Husband & wife are like liver and kidney.

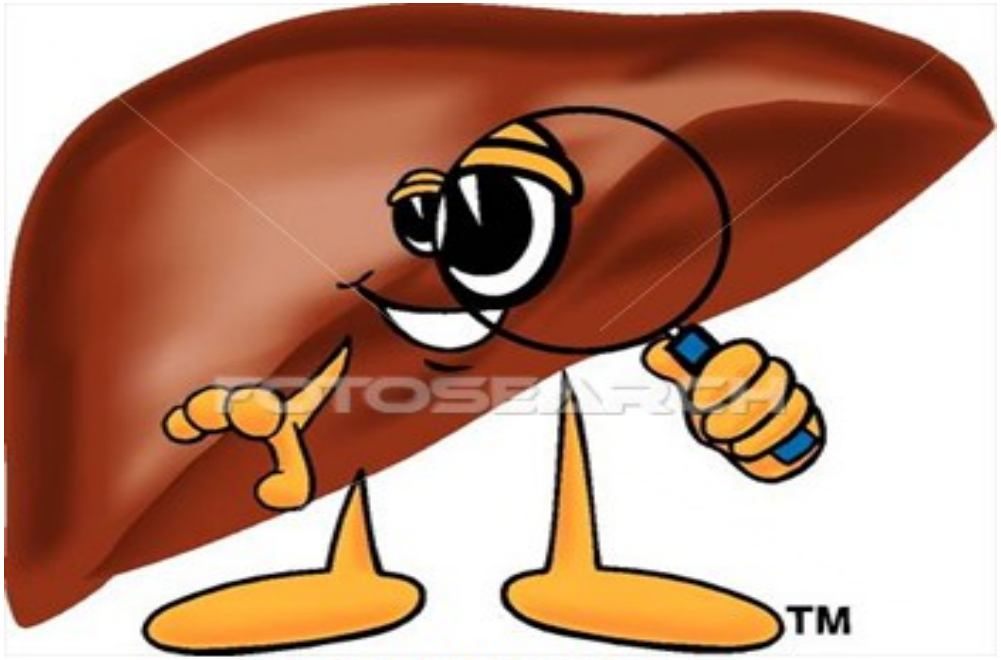
Husband is liver & wife is kidney.

If liver fails, kidney fails.

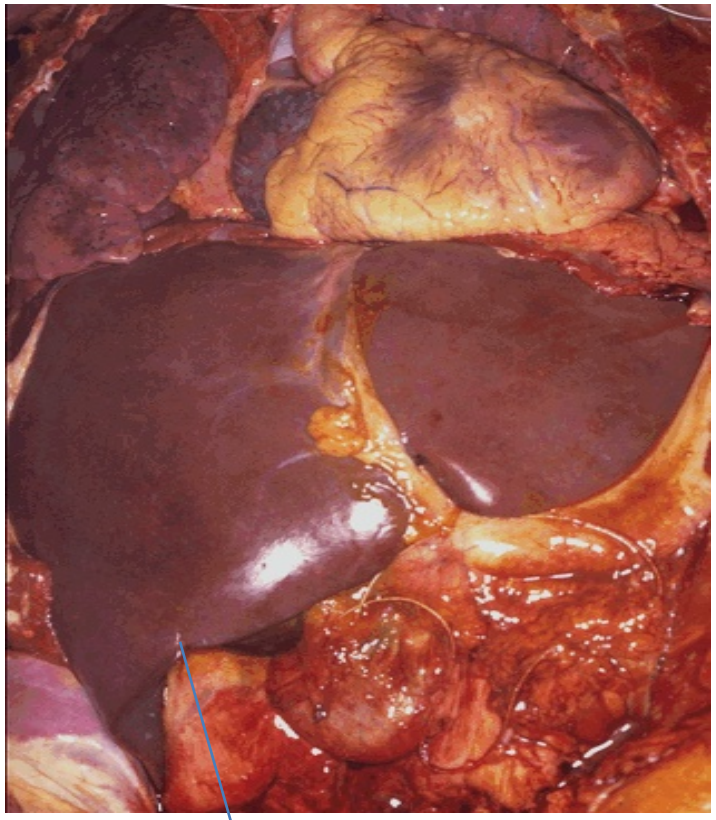
If kidney fails, liver manages with other kidney.

The Liver

Liver Panel, Liver Diseases



The Liver



Right lobe

the liver *is the largest parenchymal organ (gland), lying just below the diaphragm. The right lobe is larger than the left lobe.*

human liver normally weighs 1.5 kg

Blood supply: Portal vein, and hepatic artery

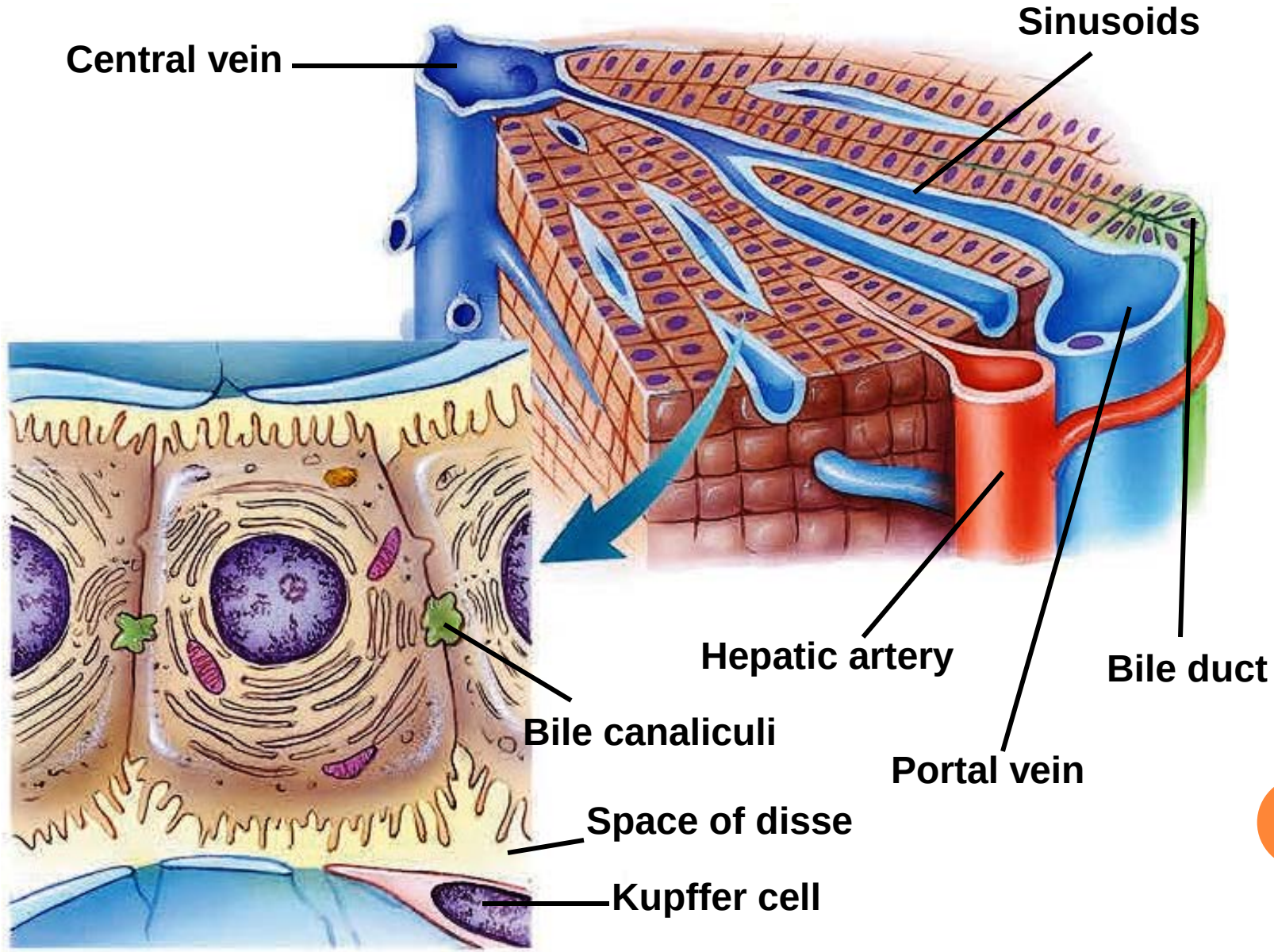
Portal circulation – brings blood to the liver from : stomach, spleen, pancreas & intestines.

FUNCTIONS OF THE LIVER

- **Carbohydrate metabolism**
  - Glycogenesis
  - Glycogenolysis
  - Gluconeogenesis
- **Fat metabolism** –
  Fatty acids and cholesterol synthesis
- **Protein metabolism**
  - anabolism
  - deamination
  - urea formation
- Secretion of bile
- Hormone production
- Detoxification
- Storage and metabolism of vitamins A,D,K,E
- Plasma protein and clotting factors synthesis, esp. prothrombin

the liver is basically an organ of homeostasis

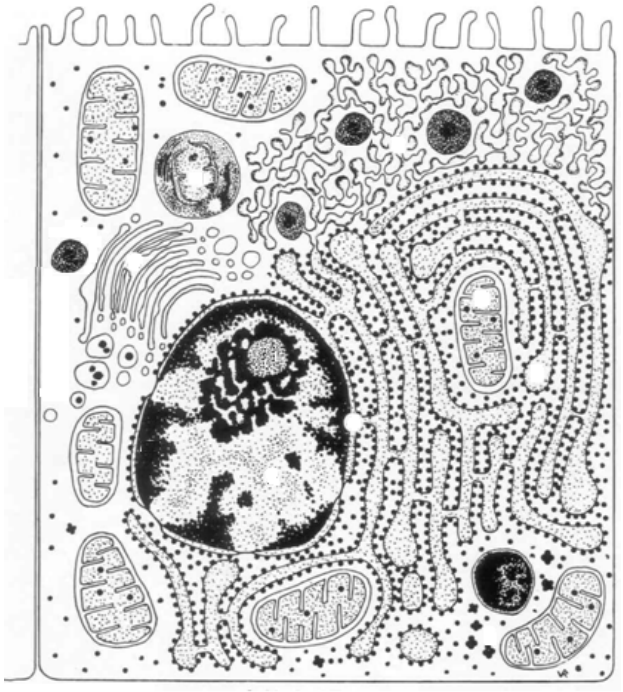
PARENCHYMA - HEPATOCYTES



Liver Cells

I- Hepatocytes:

- Are the liver cells tightly packed together



- have:-

➢ prominent nuclei and Golgi apparatus

➢ many mitochondria & lysosomes

➢ a lot of glycogen granules & fat droplets

➢ the only other cells found in the liver are:-

-nerve cells

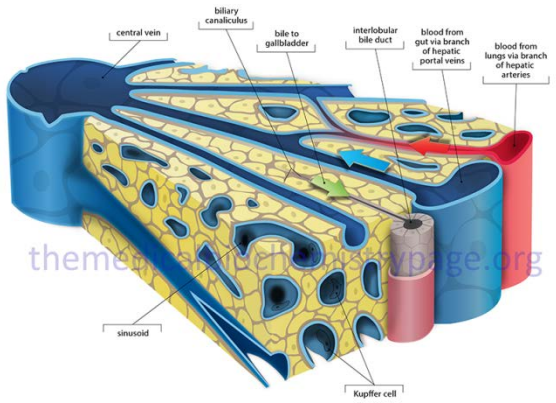
-cells associated with blood and lymph vessels

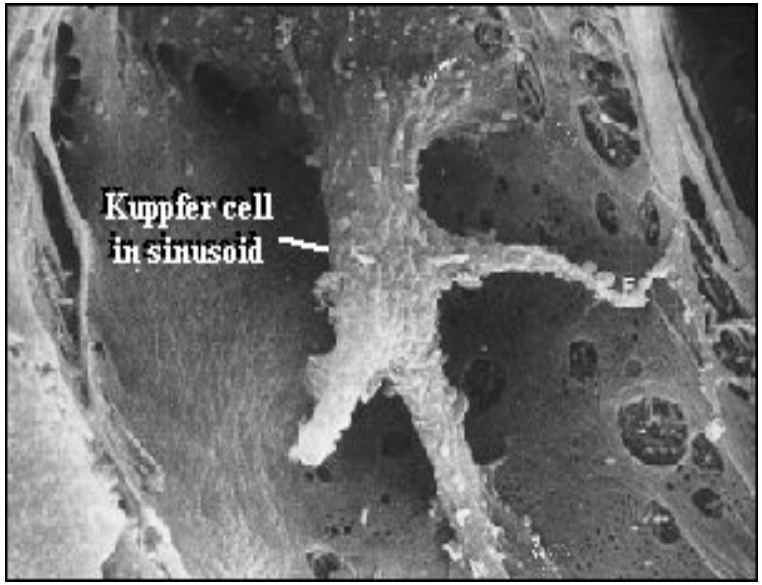
-And……

II- Kupffer cells are:

- fixed cells of the reticulo-endothelial system (part of the immune system)
- macrophages
- found attached to the walls of the sinusoids
- Function - phagocytic:

1. break down old red blood cells
2. ingest bacteria





WHAT ARE LIVER DISEASES?

Liver diseases: a collection of conditions, disorders, and infections that affect cells, structures, and tissues of the liver, causing liver damage:

- **Cells can become inflamed (such as in hepatitis).**
- **Bile flow can be obstructed (such as in cholestasis).**
- **Cholesterol or triglycerides can accumulate (fat accumulation).**
- **Blood flow to the liver may be compromised.**
- **Liver tissue can be damaged by chemicals and minerals, or infiltrated by abnormal cells.**

Bilirubin Metabolism

One of the most important functions of the liver is the processing and excretion of endogenous and exogenous substances into the bile or urine such as the major heme waste product, **bilirubin**

Bile is made up of bile acids or salts, bile pigments, cholesterol, and other substances extracted from the blood.

The body produces approximately 3 L of bile per day and excretes 1 L of what is produced. Bilirubin is the principal pigment in bile, and it is derived from the *breakdown of red blood cells*

Bilirubin is bound by albumin and transported to the liver. This form of bilirubin is referred to as unconjugated or indirect bilirubin. This form of bilirubin is insoluble in water and cannot be removed until it has been conjugated by the liver.

Once at the liver cell, unconjugated bilirubin is released from albumin so it can be picked up by a carrier protein called ligandin.

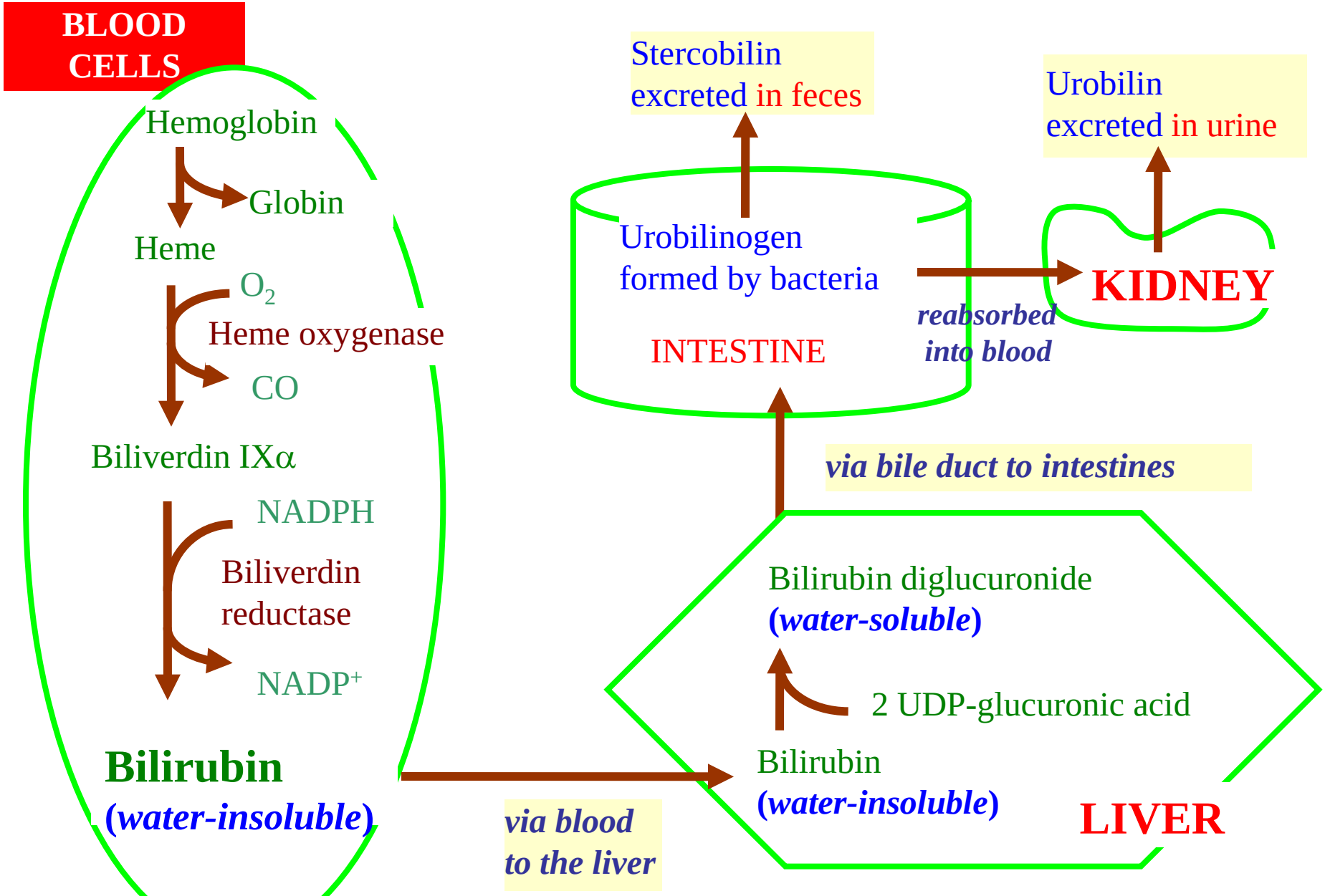
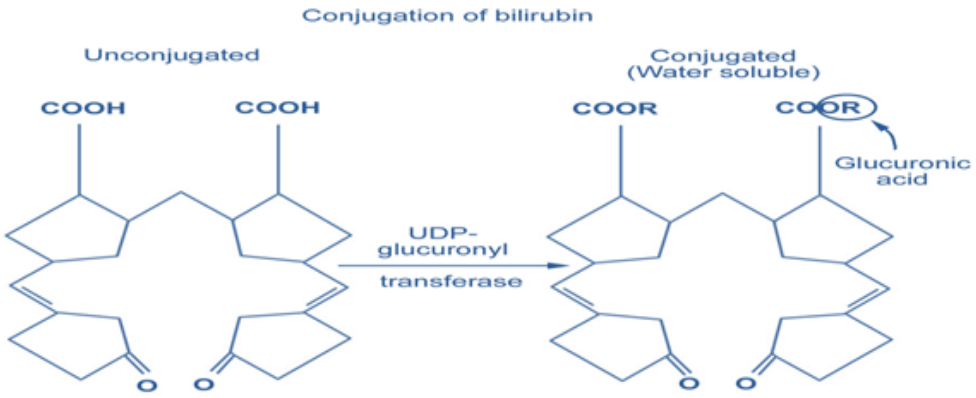
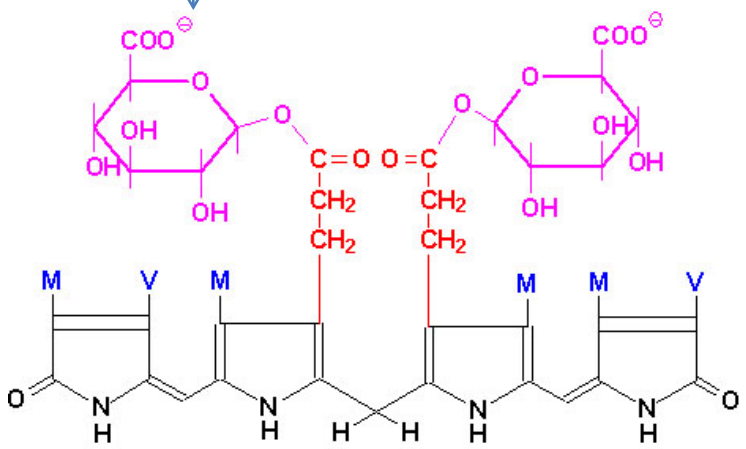
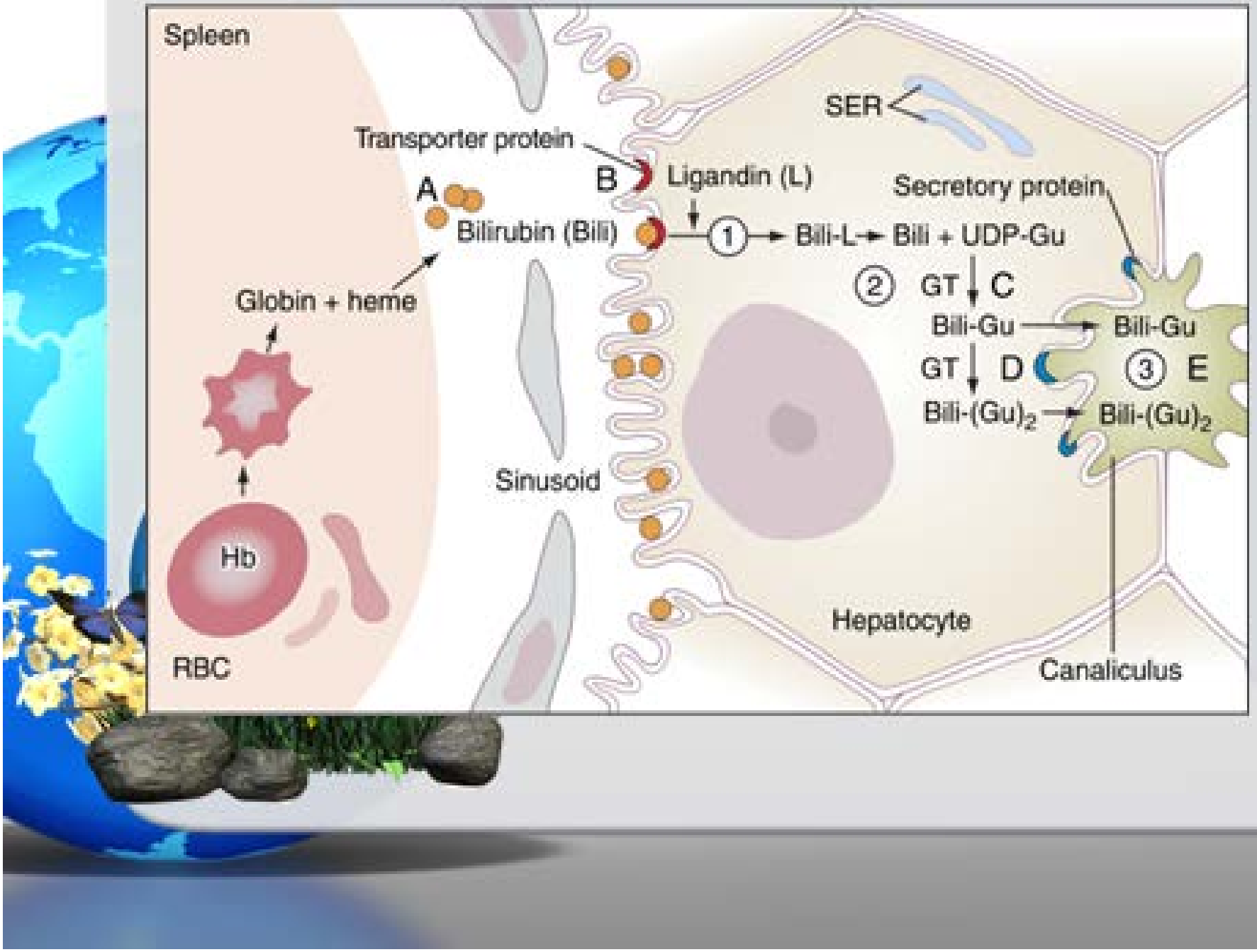


Fig. 2 metabolism of bilirubin

The conjugation (esterification) of bilirubin occurs in the presence of the enzyme **Uridyldiphosphate glucuronyl transferase (UDPGT)**, which transfers a glucuronic acid molecule to each of the two side chains of bilirubin to form **bilirubin diglucuronide**, also known **as conjugated bilirubin**. This form of bilirubin, is <u>water soluble</u> and is able to be secreted from the hepatocyte into the bile canaliculi.






Spleen
SER
Transporter protein
B
Ligandin (L)
A
Bilirubin (Bili)
1
Bili-L
Bili + UDP-Gu
Secretory protein
2
GT
C
Globin + heme
Bili-Gu
Bili-Gu
GT
D
3
E
Bili-(Gu)2
Bili-(Gu)2
Sinusoid
Hb
Hepatocyte
RBC
Canaliculus

Plasma Bilirubin

Normal plasma bilirubin: **0.4–1.2 mg/dl**.

- If the plasma bilirubin level exceeds this value, the condition is called **hyperbilirubinemia**.

When the bilirubin level exceeds 2 mg/dl, it diffuses into tissues producing yellowish discoloration of sclera, skin & mucous membrane resulting in **jaundice (or icterus).**

Van den Bergh Test: is specific test for the identificaion of increased serum **conjgated bilirubin** levels

Jaundice Types

Prehepatic jaundice occurs when the problem causing the jaundice occurs prior to liver metabolism such as in acute and chronic hemolytic anemias.

Hepatic jaundice occurs when the primary problem causing the jaundice resides in the liver (intrinsic liver defect or disease).

Posthepatic= obstructive

Newborn jaundice

Liver Function Tests (Hepatic Panel)

A liver panel, may be ordered when someone is **at risk for liver dysfunction**. Some examples include:

-People who take medications that may damage the liver

-Those who are alcoholics or heavy drinkers

-Those who have a history of known exposure to hepatitis viruses

-People who are overweight, especially if they have diabetes and/or high blood pressure

Some symptoms for liver diseases:

-Weakness, fatigue

-Nausea, vomiting

-Abdominal swelling and/or pain

-Jaundice

-Dark urine, light-colored stool

Classification of Liver Function Tests

I
- Tests based on excretory function

II
- Tests based on detoxification function

III
- Tests based on synthetic function

IV
- Tests based on metabolic function

V
- Determination of serum enzymes

I. Tests based on excretory function

Serum-Bilirubin

- Total, conjugated and unconjugated total bilirubin:0.4 -1.2 mg/dl

urine

- Bile pigments, bile salts and urobilinogen

Laboratory Results

	S Bilirubin		U Urobilinogen	U Bilirubin	F Urobilinogen
	Conjugated	Unconjugated			
Normal	0.1-0.4mg/dl	0.2-0.7mg/dl	0.4mg/day	Absent	40-280mg/day
Prehepatic	Normal	Increased	Increased	Absent	Increased
Hepatic	Increased	Increased	N/Decreased	Present	Decreased
Posthepatic	Increased	Normal	Absent	Present	Trace to absent

Bromosulphthalein (BSP) test

- Bromosulphthalein is a dye used to assess the **excretory function** of liver.
- This non-toxic compound is almost exclusively excreted by the liver
- BSP is administered & its serum concentration is measured at 45 min & at 2 hrs.
- the retention of the dye after 45minutes in normal people is less than 5%.
- **Any impairment in liver function causes an increased retention of the dye.**

II.Tests b/o detoxification function

Hippuric acid test (benzoic acid + Glycine = hippuric acid)

- 6gm of sodium benzoate dissolved in 250ml water
- Collect urine for next 4 hour

- Normal: > 4.5 g of hippuric acid

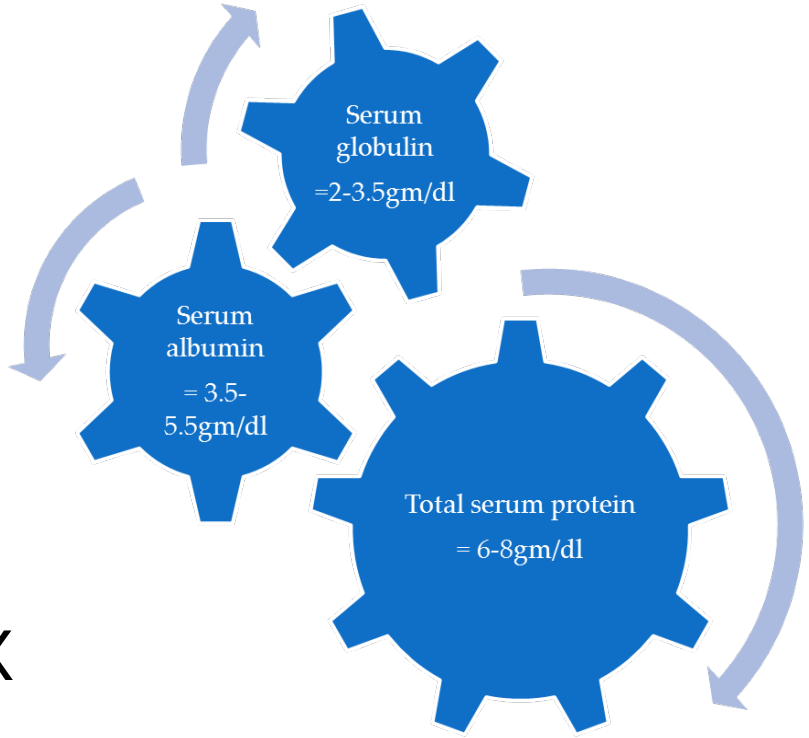
Determination of blood ammonia

- Liver detoxicates ammonia to form urea
- Normal: 40-70μg/100ml

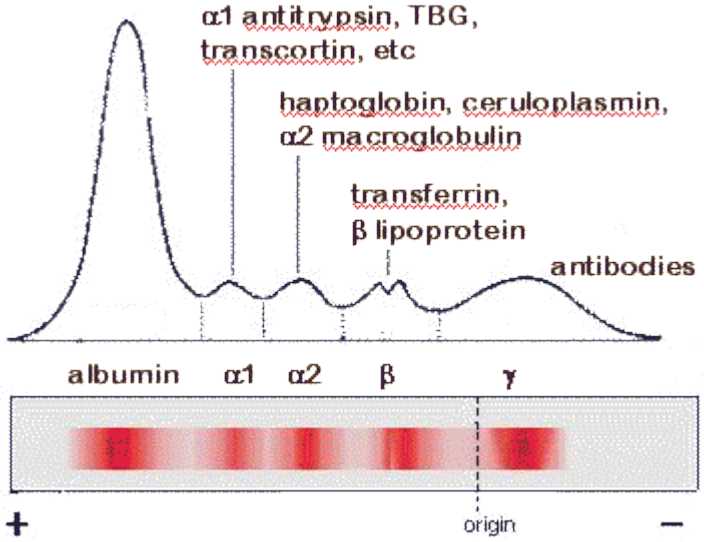
III. Tests b/o Synthetic Function

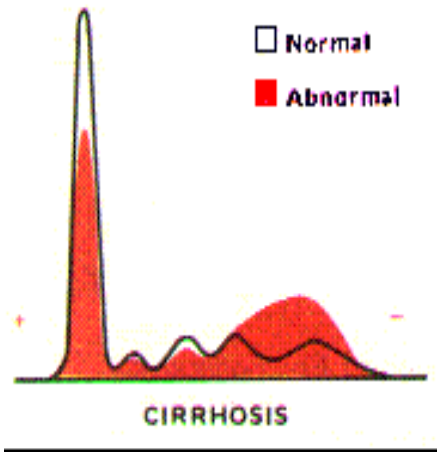
Liver is the main source of synthesis of

- Plasma proteins
  - Albumin
  - Globulin (except γ)
    Albumin/globulin ratio=1.2 – 1.8: 1
  - Fibrinogen
- Blood clotting factors
  - Prothrombin
  - Factors V, VII and X



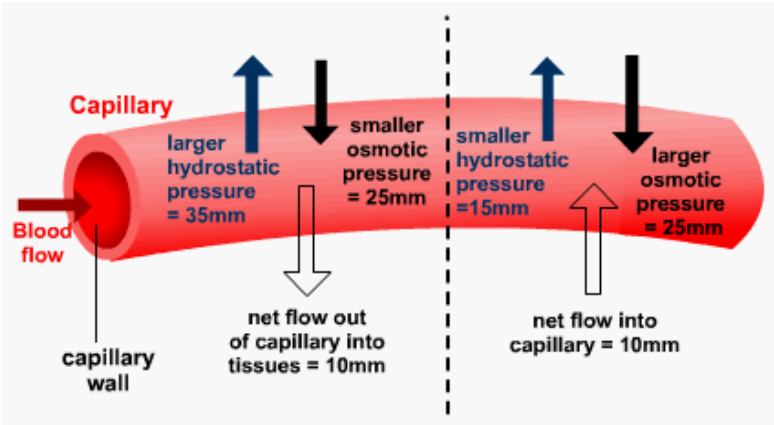
Albumin is the commonest Protein





Albumin constitutes about half of the blood serum protein. **A proper alb. balance is required to prevent fluids from leaking out of blood vessels**

Albumin transports hormones, calcium, fatty acids, and other compounds, buffers pH, and maintains osmotic pressure.



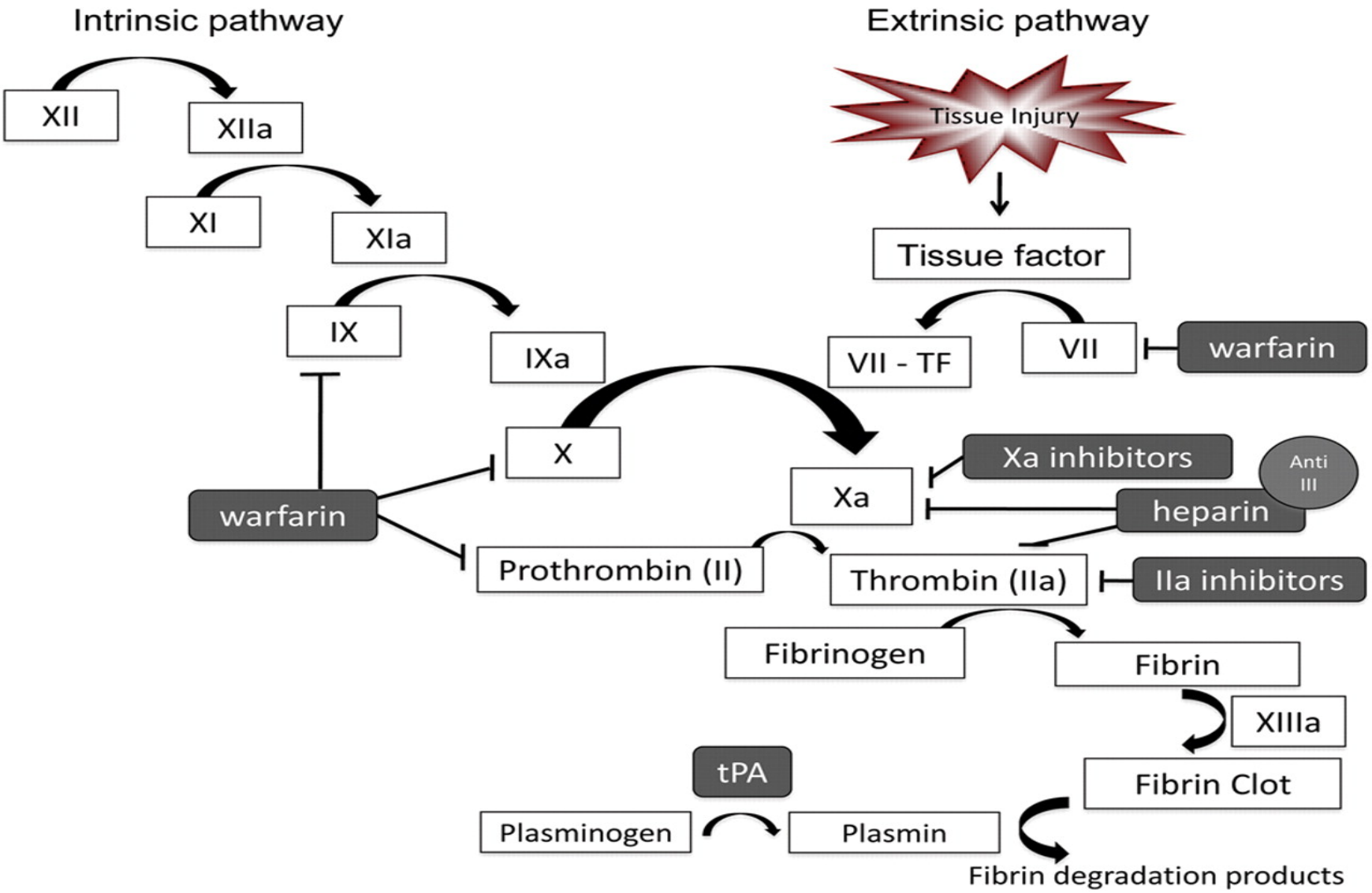
Prothrombin time (PT) and INR

Prothrombin time (PT): A test of the **time** it takes for a blood sample to clot, under specific conditions in a lab. If low levels of clotting factors are present, the prothrombin time is longer.

THUS, The prothrombin time (PT) and prothrombin ratio (PR) and international normalized ratio (INR) are measures of the **extrinsic pathway** of coagulation.

They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (fibrinogen), II (prothrombin), V, VII, and X. It is used in conjunction with the activated partial thromboplastin time (aPTT)

Coagulation Cascade

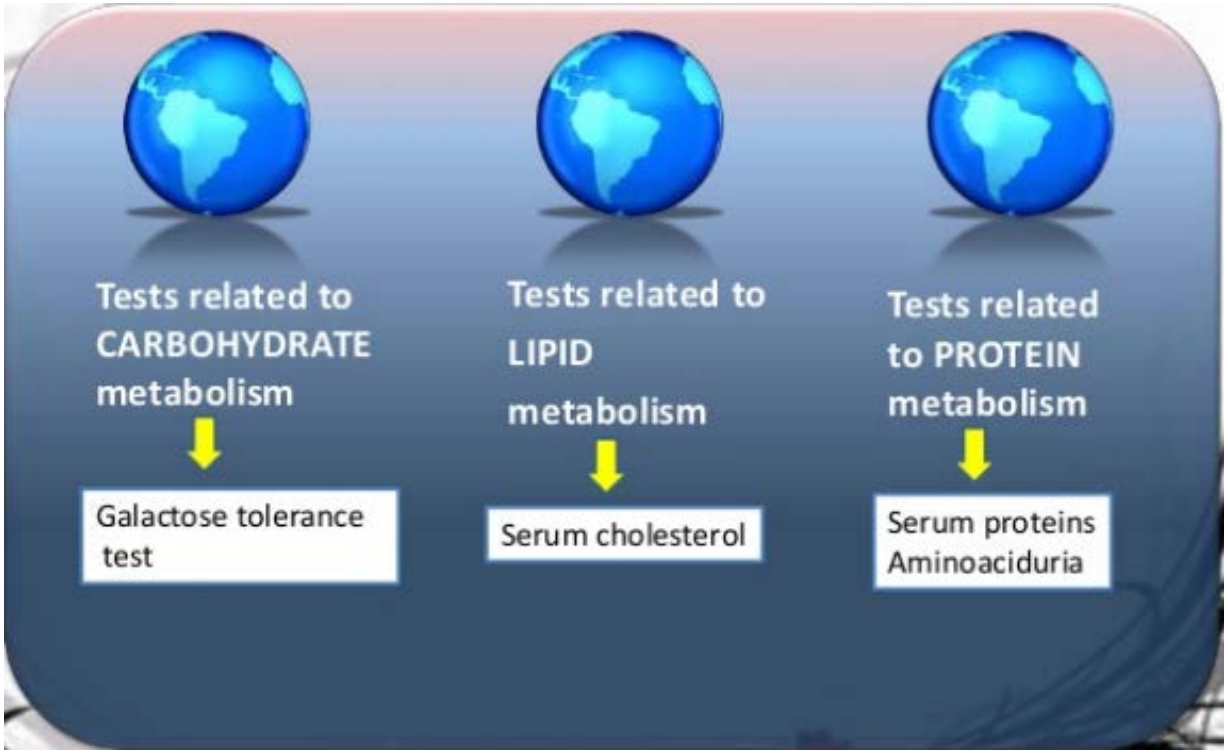


IV. Tests based on Metabolic Capacity:

carbohydrate metabolism

lipid metabolism

protein metabolism



Metabolic Function

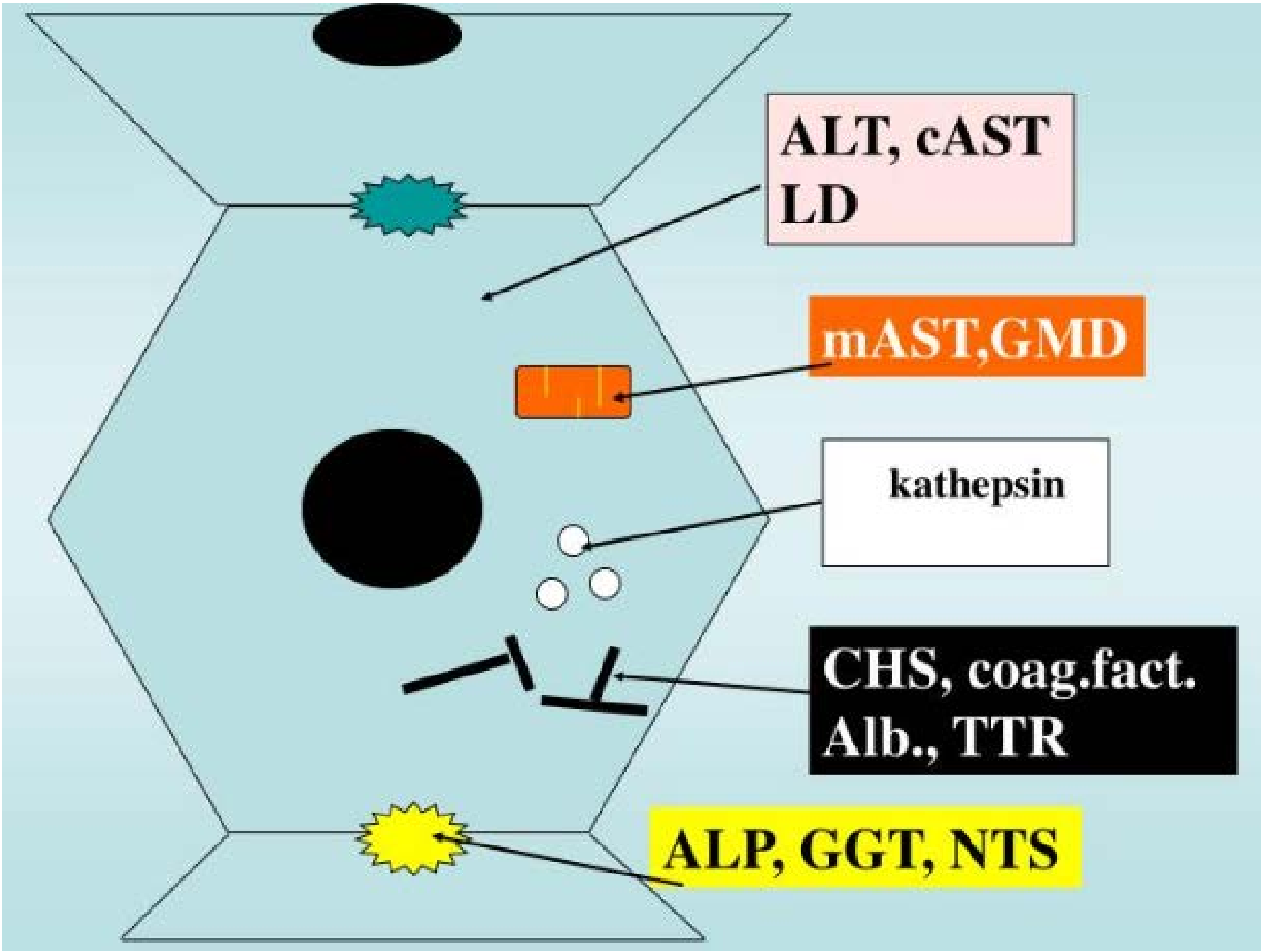
- is almost exclusively metabolized by the liver. the normal liver is able to convert galactose into glucose; but this function *is impaired in intrahepatic disease* and the amount of blood and urine galactose is excessive.

The subject is given intravenous administration of galactose (about 300 mg/kg body weight).

In the normal individuals, the half-life of galactose is about 10-15 minutes. This is markedly elevated in hepatocellular damage (infective hepatitis, cirrhosis).

V. Liver Enzymes

- Serum aminotransferases:
  - alanine aminotransferase (ALT, formerly called SGPT)
  - aspartate aminotransferase (AST, formerly called SGOT)
- Alkaline phosphatase (Alk Phos)
- Gamma-glutamyl transpeptidase (GGT)
- 5'-nucleotidase
- Lactate dehydrogenase (LDH)


ALT, cAST
LD
mAST,GMD
kathepsin
CHS, coag.fact.
Alb., TTR
ALP, GGT, NTS

DIAGNOSTIC ENZYMES

Cytoplasm: ALT, cAST (30 % of total liver AST) , LD

permeability

dysfunction

Mitochondria: mAST, GMD (glutamate dehydrogenase) necrosis

Membranes of bile duct endothelium and sinusoids:

ALP, GGT, 5-NTS (5´-nukleotidase) cholestasis

Lysosomes: hydrolytic enzymes:

proteinases (kathepsin) a β-glucuronidase (Gaucher´s disease)

Rough endoplasmic reticulum: CHS (cholinesterase),

coagulations factors, plasmat. proteines (albumin, transthyretin, transferrin)

protein synthesis defect (decrease !)

Transaminases:

ALT(SGPT) 10 to 45 U/L

AST(SGOT) 5 to 40 U/L

ALT is primarily localized to the liver. It is the marker enzyme of the liver.

ALT is present in the cytosol of hepatocytes.

AST is present in a wide variety of tissues like heart, skeletal muscles, liver, kidney, brain.

AST is present both in the cytosol and mitochondria of the hepatocytes.

Liver contains both enzymes but more of ALT

Estimation is very useful in **assessing severity and prognosis** of liver parenchymal disease especially infective hepatitis. Elevated levels :

Highly elevated > 20 times

Viral hepatitis

Drug or Toxin-induced hepatic necrosis

Moderately elevated - 3 to 20 times

Chronic hepatitis

Alcoholic hepatitis

Acute biliary tract obstruction

When AST and ALT are both over 1000 IU/L, the differential can include acetaminophen (paracetamol) toxicity, or fulminant liver failure.

Other Enzymes

- Alkaline Phosphatase ALP / Gamm GT: are:
  - Canalicular enzymes: Liver ALP rises with obstruction or infiltrative diseases (i.e., stones or tumors) ⟶ Gradual increase in plasma levels is seen in bile duct obstruction and intrahepatic cholestasis ركودة صفراوية
  - ➢ ALP is found in liver, bones and intestines
  - ➢ GGT is more sensitive marker for cholestatic damage than ALP
  - ➢ GGT is elevated in alcohol toxicity

  Since liver is not the sole source of ALP activity (bone, small intestine…), an elevated gamma GT would suggest that the liver is the source of the increased alkaline phosphatase

- Lactate Dehydrogenase (LDH-5)

Other Enzymes

Serum γ-Glutamyl Transferase

- Normal range: 10-47 IU/L: ↑ Cholestasis, alcohol ingestion

Serum 5'-Nucleotidase

- Normal range: 2-17 IU/L

Serum Lactate Dehydrogenase

- Normal range: 70-240 IU/L: acute liver damage

Main Types of Liver Diseases

Bile duct obstruction

Gilbert's syndrome

Crigler-Najjar Syndrome

Nonalcoholic fatty liver

Hepatitis A, B, C, D, E

Toxic hepatitis

Alcoholic hepatitis

Wilson's disease

Hemochromatosis

Alpha-1-antitrypsin deficiency

Autoimmune hepatitis

Cirrhosis

Primary biliary cirrhosis

Liver adenoma

Liver cancer

Liver cyst

Liver nodule (focal nodular hyperplasia)

Parasitic infection

Portal vein thrombosis

Fatty Liver

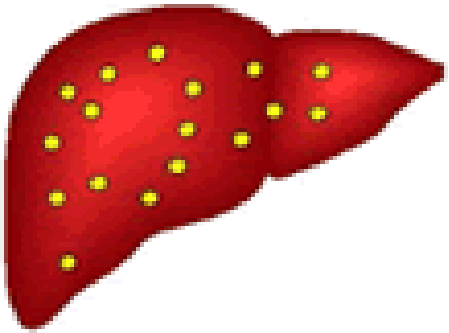
- **Fatty liver disease** (**FLD**): is a reversible condition wherein large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis التنكس الدهني (i.e., abnormal retention of lipids within a cell).
- Fatty liver occurs in those with excessive alcohol intake and the obese patients (with or without effects of insulin resistance).
- By considering the contribution by alcohol, fatty liver may be termed: 1- alcoholic steatosis

2- nonalcoholic fatty liver disease (NAFLD)

3- Non-alcoholic steatohepatitis (NASH)

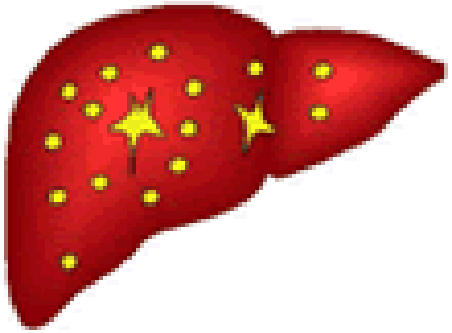
The Spectrum of NAFLD

Fatty Liver



Fat accumulates in the liver

NASH



Fat plus inflammation and scarring

Cirrhosis

Scar tissue replaces liver cells

Metabolic Disorders

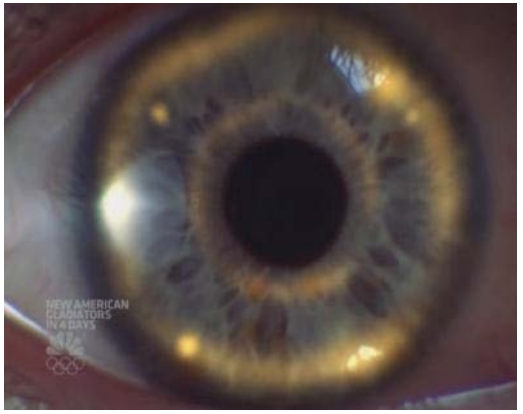
Hemochromatosis

- Excessive accumulation of body iron → deposit in parenchymal organs (e.g. heart, liver and pancreas)
- May be secondary to a genetic defect (increased absorption) OR a consequence of parenteral administration of iron
- Over 1/3 of iron accumulated stored in the liver
- Increased risk of cirrhosis and hepatocellular carcinoma

Metabolic Disorders

Wilson's Disease (Hepatolenticular degeneration)

- Copper accumulation particularly in liver, brain, and eye (demonstrated by Kayser–Fleischer rings)
- Due to mutation of Wilson's disease gene (*ATP7B*) on chr. 13 → decreased synthesis of ceruloplasmin → defective biliary excretion of copper



Metabolic Disorders

A1-Antitrypsin deficiency

Alpha-1 antitrypsin (AAT) protects the lungs and liver from damage (protects the body from a powerful enzyme called neutrophil elastase. Elastase is released from white blood cells to fight infection, but it can attack normal tissues (especially the lungs) if not tightly controlled by alpha-1 antitrypsin.).

Alpha-1 antitrypsin deficiency is an inherited disorder that may cause lung disease.

Approximately 15 percent of adults with alpha-1 antitrypsin deficiency develop liver damage (cirrhosis)

Signs and symptoms

Emphysema, shortness of breath, wheezing. A1AD also causes impaired liver function….

What is Viral Hepatitis ?

- Viral hepatitis is a **systemic** disease with primary inflammation of the liver by any one of a heterogenous group of hepatotropic viruses:

1. **Hepatitis viruses**
2. Epstein-Barr virus
3. Cytomegalovirus
4. Children & immunocompromised → rubella, adenovirus, herpesvirus, and enterovirus

Hepatitis	A	B	C	D	E
Virus	HAV	HBV	HCV	HDV	HEV
Family	Picornavirus	Hepadnavirus	Flavivirus	Satellite	Calicivirus
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Spread	Fecal-oral	parenteral, sexual,perinatal	parenteral, ?sexual	parenteral, ?sexual	Fecal-oral
Antigens	HAV-Ag	HbsAg,HBcAg, HBeAg	HCV-Ag	HDV-Ag	HEV-Ag
Antibodies	Anti_HAV	Anti-HBs,Anti-HBc,Anti-HBe	Anti-HCV	Anti-HDV	Anti-HEV
Virus markers	HAV RNA	HBV DNA, DNA polymerase	HCV RNa	HDV RNa	viruslike partiacles

Hepatitis A Virus Transmission

- Close personal contact
  (e.g., household contact, child day care centers)
- Contaminated food, water
  (e.g., infected food handlers, raw shellfish)
- **Lab diagnosis:** -Detection of Antibody :By ELISA

  - Biochemical tests:

  i) Alanine aminotransferase (ALT)

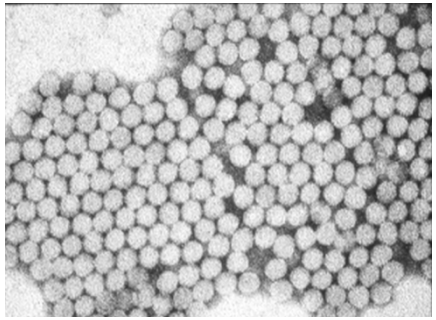
  ii) Bilirubin

  iii) Protein

Hepatitis Viruses

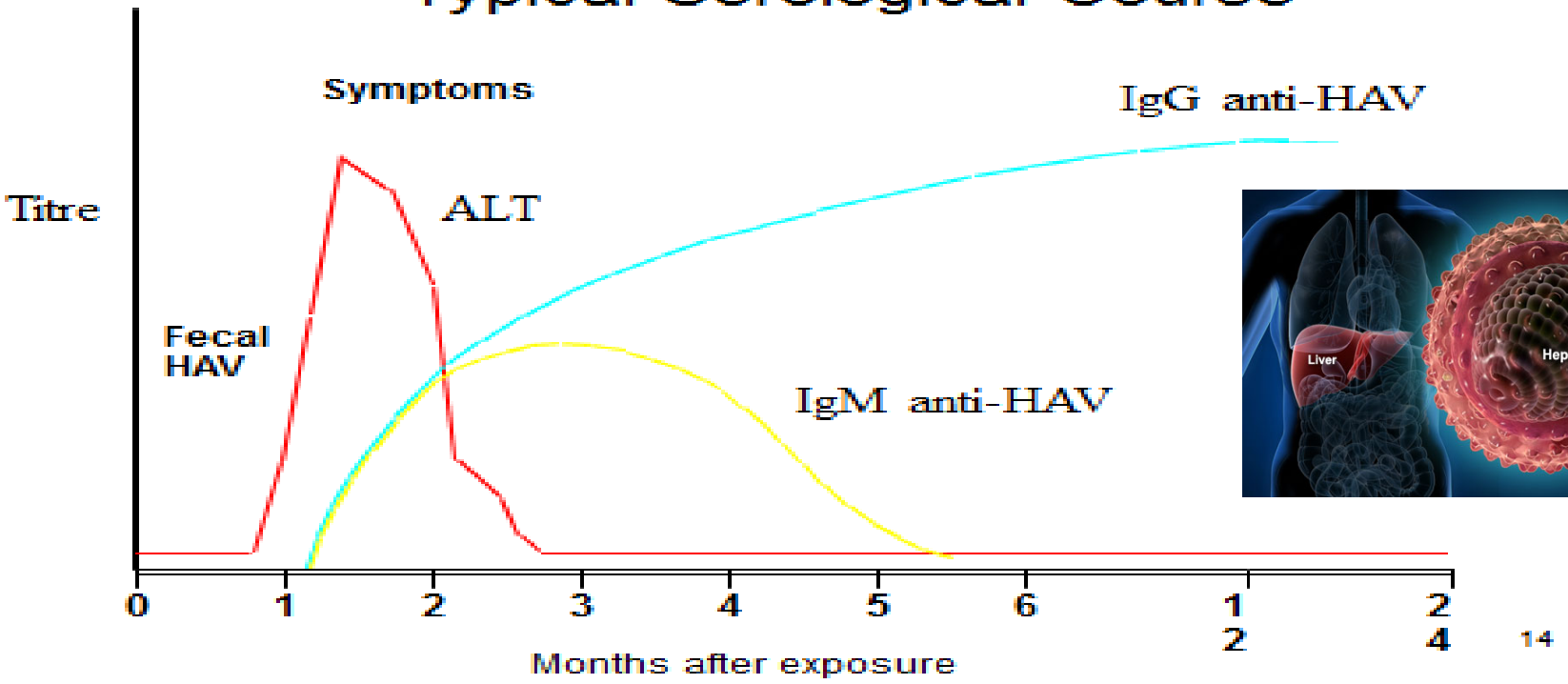
Hepatitis A

- **Small, non-enveloped, ssRNA**
- **Picornavirus family, *Hepatovirus***
- ***Incubation period: 2-6 weeks***



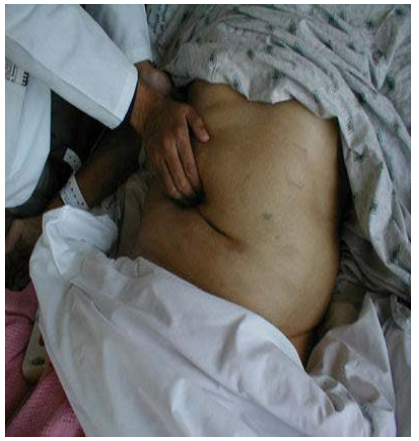
Hepatitis A Infection

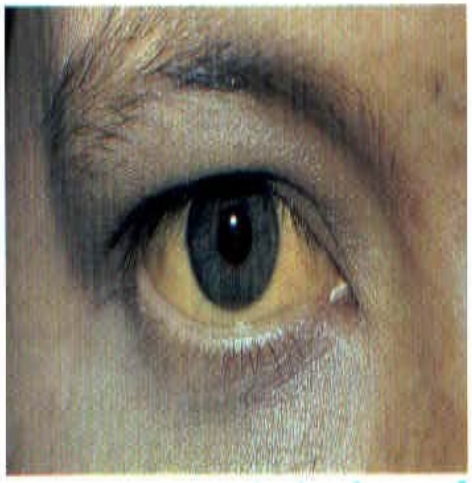
Typical Serological Course

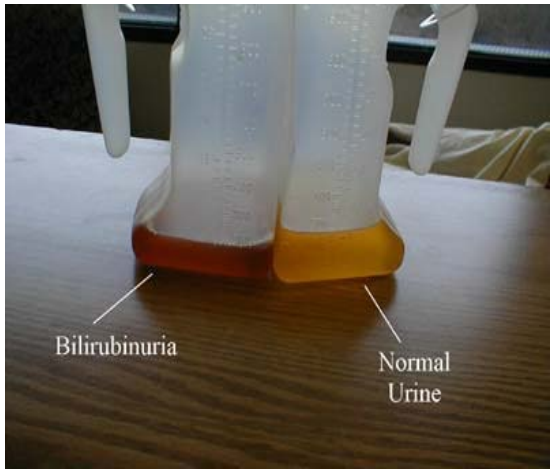


- **Preicteric phase** : (symptoms: fatigue, joint- and abdominal pain, malaise, vomiting, lack of appetite, hepatomegaly, low-grade fever)
- **Icteric phase**: Icterus: (skin, sclera, mucous membranes,

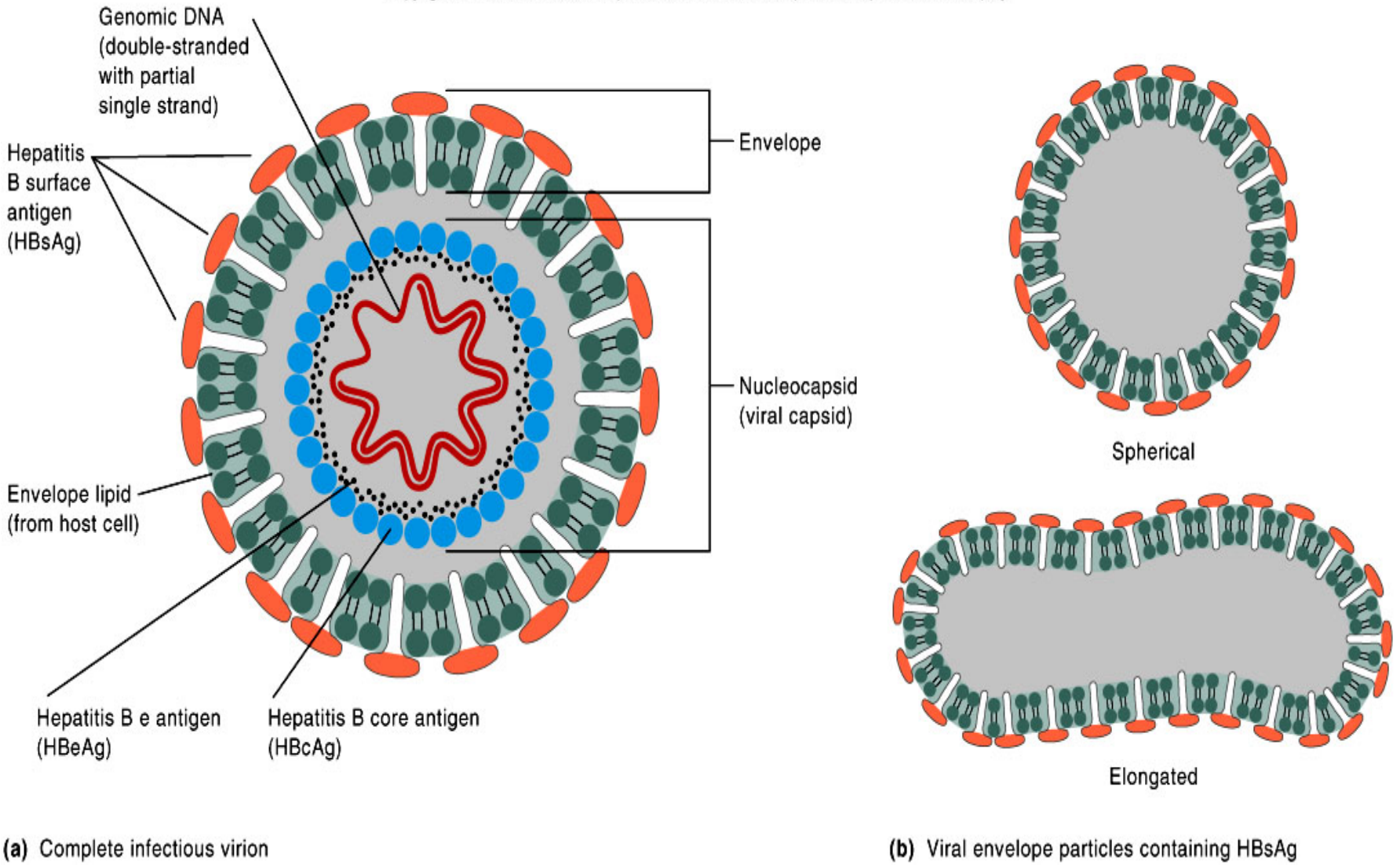
cause: elevated bilirubin level, bilirubinuria: dark urine, pale stool)







Hepatitis B HBV : Structure

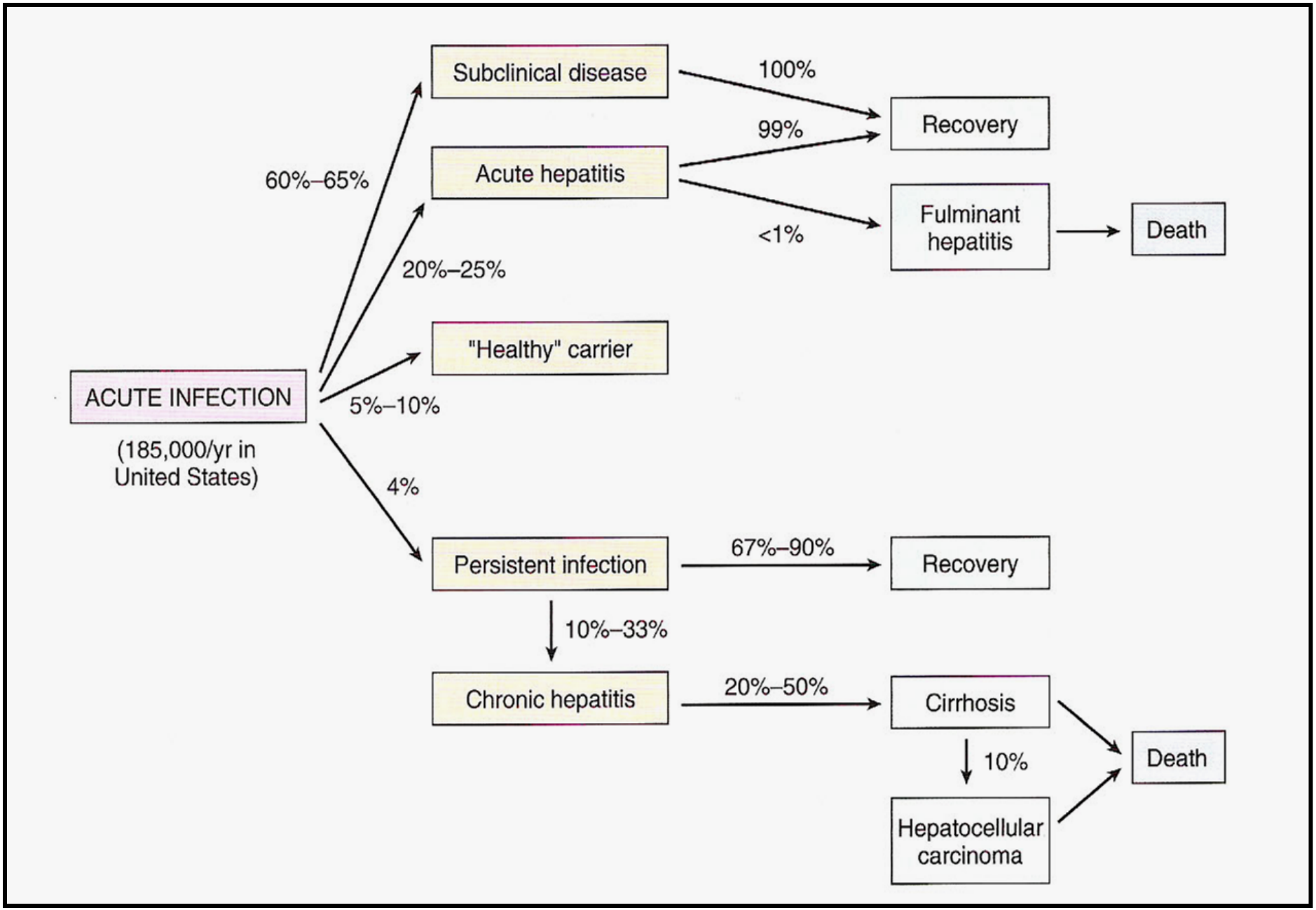


(a) Complete infectious virion

(b) Viral envelope particles containing HBsAg

Hepatitis B

- **Hepadnavirus family, ds DNA**
- present in all physiologic and pathologic body fluids → blood & body fluids (the primary vehicle for transmission)
- Incubation period: 4 – 12 weeks
- MOT:
  1. Transfusion
  2. Blood products
  3. Dialysis
  4. Needle stick accidents among health care workers
  5. IV drug abuse
  6. Sexual contact


ACUTE INFECTION
(185,000/yr in United States)
60%–65%
20%–25%
5%–10%
4%
Subclinical disease
Acute hepatitis
"Healthy" carrier
Persistent infection
Chronic hepatitis
100%
99%
<1%
Recovery
Fulminant hepatitis
Death
67%–90%
Recovery
10%–33%
20%–50%
Cirrhosis
10%
Hepatocellular carcinoma
Death

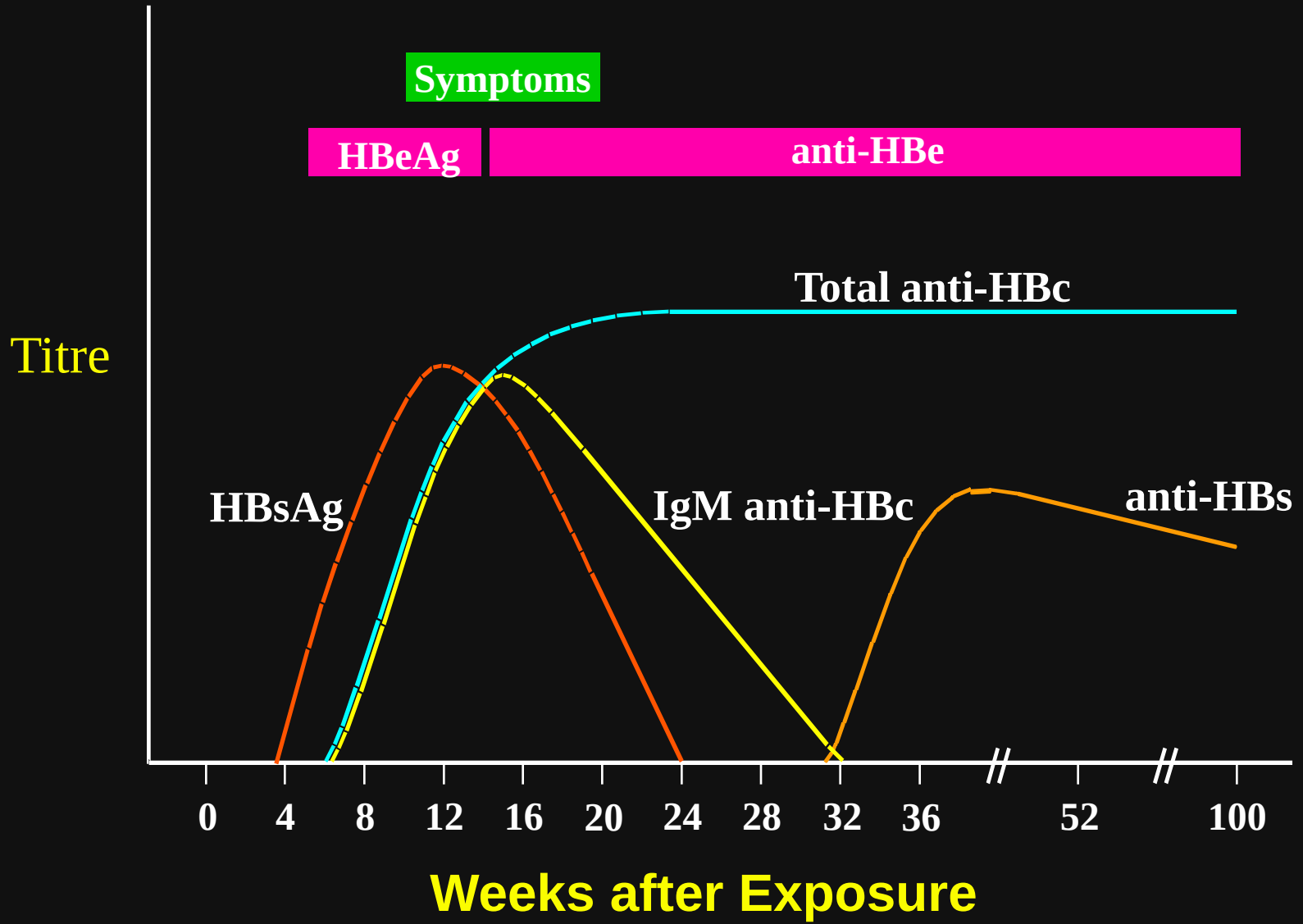
serology

- HBsAg: surface antigen
- HBeAg: e antigen (a component of HBV core); marker of viral replication
- HBcAg: core antigen (cannot be measured in serum)
- both HBsAg and HBeAg are present during acute hepatitis B
- anti-HBs follows HBsAg clearance and confers long-term immunity
- anti-HBe and anti-HBc appear during the acute and chronic phases of the illness but do not provide immunity

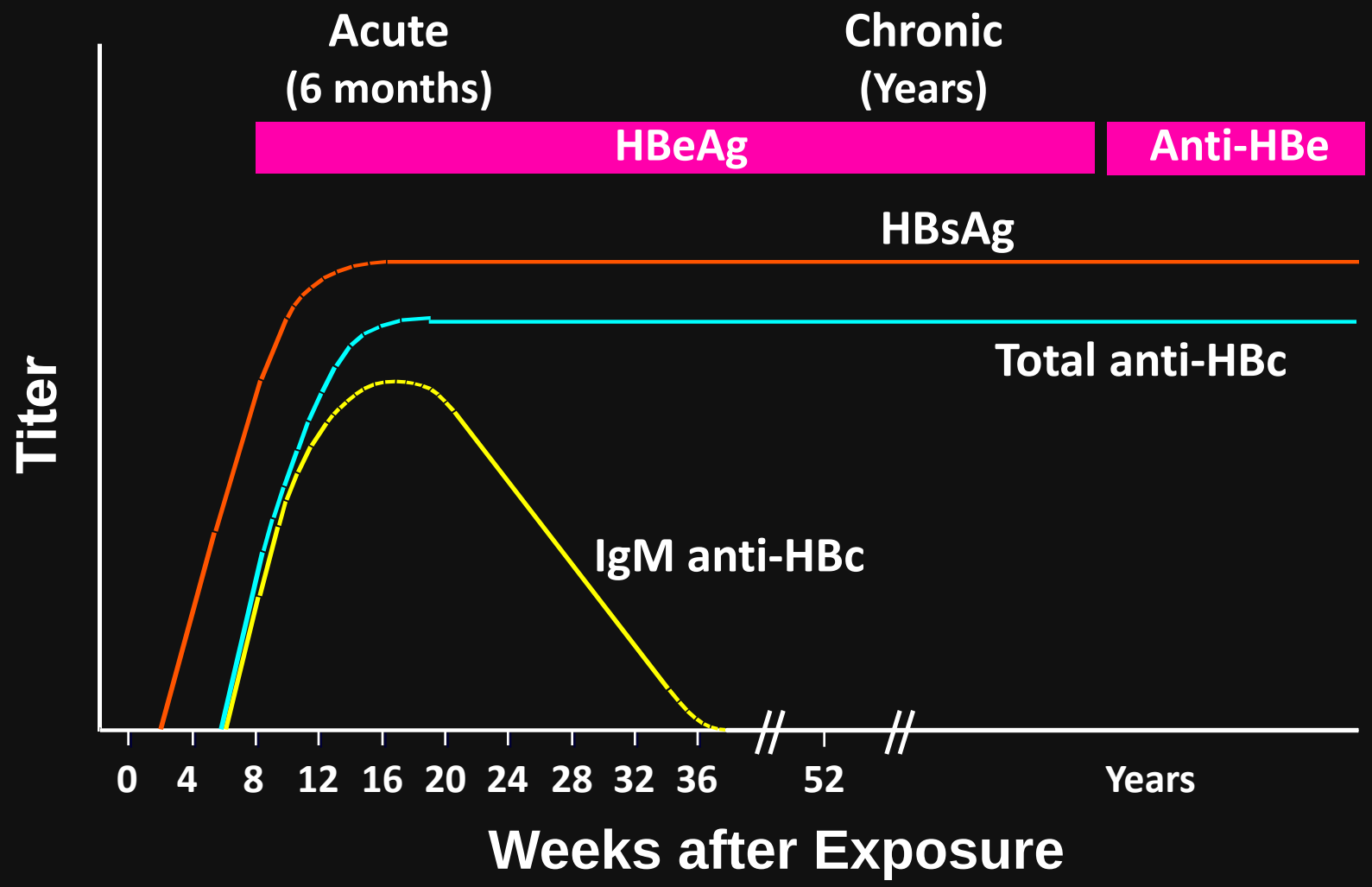
- anti-HBe indicates low infectivity

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course

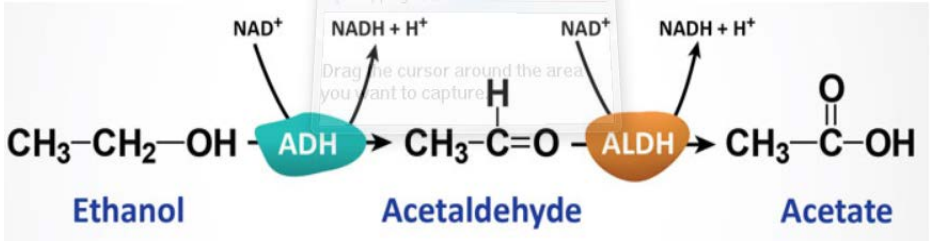


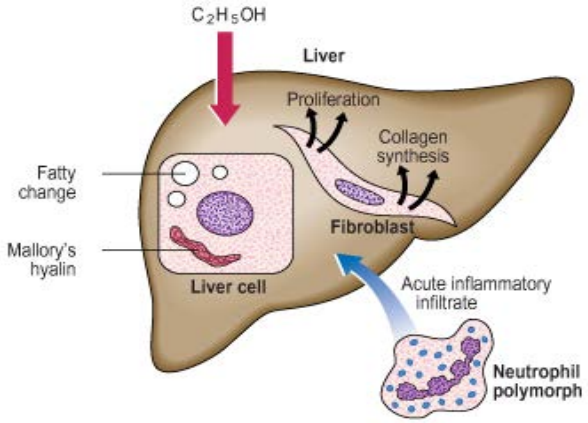
Acute HBV Infection with Progression to Chronic Infection: Typical Serologic Course



Test	Result	Interpretation
HBsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis vaccination
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	1- Resolved infection 2- False positive anti –HBc, thus susceptible 3- low level chronic infection
Anti-HBc	Positive	
Anti-HBs	Negative	

Alcoholic Hepatitis





- Cellular energy is diverted from essential metabolic pathways, such as fat metabolism, to the metabolism of alcohol so fat accumulates in the liver cells.
- The original **biochemical** explanation for an **alcoholic fatty liver** centered on the ability of ethanol metabolism to shift the redox state of the **liver** and inhibit **fatty** acid oxidation. Subsequent studies found repression of **fatty** acid oxidation and that the induction of lipogenesis can occur in **alcoholic** conditions

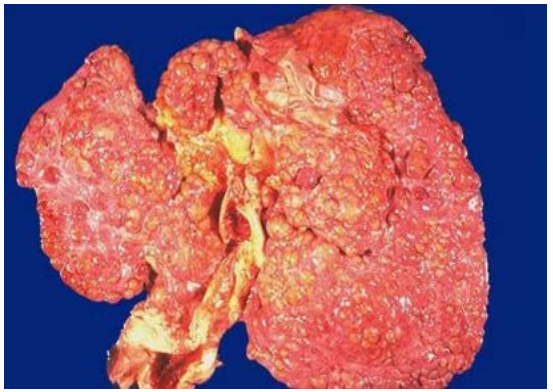
- Acetaldehyde, the main product of alcohol metabolism, binds to liver cell proteins, resulting in injured hepatocytes and an inflammatory reaction.
- Alcohol stimulates collagen synthesis in the liver, leading to *fibrosis and eventually cirrhosis*.

Liver Cirrhosis

Cirrhosis is a serious **degenerative disease** that occurs when healthy cells in the liver are damaged and replaced by **scar** tissue, usually as a result of alcohol abuse or chronic hepatitis. Severe damage can lead to liver failure and possibly death.

Hepatocytes die due to a variety of causes, including:

- Alcoholic liver disease 60-70%
- Viral hepatitis 10%
- Biliary disease 5-10%
- Primary hemochromatosis 5%
- Cryptogenic cirrhosis 10-15%
- Wilson's, α1AT def rare



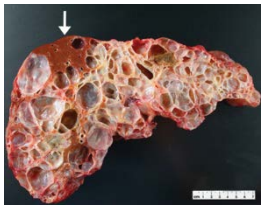
Liver Cirrhosis Symptoms

- Liver Failure
- Splenomegaly
- Ascites
- Infections
- Varices
- Portal hypertension
- Jaundice, Coagulopathy, hypoproteinemia, Encephalopathy, hepatic coma

Other liver Diseases

Liver Cyst: a simple liver cyst is a thin-walled bubble, a fluid-filled cavity in the liver, they are normally benign

Liver fibrosis: is characterized by the formation of fibroids or fibrous tissue, regenerative nodules, and liver scarring



Primary biliary cirrhosis is a serious autoimmune disease of the bile capillaries.

Primary sclerosing cholangitis **التهاب الأوعية الصفراوية التصلبي البدئي** is a serious chronic inflammatory disease of the bile duct, which is believed to be autoimmune in origin.

Budd–Chiari syndrome is the clinical picture caused by occlusion of the hepatic vein preventing the blood from leaving the liver

Tumors of the Liver

- **Benign tumors of the liver** include: liver cell adenoma, angioma , focal nodular hyperplasia.
- **Malignant**
  - *Primary malignant tumors* of the liver include:
    - liver cell carcinoma (hepatocellular carcinoma)
    - cholangiocarcinoma سرطانة الأوعية الصفراوية (adenocarcinoma of bile ducts)
    - Angiosarcoma ساركوم وعائي (malignant neoplasm of vascular endothelium غرن وعائي)
    - Hepatoblastoma ورم أرومي كبدي (primary liver tumor in childhood).
  - *Secondary metastases* include the entire gastrointestinal tract including pancreas and bowel, the lung and the breast.

Nodules & Tumors

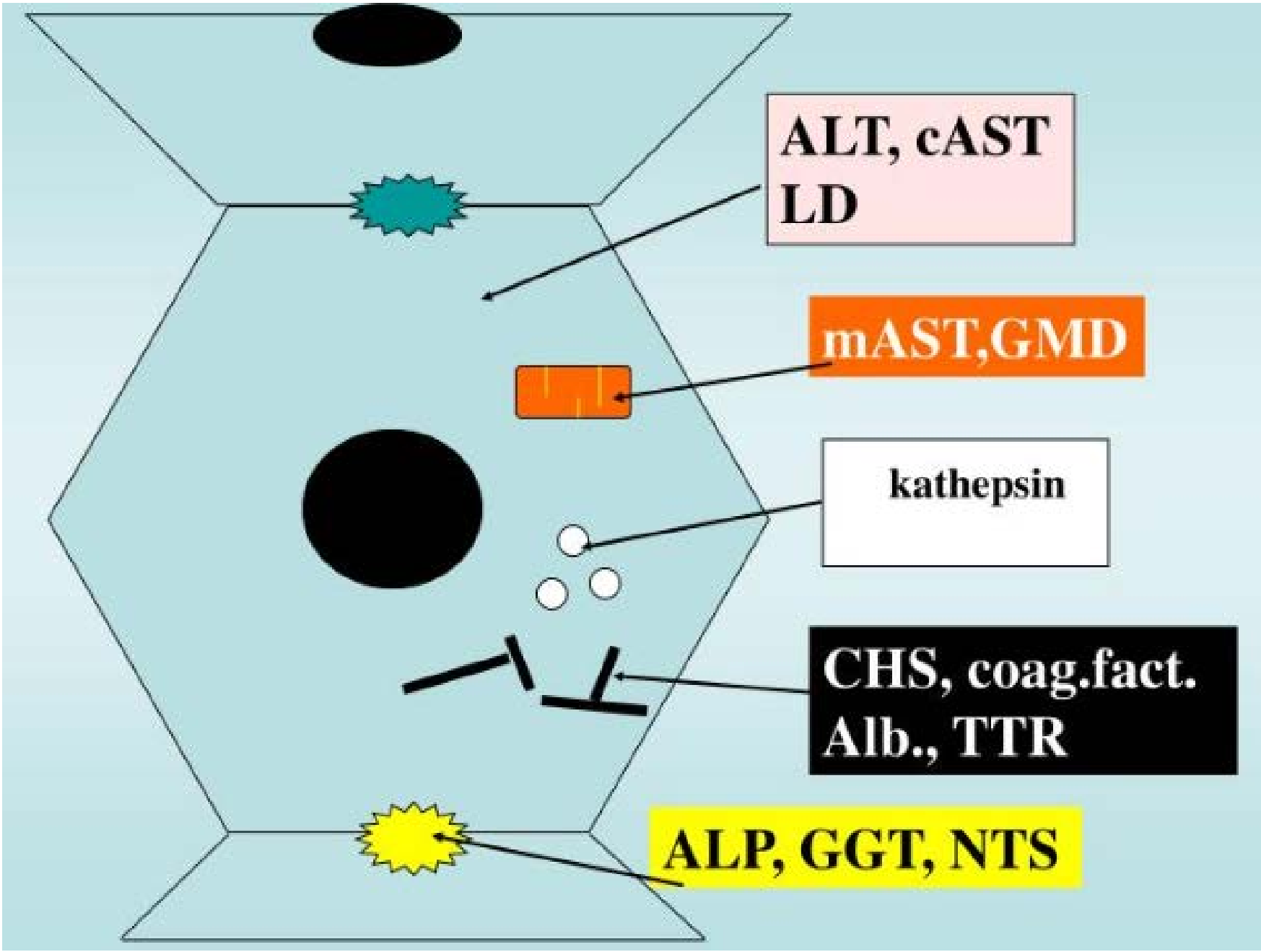
Hepatocellular Carcinoma

- male preponderance; 20 – 40 y/o
- Risk factors:
  1. Viral infection – chronic HBV & HCV infection
  2. Chronic alcoholism – (+) cirrhosis
  3. Food contaminants – aflatoxin from *Aspergillus flavus* → bind with cellular DNA → (+) p53 mutation

- Laboratory:
  - ➢ increased tumor markers – serum AFP, TAG-72, SCCA and serum CEA

V. Liver Enzymes

- Serum aminotransferases:
  - alanine aminotransferase (ALT, formerly called SGPT)
  - aspartate aminotransferase (AST, formerly called SGOT)
- Alkaline phosphatase (Alk Phos)
- Gamma-glutamyl transpeptidase (GGT)
- 5'-nucleotidase
- Lactate dehydrogenase (LDH)


ALT, cAST
LD
mAST,GMD
kathepsin
CHS, coag.fact.
Alb., TTR
ALP, GGT, NTS

DIAGNOSTIC ENZYMES

Cytoplasm: ALT, cAST (30 % of total liver AST) , LD

permeability

dysfunction

Mitochondria: mAST, GMD (glutamate dehydrogenase) necrosis

Membranes of bile duct endothelium and sinusoids:

ALP, GGT, 5-NTS (5´-nukleotidase) cholestasis

Lysosomes: hydrolytic enzymes:

proteinases (kathepsin) a β-glucuronidase (Gaucher´s disease)

Rough endoplasmic reticulum: CHS (cholinesterase),

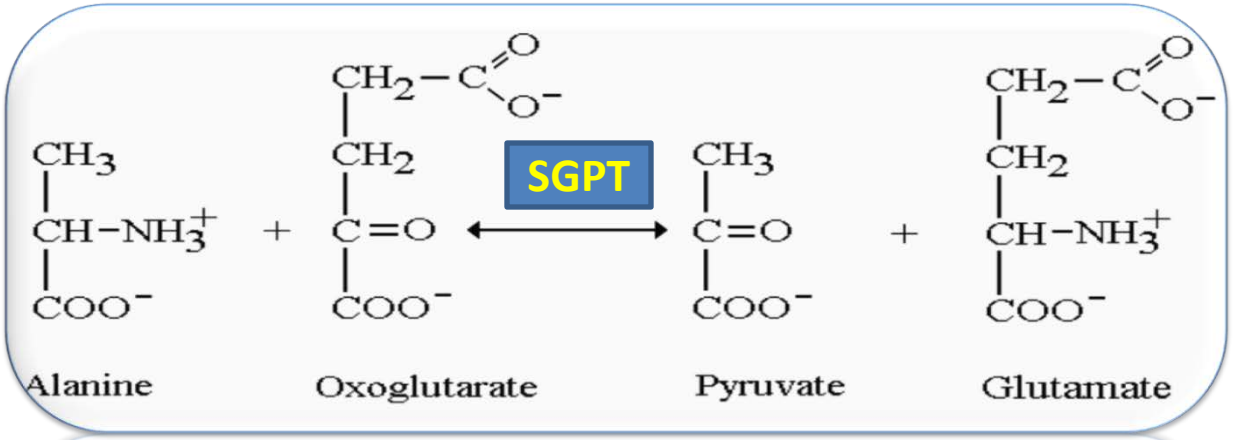
coagulations factors, plasmat. proteines (albumin, transthyretin, transferrin)

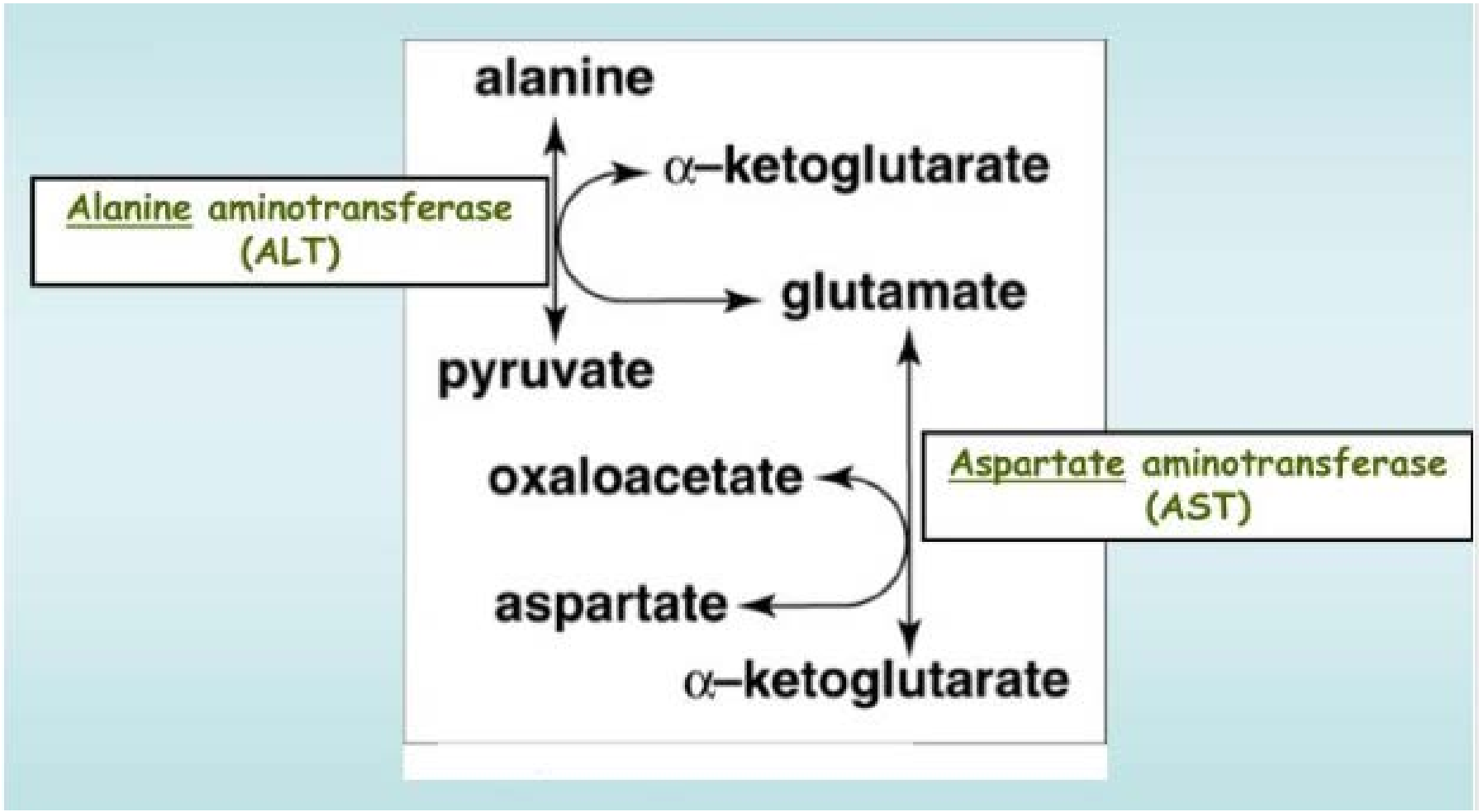
protein synthesis defect (decrease !)

Aminotranferases

Aminotransferases or transaminases are: a group of enzymes that catalyze the inter-conversion of amino acids and ketoacids by transfer of amino group. The two aminotransferases of greatest clinical significance are:

- Aspartate aminotransferase (AST), formerly termed glutamate oxaloacetate transaminase (GOT)
- and alanine aminotransferase (ALT), formerly termed glutamate pyruvate transaminase (GPT)




alanine
α–ketoglutarate
Alanine aminotransferase
(ALT)
glutamate
pyruvate
oxaloacetate
Aspartate aminotransferase
(AST)
aspartate
α–ketoglutarate

ALT and AST

Alanine aminotransferase=ALT is found predominantly in the liver (in cytoplasm of parenchymal cells), with clinically negligible quantities found in the kidneys, heart, and skeletal muscle**. ALT is a more specific indicator of liver inflammation than AST.**

- ALT (and all transaminases) require the coenzyme *pyridoxal phosphate*
- Significantly elevated levels often suggest the existence of other medical problems such as viral hepatitis, congestive heart failure, liver damage, infectious mononucleosis

Aspartate transaminase=(AST) is found in the liver (parenchymal cells), heart, skeletal muscles, kidneys, and red blood cells (it is not specific to the liver, it has also been used as a cardiac marker etc.),

- it is raised mainly in acute liver damage
- Two isoenzymes are present in humans: **cAST,** the cytosolic isoenzyme found mainly in red blood cells and heart (30 % of liver AST)
- **mAST,** the mitochondrial isoenzyme is present predominantly in liver (70 % of liver AST)

Transaminases:

ALT(SGPT) 10 to 45 U/L

AST(SGOT) 5 to 40 U/L

ALT is primarily localized to the liver. It is the marker enzyme of the liver.

ALT is present in the cytosol of hepatocytes.

AST is present in a wide variety of tissues like heart, skeletal muscles, liver, kidney, brain.

AST is present both in the cytosol and mitochondria of the hepatocytes.

Liver contains both enzymes but more of ALT

Estimation is very useful in **assessing severity and prognosis** of liver parenchymal disease especially infective hepatitis. Elevated levels :

Highly elevated > 20 times

Viral hepatitis

Drug or Toxin-induced hepatic necrosis

Moderately elevated - 3 to 20 times

Chronic hepatitis

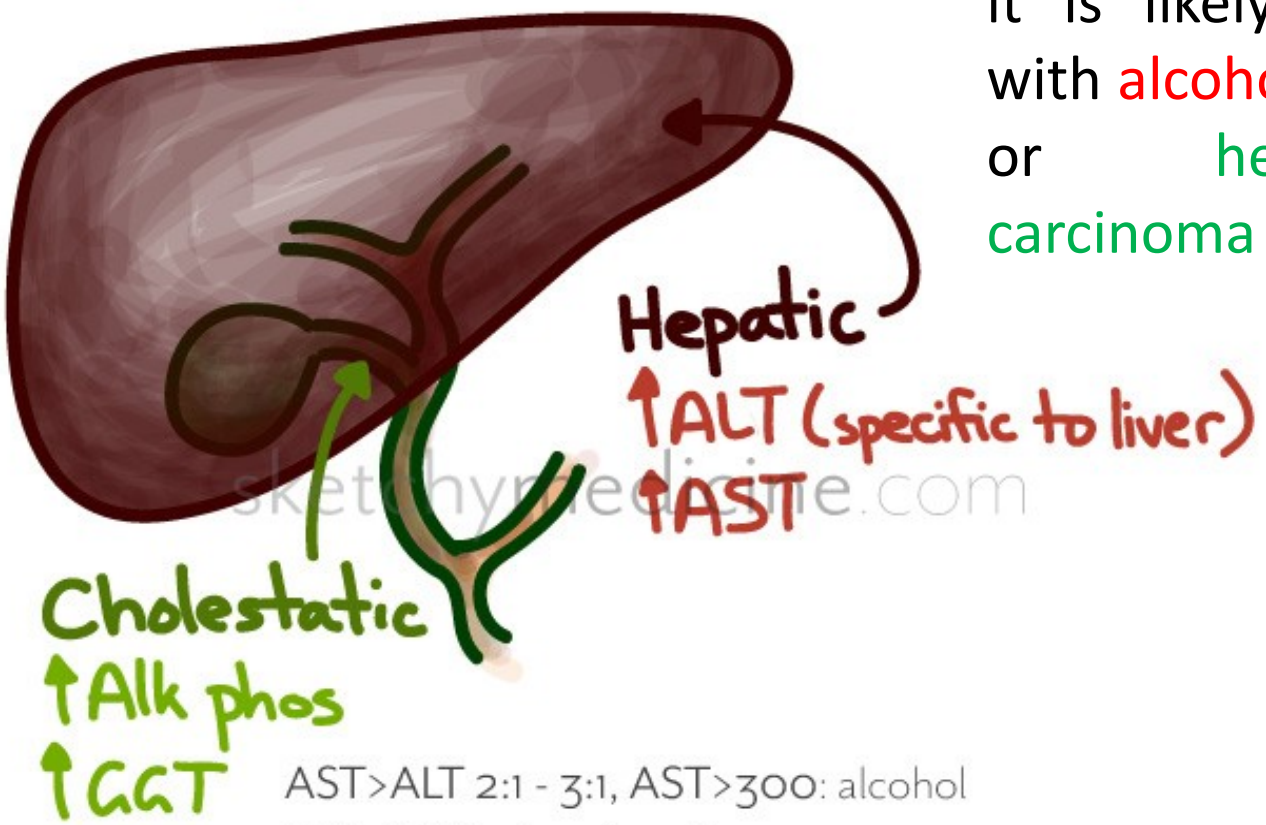
Alcoholic hepatitis

Acute biliary tract obstruction

When AST and ALT are both over 1000 IU/L, the differential can include acetaminophen (paracetamol) toxicity, or fulminant liver failure.

AST/ALT ratio (De Ritis Ratio)

Liver Enzymes



When **AST/ALT > 2.0**, it is likely associated with alcoholic hepatitis or hepatocellular carcinoma

AST>ALT 2:1 - 3:1, AST>300: alcohol

ALT>AST in fatty liver disease

ALT>AST by 1000x: acute viral hepatitis, ischemia, toxins, auto-immune, Wilson's disease

**AST can also come from muscle*

**ALP has 5 minor sources (liver, blue duct, kidney, bone, placenta)*

Other Enzymes

- Alkaline Phosphatase ALP / Gamm GT: are:
  - Canalicular enzymes: Liver ALP rises with obstruction or infiltrative diseases (i.e., stones or tumors) ⟶ Gradual increase in plasma levels is seen in bile duct obstruction and intrahepatic cholestasis ركودة صفراوية
  - ➢ ALP is found in liver, bones and intestines
  - ➢ GGT is more sensitive marker for cholestatic damage than ALP
  - ➢ GGT is elevated in alcohol toxicity

  Since liver is not the sole source of ALP activity (bone, small intestine…), an elevated gamma GT would suggest that the liver is the source of the increased alkaline phosphatase

- Lactate Dehydrogenase (LDH-5)

Other Enzymes

Serum γ-Glutamyl Transferase

- Normal range: 10-47 IU/L: ↑ Cholestasis, alcohol ingestion

Serum 5'-Nucleotidase

- Normal range: 2-17 IU/L

Serum Lactate Dehydrogenase

- Normal range: 70-240 IU/L: acute liver damage

Main Types of Liver Diseases

Bile duct obstruction

Gilbert's syndrome

Crigler-Najjar Syndrome

Nonalcoholic fatty liver

Hepatitis A, B, C, D, E

Toxic hepatitis

Alcoholic hepatitis

Wilson's disease

Hemochromatosis

Alpha-1-antitrypsin deficiency

Autoimmune hepatitis

Cirrhosis

Primary biliary cirrhosis

Liver adenoma

Liver cancer

Liver cyst

Liver nodule (focal nodular hyperplasia)

Parasitic infection

Portal vein thrombosis

Fatty Liver

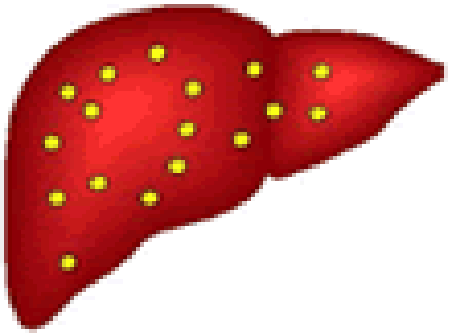
- **Fatty liver disease** (**FLD**): is a reversible condition wherein large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis التنكس الدهني (i.e., abnormal retention of lipids within a cell).
- Fatty liver occurs in those with excessive alcohol intake and the obese patients (with or without effects of insulin resistance).
- By considering the contribution by alcohol, fatty liver may be termed: 1- alcoholic steatosis

2- nonalcoholic fatty liver disease (NAFLD)

3- Non-alcoholic steatohepatitis (NASH)

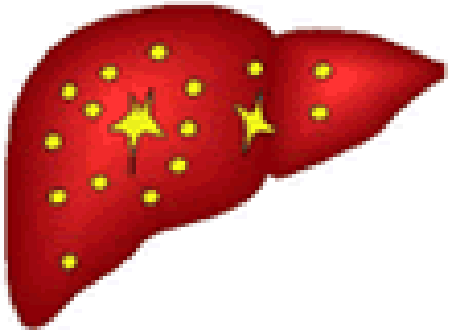
The Spectrum of NAFLD

Fatty Liver



Fat accumulates in the liver

NASH



Fat plus inflammation and scarring

Cirrhosis

Scar tissue replaces liver cells

Metabolic Disorders

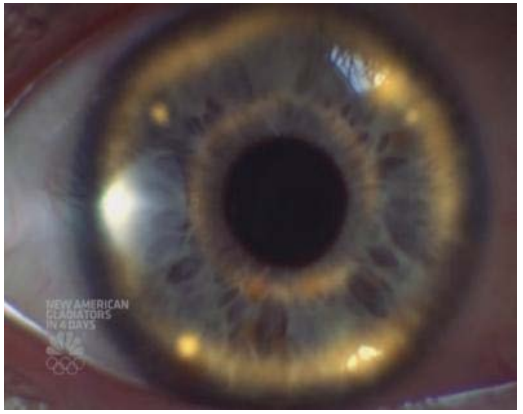
Hemochromatosis

- Excessive accumulation of body iron → deposit in parenchymal organs (e.g. heart, liver and pancreas)
- May be secondary to a genetic defect (increased absorption) OR a consequence of parenteral administration of iron
- Over 1/3 of iron accumulated stored in the liver
- Increased risk of cirrhosis and hepatocellular carcinoma

Metabolic Disorders

Wilson's Disease (Hepatolenticular degeneration)

- Copper accumulation particularly in liver, brain, and eye (demonstrated by Kayser–Fleischer rings)
- Due to mutation of Wilson's disease gene (*ATP7B*) on chr. 13 → decreased synthesis of ceruloplasmin → defective biliary excretion of copper



Metabolic Disorders

A1-Antitrypsin deficiency

Alpha-1 antitrypsin (A1AT) is a glycoprotein which is largely produced in the liver.(AAT) protects the lungs and liver from damage (protects the body from a powerful enzyme called neutrophil elastase. Elastase is released from white blood cells to fight infection, but it can attack normal tissues (especially the lungs) if not tightly controlled by alpha-1 antitrypsin.).

Alpha-1 antitrypsin deficiency is an inherited disorder that may cause lung disease.

Approximately 15 percent of adults with alpha-1 antitrypsin deficiency develop liver damage (cirrhosis)

Signs and symptoms

Emphysema, shortness of breath, wheezing. A1AD also causes impaired liver function….

What is Viral Hepatitis ?

- Viral hepatitis is a **systemic** disease with primary inflammation of the liver by any one of a heterogenous group of hepatotropic viruses:

1. **Hepatitis viruses**
2. Epstein-Barr virus
3. Cytomegalovirus
4. Children & immunocompromised → rubella, adenovirus, herpesvirus, and enterovirus

Hepatitis	A	B	C	D	E
Virus	HAV	HBV	HCV	HDV	HEV
Family	Picornavirus	Hepadnavirus	Flavivirus	Satellite	Calicivirus
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Spread	Fecal-oral	parenteral, sexual,perinatal	parenteral, ?sexual	parenteral, ?sexual	Fecal-oral
Antigens	HAV-Ag	HbsAg,HBcAg, HBeAg	HCV-Ag	HDV-Ag	HEV-Ag
Antibodies	Anti_HAV	Anti-HBs,Anti-HBc,Anti-HBe	Anti-HCV	Anti-HDV	Anti-HEV
Virus markers	HAV RNA	HBV DNA, DNA polymerase	HCV RNa	HDV RNa	viruslike partiacles

Hepatitis A Virus Transmission

- Close personal contact
  (e.g., household contact, child day care centers)
- Contaminated food, water
  (e.g., infected food handlers, raw shellfish)
- **Lab diagnosis:** -Detection of Antibody :By ELISA

  - Biochemical tests:

  i) Alanine aminotransferase (ALT)

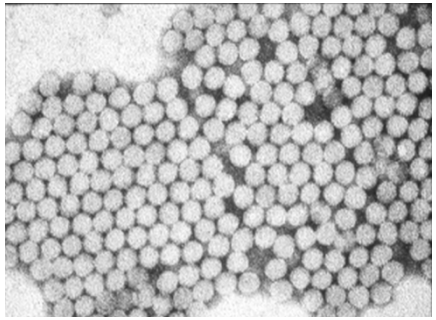
  ii) Bilirubin

  iii) Protein

Hepatitis Viruses

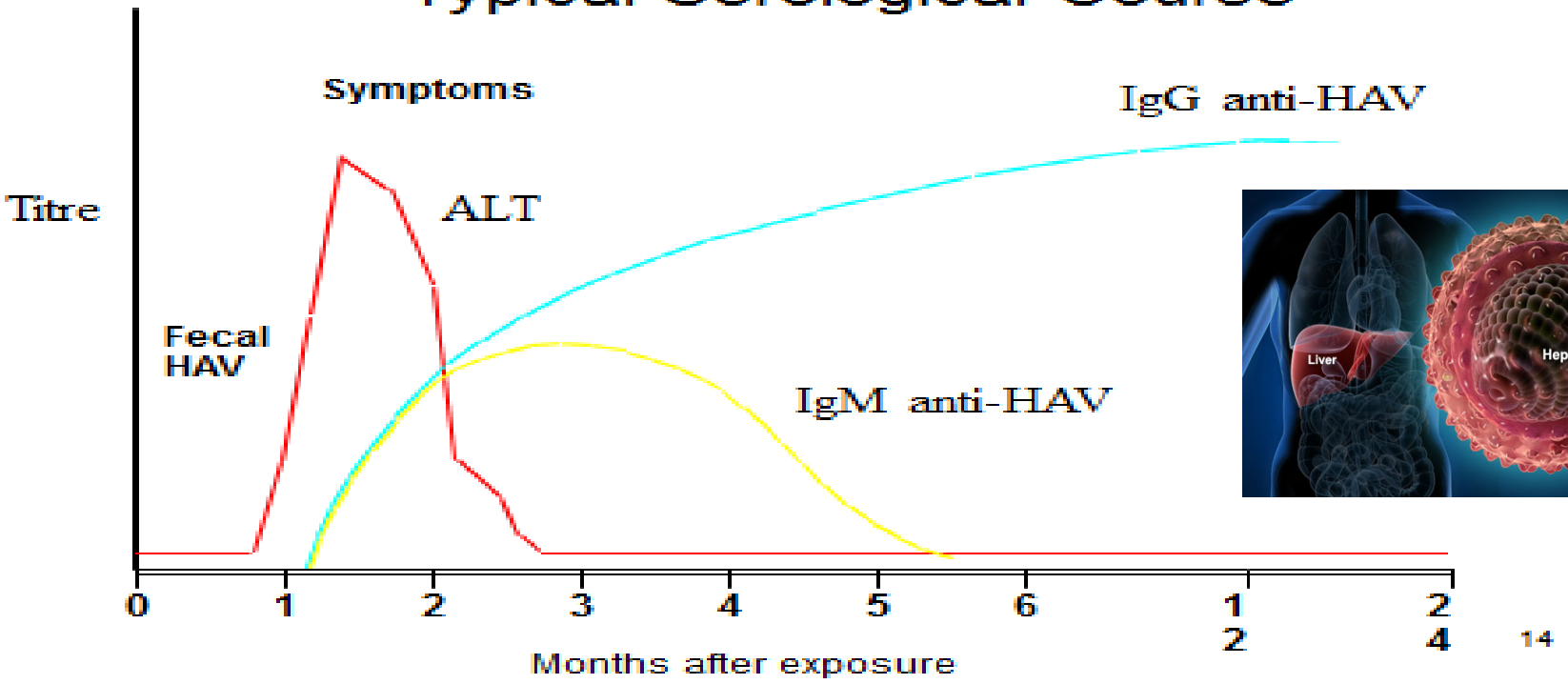
Hepatitis A

- **Small, non-enveloped, ssRNA**
- **Picornavirus family, *Hepatovirus***
- ***Incubation period: 2-6 weeks***



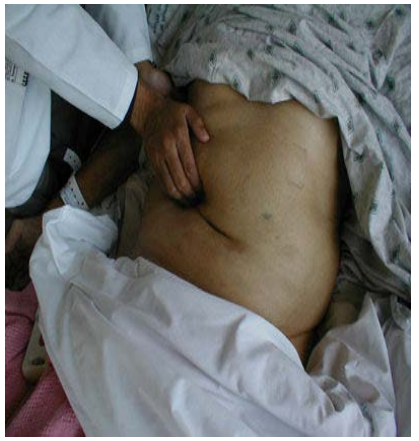
Hepatitis A Infection

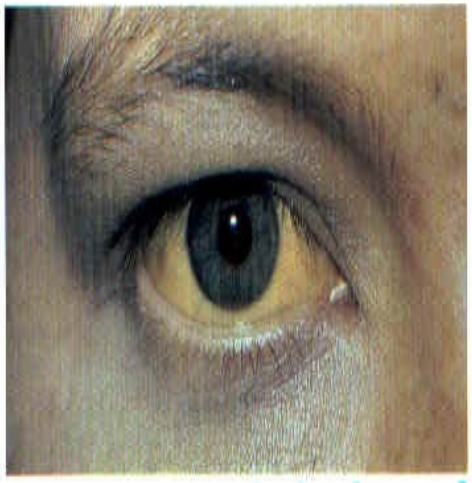
Typical Serological Course

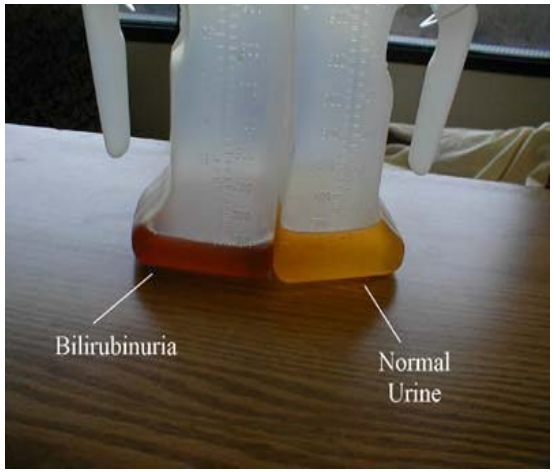


- **Preicteric phase** : (symptoms: fatigue, joint- and abdominal pain, malaise, vomiting, lack of appetite, hepatomegaly, low-grade fever)
- **Icteric phase**: Icterus: (skin, sclera, mucous membranes,

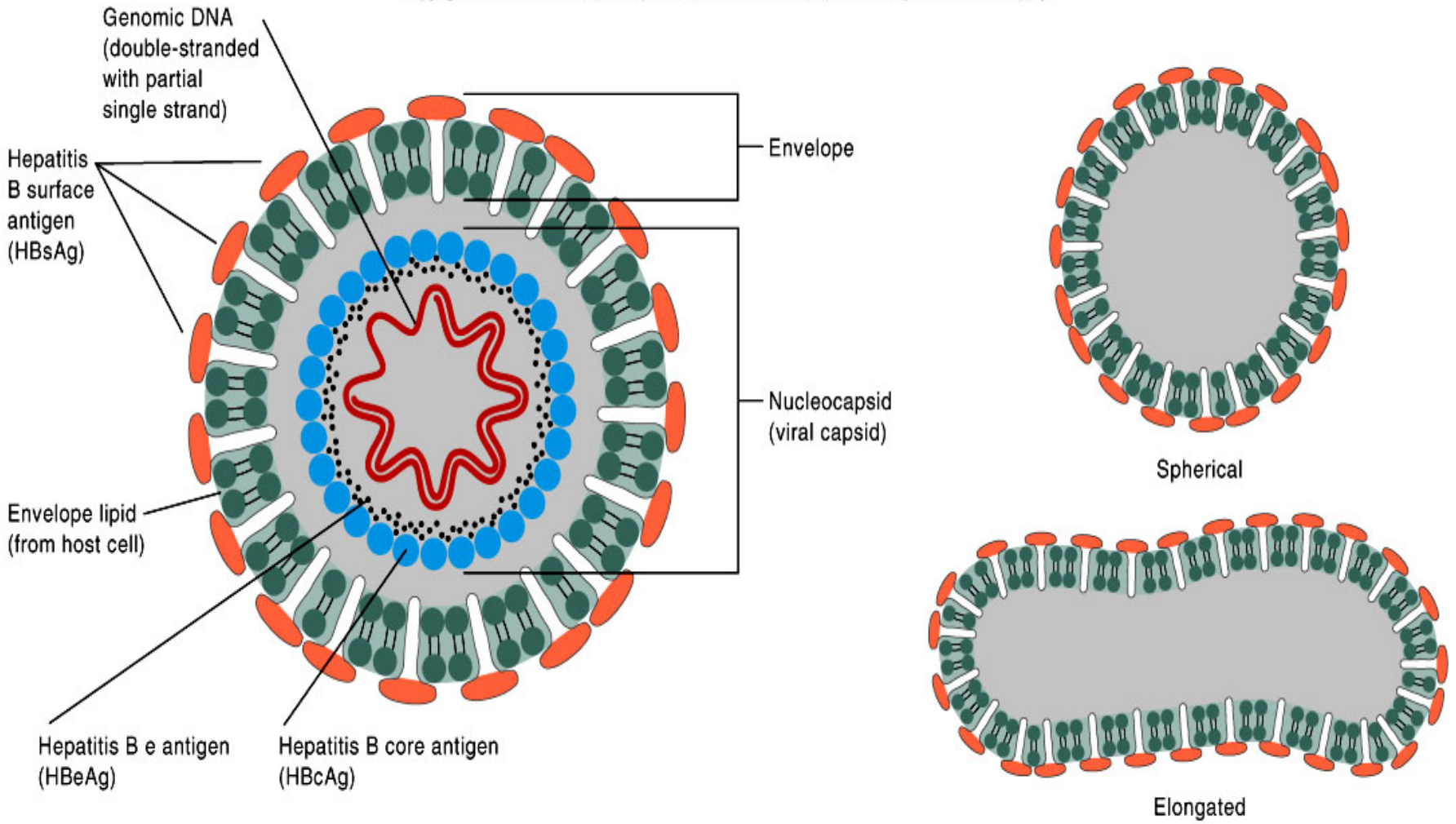
cause: elevated bilirubin level, bilirubinuria: dark urine, pale stool)







Hepatitis B HBV : Structure

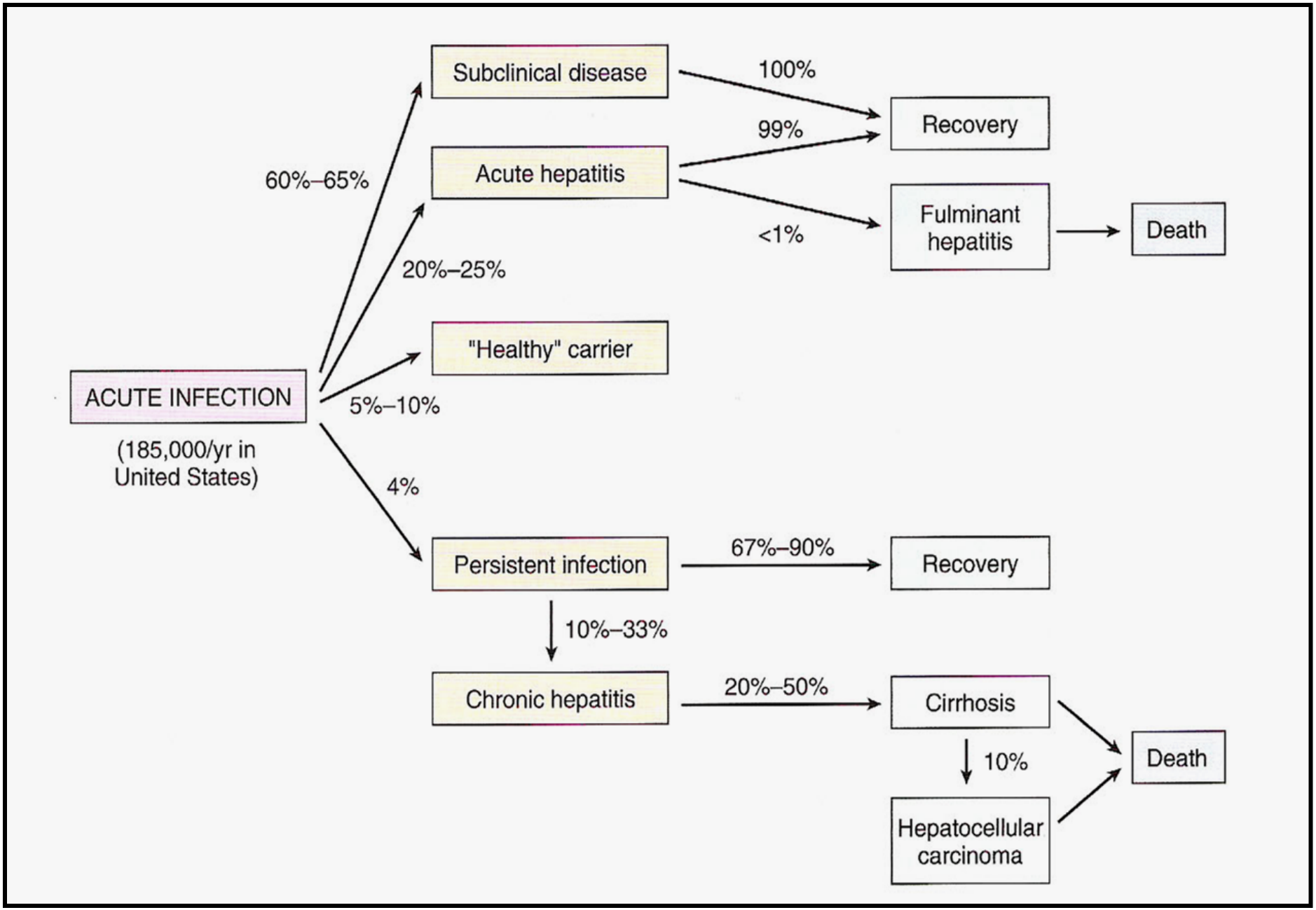


(a) Complete infectious virion

(b) Viral envelope particles containing HBsAg

Hepatitis B

- **Hepadnavirus family, ds DNA**
- present in all physiologic and pathologic body fluids → blood & body fluids (the primary vehicle for transmission)
- Incubation period: 4 – 12 weeks
- MOT:
  1. Transfusion
  2. Blood products
  3. Dialysis
  4. Needle stick accidents among health care workers
  5. IV drug abuse
  6. Sexual contact


ACUTE INFECTION
(185,000/yr in United States)
60%–65%
20%–25%
5%–10%
4%
Subclinical disease
Acute hepatitis
"Healthy" carrier
Persistent infection
Chronic hepatitis
100%
99%
<1%
Recovery
Fulminant hepatitis
Death
67%–90%
Recovery
10%–33%
20%–50%
Cirrhosis
10%
Hepatocellular carcinoma
Death

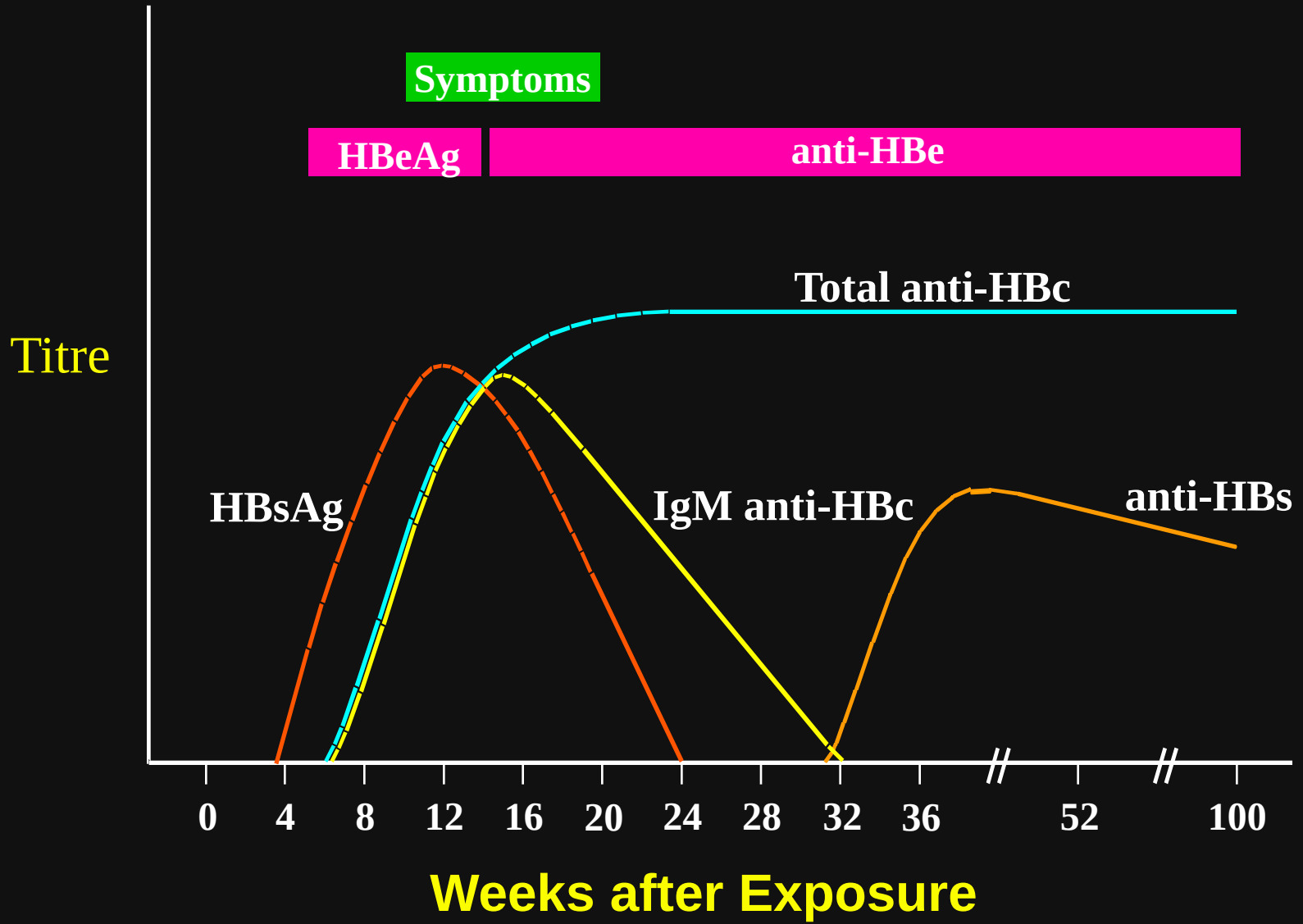
serology

- HBsAg: surface antigen
- HBeAg: e antigen (a component of HBV core); marker of viral replication
- HBcAg: core antigen (cannot be measured in serum)
- both HBsAg and HBeAg are present during acute hepatitis B
- anti-HBs follows HBsAg clearance and confers long-term immunity
- anti-HBe and anti-HBc appear during the acute and chronic phases of the illness but do not provide immunity

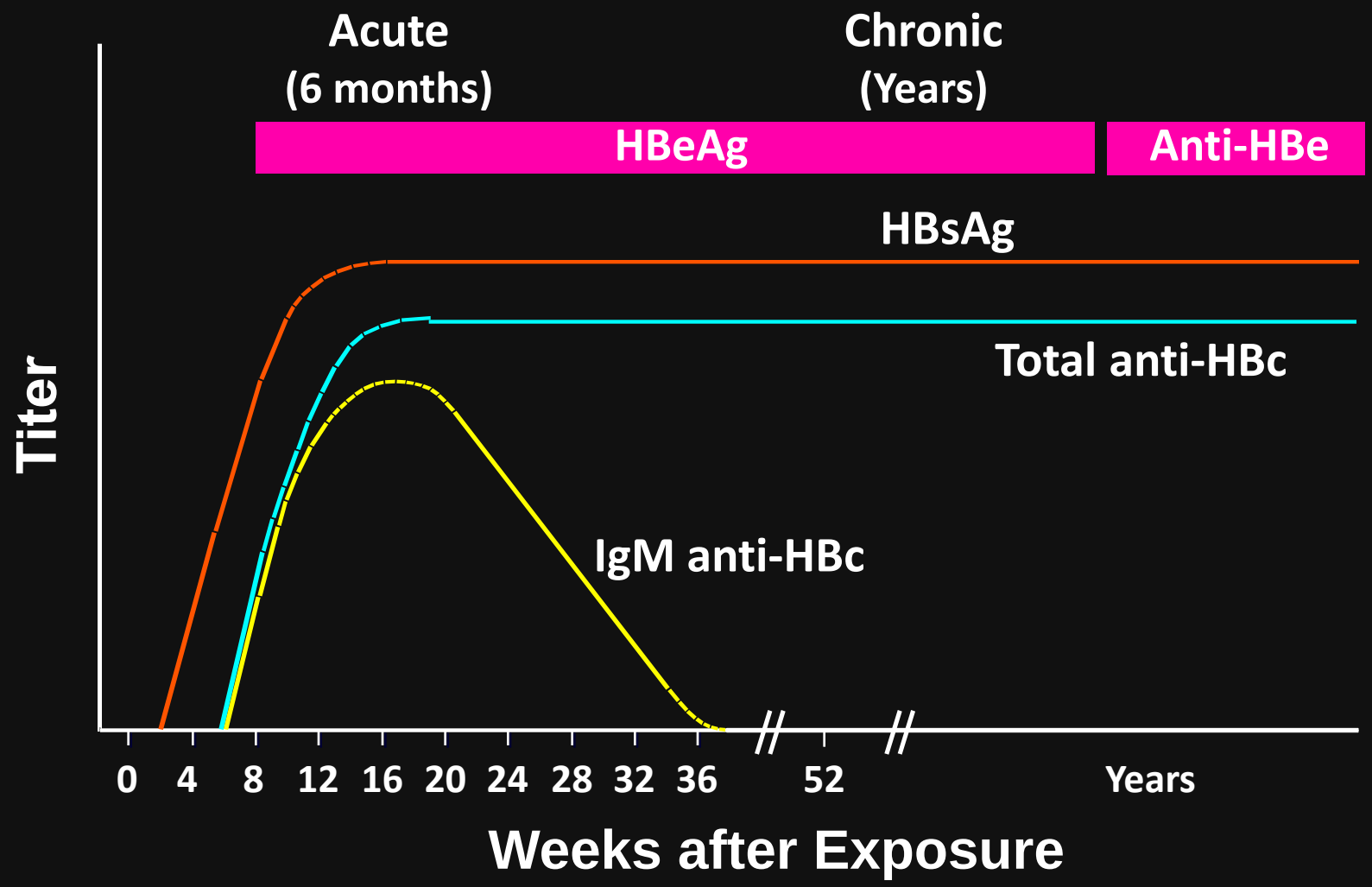
- anti-HBe indicates low infectivity

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course



Acute HBV Infection with Progression to Chronic Infection: Typical Serologic Course



Test	Result	Interpretation
HBsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
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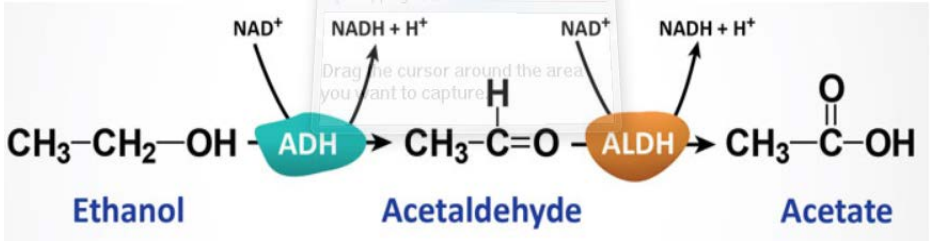
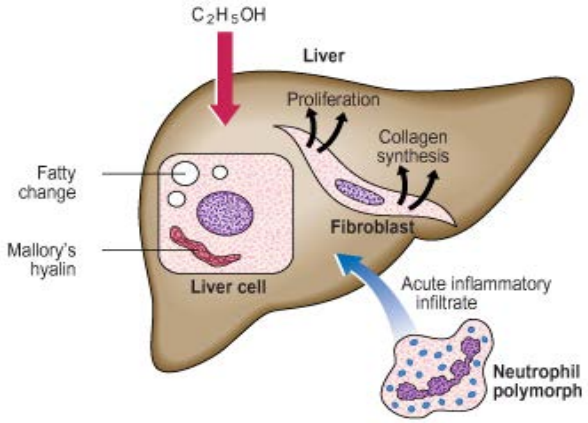
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	1- Resolved infection 2- False positive anti –HBc, thus susceptible 3- low level chronic infection
Anti-HBc	Positive	
Anti-HBs	Negative	

Alcoholic Hepatitis





- Cellular energy is diverted from essential metabolic pathways, such as fat metabolism, to the metabolism of alcohol so fat accumulates in the liver cells.
- The original **biochemical** explanation for an **alcoholic fatty liver** centered on the ability of ethanol metabolism to shift the redox state of the **liver** and inhibit **fatty** acid oxidation. Subsequent studies found repression of **fatty** acid oxidation and that the induction of lipogenesis can occur in **alcoholic** conditions

- Acetaldehyde, the main product of alcohol metabolism, binds to liver cell proteins, resulting in injured hepatocytes and an inflammatory reaction.
- Alcohol stimulates collagen synthesis in the liver, leading to *fibrosis and eventually cirrhosis*.

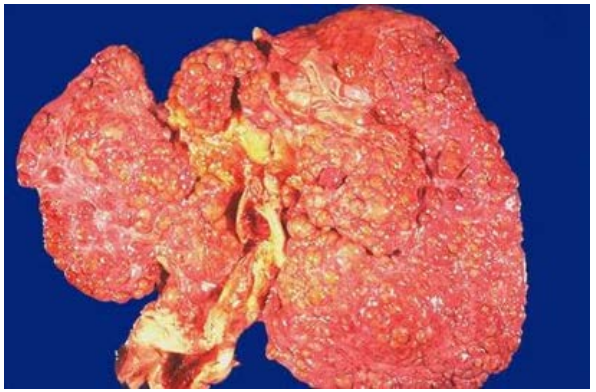
Liver Cirrhosis

Cirrhosis is a serious **degenerative disease** that occurs when healthy cells in the liver are damaged and replaced by **scar** tissue, usually as a result of alcohol abuse or chronic hepatitis. Severe damage can lead to liver failure and possibly death.

Cirrhosis poses another danger as well: Dense scarring slows the normal flow of blood through the liver, causing blood to find alternate pathways to return to the heart. This includes veins along the stomach and esophagus. The added pressure in these blood vessels, called **varices**, can cause them to enlarge and, in some cases, rupture….

Hepatocytes die due to a variety of causes, including:

- Alcoholic liver disease 60-70%
- Viral hepatitis 10%
- Biliary disease 5-10%
- Primary hemochromatosis 5%
- Cryptogenic cirrhosis 10-15%
- Wilson's, α1AT def rare



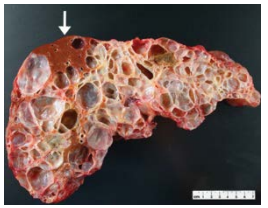
Liver Cirrhosis Symptoms

- Liver Failure
- Splenomegaly
- Ascites
- Infections
- Varices
- Portal hypertension
- Jaundice, Coagulopathy, hypoproteinemia, Encephalopathy, hepatic coma

Other liver Diseases

Liver Cyst: a simple liver cyst is a thin-walled bubble, a fluid-filled cavity in the liver, they are normally benign

Liver fibrosis: is characterized by the formation of fibroids or fibrous tissue, regenerative nodules, and liver scarring



Primary biliary cirrhosis is a serious autoimmune disease of the bile capillaries.

Primary sclerosing cholangitis **التهاب الأوعية الصفراوية التصلبي البدئي** is a serious chronic inflammatory disease of the bile duct, which is believed to be autoimmune in origin.

Budd–Chiari syndrome is the clinical picture caused by occlusion of the hepatic vein preventing the blood from leaving the liver

Tumors of the Liver

- **Benign tumors of the liver** include: liver cell adenoma, angioma , focal nodular hyperplasia.
- **Malignant**
  - *Primary malignant tumors* of the liver include:
    - liver cell carcinoma (hepatocellular carcinoma)
    - cholangiocarcinoma سرطانة الأوعية الصفراوية (adenocarcinoma of bile ducts)
    - Angiosarcoma ساركوم وعائي (malignant neoplasm of vascular endothelium غرن وعائي)
    - Hepatoblastoma ورم أرومي كبدي (primary liver tumor in childhood).
  - *Secondary metastases* include the entire gastrointestinal tract including pancreas and bowel, the lung and the breast.

Nodules & Tumors

Hepatocellular Carcinoma

- male preponderance; 20 – 40 y/o
- Risk factors:
  1. Viral infection – chronic HBV & HCV infection
  2. Chronic alcoholism – (+) cirrhosis
  3. Food contaminants – aflatoxin from *Aspergillus flavus* → bind with cellular DNA → (+) p53 mutation

- Laboratory:
  - ➢ increased tumor markers – serum AFP, TAG-72, SCCA and serum CEA