Liver Diseases

Erik Christensen. M.D., Dr.Med.Sci.
Chief Consultant Physician, Associate Professor
Center of Gastroenterology K, Medical Section
Bispebjerg Hospital
University of Copenhagen, Denmark

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Programme:

- First part:
  - Overwiew
    - Acute – chronic liver disease, symptoms, signs, blood tests, liver structure
  - Viral hepatitis
- Second part:
  - Toxic hepatitis, fatty liver, alcoholic hepatitis
  - Bilirubin, jaundice
  - Bile, gallstone
- Third part:
  - Cirrhosis, end-stage liver disease
  - Complications
    - Portal hypertension, esophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathia, hepatopulmonary syndrome

Hepatitis

- Hepatitis implies injury to liver characterized by presence of inflammatory cells in the liver tissue.
- Etymologically from ancient Greek hepar or hepato- meaning 'liver,' and suffix -itis, denoting 'inflammation'
- The condition can be self limiting, healing on its own, or can progress to scarring of the liver (cirrhosis).
- Hepatitis is acute when it lasts less than 6 months and chronic when it persists longer.
- A group of viruses known as the hepatitis viruses cause most cases of liver damage worldwide.
- Hepatitis can also be due to toxins (notably alcohol), other infections or from autoimmune process.
- It may run a subclinical course when the affected person may not feel ill. The patient becomes unwell and symptomatic when the disease impairs liver functions.

Causes - Acute hepatitis

- Viral Hepatitis: Hepatitis A to E (>95% of viral cause), Herpes simplex, Cytomegalovirus, Epstein-Barr, yellow fever virus, adenoviruses.
- Non viral infection: toxoplasma, Leptospira, Q fever, rocky mountain spotted fever
- Alcohol
- Toxins: Amanita toxin in mushrooms, carbon tetrachloride
- Drugs: Paracetamol, amoxycillin, antituberculosis medicines and many others
- Ischemic hepatitis (circulatory insufficiency)
- Pregnancy
- Auto immune conditions
- Metabolic diseases, e.g. Wilson's disease

Causes – Chronic hepatitis

- Viral hepatitis: Hepatitis B with or without hepatitis D, hepatitis C (Hepatitis A and E do not lead to chronic disease)
- Autoimmune: Autoimmune hepatitis
- Alcohol
- Drugs: methyl-dopa, nitrofurantoin, isoniazide, ketoconazole
- Non-alcoholic steatohepatitis
- Heredity: Wilson's disease, alpha 1-antitrypsin deficiency, hemochromatosis
- Primary biliary cirrhosis and primary sclerosing cholangitis occasionally mimic chronic hepatitis

Signs and symptoms - Acute hepatitis

- Clinically, the course of acute hepatitis varies widely from mild symptoms requiring no treatment to fulminant hepatic failure needing liver transplantation.
- Acute viral hepatitis is more likely to be asymptomatic in younger people. Symptomatic individuals may present after convalescent stage of 7 to 10 days, with the total illness lasting 2 to 6 weeks.
- Initial features are of nonspecific flu-like symptoms, common to almost all acute viral infections and may include malaise, muscle and joint aches, fever, nausea or vomiting, diarrhea, and headache.
- More specific symptoms, which can be present in acute hepatitis from any cause, are: profound loss of appetite, aversion to smoking among smokers, dark urine, yellowing of the eyes and skin (i.e., jaundice) and abdominal discomfort.
- Physical findings are usually minimal, apart from jaundice (33%) and tender hepatomegaly (10%). There can be occasional lymphadenopathy (5%) or splenomegaly (5%).

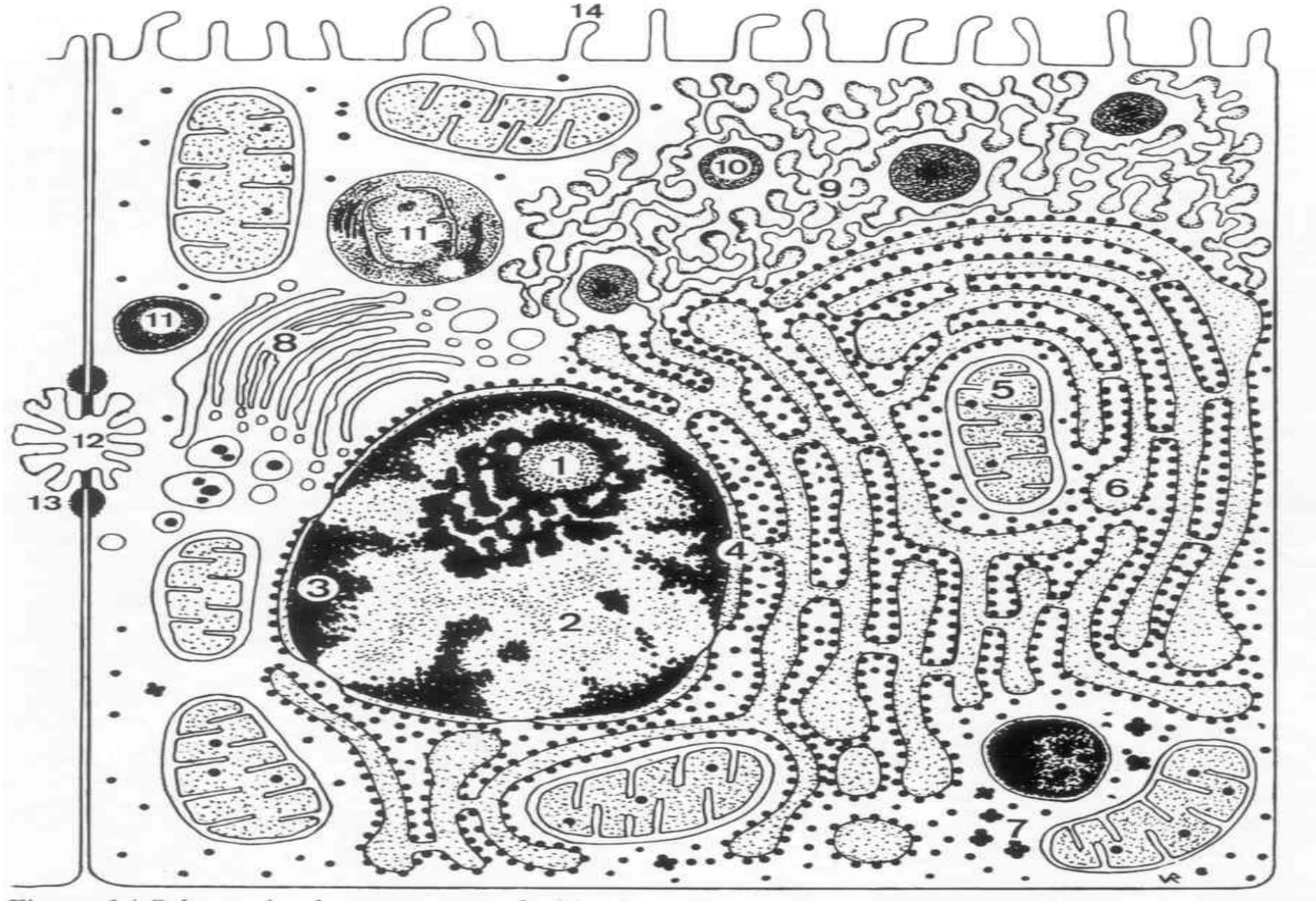
Signs and symptoms - Chronic hepatitis

- Majority of patients will remain asymptomatic or mildly symptomatic,
- abnormal blood tests being the only manifestation.
- Features may be related to the extent of liver damage or the cause of hepatitis.
- Many experience return of symptoms related to acute hepatitis.
- Jaundice can be a late feature and may indicate extensive damage.
- Other features include abdominal fullness from enlarged liver or spleen, low grade fever and fluid retention (ascites).
- Extensive damage and scarring of liver (i.e., cirrhosis) leads to weight loss, easy bruising and bleeding tendencies.
- Acne, abnormal menstruation, lung scarring, inflammation of the thyroid gland and kidneys may be present in women with autoimmune hepatitis.
- Findings on clinical examination are usually those of cirrhosis or are related to aetiology.

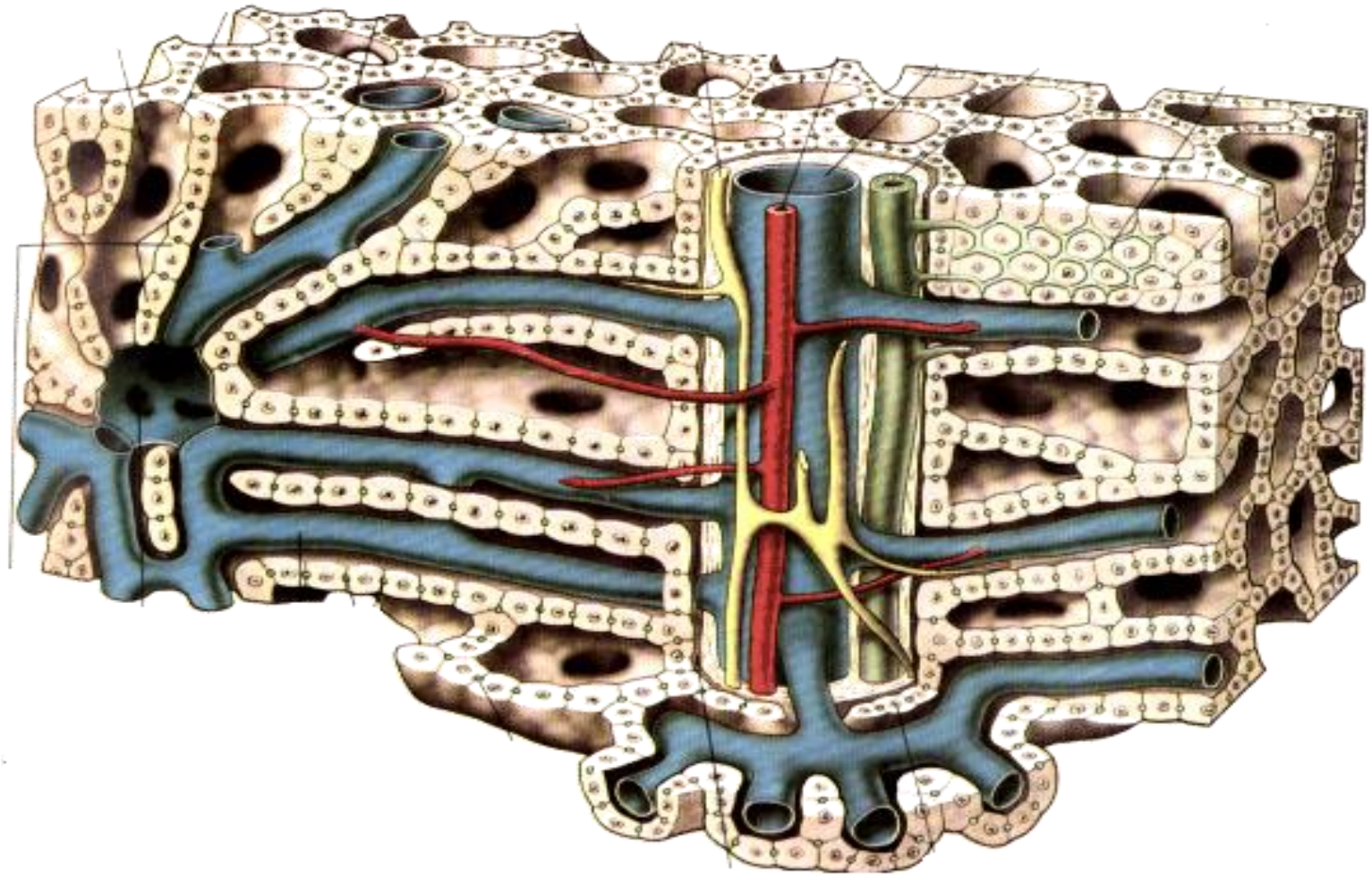
Standard Liver Function Tests

- **Alanine aminotransferase (ALT or ALAT)** is present in hepatocytes (liver cells). When a cell is damaged, it leaks this enzyme into the blood, where it is measured. ALT rises dramatically in acute liver damage.
- **Aspartate aminotransferase (AST or ASAT)** is similar to ALT.
- **Alkaline phosphatase (ALP)** is an enzyme in the cells lining the biliary ducts of the liver. ALP levels in plasma will rise with large bile duct obstruction, intrahepatic cholestasis or infiltrative diseases of the liver.
- **Bilirubin** is a breakdown product of heme (a part of haemoglobin in red blood cells). The liver is responsible for clearing the blood of bilirubin. Increased total bilirubin causes jaundice. The cause can be 1. Prehepatic, 2. Hepatic, 3. Posthepatic
- **Coagulation factor 2, 7, 10,** Prothrombin time or international normalized ratio (INR). Is produced by the liver.
- **Albumin** is produced by the liver

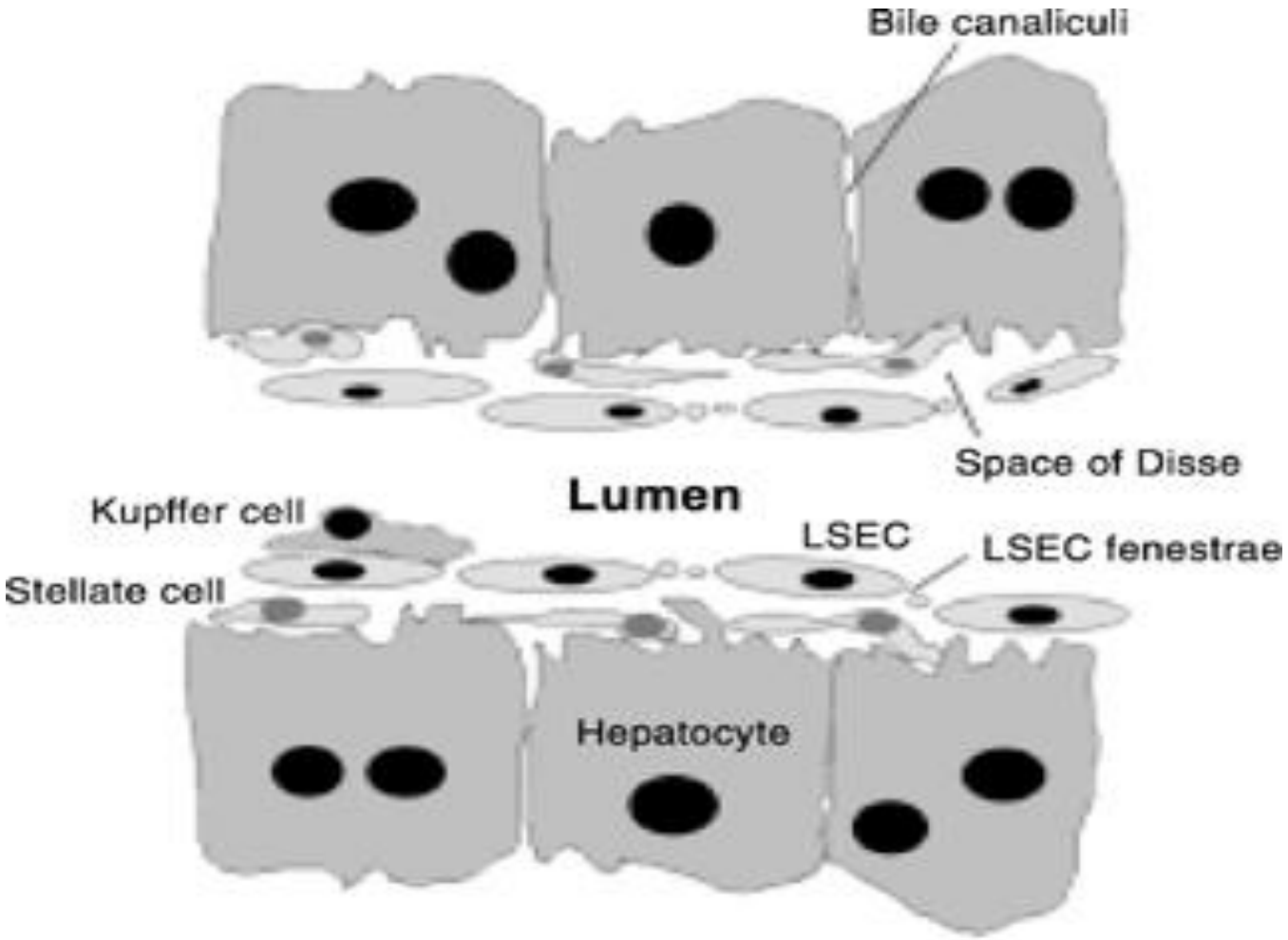
Liver cell



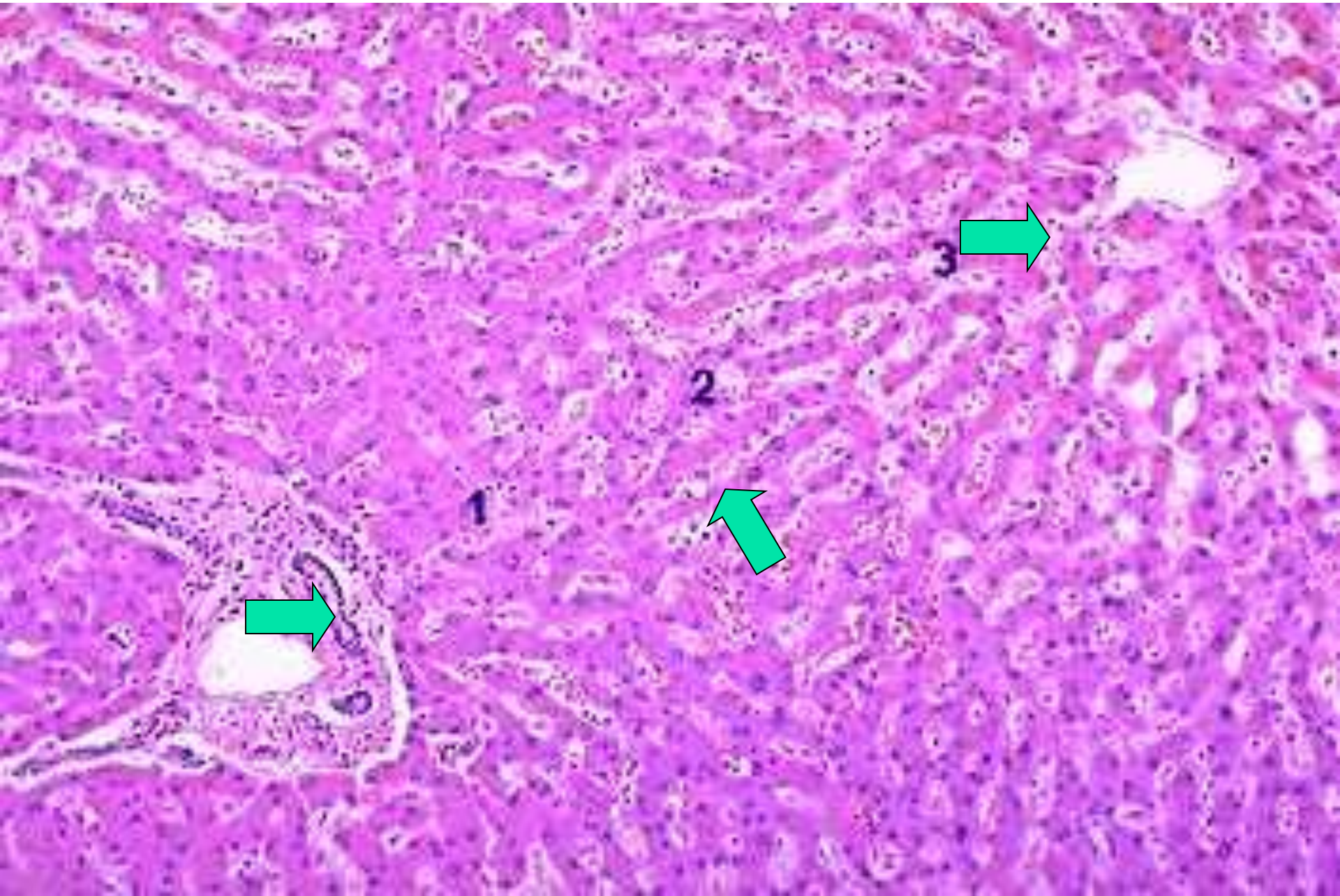
Structure of Liver Lobule



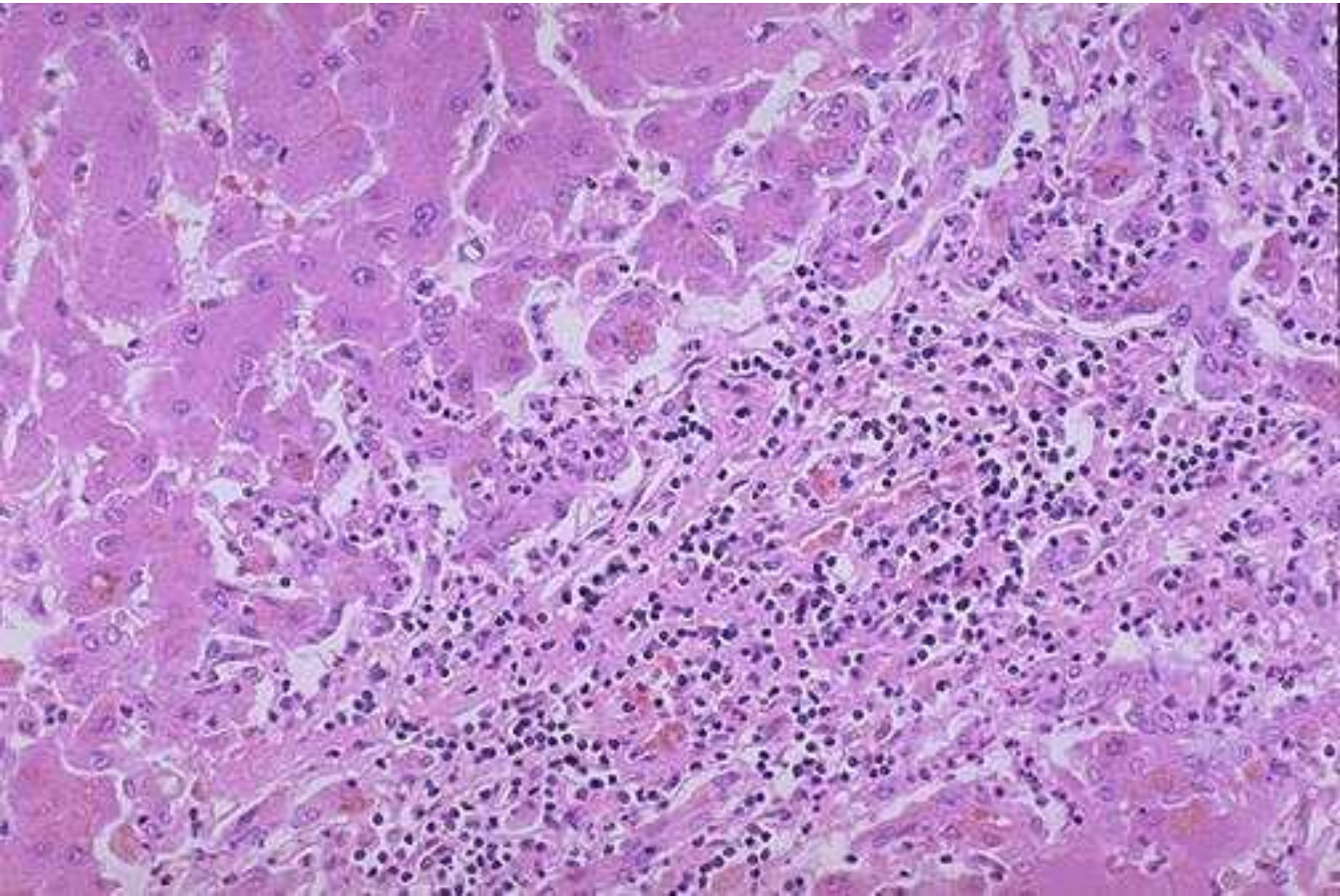
Liver sinusoid



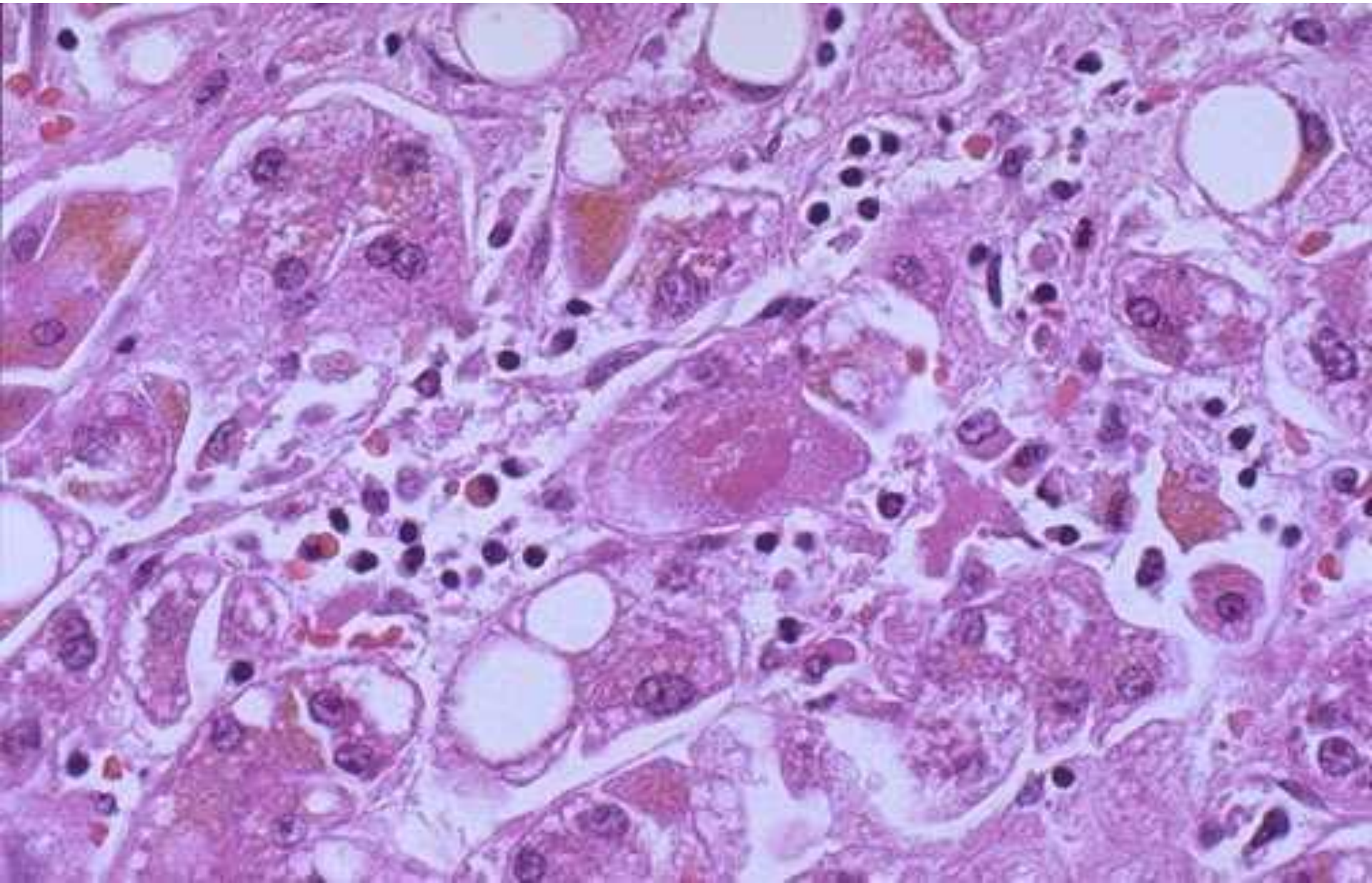
Normal Liver



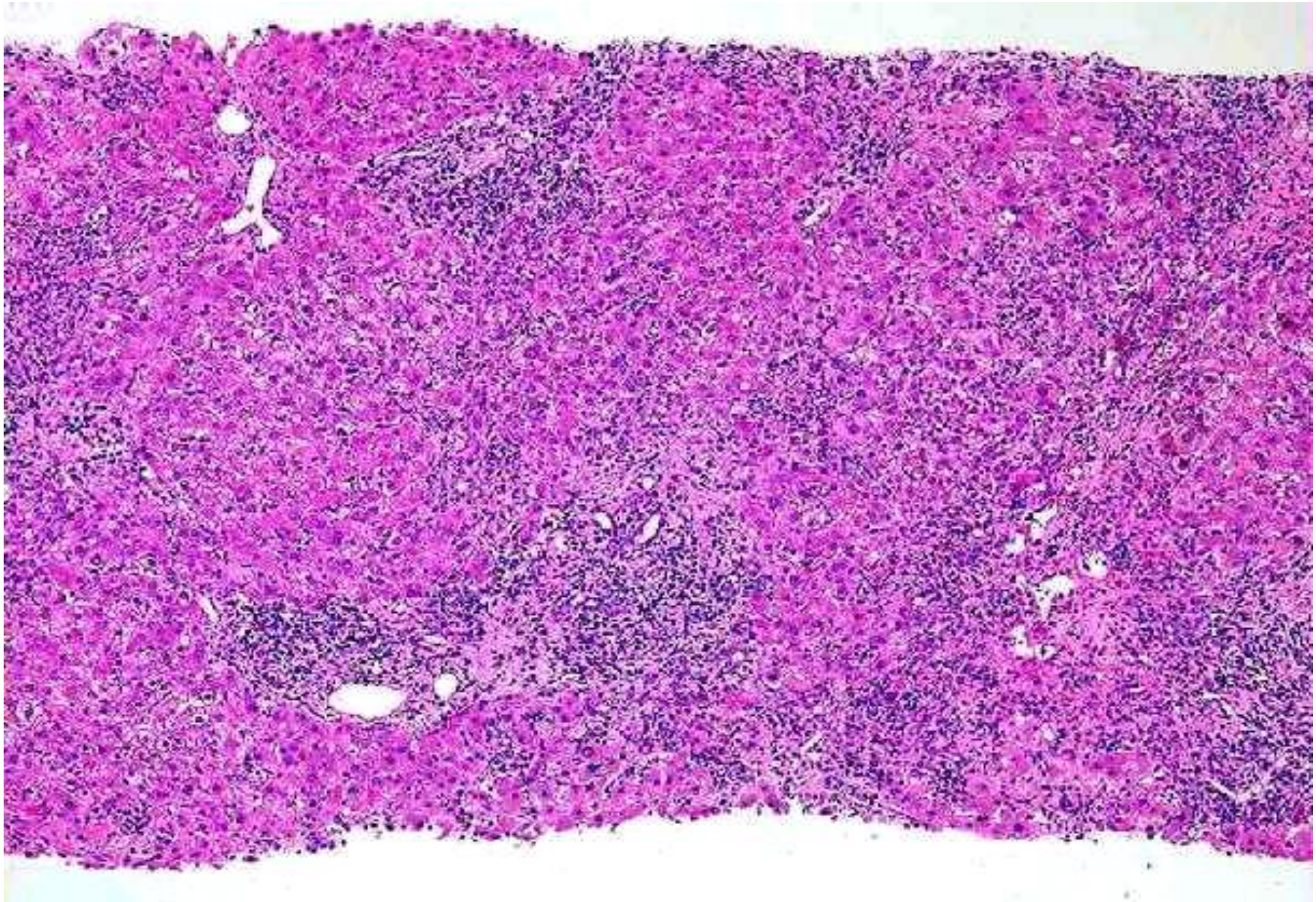
Acute viral Hepatitis



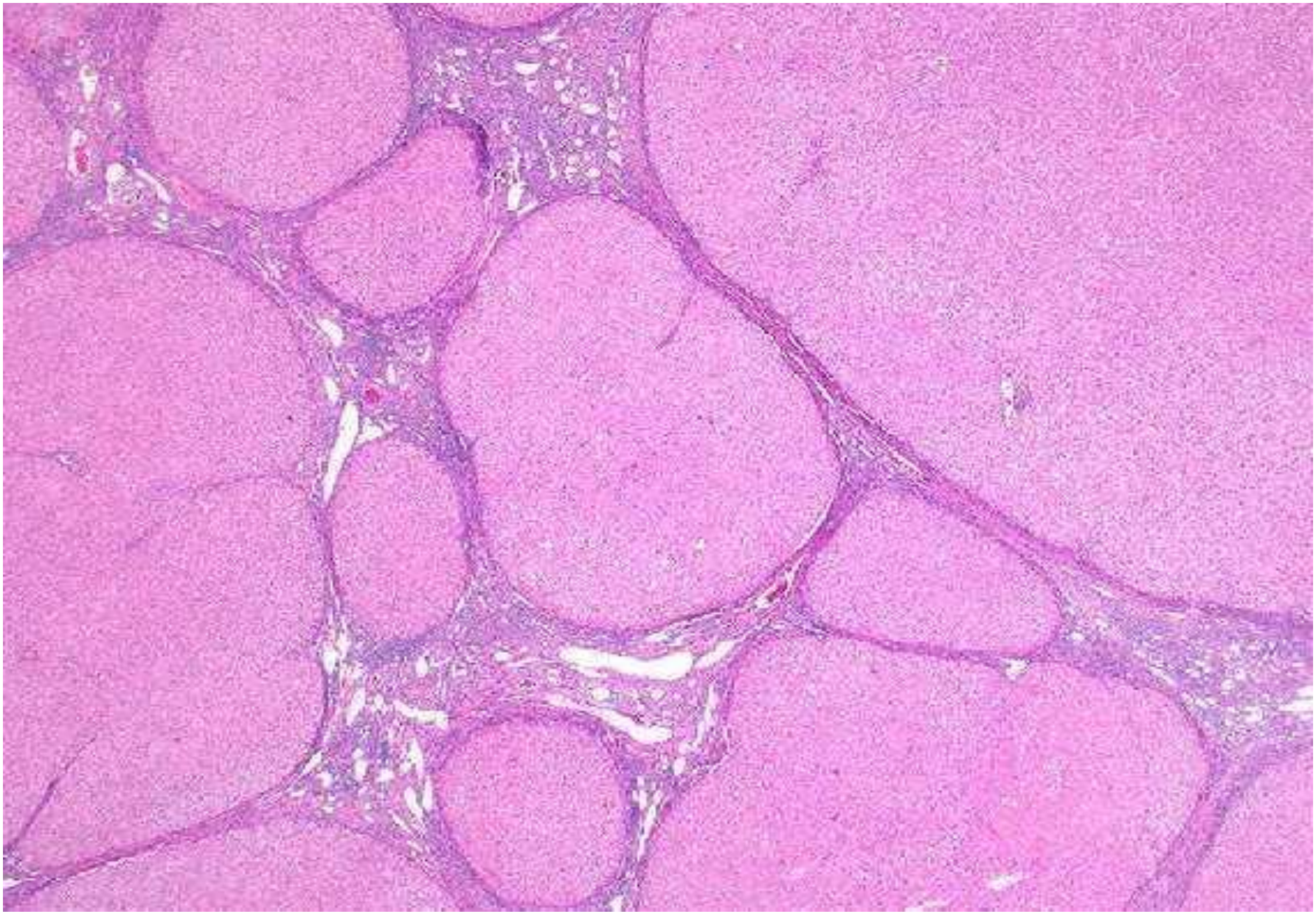
Acute viral Hepatitis



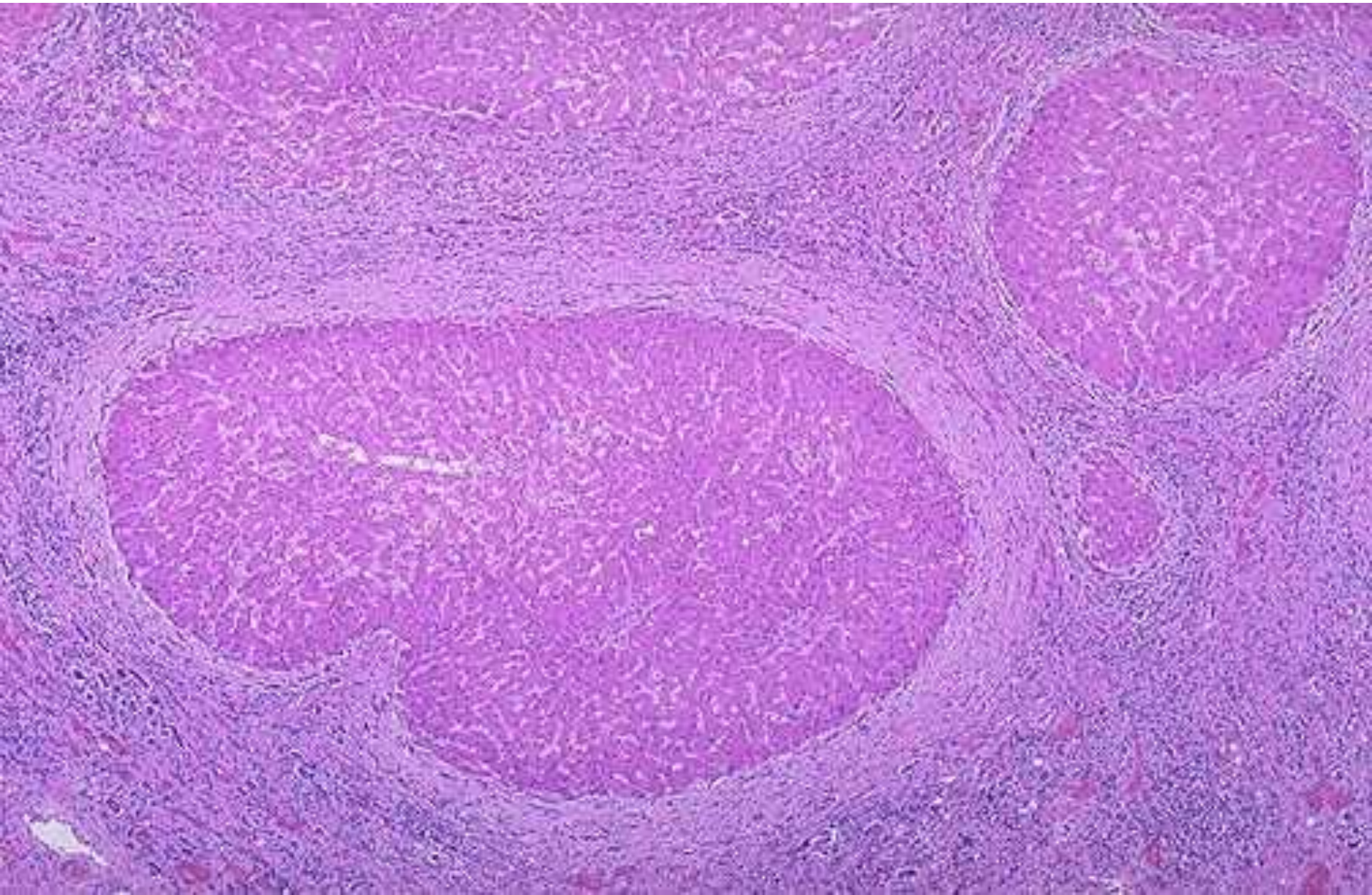
Liver Biopsy – Chronic hepatitis



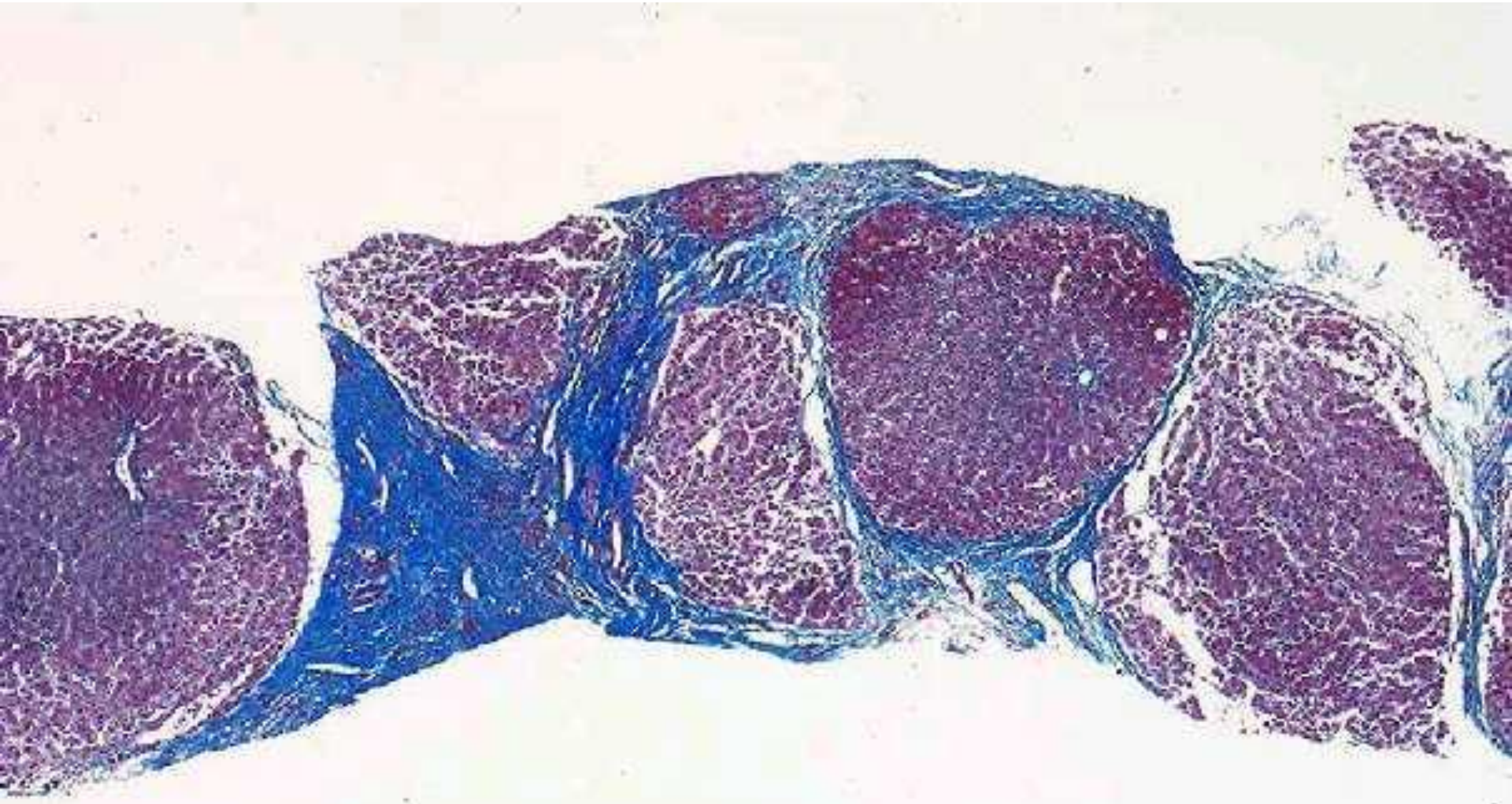
Liver Biopsy – Cirrhosis

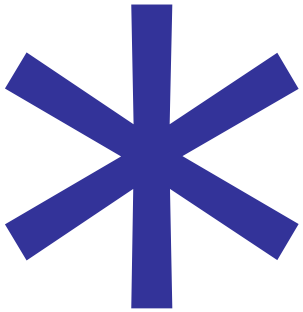


Liver Biopsy – Cirrhosis



Liver Biopsy – Cirrhosis





Viral Hepatitis

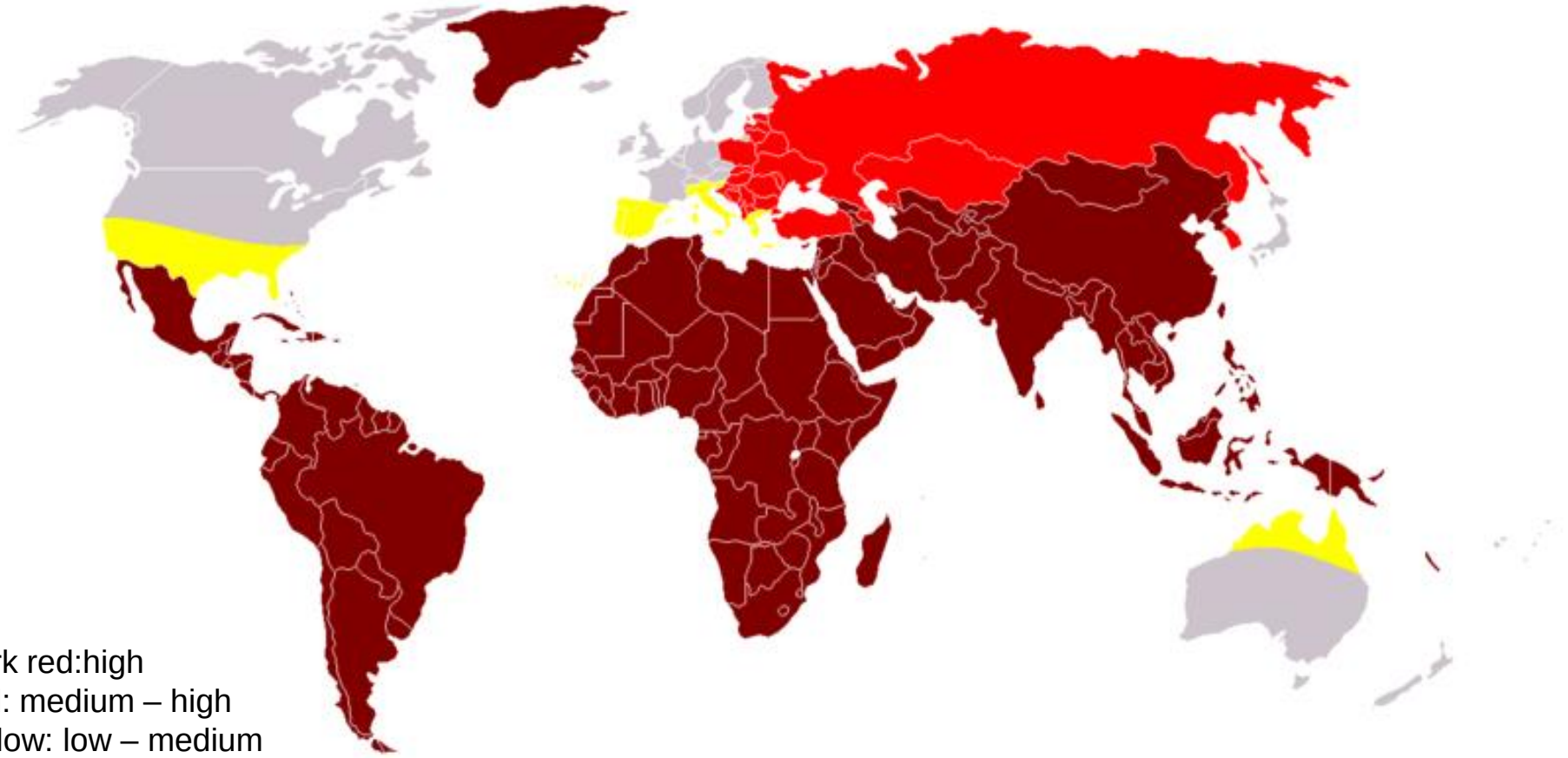
Most cases of acute hepatitis are due to viral infections:

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis B with D (delta)
- Hepatitis E
- Other viruses like cytomegalovirus, Epstein-Barr virus, yellow fever, etc.

Hepatitis A ("infectious hepatitis")

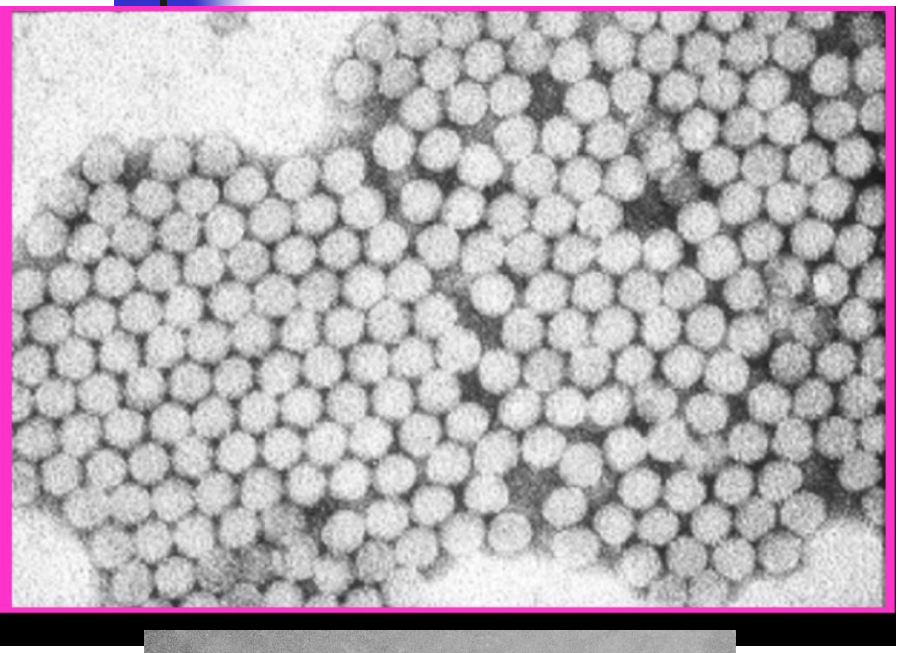
- Most commonly transmitted by the fecal-oral route via contaminated food or drinking water.
- Every year, approximately 10 million people worldwide are infected.
- Incubation period 2-6 weeks (average 28 days).
- In developing countries, and in regions with poor hygiene standards, the incidence of infection is near 100% and the illness is usually contracted in early childhood. It causes no clinical signs and symptoms in over 90% of these children.
- In Europe, the United States and other industrialised countries the infection is contracted primarily by susceptible young adults during trips to countries with a high incidence of the disease.

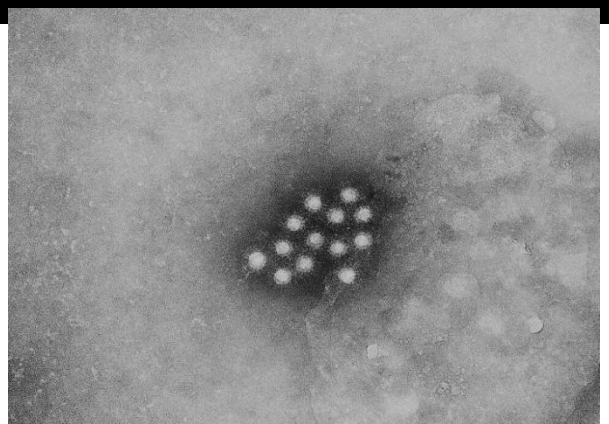
Hepatitis A Prevalence

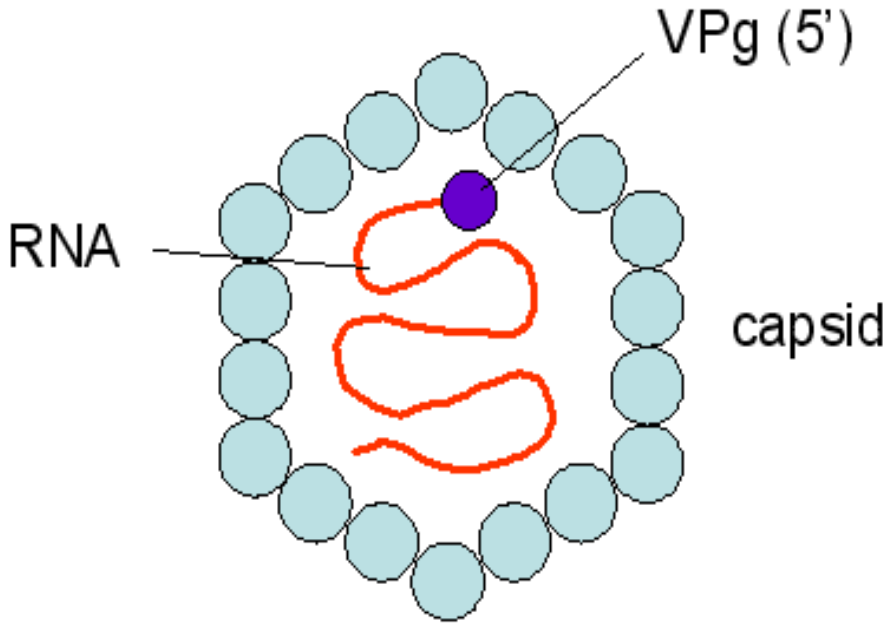


dark red:high
red: medium – high
yellow: low – medium
grey: low

Hepatitis A Virus (HAV)





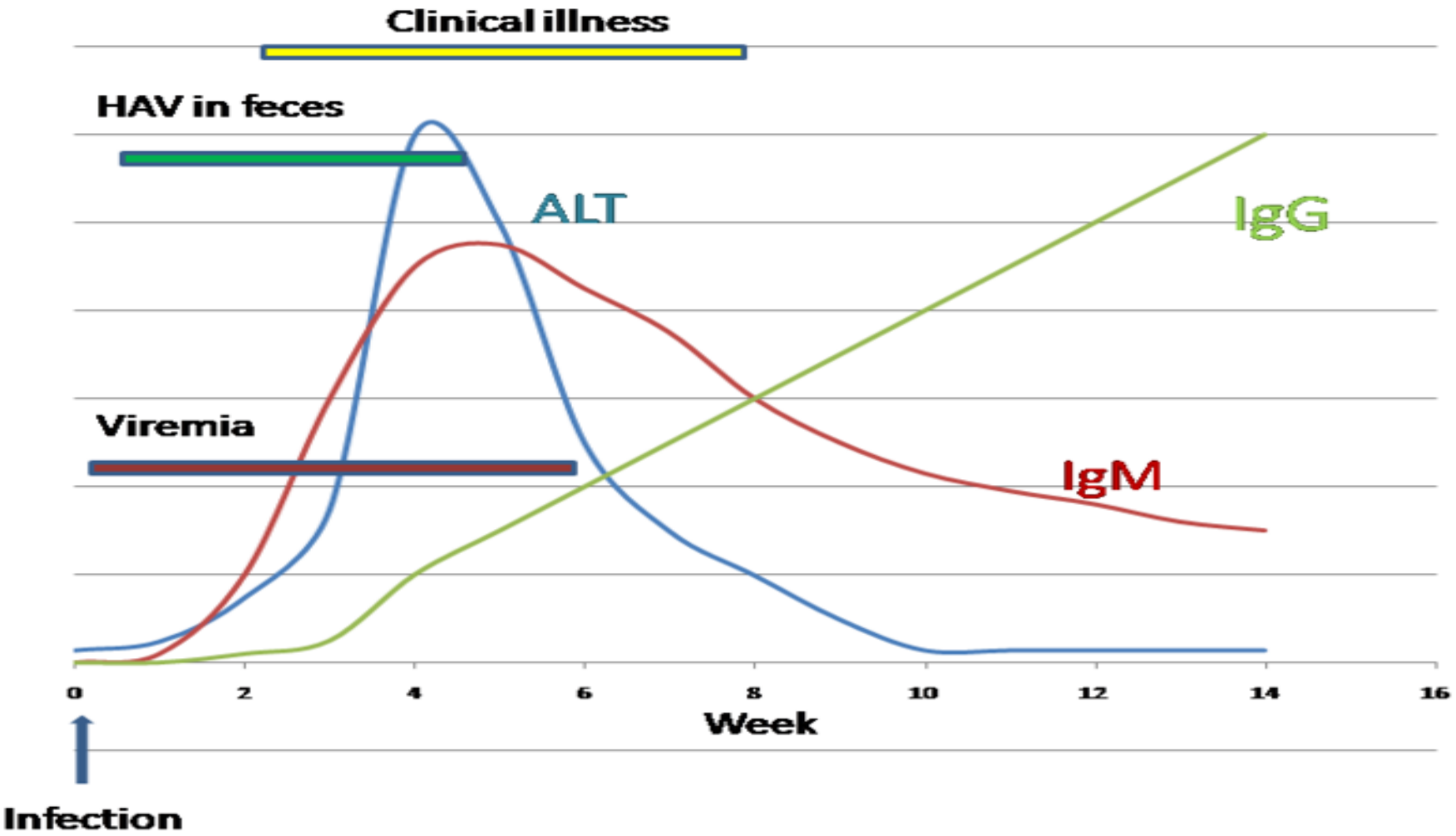


Picornavirus, single strand, positive sense RNA genome. Naked (unenveloped) icosahedral capsid 28 nm. At the 5' end of the RNA strand is a viral protein called VPg. One serotype.

Hepatitis A - Pathogenesis

- Following ingestion, HAV enters the bloodstream through the epithelium of the oropharynx or intestine.
- The blood carries the virus to its target, the liver, where it lives and multiplies within hepatocytes and Kupffer cells (i.e., liver macrophages).
- There is no apparent virus-mediated cytotoxicity, and liver pathology is likely immune-mediated.
- Virions are secreted into the bile and released in stool.
- HAV is excreted in large quantities approximately 11 days prior to appearance of symptoms or anti-HAV IgM antibodies in the blood.

Hepatitis A Course



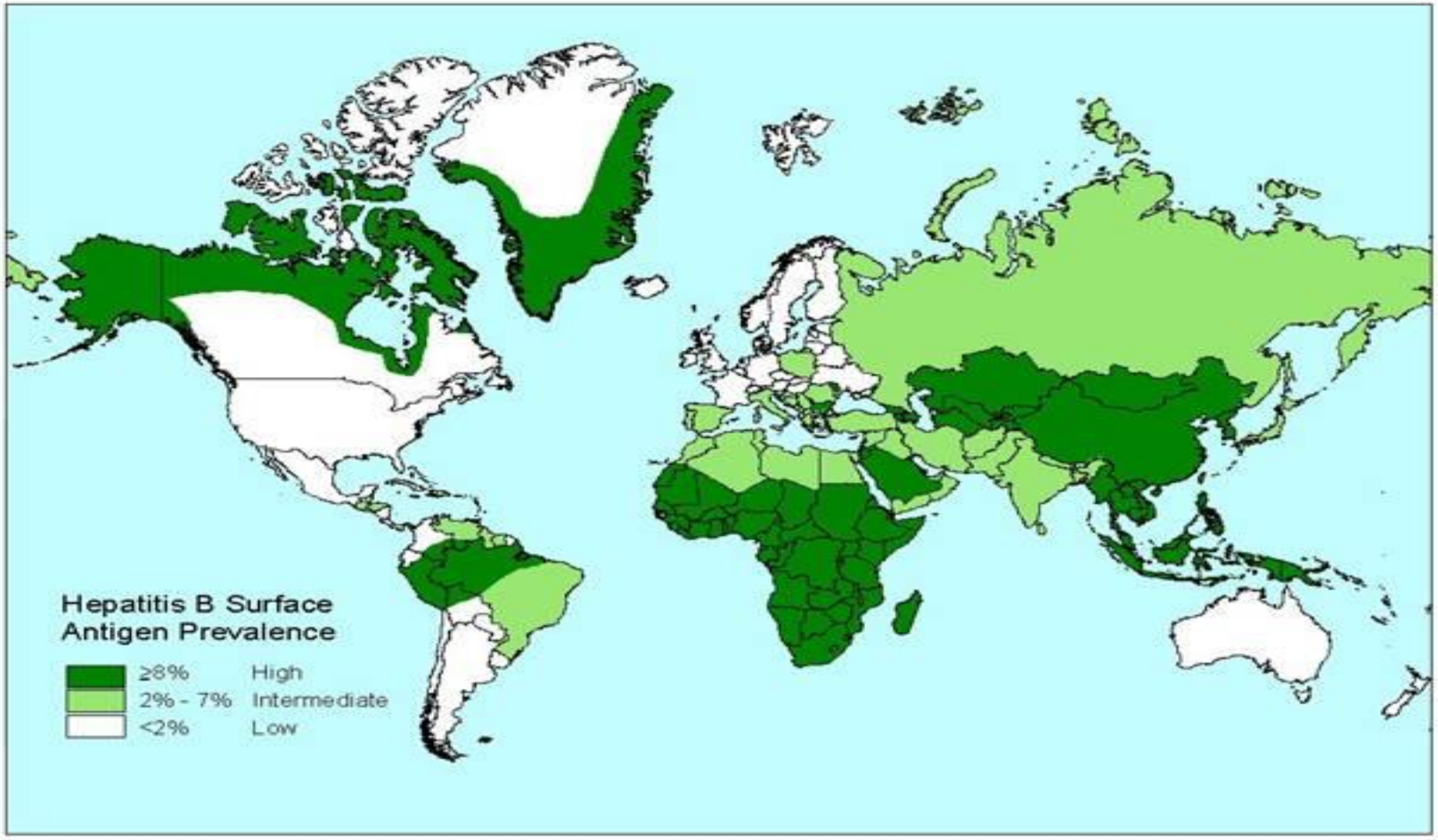
Hepatitis A - Outcome

- Mortality is less than 0.5%.
- The infection confers lifelong immunity
- Hepatitis A does not have a chronic stage and does not cause permanent liver damage.
- The disease can be prevented by vaccination and hepatitis A vaccine has been proved effective in controlling outbreaks worldwide.

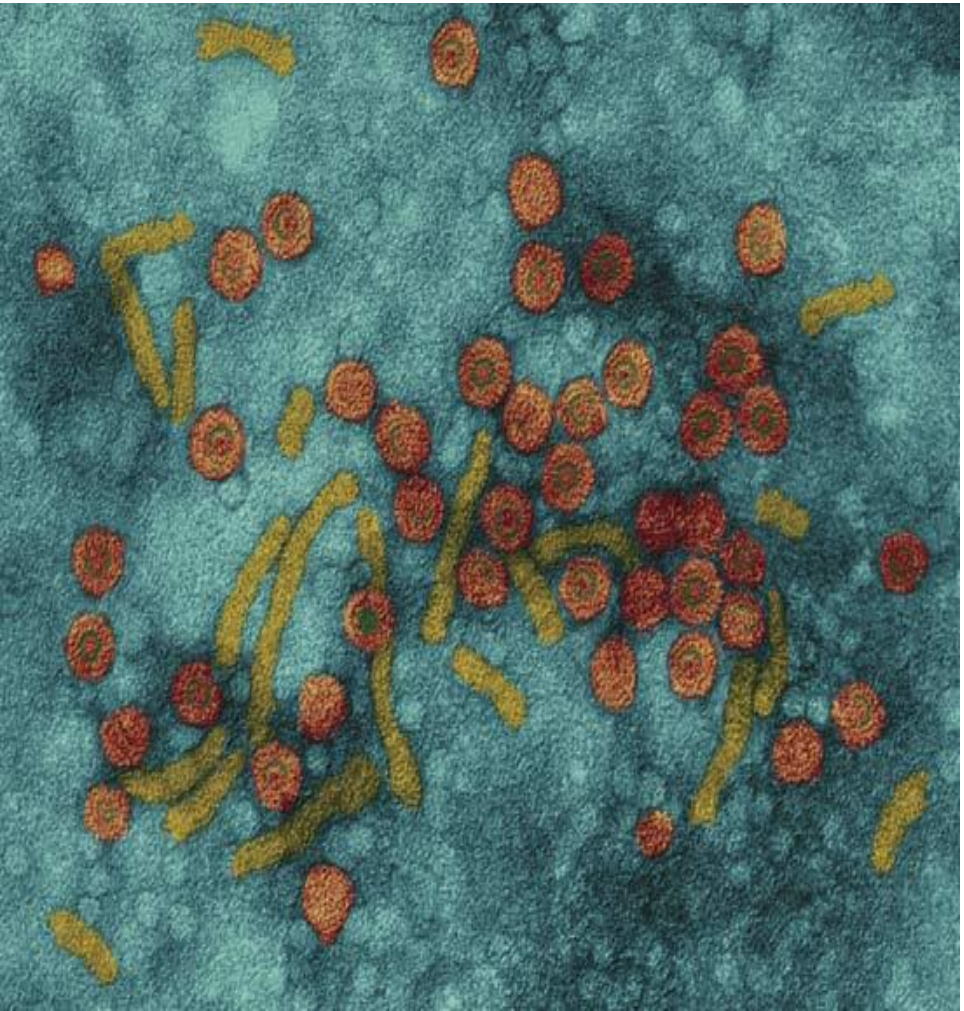
Hepatitis B – ”Serum hepatitis”

- Hepatitis B is endemic in China and various other parts of Asia.
- 3 to 6% of the world's population is currently infected, but up to a third have been exposed.
- Transmission: exposure to infectious blood or body fluids containing blood: unprotected sexual contact, blood transfusions, re-use of contaminated needles & syringes, and vertical transmission from mother to child during childbirth.
- In low prevalence areas such as the continental United States and Western Europe injection drug abuse and unprotected sex are the primary methods.
- In moderate prevalence areas, which include Eastern Europe, Russia, and Japan, where 2-7% of the population is chronically infected, the disease is predominantly spread among children.
- In high prevalence areas such as China and South East Asia, transmission during childbirth is most common,
- The prevalence of chronic HBV infection in areas of high endemicity is at least 8%.

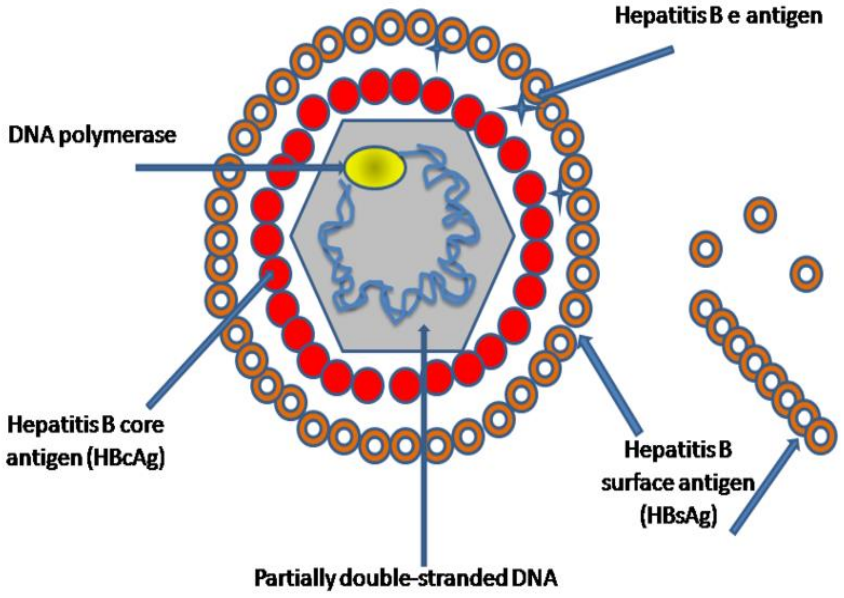
Hepatitis B Prevalence



Hepatitis B Virus



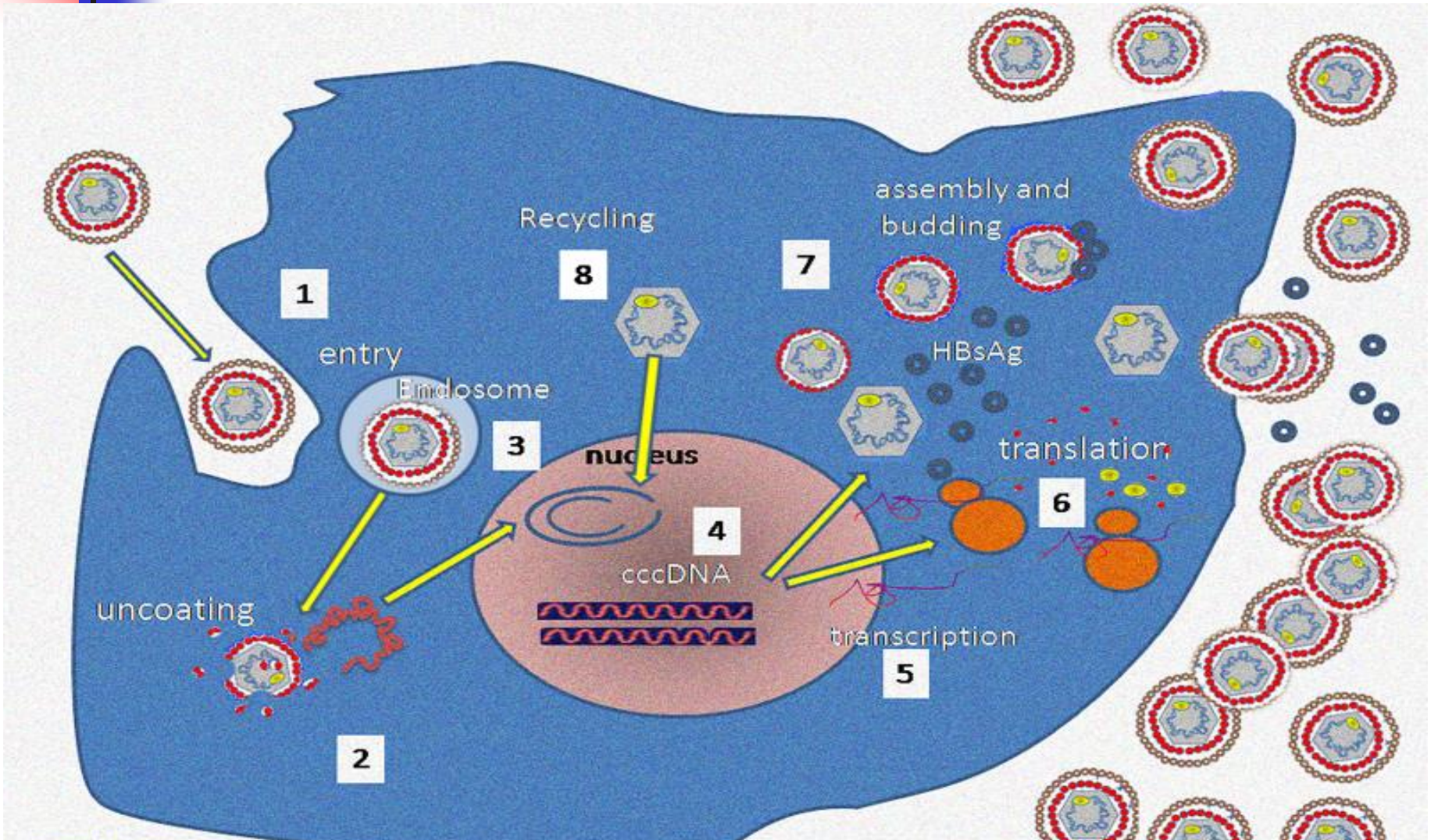
Human hepatitis B virus a hepadnavirus - enveloped DNA virus. Diameter about 40nm. The genome is associated with the P (polymerase) protein and this complex is, in turn, surrounded by the core antigens (HBcAg and HBeAg). Embedded in the surface lipid bilayer is the surface antigen (HBsAg)



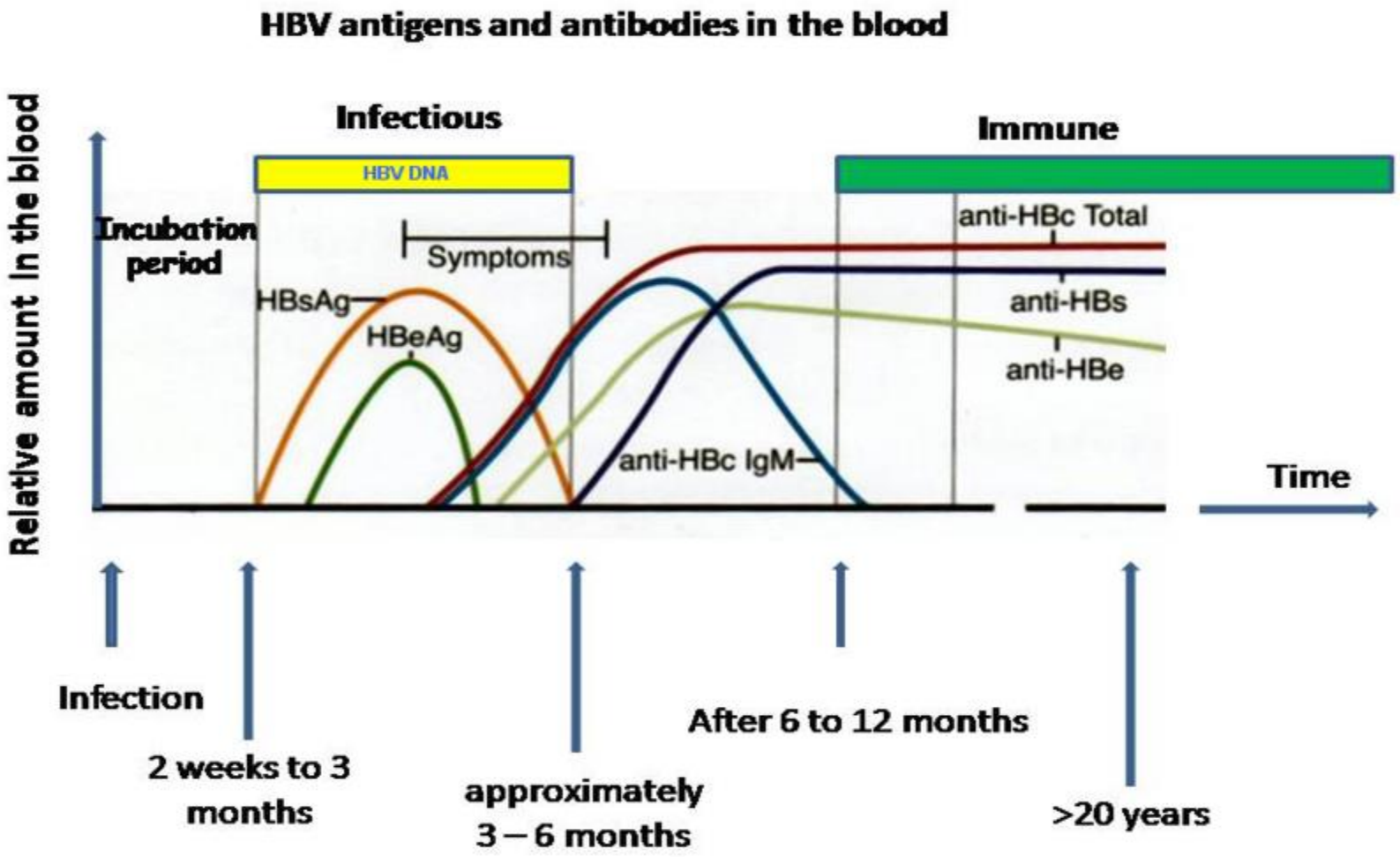
Hepatitis B - Pathogenesis

- The hepatitis B virus replicates in hepatocytes.
- During HBV infection, the host immune response causes both hepatocellular damage and viral clearance.
- The adaptive immune response, particularly virus-specific cytotoxic T lymphocytes (CTLs), contributes to most of the liver injury.
- By killing infected cells and by producing antiviral cytokines capable of purging HBV from viable hepatocytes, CTLs eliminate the virus.
- Hepatitis B virus DNA persists in the body after infection and in some people the disease re-occurs. Although rare, reactivation is seen most often in people with impaired immunity.

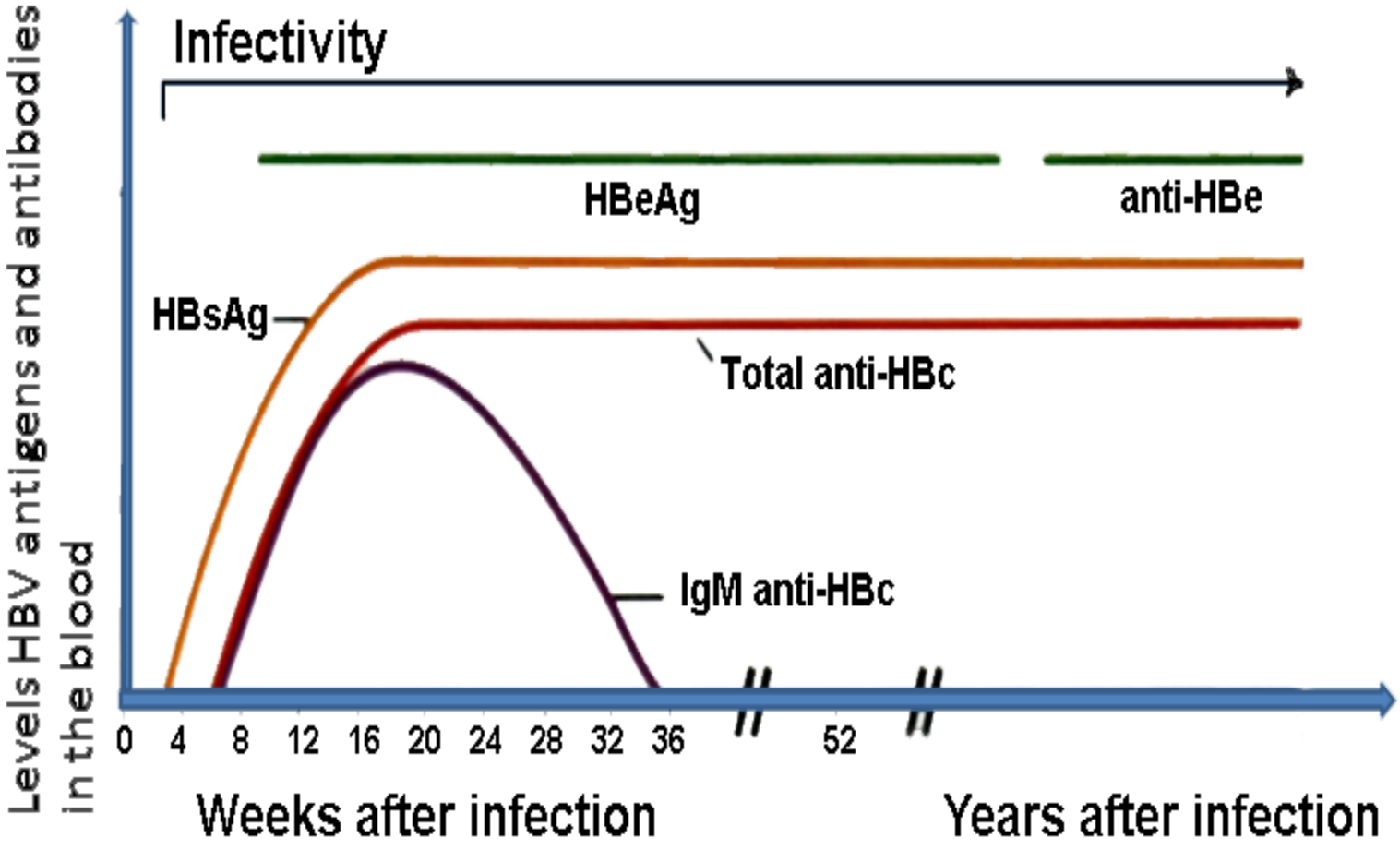
Hepatitis B Virus Replication



Acute Hepatitis B



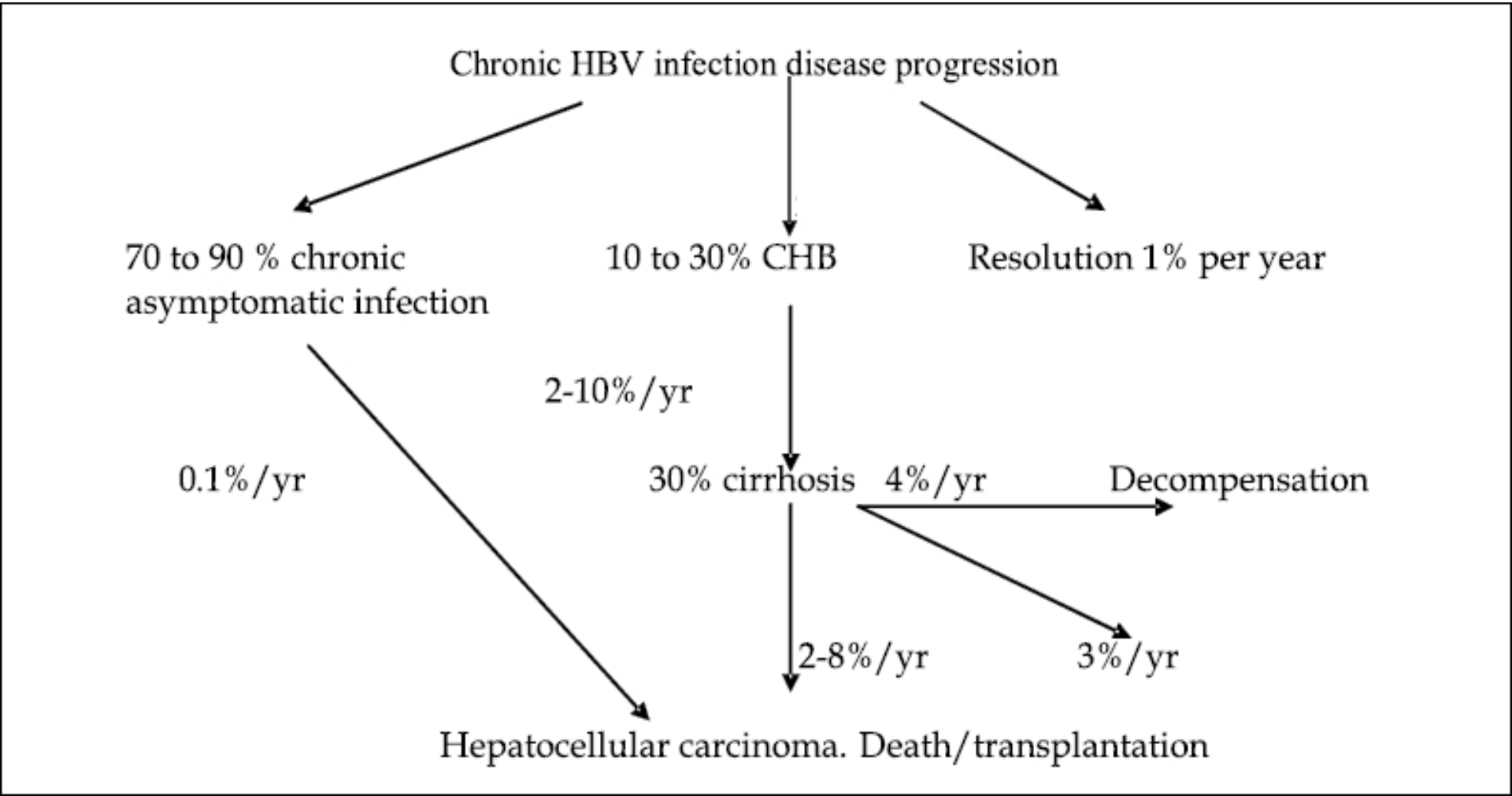
Chronic Hepatitis B



Hepatitis B - Outcome

- The infection may either be acute (self-limiting) or chronic (long-standing). Persons with self-limiting infection clear the infection spontaneously within weeks to months.
- A few patients may have more severe liver disease (fulminant hepatic failure), and may die as a result of it. The infection may be entirely asymptomatic and may go unrecognized.
- Children are less likely than adults to clear the infection. More than 95% adults or older children will recover fully and develop protective immunity to the virus. However, only 5% of newborns that acquire the infection from their mother at birth will clear the infection. Of those infected between the age of one to six, 70% will clear the infection.
- Chronic infection with Hepatitis B virus may be either asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma (liver cancer). Chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis and liver cancer.
- There is an effective vaccine

Chronic Hepatitis B Infection



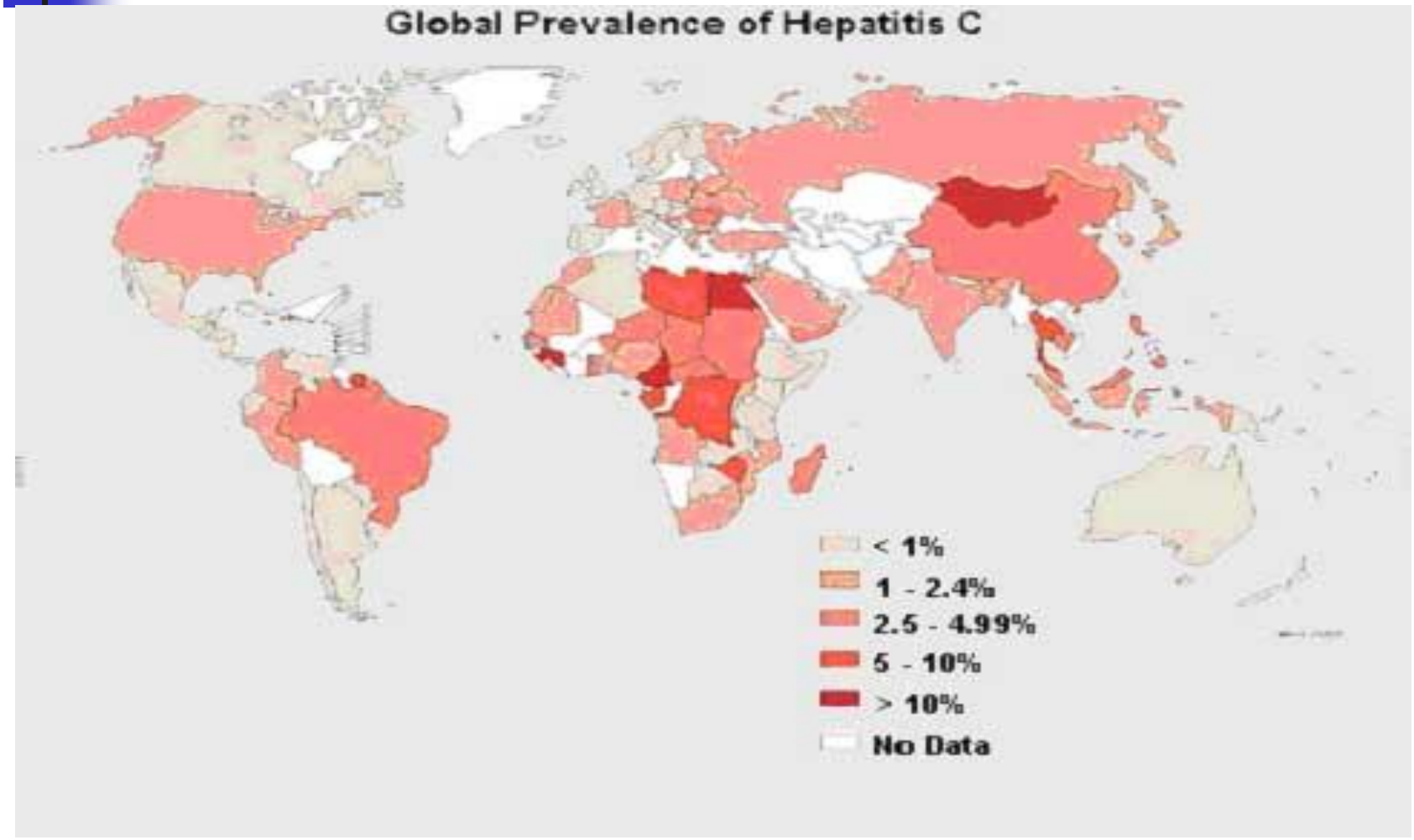
Hepatitis C

- Infected: 170 million people worldwide.
- Egypt has the highest seroprevalence for HCV, up to 20% in some areas. Regardless of how the epidemic started, a high rate of HCV transmission continues in Egypt, both iatrogenically and within the community and household.
- Co-infection with HIV
- Approximately 35% of patients in the USA infected with HIV are also infected with the hepatitis C virus.
- In other countries co-infection is less common, and this is possibly related to differing drug policies. HIV infection causes a more rapid progression of chronic hepatitis C to cirrhosis and liver failure.

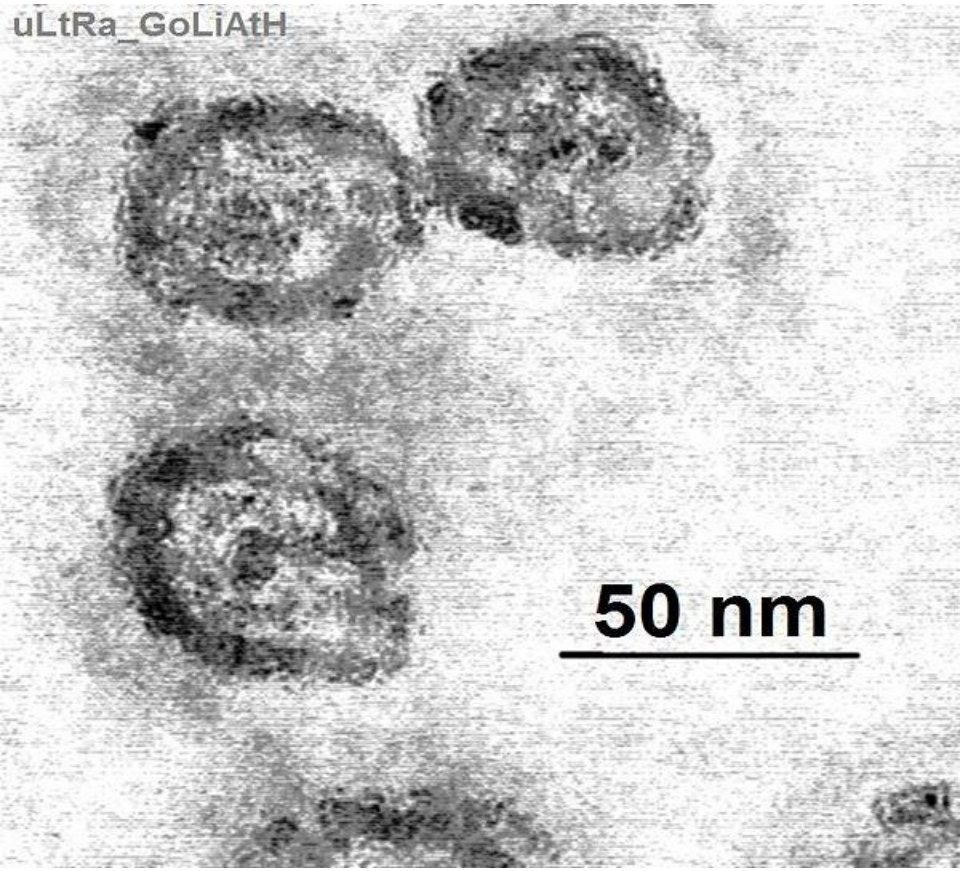
Hepatitis C

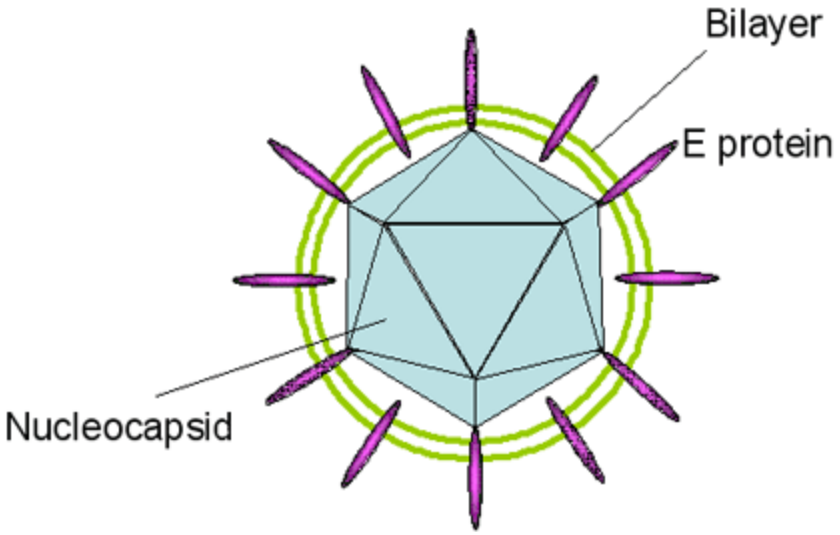
- The hepatitis C virus (HCV) is transmitted by blood-to-blood contact. Transfusion of unscreened blood or blood products or via injecting drug use.
- Inadequately or improperly sterilized medical or dental equipment: needles or syringes, hemodialysis equipment, oral hygiene instruments.
- Accidental needlesticks or blood spatter to the eyes or open wounds
- Tattooing dyes, ink pots, stylets and piercing
- Razors, toothbrushes, cuticle scissors, and other manicuring or pedicuring equipment
- The virus may be sexually transmitted, although this is rare.
- Mother-to-child transmission of hepatitis C has been well described, but occurs relatively infrequently.

Hepatitis C Prevalence



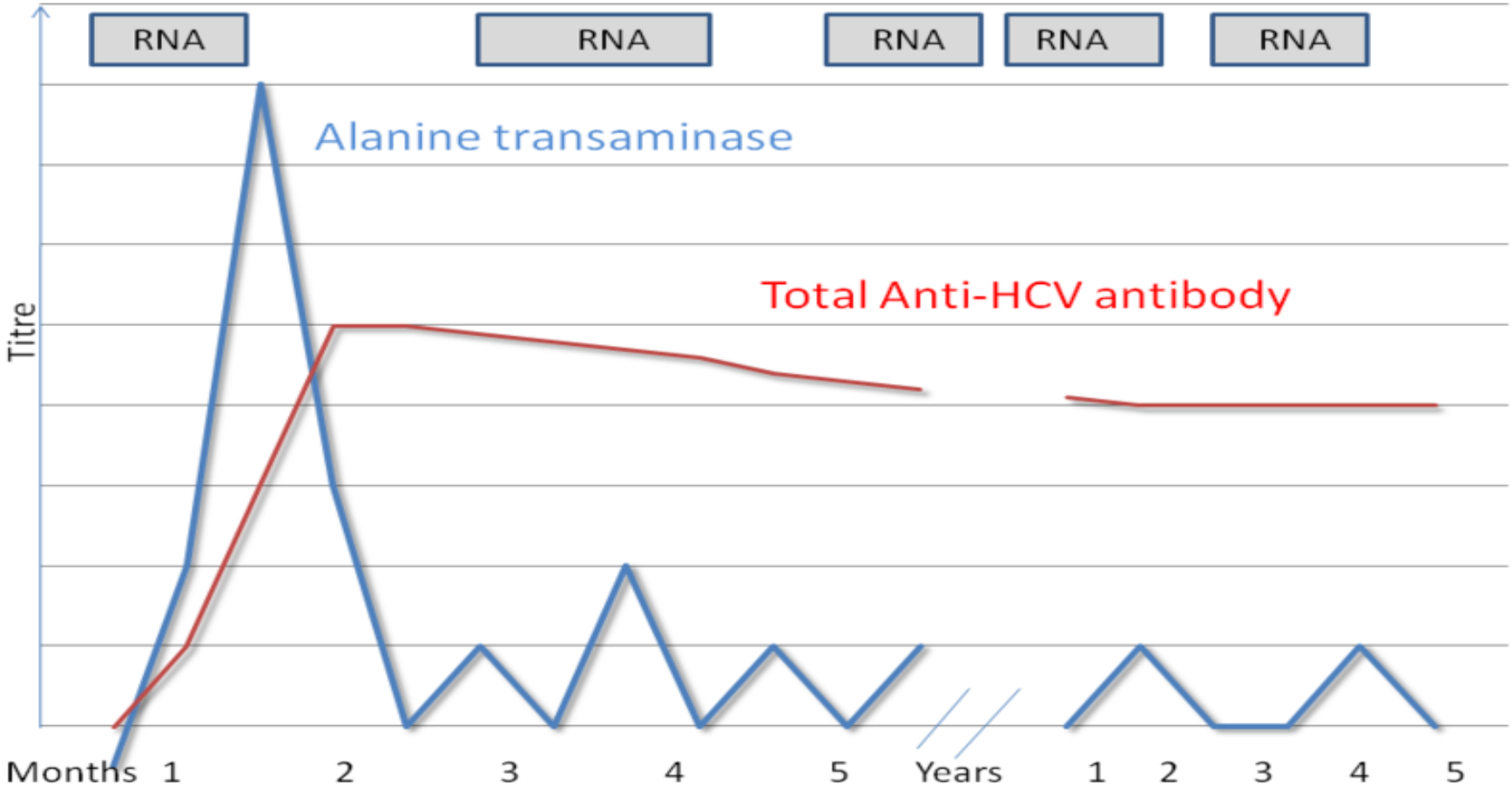
Hepatitis C Virus





Hepatitis C is a flavivirus (of which yellow fever is the prototype).Icosahedral, positive strand RNA viruses. They gain an envelope from their host cell. The virus particle is about 30 to 60 nm across. There are six major genotypes.

Chronic Hepatitis C



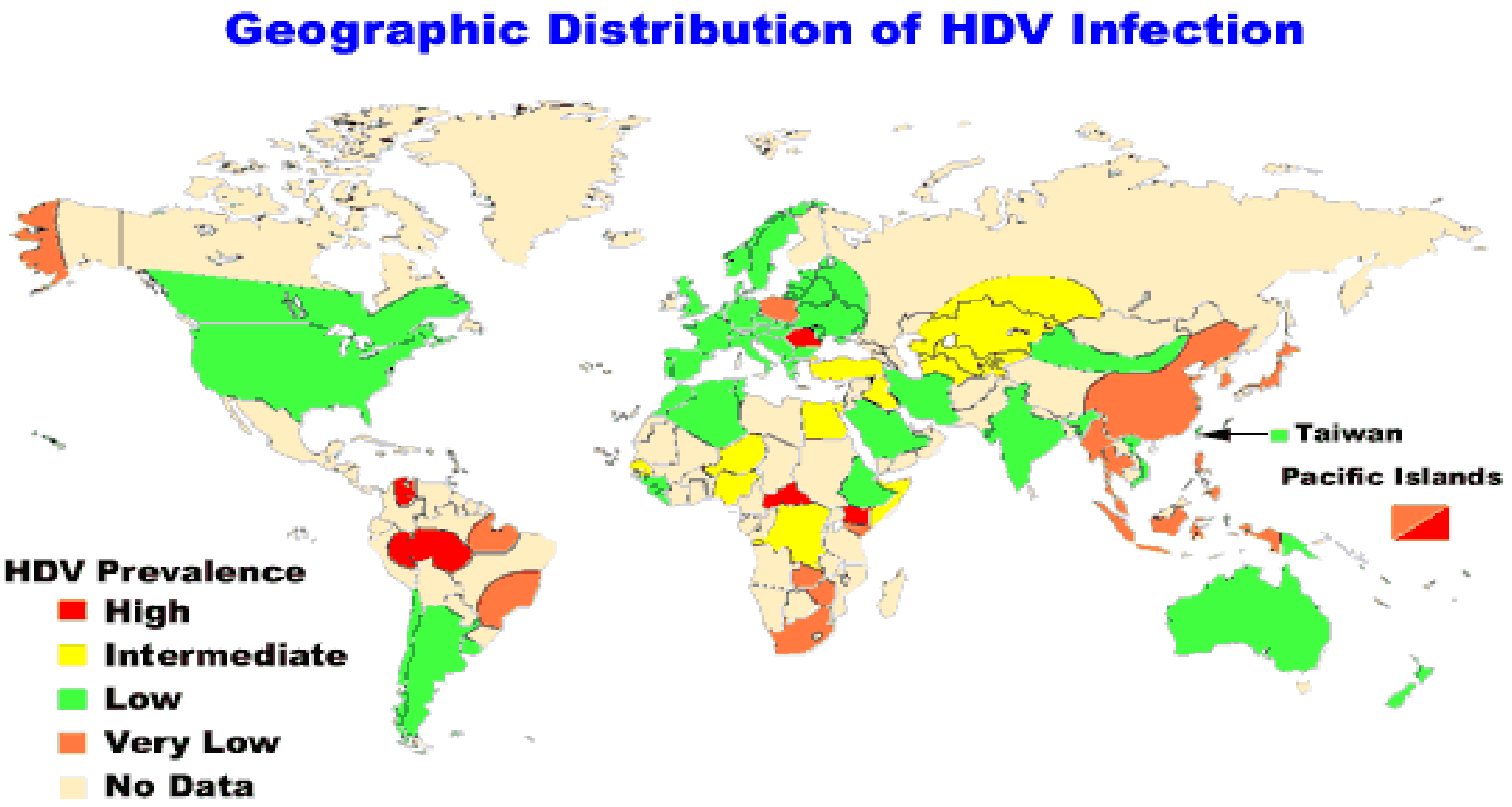
Hepatitis C - Outcome

- Between 60% to 70% of people infected develop no symptoms during the acute phase. In the minority of patients who experience acute phase symptoms, they are generally mild and nonspecific.
- The hepatitis C virus is detectable in the blood within one to three weeks after infection, and antibodies to the virus are generally detectable within 3 to 12 weeks.
- Approximately 15-40% of persons infected with HCV clear the virus during the acute phase
- The remaining 60-85% of patients infected with HCV develop chronic hepatitis C
- Roughly one-third progress to liver cirrhosis in less than 20 years. Another third progress to cirrhosis within 30 years. The remainder of patients appear to progress so slowly that they are unlikely to develop cirrhosis within their lifetimes.
- Factors associated with more rapid progression are older age, male gender, alcohol consumption, HIV coinfection and fatty liver.

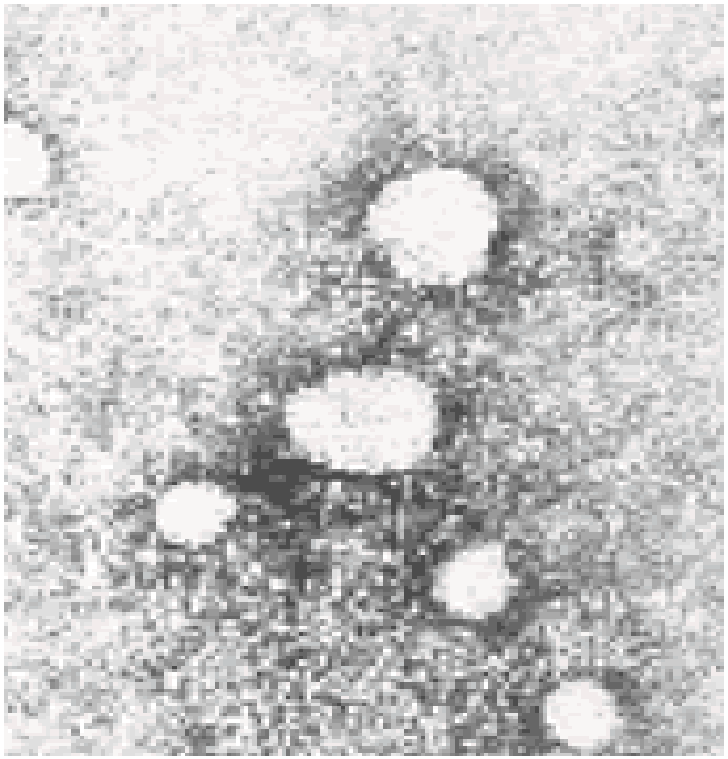
Hepatitis D (delta)

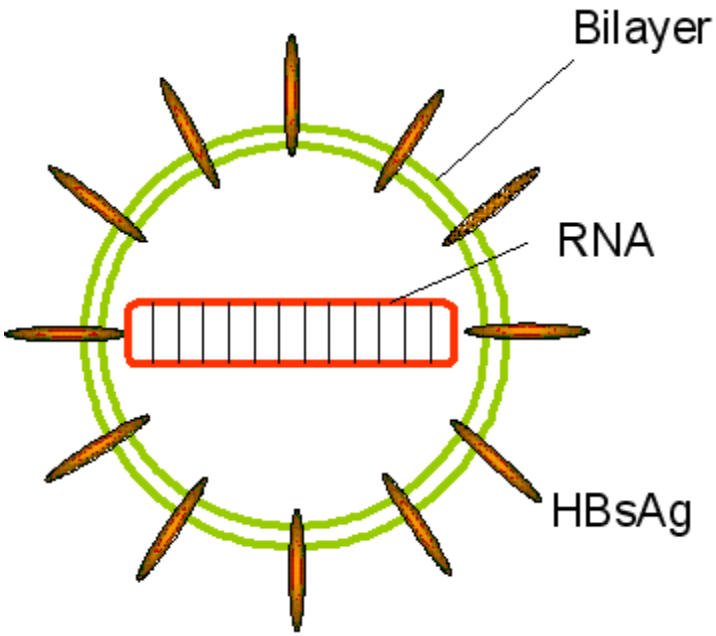
- Hepatitis delta virus or hepatitis D virus (HDV) is considered to be a subviral satellite because it can propagate only in the presence of another virus, the hepatitis B virus (HBV).
- Transmission of HDV can occur either via simultaneous infection with HBV (coinfection) or via infection of an individual previously infected with HBV (superinfection).

Hepatitis D (Delta) Virus



Hepatitis D (Delta) Virus





Hepatitis D is a highly defective virus since it cannot produce infective virions without the help of hepatitis B virus that supplies the HBsAg surface protein. In budding out of the cell, HDV acquires a membrane containing HBsAg.

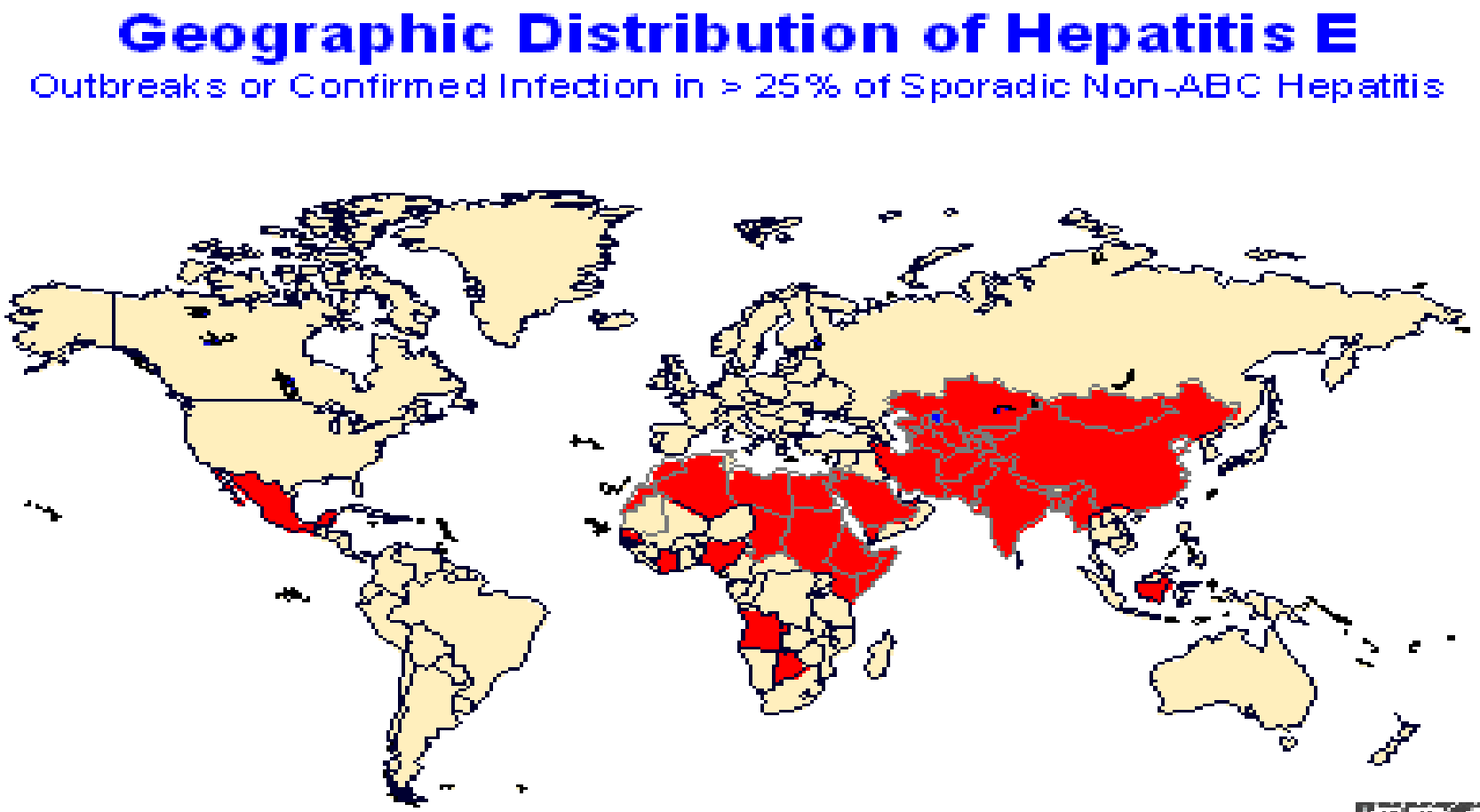
Hepatitis D (delta) - Outcome

- Both superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone: liver failure in acute infections and liver cancer in chronic infections.
- In combination with hepatitis B virus, hepatitis D has the highest mortality rate of all the hepatitis infections of 20%.

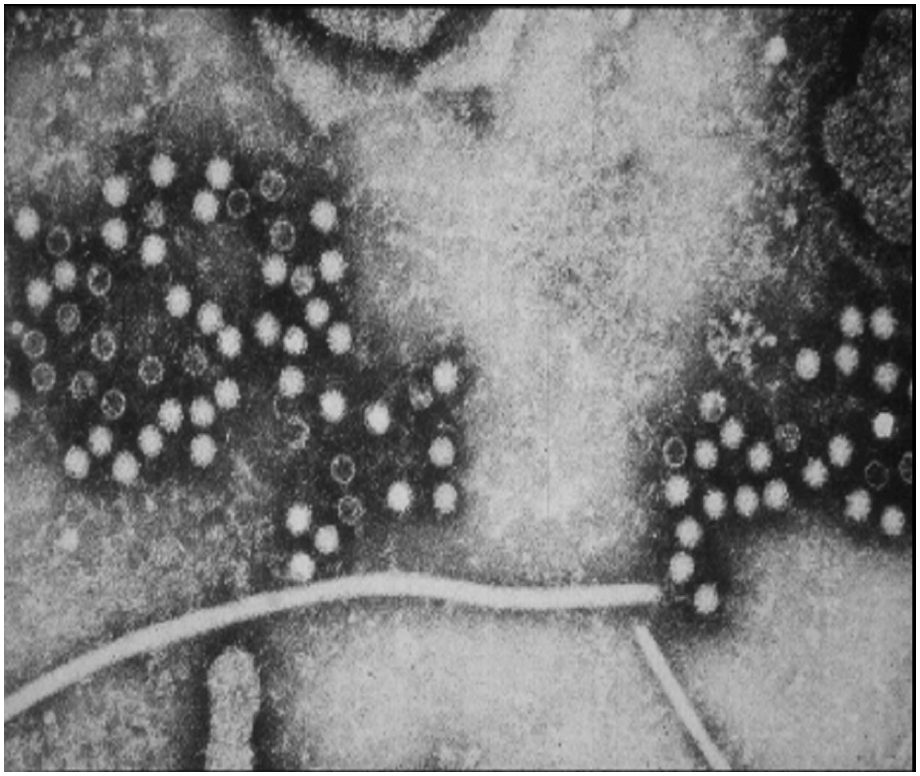
Hepatitis E

- Hepatitis E is prevalent in most developing countries, and common in any country with a hot climate.
- It is spread mainly through fecal contamination of water supplies or food; person-to-person transmission is uncommon.
- Outbreaks of epidemic Hepatitis E most commonly occur after heavy rainfalls and monsoons because of their disruption of water supplies.
- Domestic animals have been reported as a reservoir for the hepatitis E virus, with some surveys showing infection rates exceeding 95% among domestic pigs. Transmission after consumption of wild boar meat and uncooked deer meat has been reported as well. Rats also carry the virus.
- The incidence of hepatitis E is highest in adults between the ages of 15 and 40. Though children often contract this infection as well, they less frequently become symptomatic.

Hepatitis E Prevalence



Hepatitis E Virus



This virus seems to be related to the Caliciviruses but its classification is undecided. In sequence, HEV is more similar to rubella which is a Togavirus.
HEV is an approximately 34nm round, icosahedral, positive strand RNA virus without an envelope.

Hepatitis E - Outcome

- Mortality rates are generally low, for Hepatitis E is a "self-limiting" disease, in that it usually goes away by itself and the patient recovers. It never becomes chronic.
- However, during the duration of the infection (usually several weeks), the disease severely impairs a person's ability to work, care for family members, and obtain food.
- Hepatitis E occasionally develops into an acute severe liver disease, and is fatal in about 2% of all cases.
- Clinically, it is comparable to hepatitis A.
- Pregnant women, especially those in the third trimester, suffer an elevated mortality rate from the disease ~20% because of ”fulminant hepatic failure”.
- A vaccine is being developed.

Other Viruses Associated with Acute Hepatitis

Seen in E.U.*

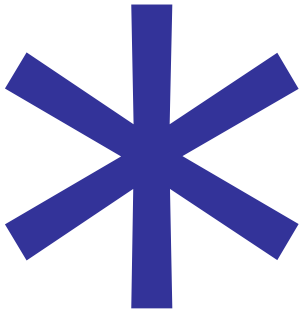
- Cytomegalovirus
- Epstein-Barr
- Herpes simplex
- Varicella zoster
- Measles
- Rubella
- Coxsackie

Exotic**

- Yellow fever
- Argentinean hemorrhagic fever
- Bolivian hemorrhagic fever
- Lassa fever
- Rift Valley fever
- Marburg
- Ebola

* Each causes less than 1% of acute hepatitis.

** Not seen in the E.U..



Programme:

- First part:
  - Overwiew
    - Acute – chronic liver disease, symptoms, signs, blood tests, liver structure
  - Viral hepatitis
- Second part:
  - Toxic hepatitis, fatty liver, alcoholic hepatitis
  - Bilirubin, jaundice
  - Bile, gallstone
- Third part:
  - Cirrhosis, end-stage liver disease
  - Complications
    - Portal hypertension, esophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathia, hepatopulmonary syndrome

Toxic hepatitis

- Hepatotoxicity (from hepatic toxicity) implies chemical-driven liver damage.
- The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents.
- Certain medicinal agents when taken in overdoses and sometime even when introduced within therapeutic ranges may injure the organ.
- Other chemical agents used in laboratories and industries, natural chemicals and herbal remedies can induce hepatotoxicity.
- More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market.
- Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests.
- Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures.

Toxic hepatitis

- The human body identifies almost all drugs as foreign substances (i.e. xenobiotics) and subjects them to various chemical processes to make them suitable for elimination.
- This involves chemical transformations to (a) reduce fat solubility and (b) to change biological activity.
- The smooth endoplasmic reticulum in liver is the principal "metabolic clearing house" for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acids, and proteins), and exogenous substances (e.g. drugs). The central role played by liver in the clearance and transformation of chemicals also makes it susceptible to drug induced injury.

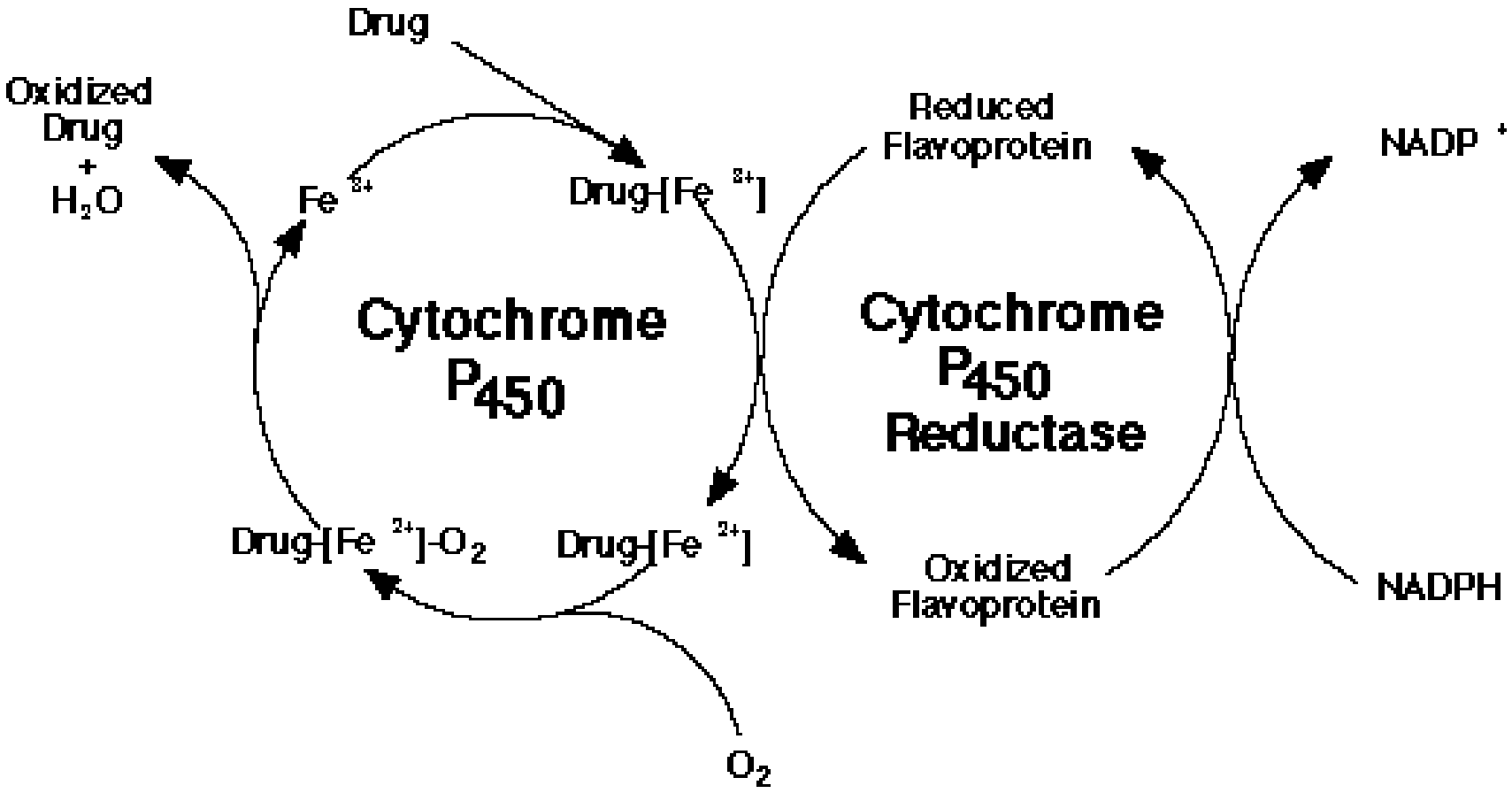
Toxic hepatitis – Drug metabolism

- **Phase 1 reaction** involves oxidation, reduction, hydrolysis, hydration and many other rare chemical reactions. These processes tend to increase water solubility of the drug and can generate metabolites which are more chemically active and potentially toxic.
- Most of **phase 2 reactions** take place in cytosol and involve conjugation with endogenous compounds via transferase enzymes. Chemically active phase 1 products are rendered relatively inert and suitable for elimination by this step.
- A group of enzymes located in the endoplasmic reticulum, known as cytochrome P-450, is the most important family of metabolizing enzymes in the liver. Cytochrome P-450 is the terminal oxidase component of an electron transport chain. It consists of a family of closely related 50 isoforms, six of them metabolize 90% of drugs. There is a tremendous diversity of individual P-450 gene products and this heterogeneity allows the liver to perform oxidation on a vast array of chemicals (including almost all drugs) in phase 1.

Cytochrome P-450 - Characteristics

- Three important characteristics of the P450 system have roles in drug induced toxicity:
- **1. Genetic diversity**: Each of the P-450 proteins is unique and accounts to some extent for the variation in drug metabolism between individuals. Genetic variations (polymorphism) in CYP450 metabolism should be considered when patients exhibit unusual sensitivity or resistance to drug effects at normal doses.
- **2. Change in enzyme activity**: Many substances can influence P-450 enzyme mechanism. Enzyme inhibitors block the metabolic activity of one or several P-450 enzymes. This effect usually occurs immediately. Inducers increase P-450 activity by increasing its synthesis.
- **3. Competitive inhibition**: Some drugs may share the same P-450 specificity and thus competitively block their biotransformation. This may lead to accumulation of drugs metabolised by the enzyme. This type of drug interaction may also reduce the rate of generation of toxic substrate.

Cytochrome P-450 - action



Adverse drug Reactions

- Adverse drug reactions are classified as type A (intrinsic or pharmacological) or type B (idiosyncratic). Type A drug reaction accounts for 80% of all toxicities.
- Drugs or toxins that have a **pharmacological (type A) hepatotoxicity** are those that have predictable dose-response curves (higher concentrations cause more liver damage) and well characterized mechanisms of toxicity such as directly damaging liver tissue or blocking a metabolic process. As in the case of Acetaminophen overdose, this type of injury occurs shortly after some threshold for toxicity is reached.
- **Idiosyncratic (type B) injury** occurs without warning; when agents cause non-predictable hepatotoxicity in susceptible individuals which is not related to dose and has variable latency period. This type of injury does not have a clear dose-response or temporal relationship, and most often do not have predictive models.

Fatty liver disease (FLD) - steatosis hepatis

- Fatty liver (steatosis hepatis) is a reversible condition where large vacuoles of triglyceride fat accumulate in liver cells.
- Despite having multiple causes, fatty liver disease (FLD) can be considered a single disease that occurs worldwide in those with excessive alcohol intake and those who are obese (with or without effects of insulin resistance). The condition is also associated with other diseases that influence fat metabolism.

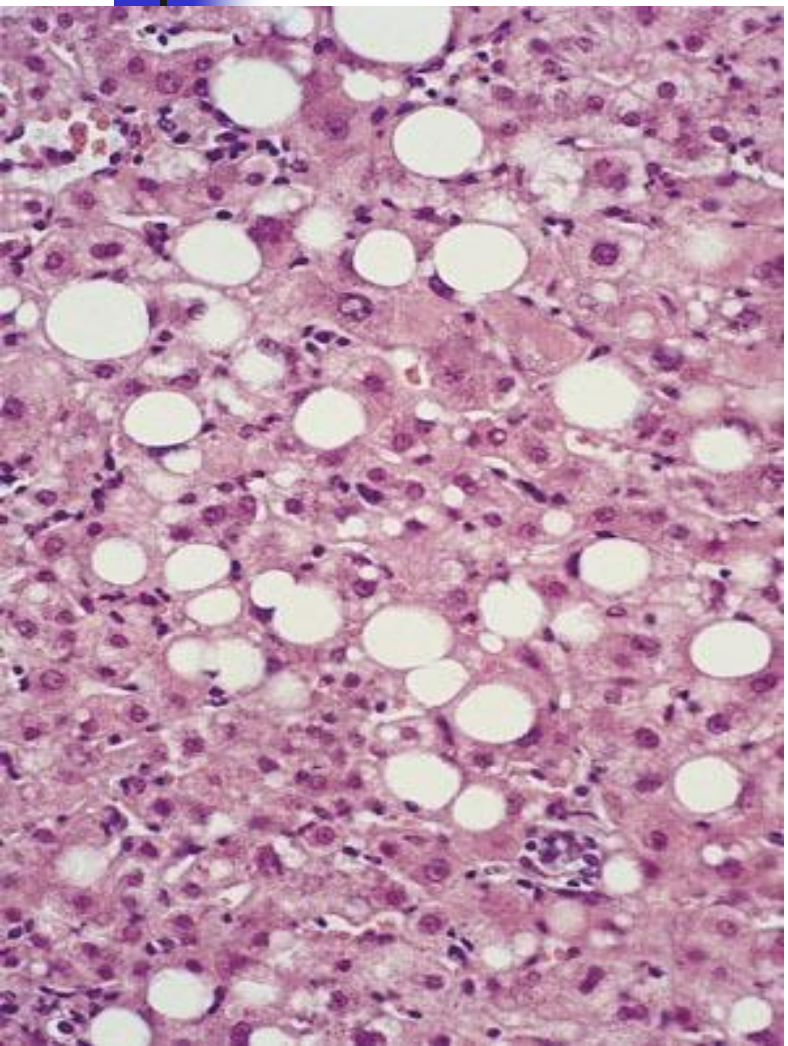
Steatosis - causes

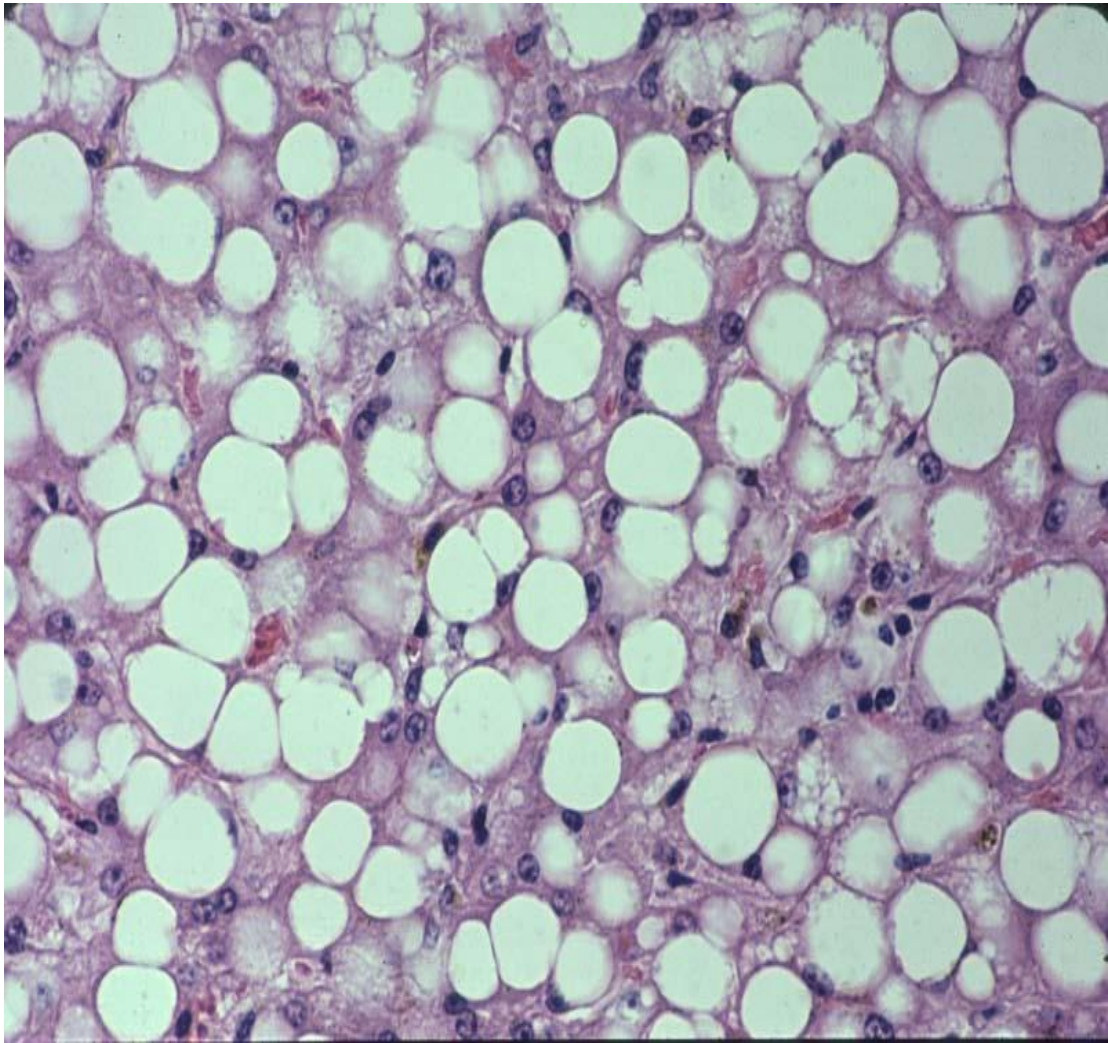
- Alcohol
- Metabolic syndrome (diabetes, hypertension and dyslipidemia)
- Metabolic: Abetalipoproteinemia, glycogen storage diseases, Weber-Christian disease, Wolman disease, acute fatty liver of pregnancy, lipodystrophy
- Nutritional: Malnutrition, total parenteral nutrition, severe weight loss, refeeding syndrome, jejuno-ileal bypass, gastric bypass, jejunal diverticulosis with bacterial overgrowth
- Drugs and toxins: Amiodarone, methotrexate, diltiazem, glucocorticoids, tamoxifen, environmental hepatotoxins (e.g. phosphorus, toxic mushroom)

Steatosis - histopathology

- Intra-cytoplasmic accumulation of triglyceride (neutral fats).
- At the beginning, the hepatocytes present small fat vacuoles (liposomes) around the nucleus - microvesicular fatty change. In this stage liver cells are filled with multiple fat droplets that do not displace centrally located nucleus.
- In the late stages, the size of the vacuoles increases pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance - macrovesicular fatty change.
- Large vacuoles may coalesce, producing fatty cysts - which are irreversible lesions.

Steatosis - histopathology





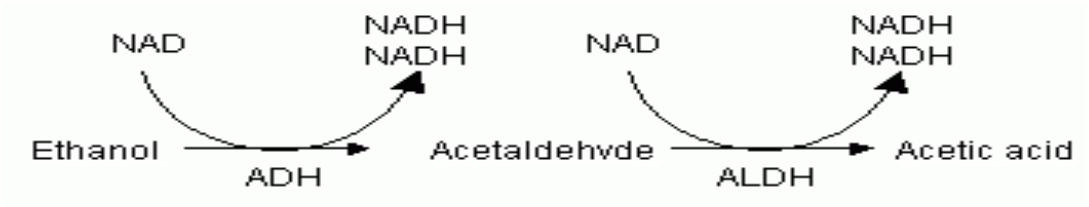
Steatosis - Pathogenesis

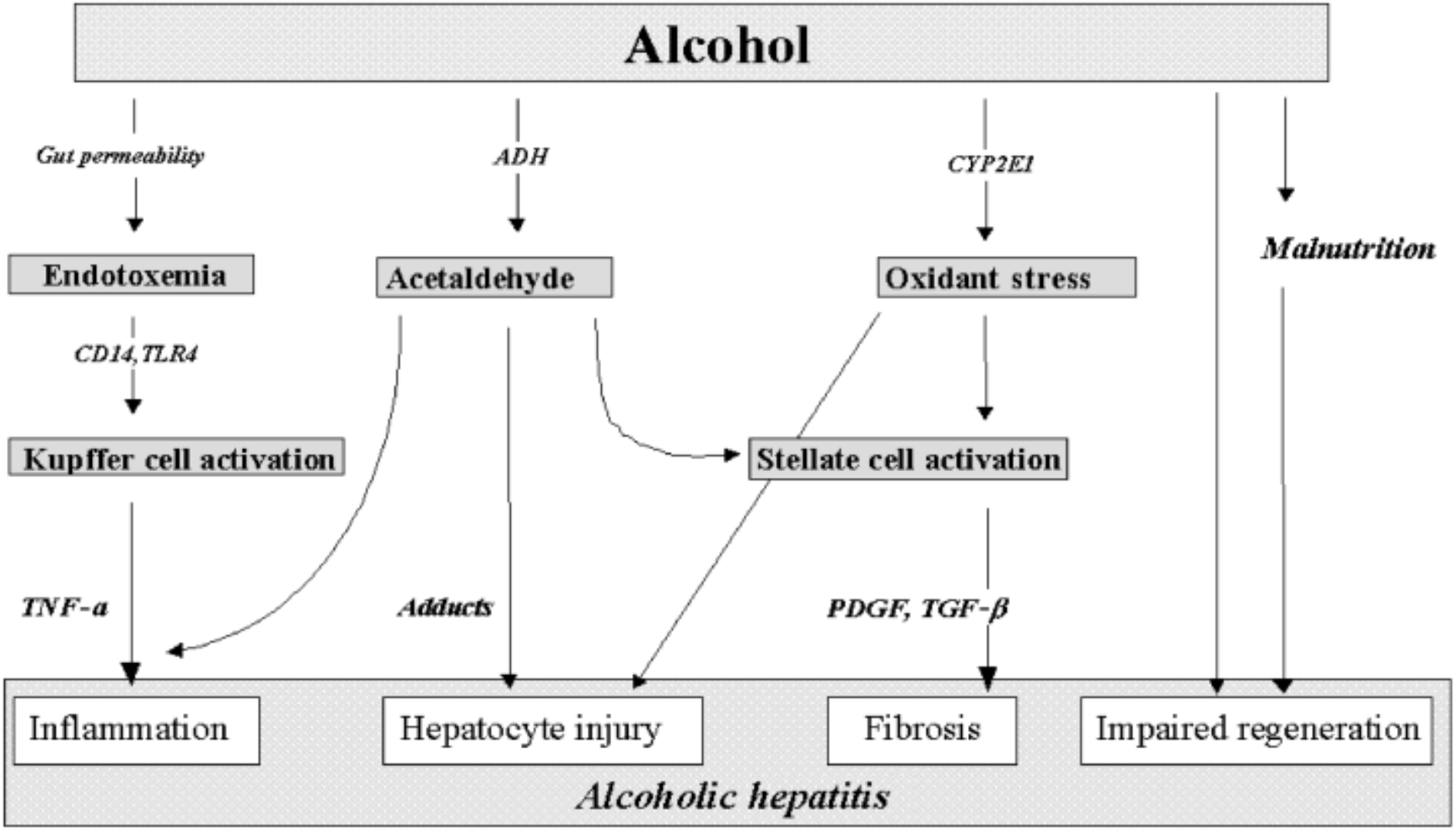
- Defects in fat metabolism: a) imbalance in energy consumption and its combustion resulting in lipid storage, b) a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from adipose tissue to the liver is increased.
- Impairment or inhibition of receptor molecules (PPAR-a, PPAR-? and SREBP1) that control the enzymes responsible for the oxidation and synthesis of fatty acids appears to contribute towards fat accumulation.
- Alcoholism is known to damage mitochondria and other cellular structure further impairing cellular energy mechanism.
- Non alcoholic FLD may begin as excess of unmetabolised energy in liver cells.
- Hepatic steatosis is considered reversible and to some extent nonprogressive if there is cessation or removal of underlying cause.
- Severe fatty liver is accompanied by inflammation.
- Liver with extensive inflammation and high degree of steatosis often progresses to more severe forms of the disease (fibrosis, cirrhosis).

Alcoholic hepatitis

- Alcoholic hepatitis is hepatitis (inflammation of the liver) due to excessive intake of alcohol.
- Some alcoholics get an acute hepatitis or inflammatory reaction to cells affected by fatty change. This is not directly related to the dose of alcohol.
- It is distinct from cirrhosis and can be an early stage of alcoholic liver disease.
- Symptoms are jaundice, ascites (fluid accumulation in the abdominal cavity), fatigue and hepatic encephalopathy (brain dysfunction due to liver failure).
- Mild cases are self-limiting, but severe cases have a high risk of death.

Alcohol – toxic effects

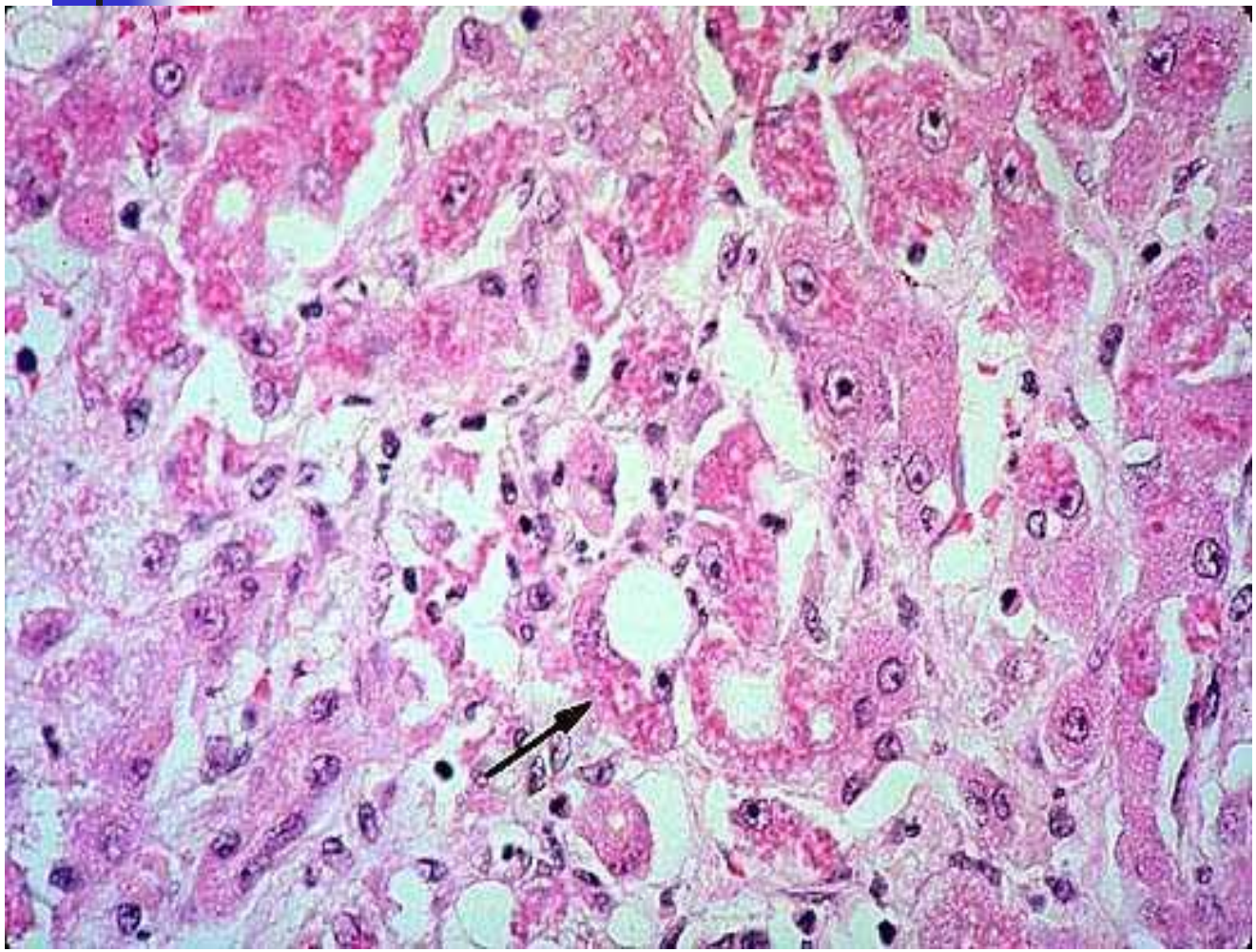




Alcoholic hepatitis - histopathology

- Pathological changes in liver histology include:
- Mallory's Hyaline - a condition where pre-keratin filaments accumulate in hepatocytes.
- Ballooning degeneration - hepatocytes in the setting of alcoholic change often swell up with excess fat, water and protein. Accompanied with ballooning, there is necrotic damage. The swelling is capable of blocking nearby biliary ducts, leading to diffuse cholestasis.
- Inflammation - Neutrophilic invasion is triggered by the necrotic changes and presence of cellular debris within the lobules.

Alcoholic hepatitis - histopathology



Mallory bodies (arrow) appear as violaceous, ropy, hyaline inclusions located in the perinuclear region of the cytoplasm of the hepatocytes. They are composed of degenerated intermediate (cytokeratin) filaments of the cytoskeleton of the liver cells.

Bilirubin

- Bilirubin is the yellow breakdown product of normal heme catabolism.
- Bilirubin is excreted in bile, and its levels are elevated in certain diseases.
- It is responsible for the yellow colour of bruises and the yellow discolouration in jaundice.

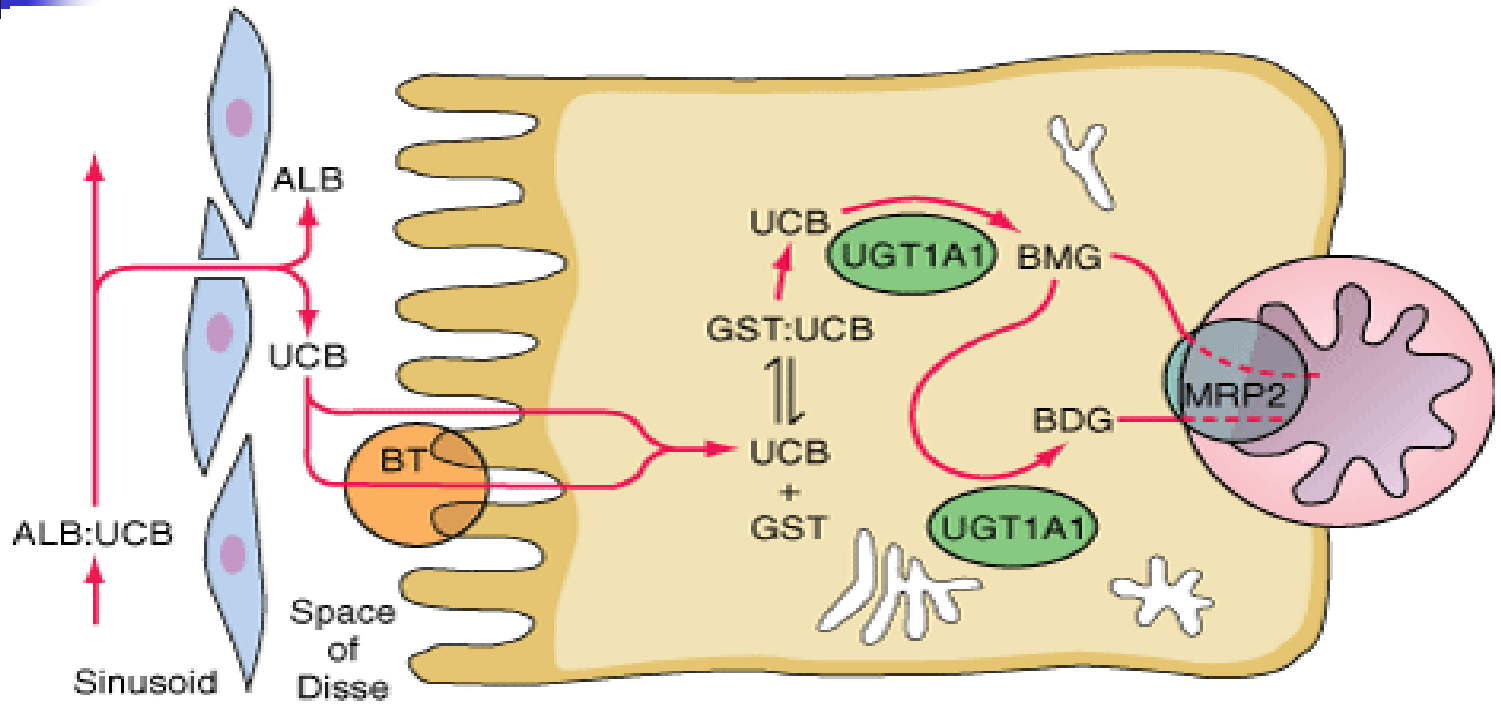
Bilirubin metabolism (1: ”prehepatic”) – Unconjugated Bilirubin

- After 120 days the red blood cells become fragile and prone to rupture.
- As the cell traverses through the reticuloendothelial system, their cell membranes rupture and hemoglobin is released, phagocytosed and split into **heme** and globin. Heme is oxidized to **biliverdin** by the microsomal enzyme **heme oxygenase**.
- Next step is reduction of biliverdin to yellow color tetrapyrol pigment **bilirubin** by cytosolic enzyme **biliverdin reductase**. This bilirubin is known as "unconjugated", "free" or "indirect" bilirubin. Approximately 4 mg per kg of bilirubin is produced each day.

Bilirubin metabolism (2. ”hepatic”) – Conjugated Bilirubin

- The unconjugated bilirubin travels to the liver through the bloodstream.
- Because this bilirubin is not soluble, however, it is transported through the blood bound to serum albumin.
- Once it arrives at the liver, it is conjugated with glucuronic acid (to form bilirubin diglucuronide, or just ”bound”, ”direct” "conjugated bilirubin") to become more water soluble. The reaction is catalyzed by the enzyme **UDP-glucuronide transferase**.

Hepatocellular bilirubin transport



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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ALB, albumin; UCB, unconjugated bilirubin, UGT1A1, bilirubin-UDP-glucuronosyltransferase; BMG, bilirubin monoglucuronide; GST, glutathione-S-transferase; MRP2, multidrug resistance–associated protein 2; BDG, bilirubin diglucuronide; BT, proposed bilirubin transporter.

Bilirubin metabolism (3. ”Post Hepatic”) – Conjugated Bilirubin

- The conjugated bilirubin is excreted from the liver into the biliary and cystic ducts as part of bile.
- Intestinal bacteria convert the bilirubin into urobilinogen.
- From here the urobilinogen can take two pathways.
- It can either be further converted into stercobilinogen, which is then oxidized to stercobilin and passed out in the faeces,
- or it can be reabsorbed by the intestinal cells, transported in the blood to the kidneys, and passed out in the urine as the oxidised product urobilin.
- Stercobilin and urobilin are the products responsible for the coloration of faeces and urine, respectively.

Jaundice – ”prehepatic” (unconjugated hyperbilirubinemia). Causes:

- Hemolysis and hemolytic anemias including sickle cell anemia, spherocytosis and glucose 6-phosphate dehydrogenase deficiency.
- Ineffective erythropoiesis (pernicious anemia, thalassemia)
- Laboratory findings include:
- Urine: no bilirubin present, urobilirubin > 2 units (except in infants where gut flora has not developed).
- Serum: increased unconjugated bilirubin.

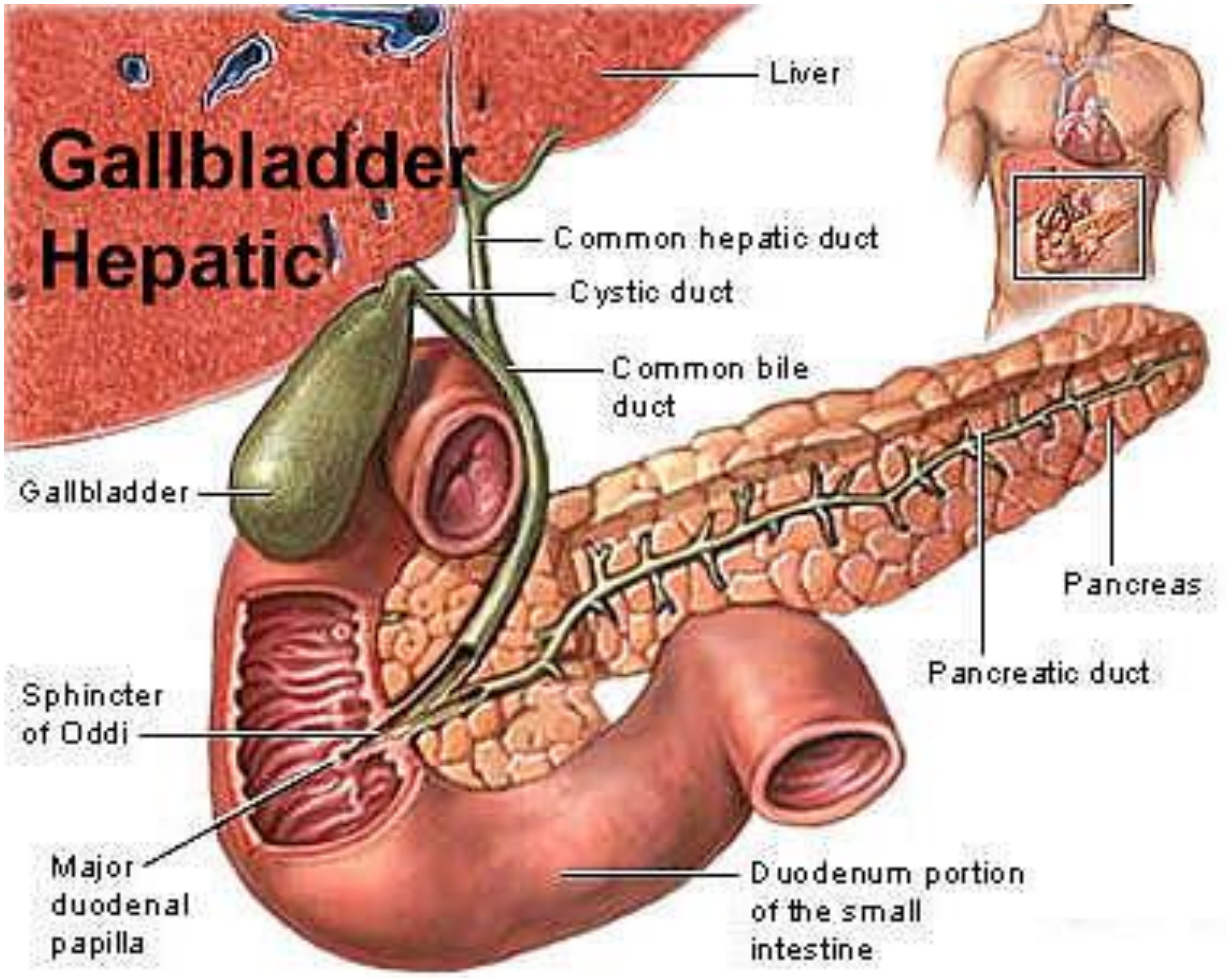
Jaundice – ”hepatic” (combined conjugated and unconjugated hyperbilirubinemia). Causes:

- Parenchymal disease: acute hepatitis, hepatotoxicity and alcoholic liver disease, whereby cell necrosis reduces the liver's ability to metabolise and excrete bilirubin leading to a buildup in the blood. Less common causes include primary biliary cirrhosis,
- Gilbert-Meulengracht's syndrome (a dominant genetic disorder of bilirubin metabolism which can result in mild jaundice, which is found in 5%-10% of the population) (decreased bilirubin UGT activity)
- Crigler-Najjar syndrome (I and II) (Absent or markedly decreased bilirubin UGT activity)
- Metastatic carcinoma.
- Neonatal jaundice, is common, occurring in almost every newborn (the conjugation and excretion of bilirubin not fully matured until approximately two weeks of age).
- Laboratory Findings include:
- Urine: Conjugated bilirubin present, Urobilirubin > 2 units but variable (Except in children)

Jaundice – ”Post-hepatic” (conjugated hyperbilirubinemia). Causes:

- Interruption (obstruction) to the drainage of bile in the biliary system.
- The most common causes are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" live in the common bile duct, causing obstructive jaundice.
- Strictures of the common bile duct, biliary atresia, ductal carcinoma, pancreatitis and pancreatic pseudocysts.
- The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments.
- (Dubin-Johnson syndrome (recessive defect in secretion of conjugated bilirubin from liver cells))
- (Rotor’s syndrome (recessive defect in secretion of conjugated bilirubin from liver cells))
- Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus".

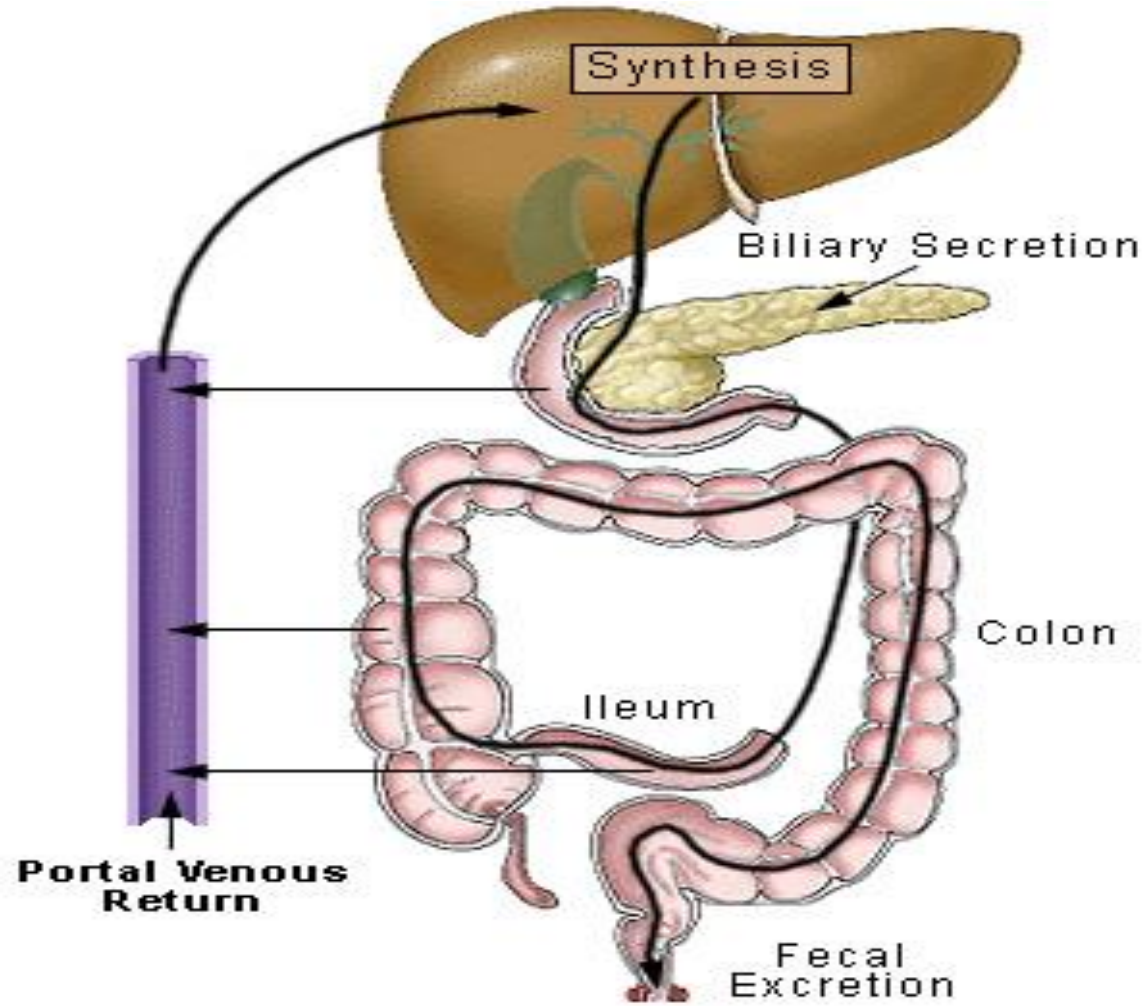
Biliary tract



Bile

- The bile salts sodium glycocholate and sodium taurocholate are produced by the liver from cholesterol.
- They are secreted in bile by hepatocytes along the bile canaliculi, which then join the bile duct, and goes into the gall bladder.
- Ordinarily the concentration of bile salts in bile is 0.8%, however the gall bladder removes water and electrolytes from the bile, concentrating it between meals.
- It concentrates it up to 5 times (increasing concentration to 4%), before contracting the walls and releasing it into the duodenum once chyme has entered the small intestine.
- The human liver can produce close to one litre of bile per day (depending on body size). 95% of the salts secreted in bile are reabsorbed in the terminal ileum and re-used sometimes two to three times with each meal (enterohepatic circulation).

Enterohepatic circulation



Bile - Physiological function

- Bile salts are composed of a hydrophilic side, and a hydrophobic side. Thus they can to form micelles, with the hydrophobic sides towards the centre and hydrophilic towards the outside. In the centre of these micelles are triglycerides.
- Pancreatic lipase is able to get to the molecules of triglyceride through gaps between the bile salts, providing a largely increased surface area for digestion. The micelles in the duodenum have a diameter of around 14-33µm.
- Taurocholic acid and deoxycholic acid combine with phospholipids to break down fat globules in the process of emulsification by associating its hydrophobic side with lipids and the hydrophilic side with water. Emulsified droplets then are organized into many micelles which increases absorption. Since bile increases the absorption of fats, it is an important part of the absorption of the fat-soluble vitamins D, E, K and A.

Consequences of cholestasis

- In the absence of bile, fats become indigestible and are instead excreted in feces, a condition called steatorrhea.
- Feces lack their characteristic brown colour and instead are white or grey, and greasy.
- Steatorrhea can lead to deficiencies in essential fatty acids and fat-soluble vitamins.

Gallstone - Cholelithiasis

- Gallstones (choleliths) are crystalline bodies formed within the body by accretion or concretion of normal or abnormal bile components.
- Gallstones can occur anywhere within the biliary tree, including the gallbladder and the common bile duct.
- Obstruction of the common bile duct is choledocholithiasis.
- Obstruction of the biliary tree can cause jaundice
- Obstruction of the outlet of the pancreatic exocrine system can cause pancreatitis
- Cholelithiasis is the presence of stones in the gallbladder-chole- means "bile", lithia means "stone", and -sis means "process".

Gallstones

- Cholesterol stones (20%) are usually green, but are sometimes white or yellow in color. They are made primarily of cholesterol.
- Pigment stones (20%) are small, dark stones made of bilirubin and calcium salts that are found in bile. Risk factors for pigment stones include hemolytic anemia, cirrhosis, biliary tract infections, and hereditary blood cell disorders, such as sickle cell anemia and spherocytosis.
- Mixed stones account for the majority of stones. Most of these are a mixture of cholesterol and calcium salts. Because of their calcium content, they can often be visualized radiographically.

Gallstones

Gallstones - Pathogenesis

- Gallstones may be caused by a combination of factors, including inherited body chemistry, body weight, gallbladder motility (movement), and perhaps diet.
- Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts.
- Incomplete and infrequent emptying of the gallbladder may cause the bile to become overconcentrated and contribute to gallstone formation.
- The presence of proteins in the liver and bile that promote cholesterol crystallization into gallstones.
- Increased levels of the hormone estrogen as a result of pregnancy, hormone therapy, or the use of combined (estrogen-containing) forms of hormonal contraception, may increase cholesterol levels in bile and also decrease gallbladder movement, resulting in gallstone formation.
- Low-fibre, high-cholesterol diets, and diets high in starchy foods have been suggested as contributing to gallstone formation.
- Rapid weight loss, constipation, eating fewer meals per day, eating less fish, and low intakes of the nutrients folate, magnesium, calcium, and vitamin C.
- Wine and whole grain bread may decrease the risk of gallstones.

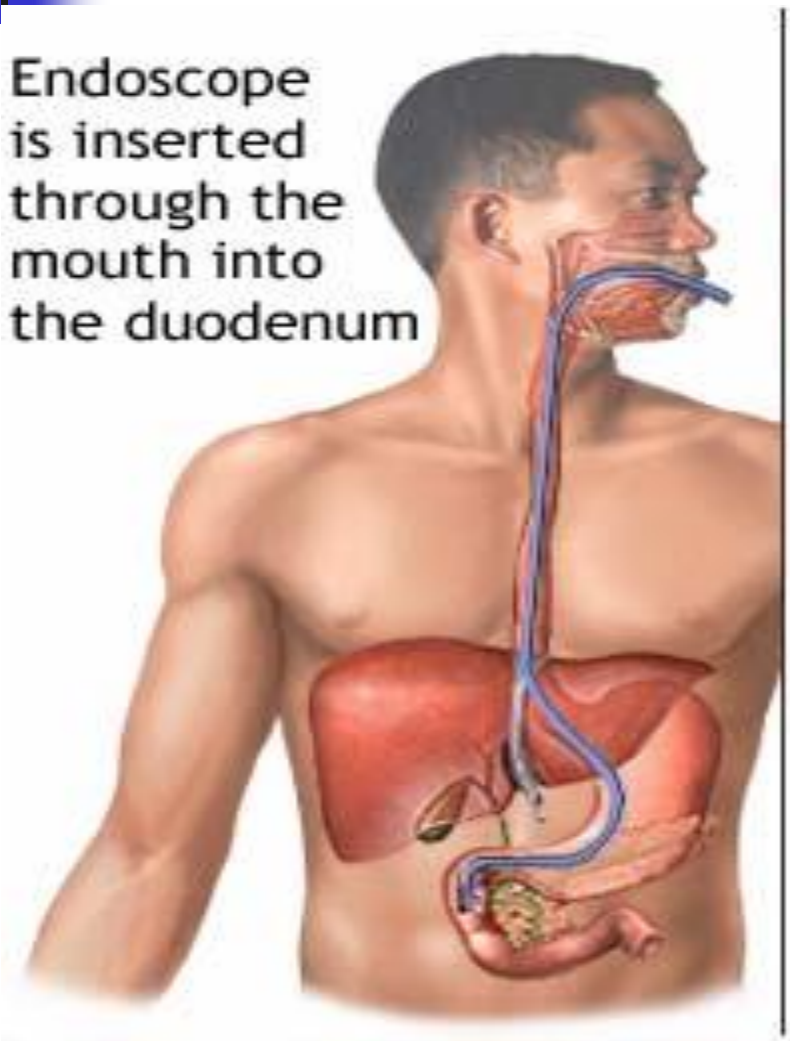
Gallstones - symptoms

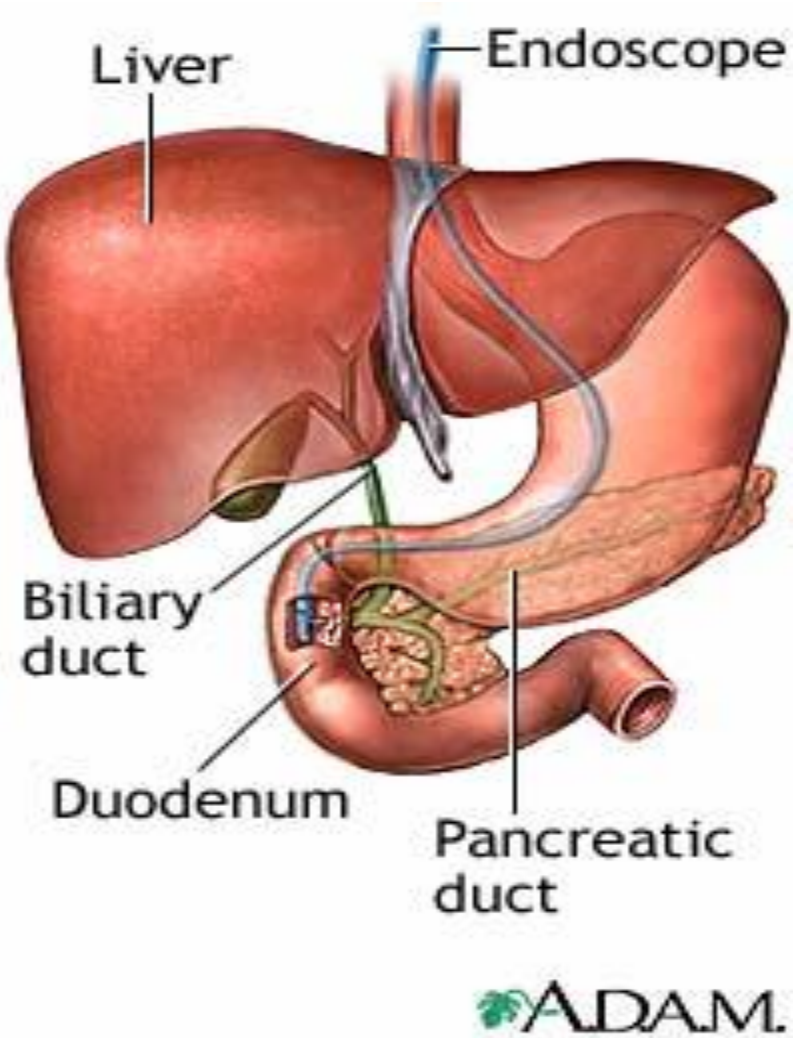
- Usually asymptomatic (”silent”) for many years.
- Symptoms start developing once the stones are >8 mm.
- A main symptom is a gallstone "attack", also known as biliary colic - intense pain in the right upper abdominal region that steadily increases for approximately thirty minutes to several hours. There may be also pain between the shoulder blades, or under the right shoulder. Nausea and vomiting may occur.
- Often, these attacks occur after a particularly fatty meal and almost always happen at night.
- Other symptoms include abdominal bloating, intolerance of fatty foods, belching, gas, and indigestion.
- If the above symptoms coincide with chills, lowgrade fever, yellowing of the skin or eyes, and/or clay-colored stool the patient should be admitted to hospital.

Gallstones - therapy

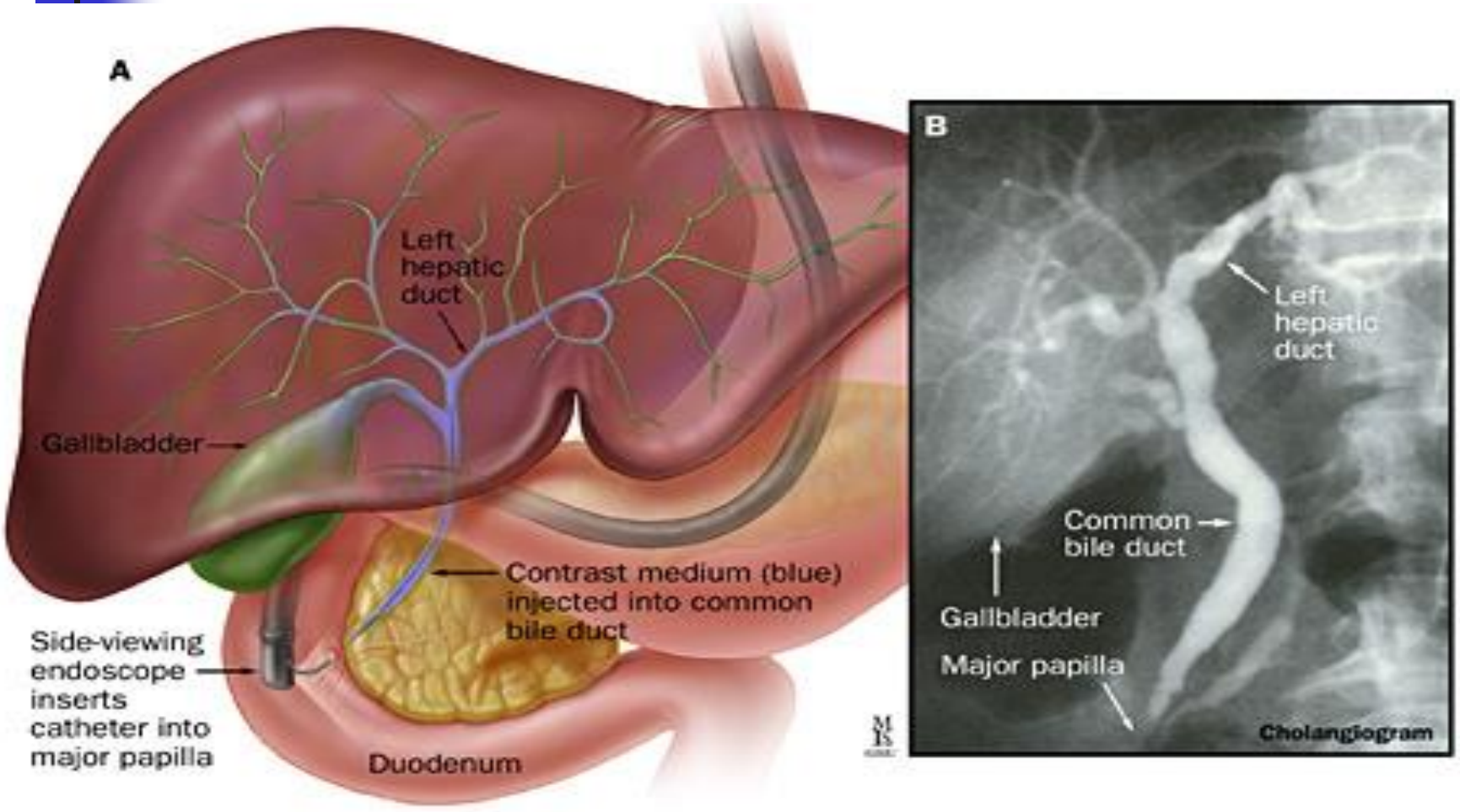
- Long-time therapy with ursodeoxycholic acid
- Endoscopic retrograde sphincterotomy (ERS) following endoscopic retrograde cholangiopancretaography (ERCP).
- Cholecystectomy – open or laparoscopic

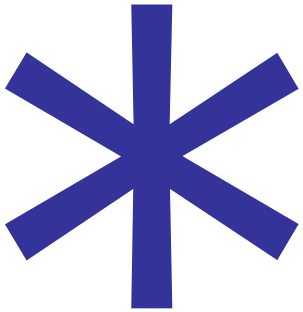
ERCP


Endoscope is inserted through the mouth into the duodenum


Liver
Endoscope
Biliary duct
Duodenum
Pancreatic duct
A.D.A.M.

ERCP


A
Left hepatic duct
Gallbladder
Contrast medium (blue) injected into common bile duct
Side-viewing endoscope inserts catheter into major papilla
Duodenum
B
Left hepatic duct
Common bile duct
Gallbladder
Major papilla
Cholangiogram



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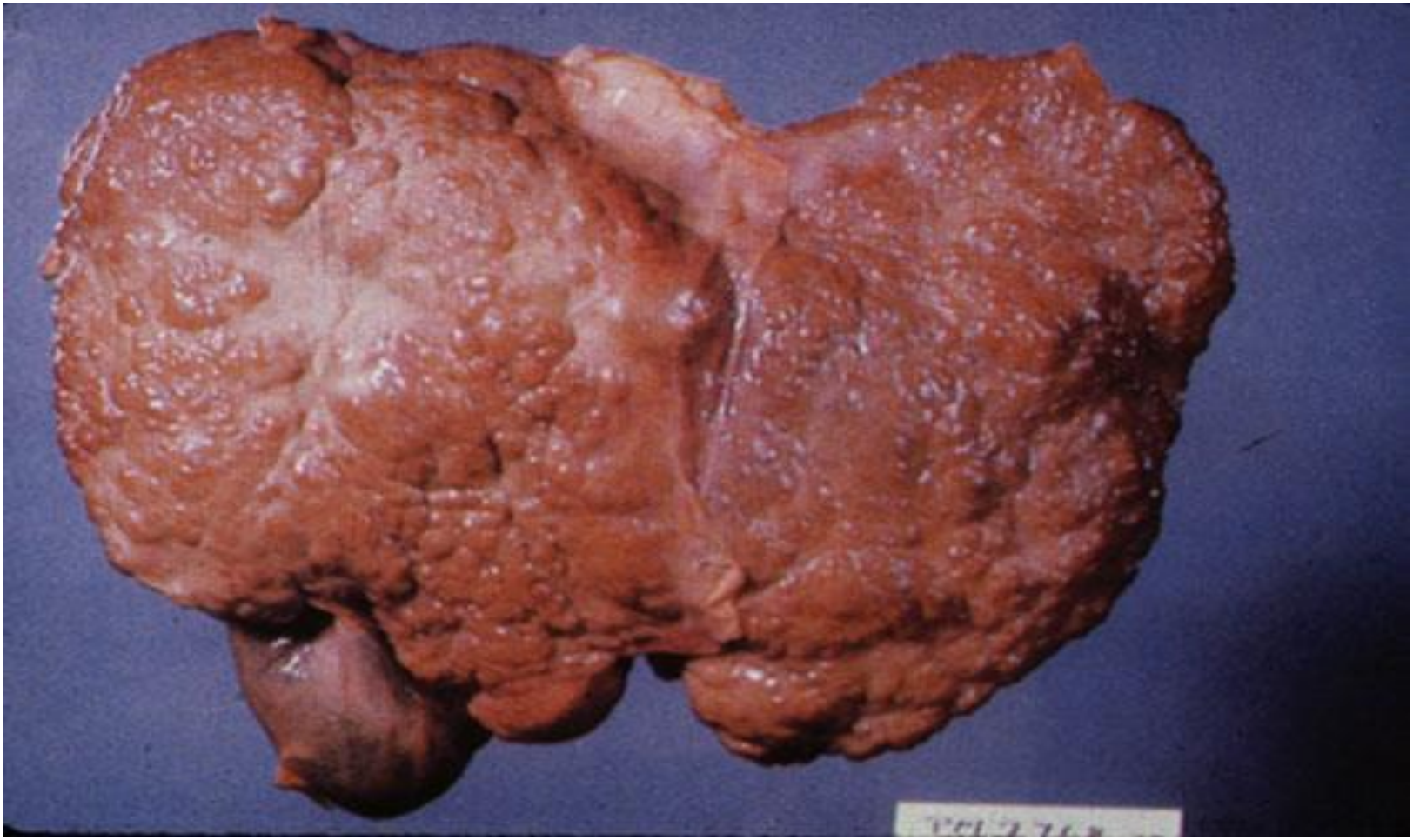
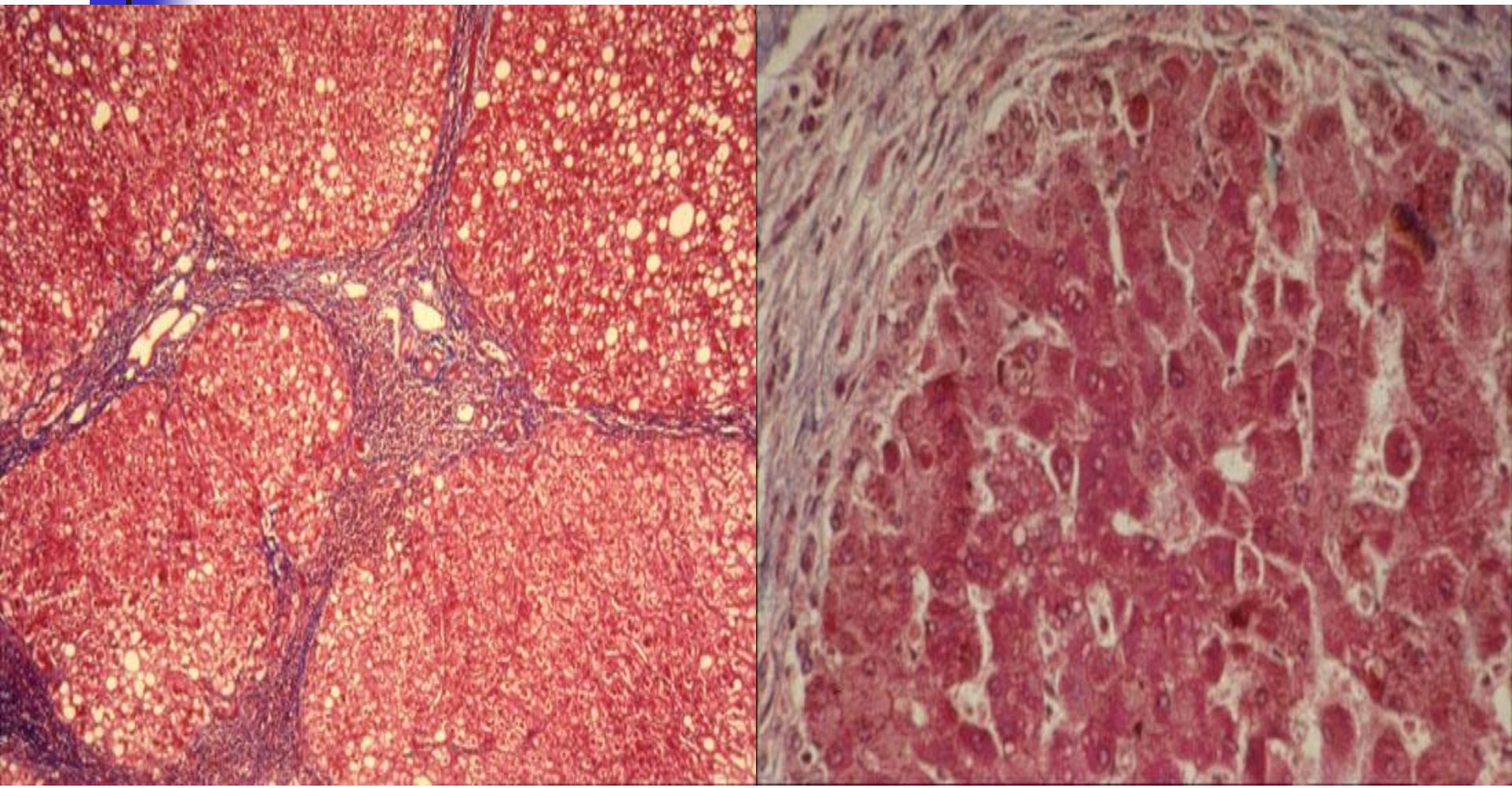
Cirrhosis

- Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrous scar tissue as well as regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated), leading to progressive loss of liver function.
- The word "cirrhosis" is a neologism that derives from Greek kirrhos, meaning "tawny" (the orange-yellow colour of the diseased liver). While the clinical entity was known before, it was René Laennec who gave it the name "cirrhosis" in his 1819 work in which he also describes the stethoscope.

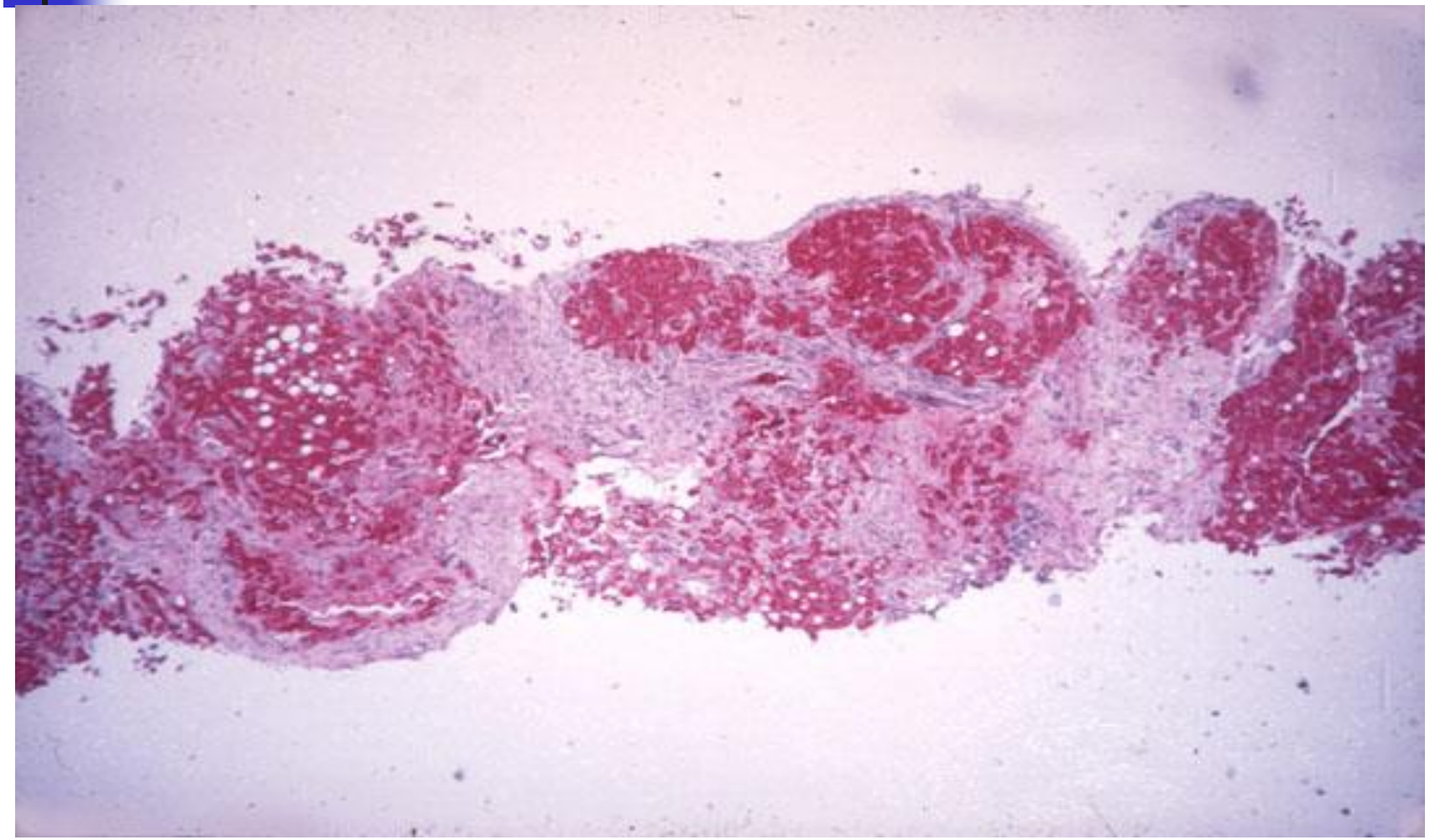
Cirrhosis



Cirrhosis – fibrosis, nodular regeneration



Advanced cirrhosis



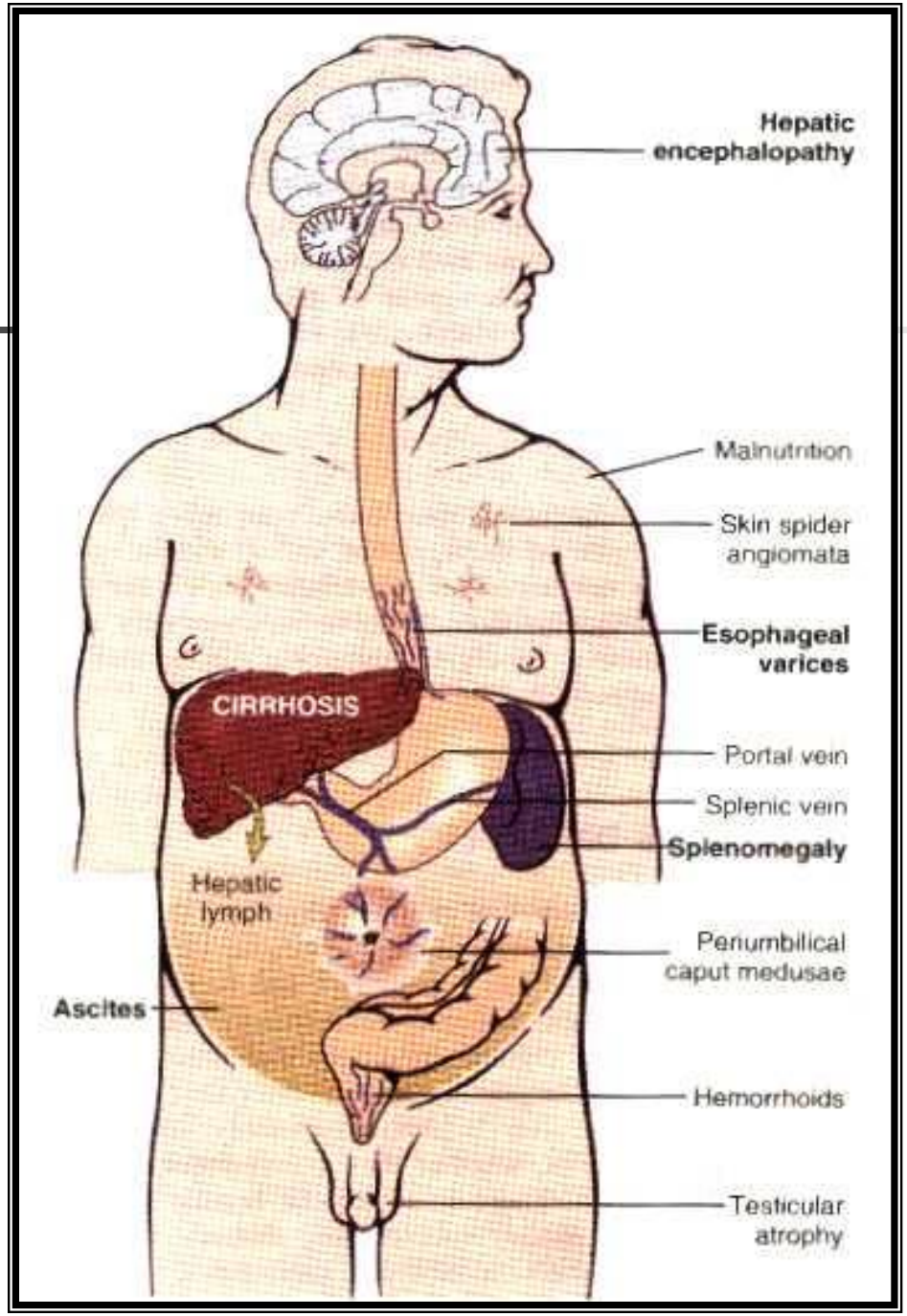
Cirrhosis - Pathophysiology

- Cirrhosis is often preceded by hepatitis and fatty liver (steatosis), independent of the cause. These changes are fully reversible.
- The pathological hallmark of cirrhosis is the development of scar tissue that replaces normal parenchyma, blocking the portal flow of blood through the organ and disturbing normal function.
- Recent research shows the pivotal role of stellate cell, a cell type that normally stores vitamin A, in the development of cirrhosis. Damage to the hepatic parenchyma leads to activation of the stellate cell, which becomes contractile (called myofibroblast) and obstructs blood flow in the circulation. In addition, it secretes TGF-ß1, which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it disturbs the balance between matrix metalloproteinases and the naturally occurring inhibitors (TIMP 1 and 2), leading to matrix breakdown and replacement by connective tissue-secreted matrix
- The fibrous tissue bands (septa) separate hepatocyte nodules, which eventually replace the entire liver architecture, leading to decreased blood flow throughout. The spleen becomes congested, which leads to hypersplenism and increased sequestration of platelets. Portal hypertension is responsible for most severe complications of cirrhosis.

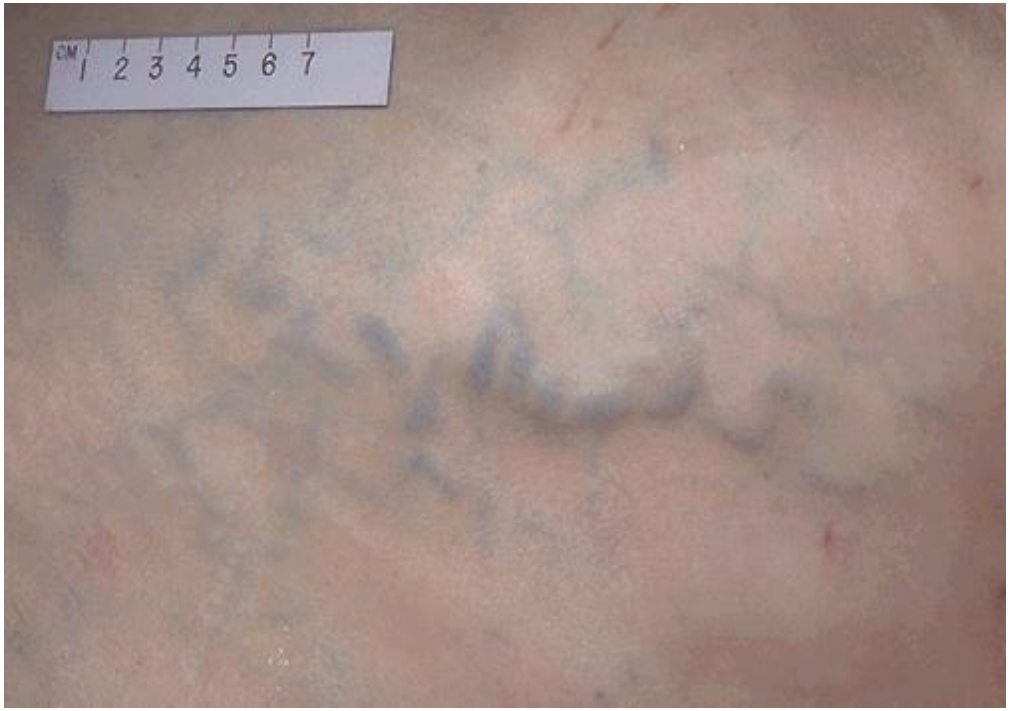
Cirrhosis - Causes

- **Alcoholic liver disease (ALD).**
- **Chronic hepatitis C.**
- **Chronic hepatitis B.**
- Non-alcoholic steatohepatitis (NASH). Associated with diabetes, protein malnutrition, obesity, coronary artery disease.
- **Primary biliary cirrhosis.**
- **Primary sclerosing cholangitis.**
- **Autoimmune hepatitis.**
- **Hereditary hemochromatosis**
- Wilson's disease.
- Alpha 1-antitrypsin deficiency (AAT).
- Cardiac cirrhosis. Due to chronic right sided heart failure which leads to liver congestion.
- Galactosemia
- Glycogen storage disease type IV
- Cystic fibrosis
- Drugs or toxins
- Certain parasitic infections (such as schistosomiasis

Cirrhosis Clinical Features

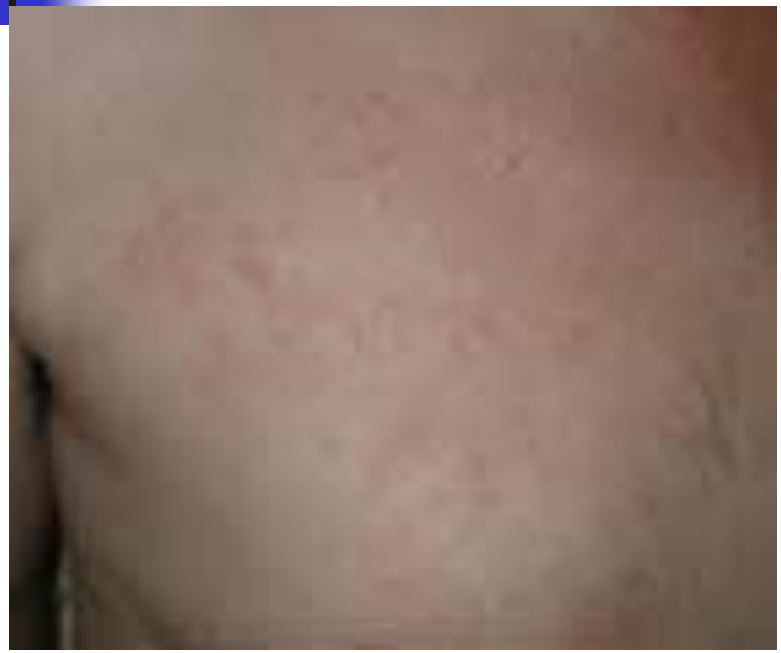


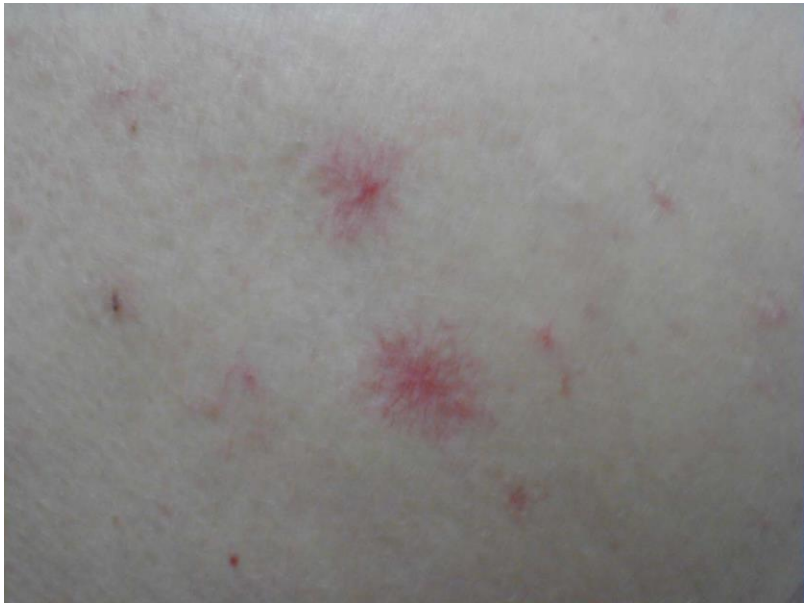
Dilated abdominal veins - Caput Medusae



In portal hypertension, the umbilical vein may open. Blood from the portal venous system may be shunted through the periumbilical veins into the umbilical vein and ultimately to the abdominal wall veins becoming dilated, manifesting as caput medusa.

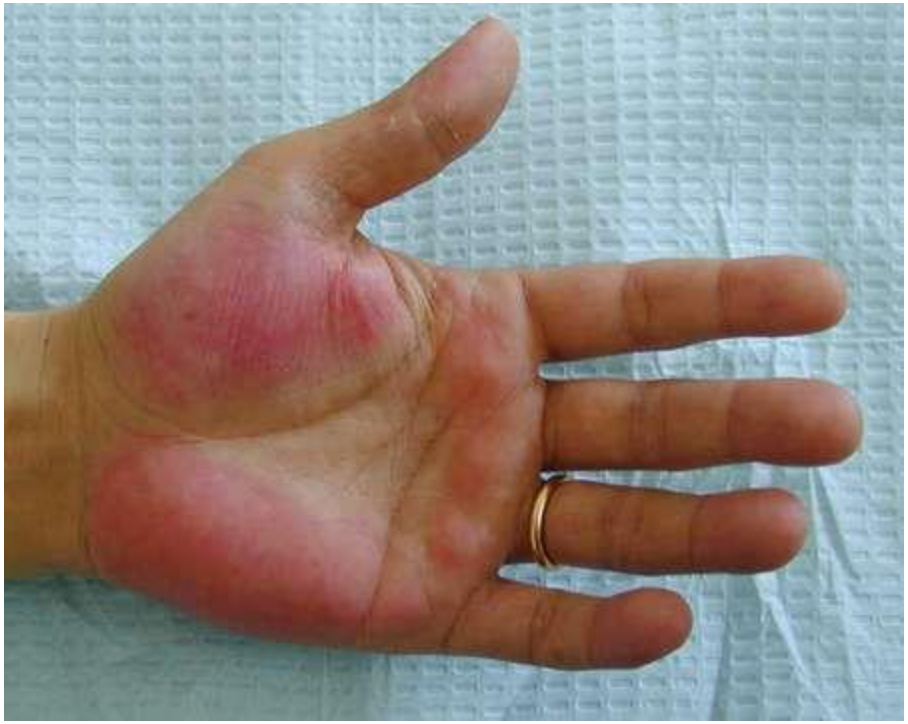
Spider angiomata or spider nevi





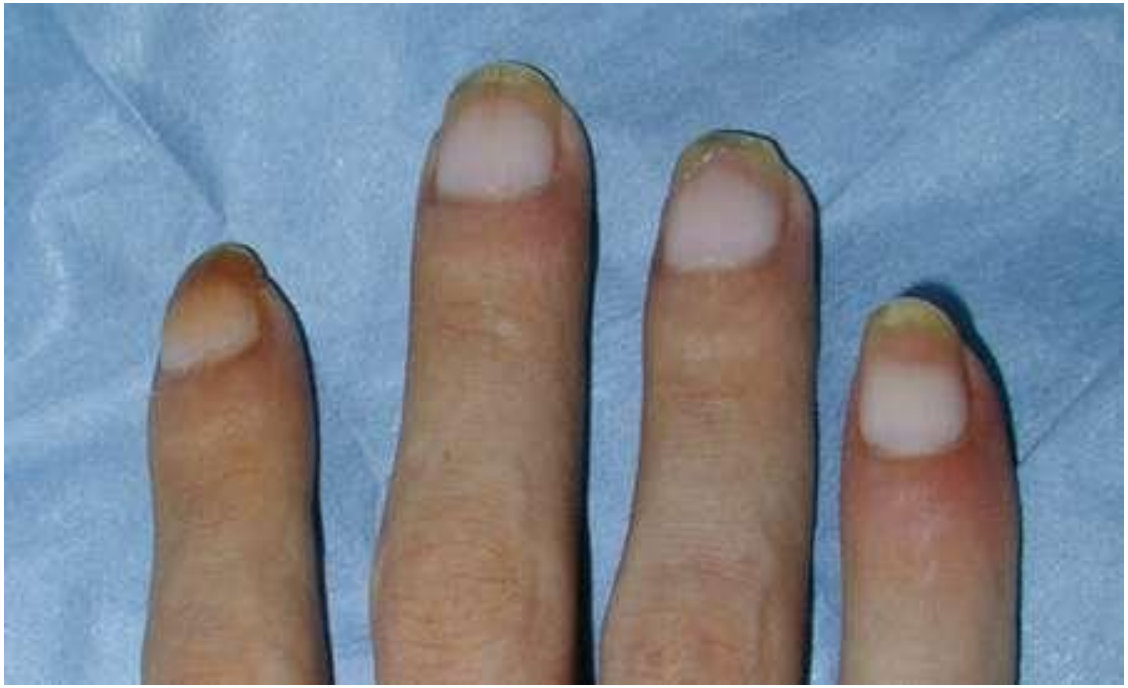
Vascular lesions consisting of a central arteriole surrounded by many smaller vessels due to an increase in estradiol. These occur in about 1/3 of cases.

Palmar Erythema



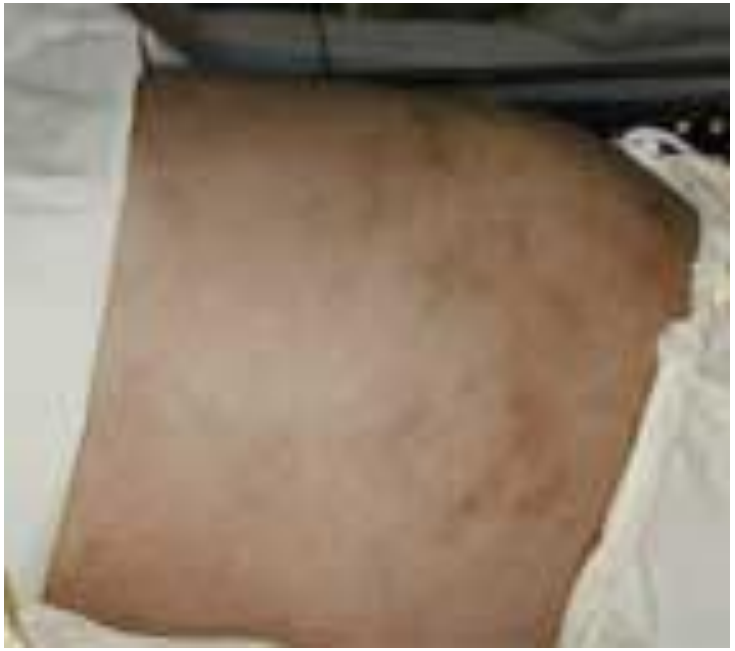
Palmar erythema. Exaggerations of normal speckled mottling of the palm, due to altered sex hormone metabolism.

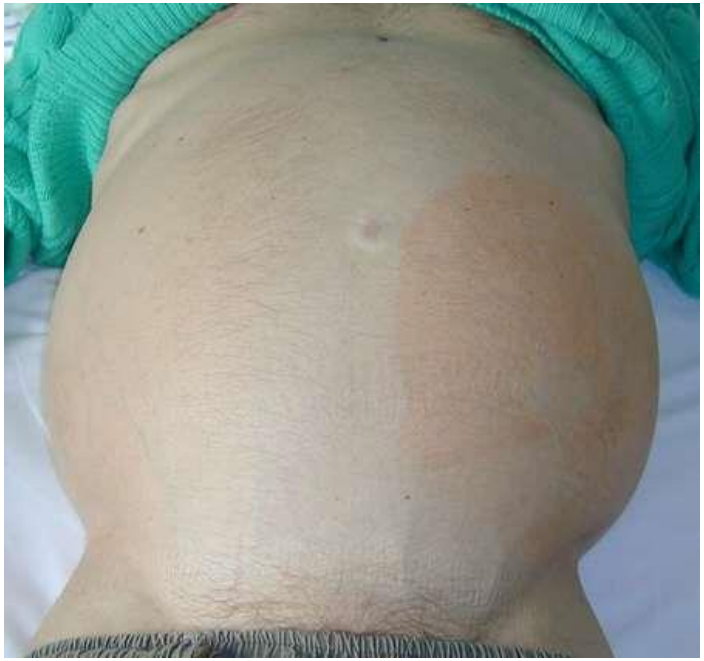
“White Nails”



Due to hypoalbuminemia

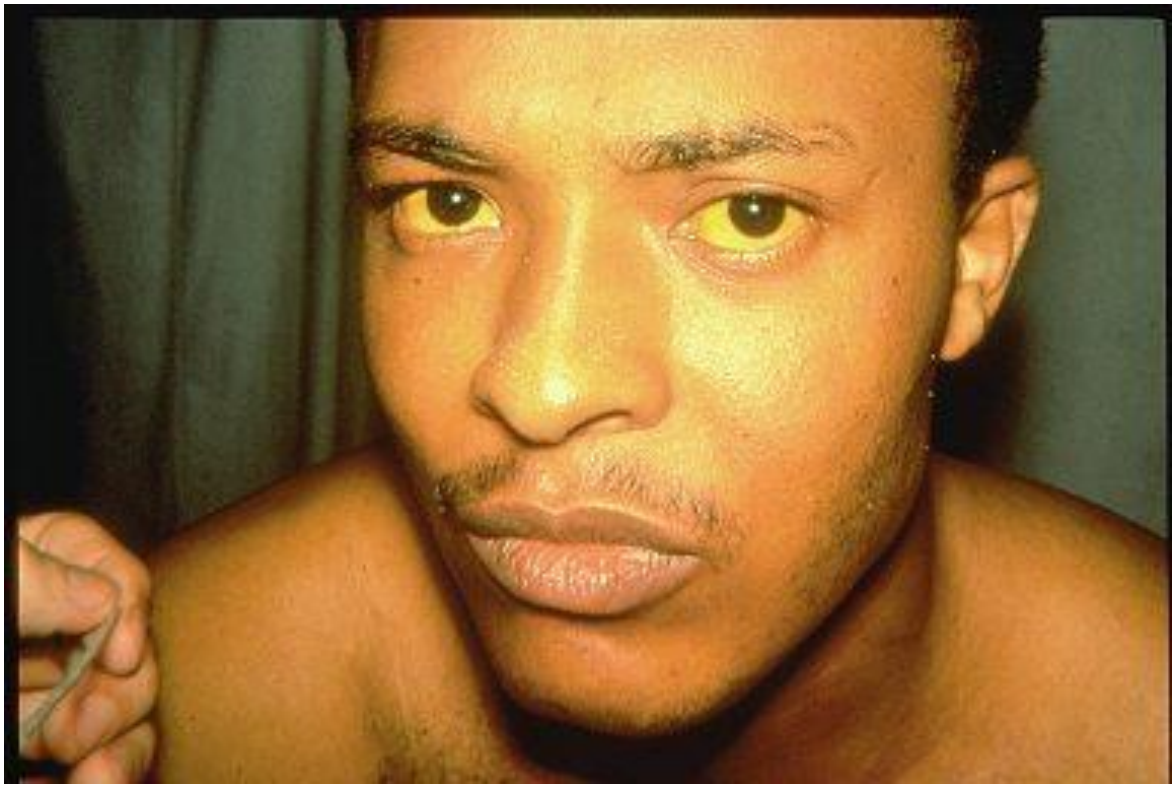
Ascites





Accumulation of fluid in the peritoneal cavity

Jaundice



Yellow discoloring of the skin, eye, and mucus membranes due to increased bilirubin. Urine may also appear dark.

Cirrhosis – Other signs and symptoms

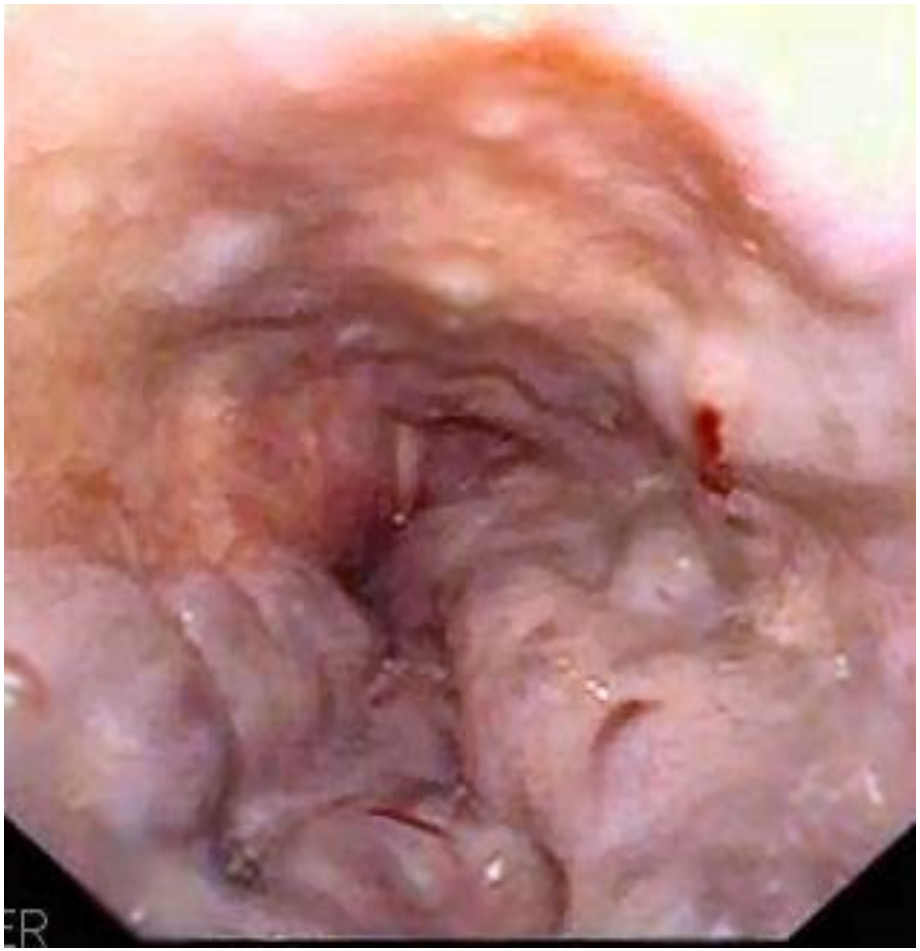
- Gynecomastia. This is due to increased estradiol and can occur in up to 66% of patients.
- Hypogonadism. Manifested as impotence, infertility, loss of sexual drive, and testicular atrophy due to primary gonadal injury or suppression of hypothalamic or pituitary function.
- Liver size. Can be enlarged, normal, or shrunken.
- Fetor hepaticus. Musty odor in breath due to increased dimethyl sulfide.
- Asterixis. Bilateral asynchronous flapping of outstretched, dorsiflexed hands seen in patients with hepatic encephalopathy.
- Weakness
- Fatigue
- Anorexia
- Weight loss
- Bruising and bleeding
- Itching (pruritus) due to bile products deposited in the skin.

Cirrhosis - Complications

- Portal hypertension
- **Esophageal varices**
- **Ascites** - fluid leaks through the vasculature into the abdominal cavity.
- **Hepatorenal syndrome** - insufficient blood supply to the kidneys, causing acute renal failure. This complication has a very high mortality (over 50%).
- **Hepatic encephalopathy** - the liver does not clear ammonia and related nitrogenous substances from the blood
- Hepatopulmonary syndrome - blood bypassing the normal lung circulation (shunting), leading to cyanosis and dyspnea (shortness of breath).
- Hepatocellular carcinoma is primary liver cancer, a frequent complication of cirrhosis. It has a high mortality rate.
- Immune system dysfunction, leading to infection.
- Spontaneous bacterial peritonitis

Esophageal varices

- Esophageal varices are extremely dilated sub-mucosal veins in the esophagus. They are most often a consequence of portal hypertension, such as may be seen with cirrhosis; patients with esophageal varices have a strong tendency to develop bleeding.
- Esophageal varices are diagnosed with endoscopy.



Bleeding esophageal varix

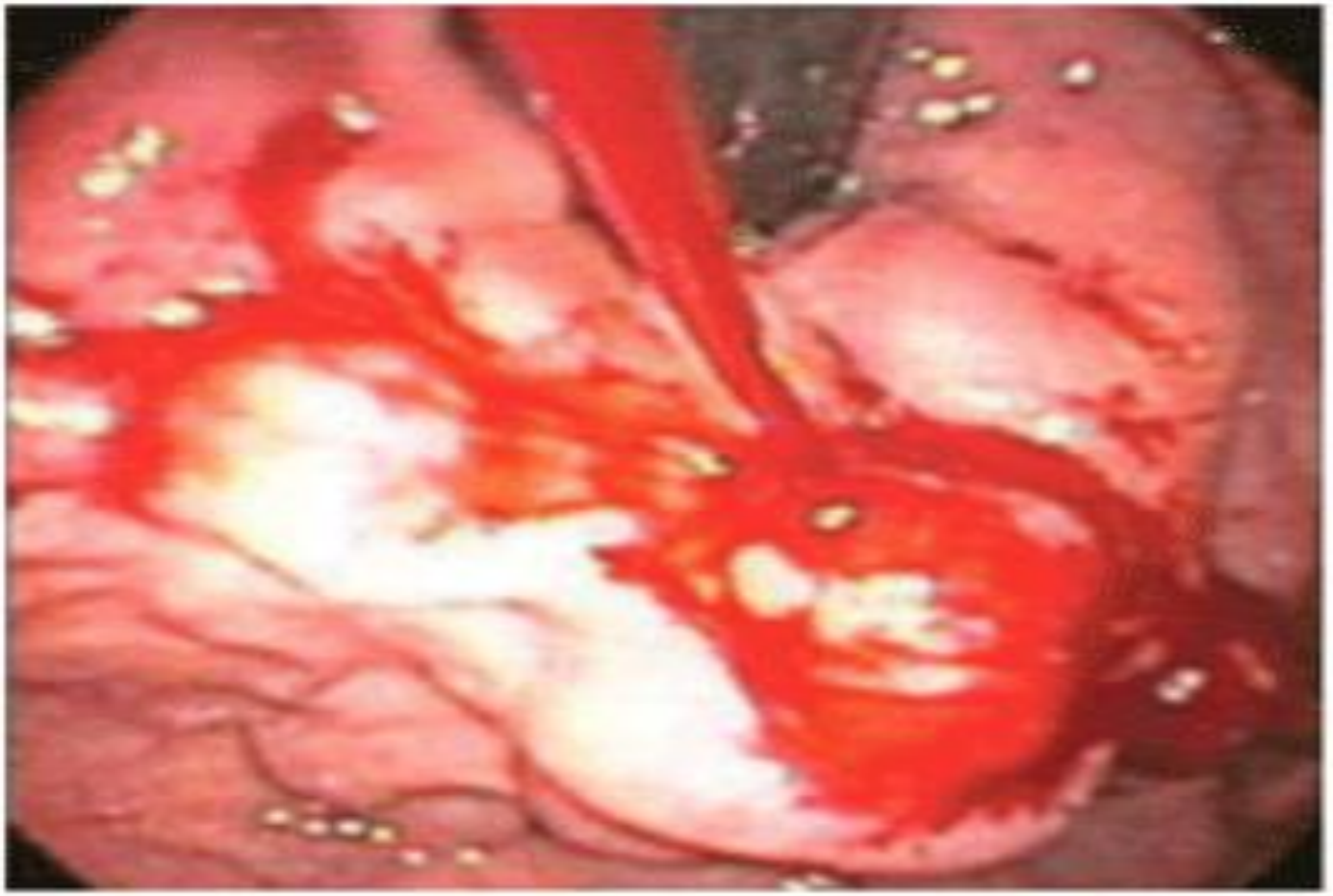


Figure 2—Bleeding varix. Endoscopic imaging showed an actively bleeding varix in the stomach.

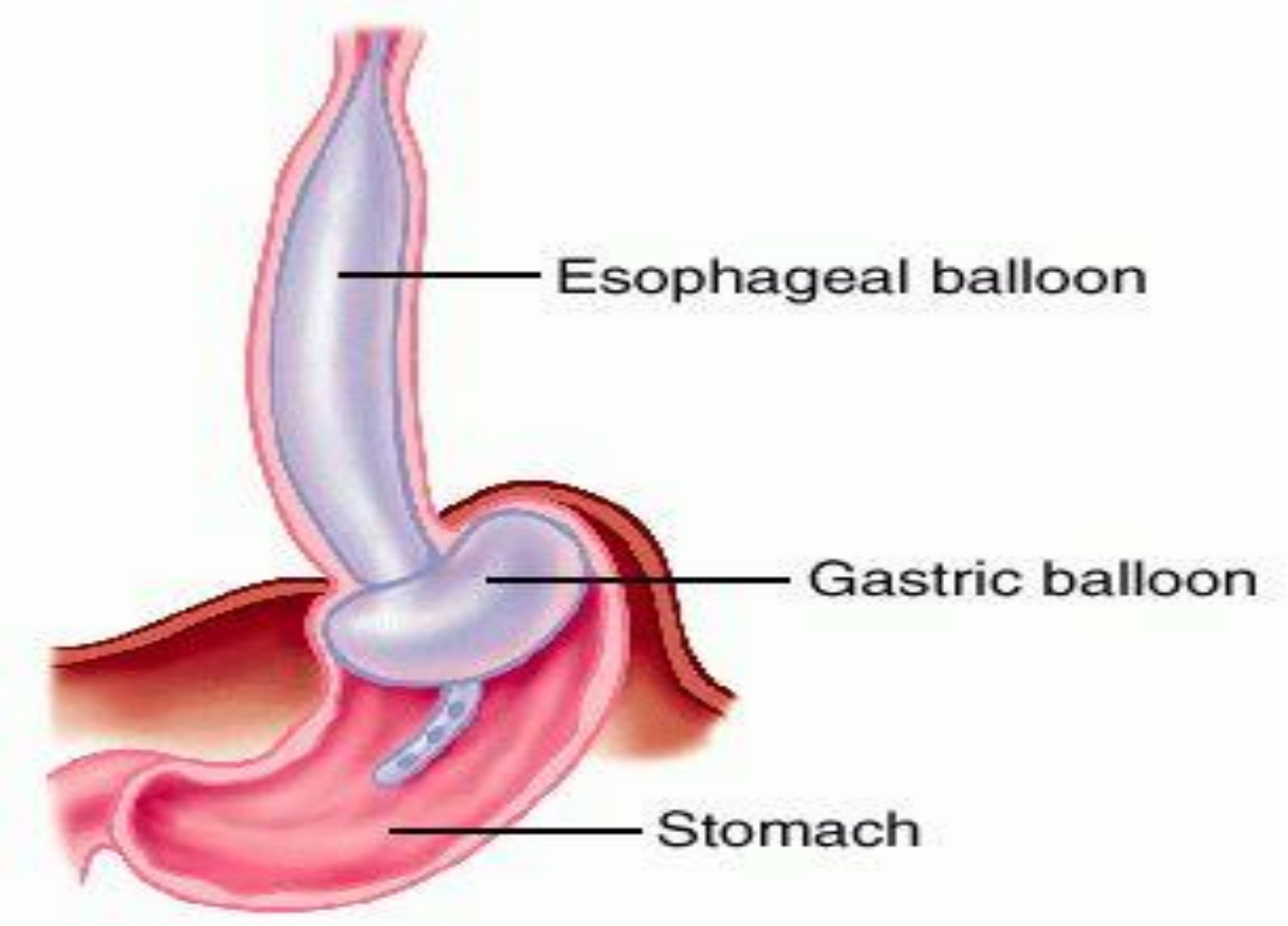
Esophageal varices - Pathogenesis

- The majority of blood from the esophagus is drained away via the esophageal veins, which drain to the azygos vein, which into the superior vena cava.
- The remaining blood from the esophagus is drained away via the superficial veins lining the esophagus interior, which drain into the coronary vein (left gastric vein) which in turn, drains directly into the portal vein.
- In portal hypertension these superficial veins lining the esophagus interior (normally only approximately 1 mm in diameter) become distended up to 1-2 cm in diameter.
- Normal portal pressure is approximately 9 mmHg compared to an inferior vena cava pressure of 2-6 mmHg. This creates a normal pressure gradient of 3-7 mmHg.
- A gradient greater than 10 mmHg is considered portal hypertension.
- At gradients greater than 10 mmHg, blood flow though the hepatic portal system is redirected from the liver into areas with lower venous pressures. This means that collateral circulation develops in the lower esophagus, abdominal wall, stomach and rectum.
- Varices develop in esophagus. Varices can also form in the stomach (gastric varices), duodenum (duodenal varices), and rectum (rectal varices).

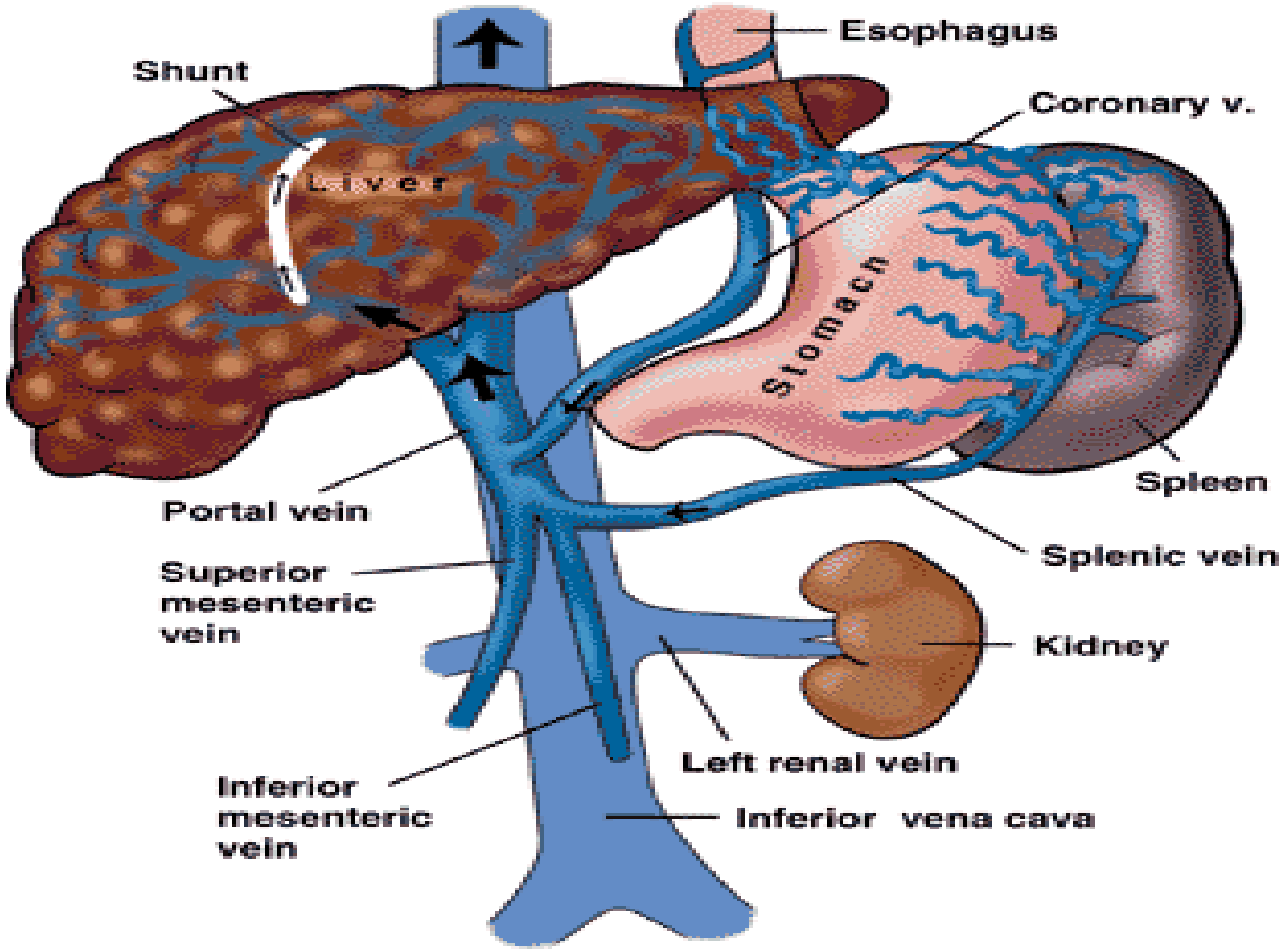
Bleeding esophageal varices – Therapy

- Variceal ligation, or banding
- Sclerotherapy
- Balloon tamponade
- Transjugular intrahepatic portosystemic shunt (TIPS)
- Distal splenorenal shunt procedure
- Liver transplantation

Balloon tamponade



Transjugular intrahepatic portosystemic shunt (TIPS)



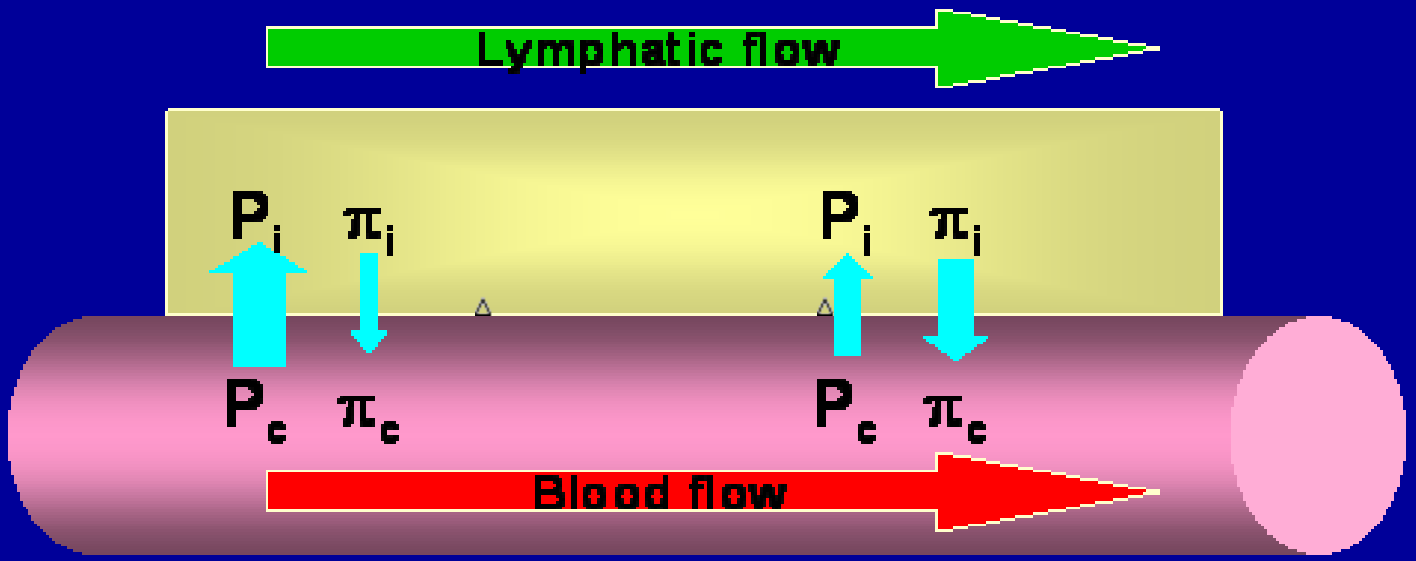
Ascites in cirrhosis

- Accumulation of fluid in the peritoneal cavity
- Amounts of up to 25 liters are fully possible.
- Transudate, a result of increased pressure in the portal vein due to cirrhosis. A transudate has low protein (<30g/L).
- Portal hypertension plays an important role in the production of ascites by raising capillary hydrostatic pressure within the splanchnic bed.

Formation of ascites – mechanical factors

- Increase in hydrostatic pressure (portal hypertension)
- Peripheral vasodilatation in particular in the splancnic area
- Increased capillary permeability (endotoxins, inflammation, immunological processes etc.)
- Reduced colloid osmotic pressure
- Insufficiency of lymphatic drainage

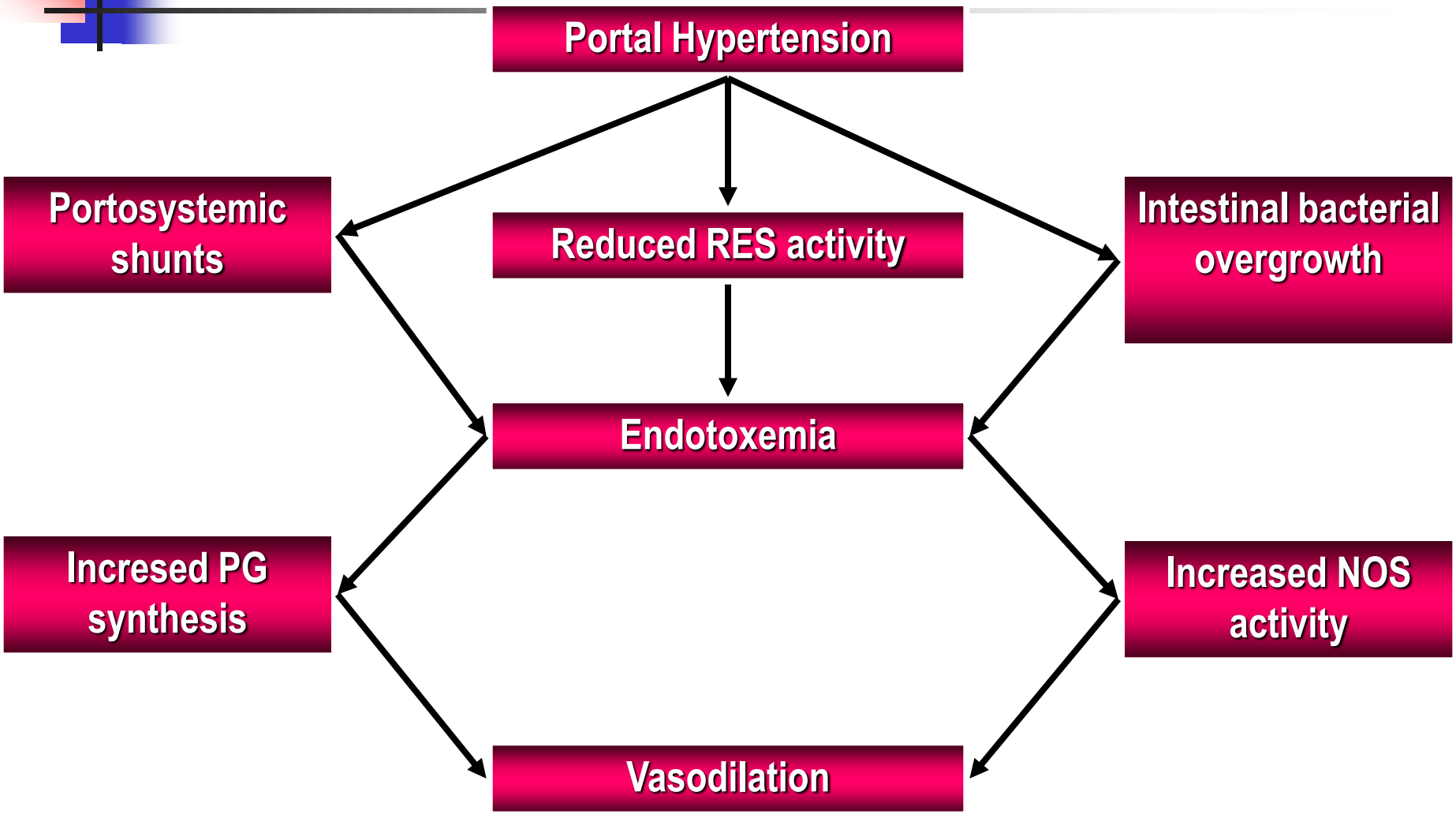
Pressures across the systemic capillary bed



$$\text{Net flux} = LpS\,[(P_c - P_i) - s(\pi_c - \pi_i)]$$

Lp, hydraulic permeability
S, surface area
P, hydraulic pressure
π, oncotic pressure
s, reflection coefficient of proteins

Mechanisms of vasodilation in cirrhosis

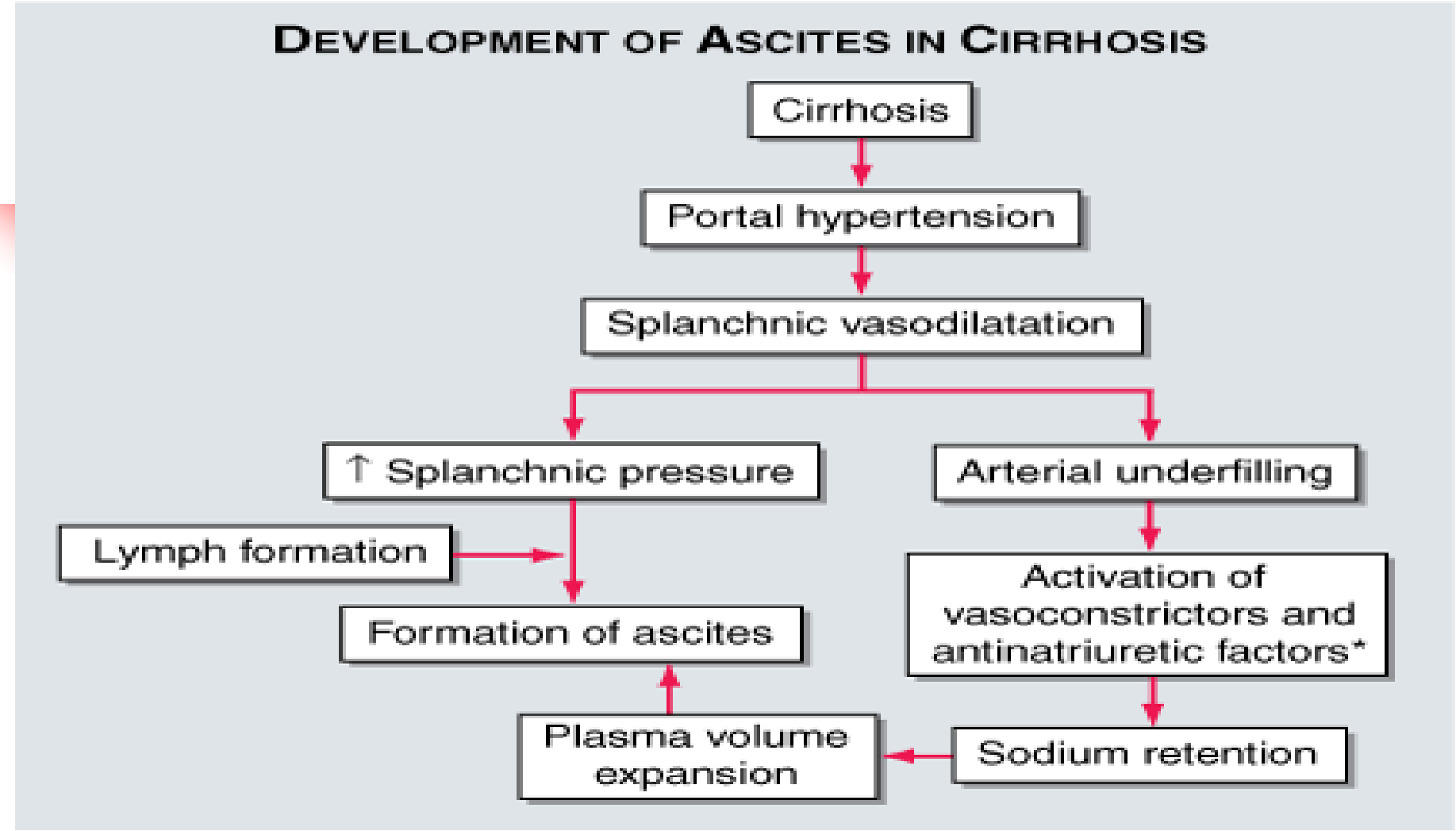


Formation of ascites – Biochemical factors

- Renin-angiotensin-aldosteron system (RAAS) stimulated → sodium retention
- Antidiuretic hormone (ADH) elevated → water retention
- Sympaticoadrenergic (noradrenalin, adrenalin) stimulation → renal vasoconstriction → sodium and water retention

Ascites formation – Theories

- **”The underfill theory”:** The ascites formation is set off by the mechanical factors (imbalance of the Starling forces)
- **”The owerflow theory”:** The sodium retention is the primary event
- **”The vasodilatition theory”:** The primary event is the peripheral arterial vasodilatation



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Lo
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.
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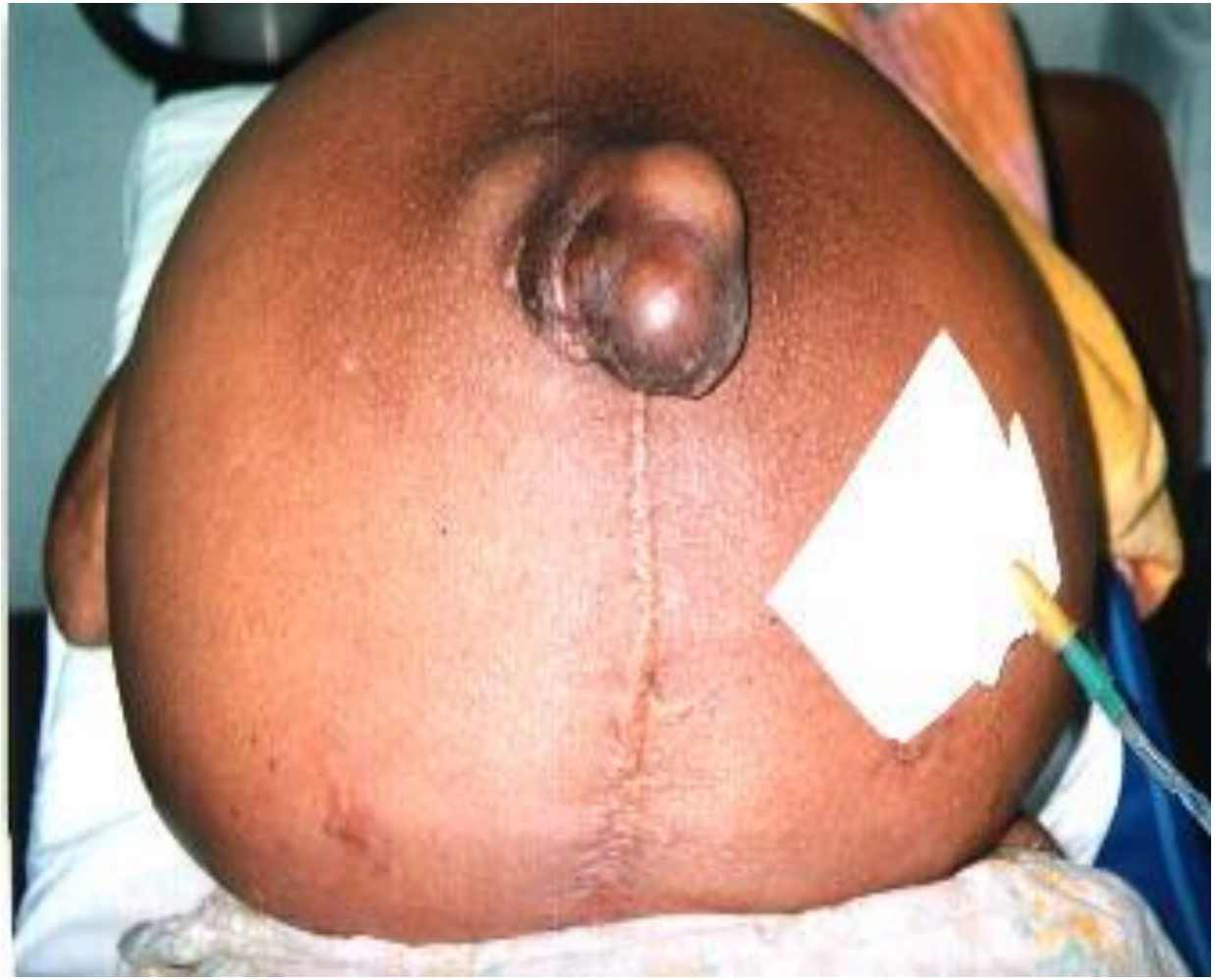
*Antinatriuretic factors include the renin-angiotensin-aldosterone system and the sympathetic nervous system.

Ascites - therapy

- Salt restriction
- Aldosterone-antagonist: Spironolactone (+/- loop diuretic)
- Water restriction
- Paracentesis
- Transjugular intrahepatic portosystemic shunt (TIPS)



Hepatorenal Syndrome (HRS)

- Acute renal failure that occurs in cirrhosis
- There is activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, and profound vasoconstriction in the kidneys. Many vasocontrictor chemicals have been hypothesized as being involved in this pathway, including vasopressin, prostacyclin and thromboxane A2, and endotoxin.
- It is usually indicative of an end-stage of perfusion to the kidney, due to deteriorating liver function.
- Patients with hepatorenal syndrome are very ill, and, if untreated, the condition is usually fatal.
- Interestingly, kidneys from patients with the hepatorenal syndrome have been used successfully for renal transplant.

Hepatorenal Syndrome (HRS)

- **Type I HRS** is characterized by rapidly progressive renal failure with a doubling of serum creatinine to a level greater than 221 µmol/L or a halving of the creatinine clearance to less than 20 mL/min in less than 2 weeks. Type I HRS carries a very poor prognosis
- **Type II HRS** is characterized by a slowly progressive:
- increase in serum creatinine level to greater than 133 µmol/L (1.5 mg/dL) or a creatinine clearance of less than 40 mL/min
- urine sodium < 10 meq/dl
- It is typically associated with ascites that is unresponsive to diuretic medications, and also carries a poor, if somewhat longer (median survival ~6 months) outlook

Hepatic encephalopathy

- A potentially-reversible neuropsychiatric abnormality in the setting of liver failure, whether chronic (as in cirrhosis), or acutely.
- With severe liver impairment, toxic substances normally removed by the liver accumulate in the blood and impair the function of brain cells.
- Signs can include impaired cognition, a flapping tremor (asterixis), and a decreased level of consciousness including coma (hepatic coma or coma hepaticum), cerebral edema, and, ultimately, death.

Hepatic encephalopathy - Pathogenesis

- Cirrhosis leads to portal hypertension. Portal-systemic anastamoses ("shunts") develop, and portal blood (from the intestinal veins) will bypass the liver and return to the heart via another route without undergoing first-pass detoxification by the liver.
- The decreased liver function means that blood that does travel through the liver may not be detoxified.
- The toxic substances include ammonia (NH_3) and mercaptans. Ammonia is normally converted to urea by the liver and, as with mercaptans, is produced by the bacterial breakdown of protein in the intestines.
- Ammonia can cross the blood-brain barrier, where it causes the support cells of the brain (astrocytes) to swell. The swelling of the brain tissue increases intracranial pressure, and can lead to coma or death via herniation of the brainstem.

Grading of encephalopathy (West Haven Criteria)

- Grade 1 - Trivial lack of awareness; Euphoria or anxiety; Shortened attention span; Impaired performance of addition. 67% of cirrhotic patients may have 'minimal hepatic encephalopathy'.
- Grade 2 - Lethargy or apathy; Minimal disorientation for time or place; Subtle personality change; Inappropriate behavior; Impaired performance of subtraction
- Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; Confusion; Gross disorientation
- Grade 4 - Coma (unresponsive to verbal or noxious stimuli)

Precipitants of hepatic encephalopathy

- Virtually any metabolic disturbance may precipitate hepatic encephalopathy. Common culprits are hyponatremia, hypokalemia, alkalosis, dehydration, hypoglycemia and renal failure of even mild degree.
- Likewise, there are several medications the use of which may bring on hepatic encephalopathy. These include benzodiazepines (e.g., diazepam, lorazepam), narcotics, and diuretics. Alcohol ingestion,
- Infection is an important precipitant of hepatic encephalopathy.
- Sometimes, hepatic encephalopathy arises as a result of patient non-compliance with dietary protein restriction.
- Bleeding into the stomach or small intestine (both of which occur with increased frequency in people with liver disease and/or portal hypertension) may also lead to hepatic encephalopathy. The presence of blood in the stomach or small intestine represents a protein load which, as a result of bacterial metabolism in the lumen of the gut, is converted to potentially toxic products such as ammonia.
- The "TIPS" procedure (transjugular intrahepatic portosystemic shunt) often precipitates hepatic encephalopathy (~30 percent)

Hepatic encephalopathy – therapy (summary)

- Reduce protein intake
- Correction of hypokalemia
- Lactulose - cause osmotic diarrhoea and acidifies the environment in the lumen of the bowel. This promotes the conversion of lumenal ammonia (NH3) to ammonium (NH4+), which is less readily absorbed into the bloodstream from the bowel lumen.
- Antibiotics may be given to kill bacteria present in the bowel, thereby decreasing bacterial conversion of protein to ammonia (and other toxic substances) there.
- Treat any precipitating factor

Hepatopulmonary syndrome

- Hypoxemia caused by vasodilation in patients with portal hypertension
- Dyspnea and hypoxemia are worse in the upright position (platypnea).
- It is defined as the triad of liver disease, an increased alveolar-arterial gradient while breathing room air, and evidence of intrapulmonary vascular dilatations.
- It results from the formation of microscopic intrapulmonary arteriovenous dilatations in patients with chronic liver disease.
- The mechanism is thought to be due to increased hepatic production or decreased hepatic clearance of vasodilators, possibly involving nitric oxide. The vascular dilatations cause overperfusion relative to ventilation, leading to hypoxemia.

Hepatopulmonary syndrome

- Patients with clinically significant symptoms should undergo pulse oximetry. If the syndrome is advanced, Arterial Blood Gasses should be measured on air.
- A useful diagnostic test is contrast echocardiography. IV microbubbles from agitated saline that are normally obstructed by pulmonary capillaries rapidly transit the lung and appear in the left atrium within 7 beats. Pulmonary angiography may reveal diffusely fine or blotchy vascular configuration.
- The main treatment is supplemental O_2 for symptoms.
- Hepatopulmonary syndrome may regress after liver transplantation or if the underlying liver disease subsides.
- Prognosis is poor without treatment.