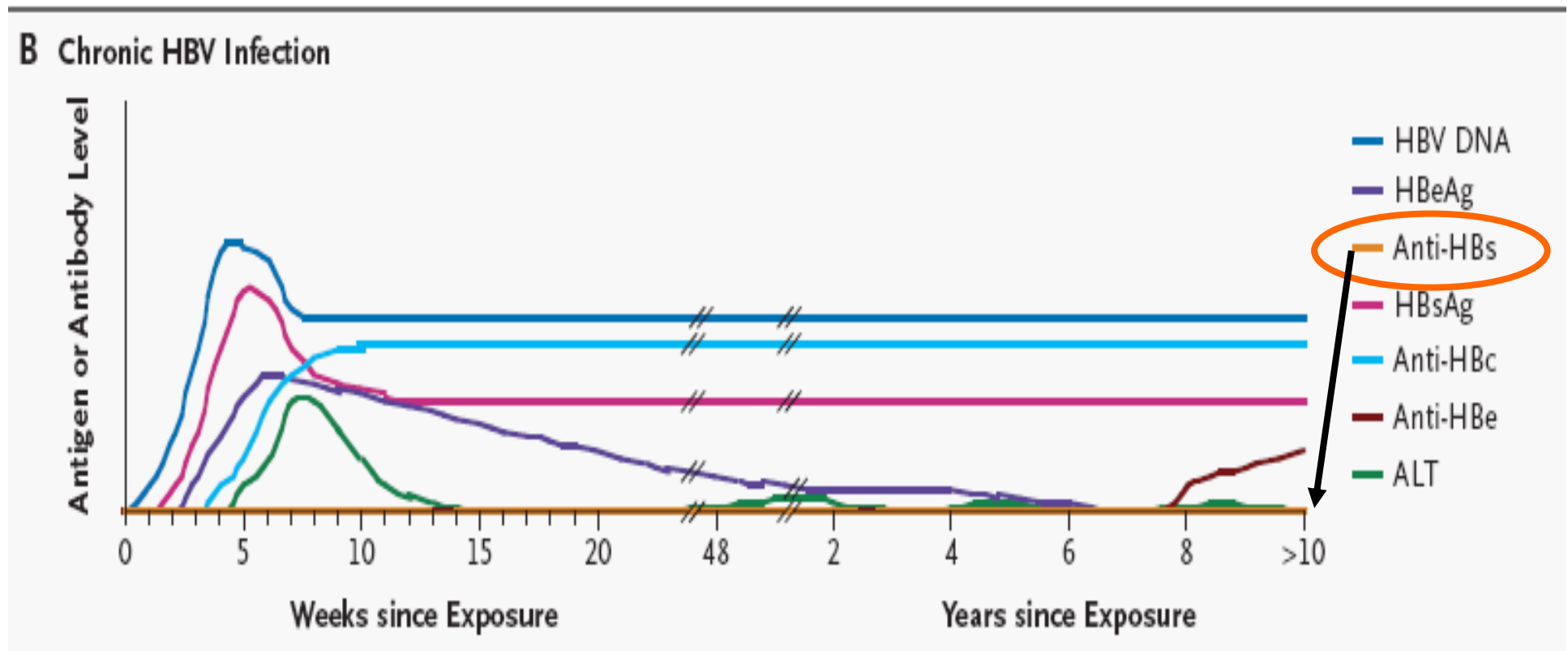
- HBsAg – surface antigen of hepatitis B virus
  - positive 1–7 weeks before clinical manifestation of disease, during, and 1–6 weeks after and in chronic form
- HBeAg – marker of infectivity of hepatitis B
- Antigen specific antibodies (Ab):
  - antibodies IgM (acute) and IgG for hepatitis A virus
  - anti-HBs – to surface antigen
    - Positive after course of hepatitis type B and after immunization
  - anti-HBc - during acute phase of hepatitis B

# Patterns of Serologic and Molecular Markers in HBV Infection

A Acute Self-Limited HBV Infection



# Patterns of Serologic and Molecular Markers in HBV Infection

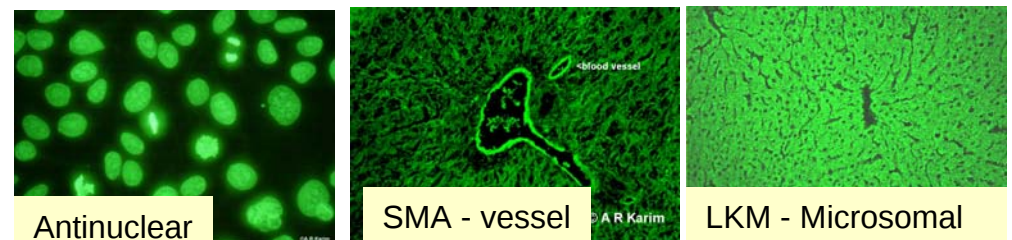
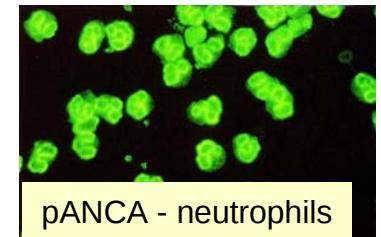
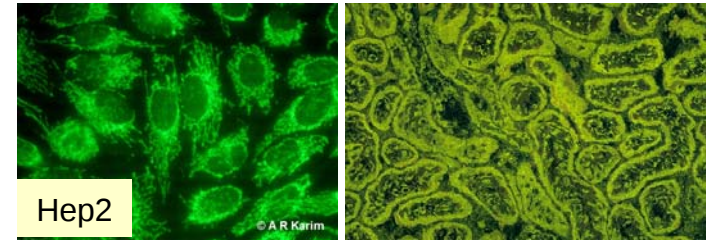


# Autoimmune markers

- Immunohistochemistry
- On human cells (neutrophils), cell lines (Hep2) or rodent tissues (liver, kidney, stomach)
- Detection of autoantibodies in patients serum

# Autoimmune markers

- Antimitochondrial antibody (AMA)
  - primary biliary cirrhosis
  - in 95% of patients
  - pyruvate dehydrogenase complex
- Peripheral antineutrophil cytoplasmic antibody (p-ANCA)
  - sclerosing cholangitis
- Antinuclear, smooth-muscle, and liver-kidney microsomal antibody
  - autoimmune hepatitis



|                   |             |                                                                                                                         |
|-------------------|-------------|-------------------------------------------------------------------------------------------------------------------------|
| pANCA             | Elastase    | Ulcerative colitis, Crohn's disease, primary sclerosing cholangitis, systemic lupus erythematosus                       |
| pANCA             | Kathepsin G | Ulcerative colitis, primary sclerosing cholangitis, Crohn's disease                                                     |
| pANCA             | Lysozym     | Ulcerative colitis, primary sclerosing cholangitis, Crohn's disease                                                     |
| pANCA             | Laktoferrin | Ulcerative colitis, primary sclerosing cholangitis, Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis |
| pANCA o.<br>cANCA | BPI         | Primary sclerosing cholangitis, ulcerative colitis, or pANCA Crohn's disease                                            |

# Other Diagnostic Tests

- Percutaneous Liver Biopsy
- Ultrasonography

# Percutaneous Liver Biopsy

- Performed at the bedside with local anesthesia and ultrasound guidance

## Indications

- hepatocellular disease of uncertain cause
  - prolonged hepatitis with the possibility of chronic active hepatitis
  - unexplained hepatomegaly
  - unexplained splenomegaly
  - hepatic filling defects by radiologic imaging
  - fever of unknown origin
  - staging of malignant lymphoma.
- 
- Most accurate in disorders causing diffuse changes

# Liver biopsy

## Acute liver disease (limited role)

- Drug-induced liver disease
- Establishing the diagnosis of acute alcoholic hepatitis

## Chronic liver disease: important part of diagnosis of

- autoimmune hepatitis
- primary biliary cirrhosis
- nonalcoholic and alcoholic steatohepatitis
- Wilson's disease (with a quantitative hepatic copper level)

# Ultrasonography

- The first diagnostic test to use in patients whose liver tests suggest cholestasis
  - presence of a dilated intrahepatic or extrahepatic biliary tree
  - identify gallstones
  - shows space-occupying lesions within the liver (cystic or solid masses)
  - Ultrasound with Doppler imaging can detect the patency of the portal vein, hepatic artery, and hepatic veins and determine the direction of blood flow.
    - The first test in patients suspected of having Budd-Chiari syndrome

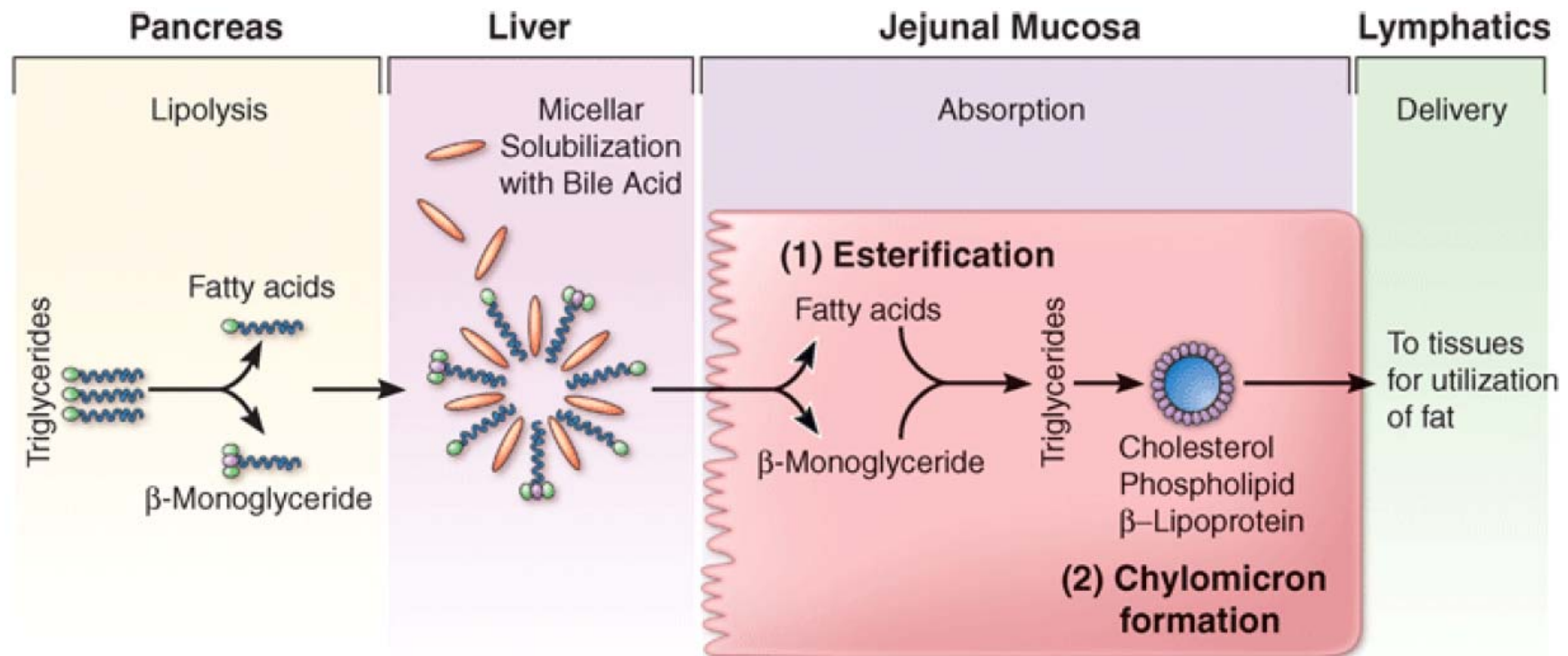
# Detecting alcoholism

## **CAGE questionnaire**

- The questionnaire asks the following questions:
  - Have you ever felt you needed to **C**ut down on your drinking?
  - Have people **A**nnoyed you by criticizing your drinking?
  - Have you ever felt **G**uilty about drinking?
  - Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?

# **PANKREAS EXOCRINE FUNCTION**

# Steps in lipid digestion



# Direct pancreatic stimulation or indirect stimulation by diet or test diet

- i.v. administration
  - secretin
  - secretin + Cholecystokinin (CCK)
  - ingestion of test meal

## Direct pancreatic stimulation or indirect stimulation by diet or test diet

- Measurement of pancreatic secretion in duodenum (45 – 120 minut)
  - Volume ( $>2\text{mL/kg/h}$ )
  - Bicarbonate ( $>80\text{ mmol/L}$  and  $10\text{ mmol/h}$ )
  - When S + CCK or diet
    - measurement of pancreatic enzyme activity
      - amylase, lipase, chymotrypsin, trypsin

# Analysis of stool

- **Nutrient digestion**
  - standard amount of fat in diet for 72 h
  - expected digestion of more than 93% of ingested fat
  - more than 20% of ingested fat in stool = pancreatic insufficiency
- **Fecal pancreatic enzyme measurement**
  - trypsin and chymotrypsin

# Pancreas function test: Bentiromide test

- Bentiromide bound on para-aminobenzoic acid (PABA) is administered orally
- Bentiromide is hydrolyzed by chymotrypsin in duodenum and free PABA is absorbed in proximal part of small intestine, conjugated in the liver and PABA metabolites are excreted in the urine
- The amount of PABA in the urine correlate with the activity of chymotrypsin
- The results may be influenced by intestinal mucosal defects, liver diseases, and kidney diseases.

Bentiromid was withdrawn in the US in October 1996

# Pancreatic Enzymes In Body Fluids

- **Serum amylase**

- pancreatic isoamylase (33% of total serum amylases)
- screening for acute pancreatitis (pts with acute abdominal or back pain)
- 20-40 % fals positive,
- sensitivity 70-75%
- values 3x of normal AP very likely
- elevated within 24 h, up for 3-5 days

- **Serum lipase**

- specificity is higher than amylase
- sensitivity 70-85%

# Measurement of fecal pancreatic enzymes of intraluminal digestion products

- Undigested
  - muscle fibers, stool fat, and fecal nitrogen
- Human elastase in stool
  - reflects the pancreatic output of this proteolytic enzyme.
  - To detect severe pancreatic exocrine insufficiency in patients with chronic pancreatitis and cystic fibrosis (solid stool specimen)

The End