Liver

Case based discussion

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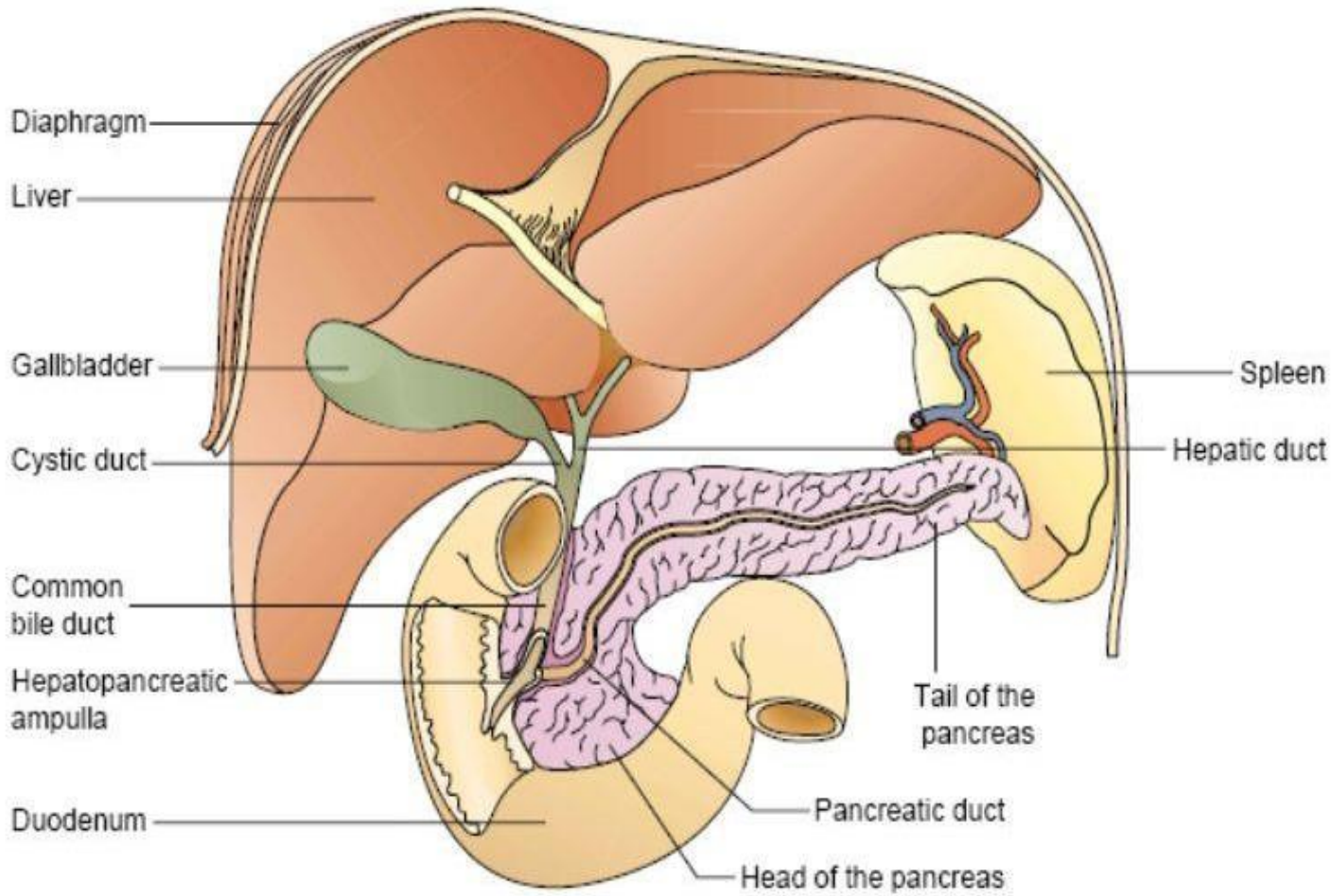
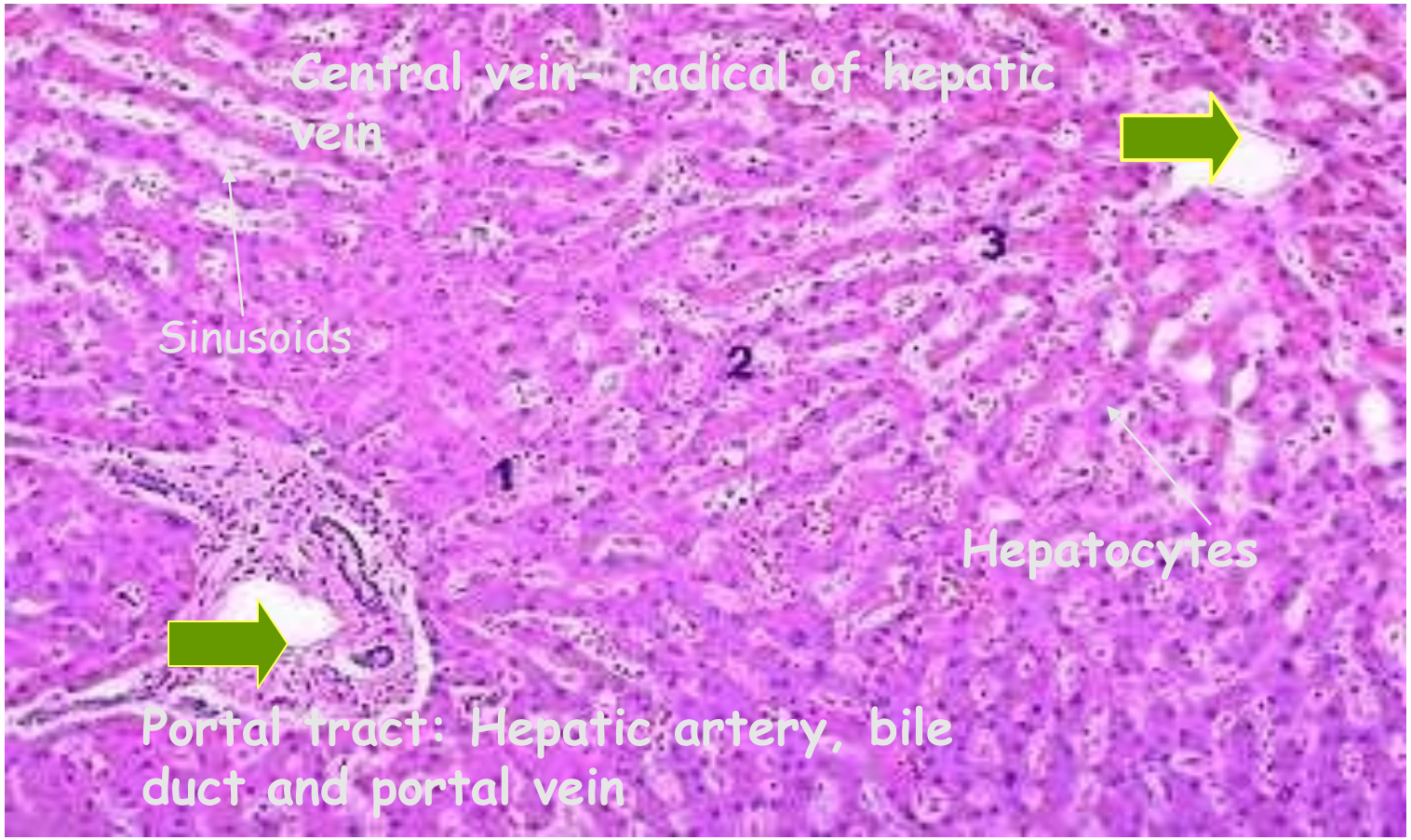
The liver and biliary system



Normal Liver - Microscopy



Liver Functions

- Metabolic – glucose homeostasis, lipoproteins
- Synthetic – albumin, coagulation factors, complement, binding proteins
- Storage – glycogen, FAT, vitamins, metals (Fe, Co)
- Catabolic – hormones, xenobiotics
- Excretory – bile (bilirubin, bile acids, cholesterol, phospholipids, copper)

Liver function tests

Enzymes

- In liver cell injury leakage of intracellular enzymes into blood causes elevated concentrations of these enzymes which can be measured
- Eg ALT, AST,GGT, Alkaline Phosphatase

Transaminases

- AST (SGOT)- a mitochondrial enzyme; ALT (SGPT)- a cytosolic enzyme
- ALT is more specific than AST for liver disease
- • Alanine amino transferase (ALT or SGPT) < 45 units per liter (U/L)
- • Aspartate amino transferase (AST or SGOT) <35 U/L

- AST>ALT in alcoholic liver disease;
- ALT > AST in viral hepatitis;

Other enzymes

- Alkaline phosphatase

Normally present in bile canaliculi

Obstruction causes regurgitation of enzyme into blood resulting in increased concentration

- Gamma glutamyl transferase [GGT]

Disproportionately increased in alcoholic liver disease

Albumin

- Major serum protein synthesized by liver cells
- Relatively long half life so liver damage has to be sustained for some time before decreased levels are found
- Indicates severe functional impairment of liver

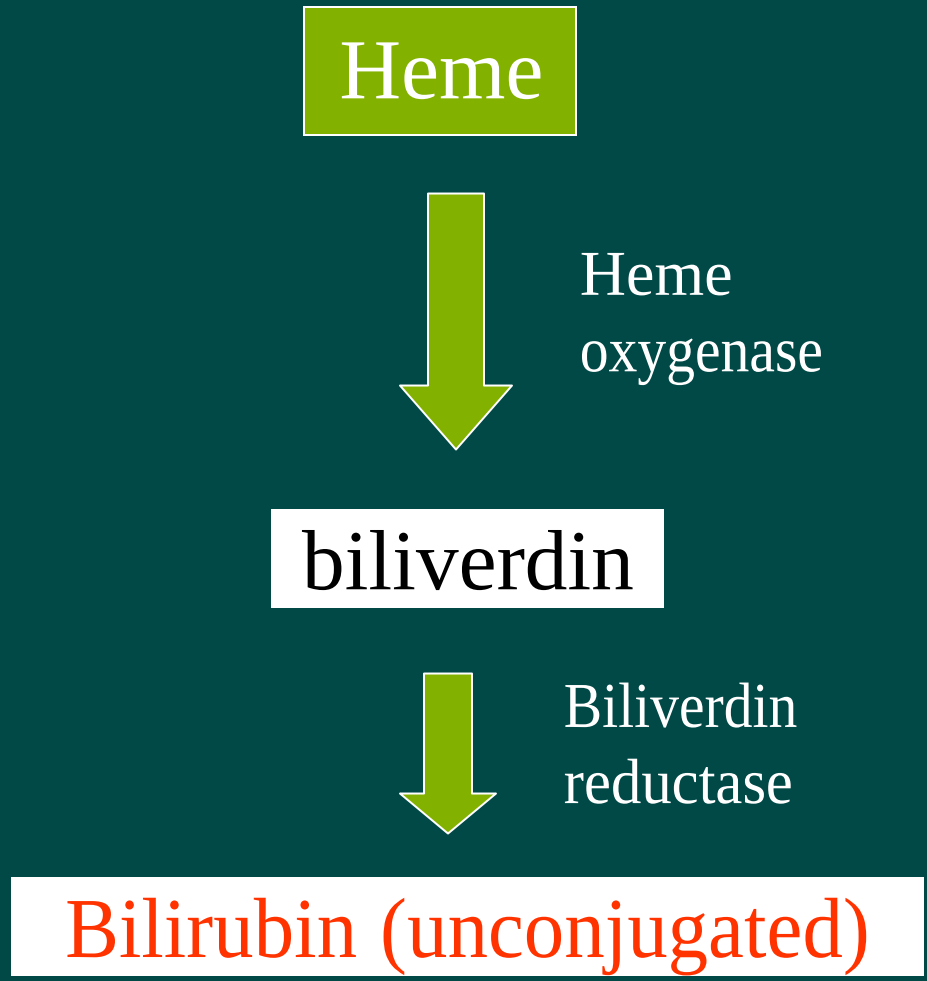
Clotting factors

- Liver synthesizes vitamin K dependant clotting factors
- Relatively shorter half life; deficiency may be found early in the course of the disease.
- Detected in lab by Prothrombin Time (N<15 sec)
- Testing mandatory before liver biopsy or surgery in a patient with liver disease
- Can be corrected by Vitamin K or clotting factors

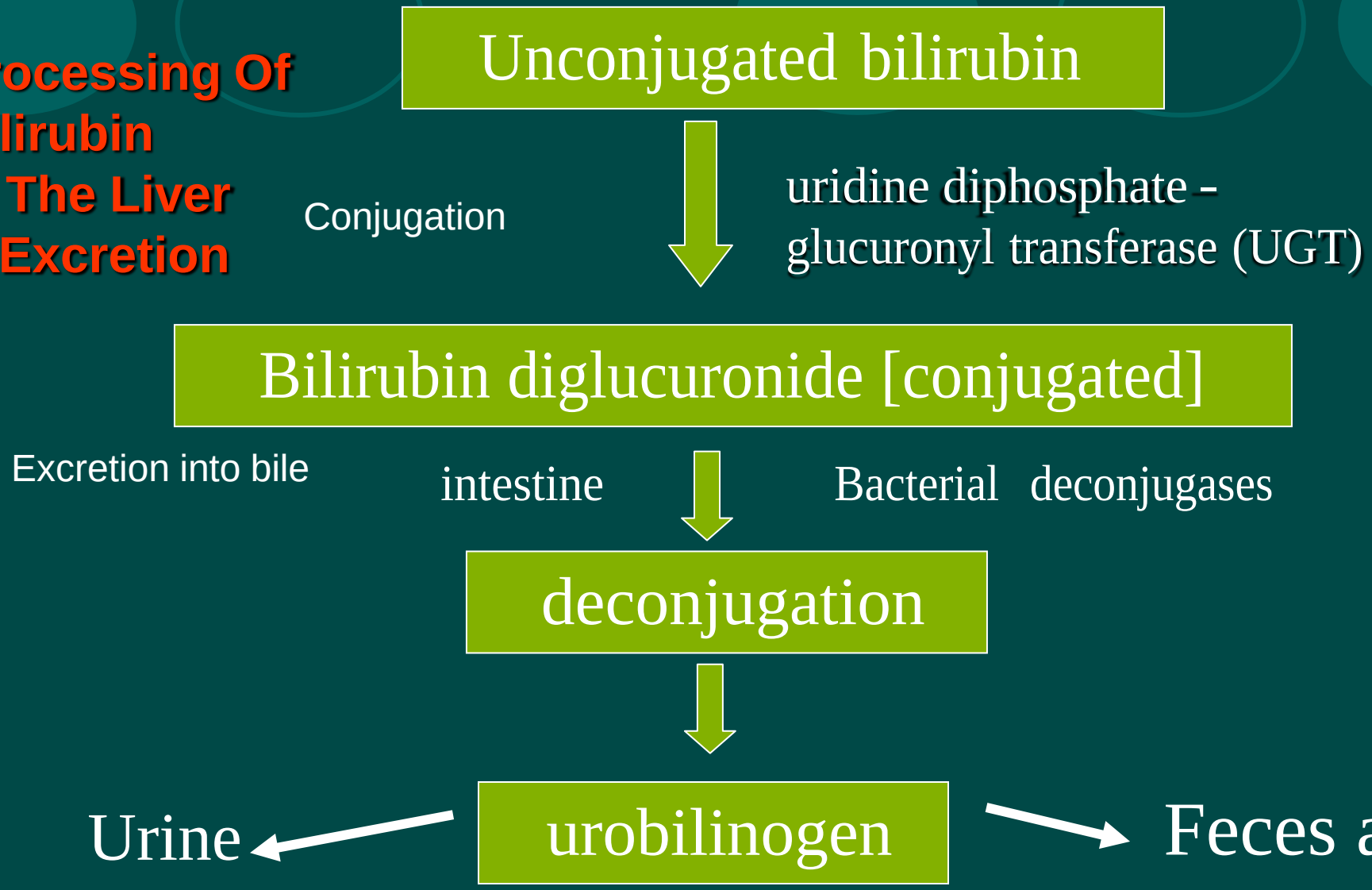
Bilirubin metabolism & Jaundice

Origin Of Bilirubin

- Senescent RBC (85%)
- Inefficient hematopoiesis (10%)
- Hemoproteins in liver, kidney cells, etc. (e.g. P450, cytochrome) 5%



Processing Of Bilirubin in The Liver & Excretion



Bilirubin in plasma and urine

- Total
- Conjugated
- Unconjugated

Jaundice/Icterus

- Yellow discoloration of skin & sclera due to **excess serum bilirubin.**
- Normal value . 0.1 to 1.2 mg/dL
- **Classification**
  - Hemolytic (prehepatic)
  - Hepatic
  - Obstructive (post hepatic)
- Conjugated & Unconjugated types
- Jaundice - Not necessarily liver disease *

Jaundice

- Predominantly unconjugated hyper-bilirubinemia
  - Excess production (**hemolytic anemia**, ineffective erythropoiesis, resorption of blood from internal bleeding)
  - Reduced hepatic uptake (drug interference, some cases of Gilbert syndrome)
  - Impaired conjugation (physiologic, Criggler – Najjar, Gilbert syndrome, diffuse hepatic disease)

Predominantly unconjugated hyper-bilirubinemia

- Physiologic jaundice of newborn
- Diffuse hepatocellular disease – Viral hepatitis, Drug induced hepatitis, Cirrhosis

Jaundice

- Predominantly conjugated hyper-bilirubinemia
  - Decreased hepatic excretion of bilirubin glucuronides- bile duct **obstruction**
  - Deficiency in canalicular membrane transporters
    - Dubin – Johnson, Rotor syndromes

Conjugated and unconjugated hyperbilirubinemia

- Liver diseases – viral hepatitis, cirrhosis, alcoholic liver disease etc

Neonatal jaundice

- Transient & mild hyperbilirubinemia in the newborn
- Physiological (liver is not fully developed until about 2 weeks of age)

Hereditary hyperbilirubinemias				
Disorder	inheritance	Defect	Pathology	Outcome
Unconjugated hyperbilirubinemia				
Criggler-Najjar I	AR	Absent B-UGT	Normal liver	neonatal Fatality
Criggler-Najjar II	AD – VP	Decreased B-UGT	Normal	Rare; mild kernicterus
Gilbert	? AD	↓ B-UGT	Normal	Innocuous
Conjugated Hyperbilirubunemia				
Dubin-Johnson	AR	Bile excre. Defect	Pigment in liver	Innocuous
Rotor	AR	?uptake defect	normal	Innocuous

Cholestasis- impaired bile formation & flow –due to obstruction/defect in secretion

- Characterized by
  - Jaundice
  - Pruritus – deposition of elevated plasma bile acids in tissues
  - Xanthomas – due to hyperlipidemia[cholesterol]
  - Elevated serum alkaline phosphatase
  - Manifestations related to deficiency of fat soluble vitamins

Viral hepatitis – hepatitis A virus infection

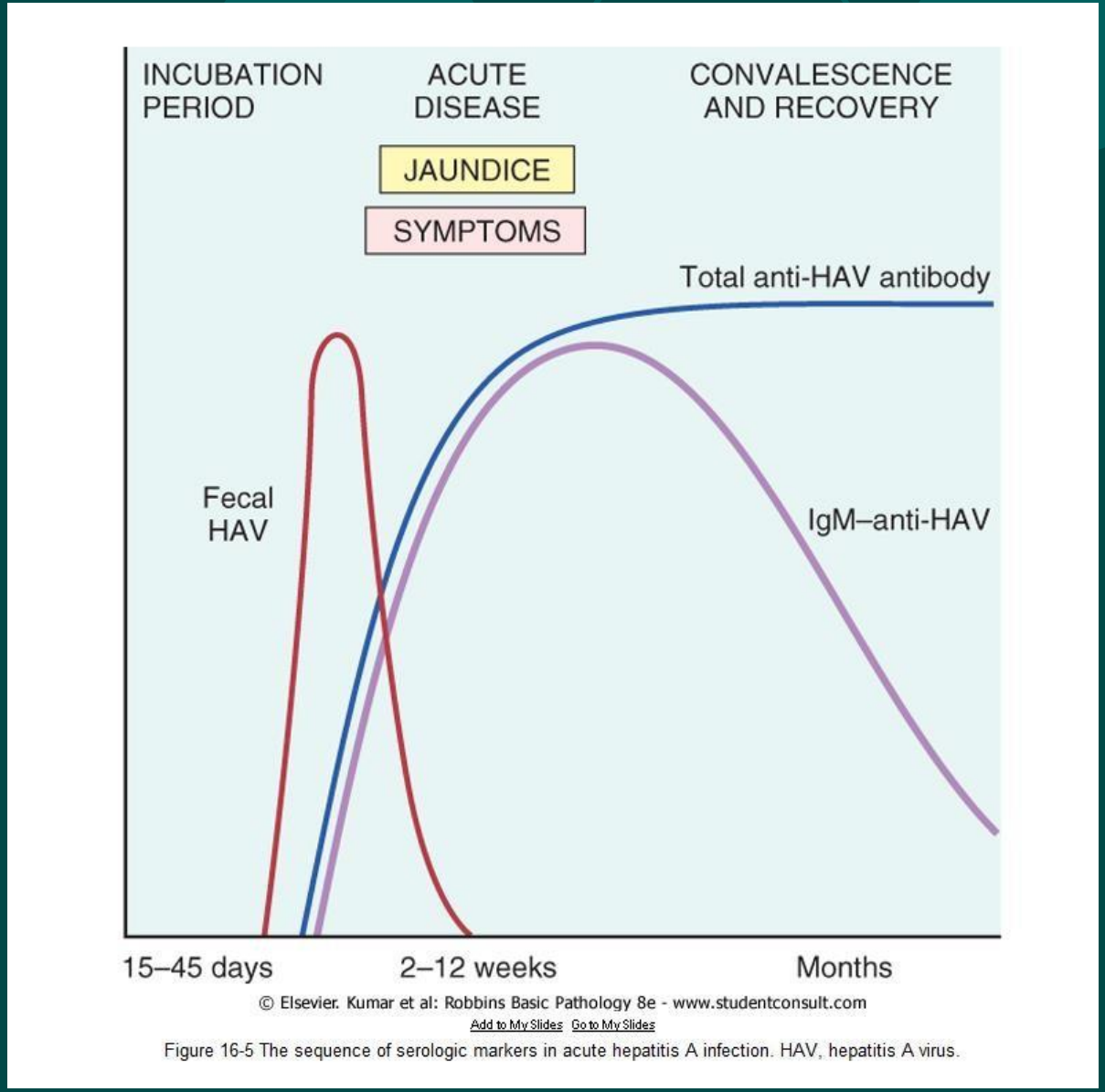
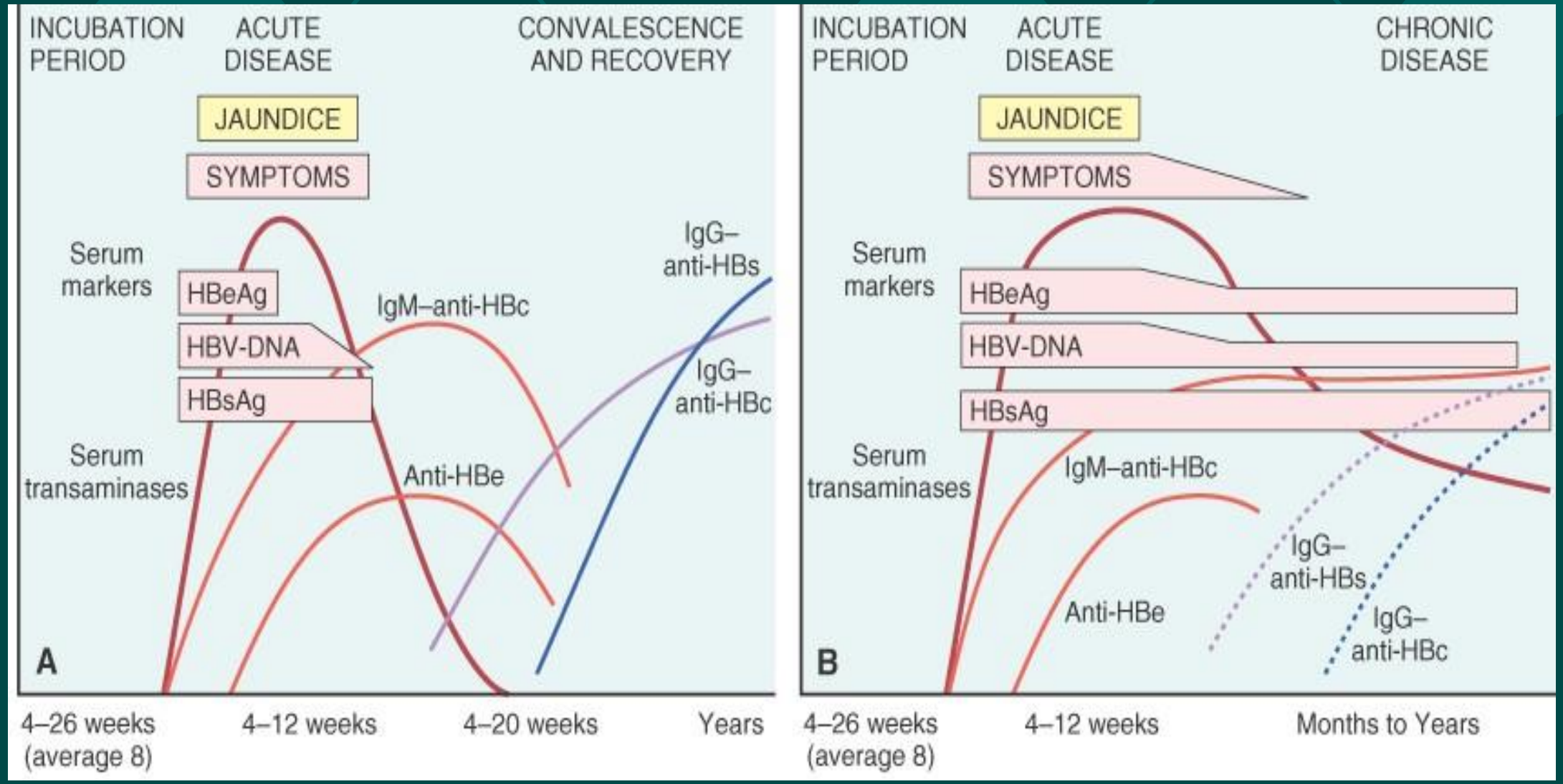
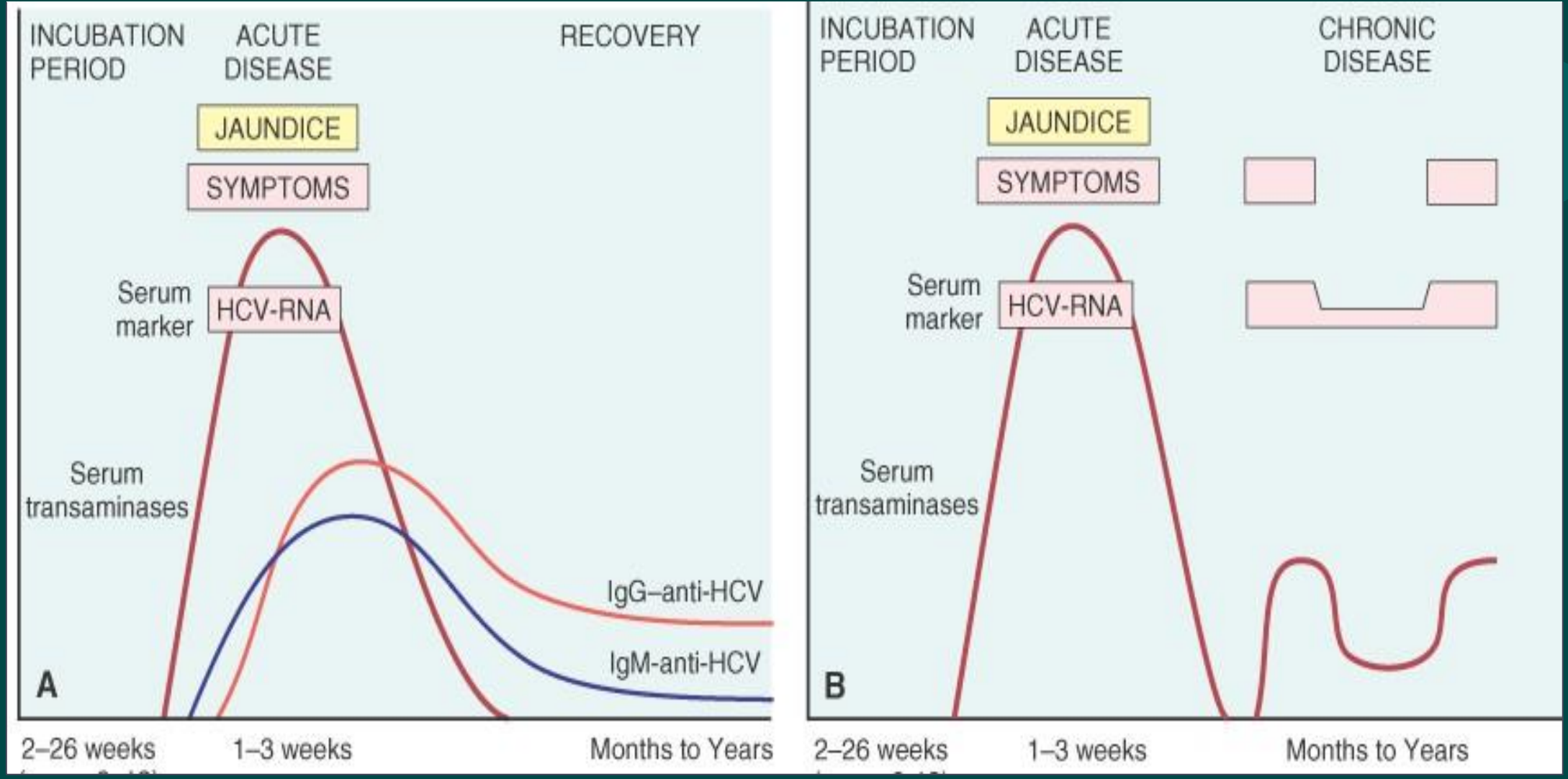


Figure 16-5 The sequence of serologic markers in acute hepatitis A infection. HAV, hepatitis A virus.



Sequence of serologic markers for hepatitis B viral hepatitis demonstrating *(A)* acute infection with resolution and *(B)* progression to chronic infection



Sequence of serologic markers for hepatitis C viral hepatitis demonstrating (*A*) acute infection with resolution and (*B*) progression to chronic relapsing infection.

Table 16-2. Laboratory Evaluation of Liver Disease

Test Category	Serum Measurement*
Hepatocyte integrity	Cytosolic hepatocellular enzymes†
	Serum aspartate aminotransferase (AST)
	Serum alanine aminotransferase (ALT)
	Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances secreted in bile†
	Serum bilirubin
	Total: unconjugated plus conjugated
	Direct: conjugated only
	Delta: covalently linked to albumin
	Urine bilirubin
	Serum bile acids
	Plasma membrane enzymes† (from damage to bile canaliculus)
	Serum alkaline phosphatase
	Serum γ-glutamyl transpeptidase
	Serum 5'-nucleotidase
Hepatocyte function	Proteins secreted into the blood
	Serum albumin‡
	Prothrombin time† (factors V, VII, X, prothrombin, fibrinogen)
	Hepatocyte metabolism Serum ammonia†
	Aminopyrine breath test (hepatic demethylation)
	Galactose elimination (intravenous injection)

Common LIVER FUNCTION TEST Reference VALUES

All tests are done in blood serum

- Aspartate amino transferase (AST or SGOT) <35 U/L
- Alanine amino transferase (ALT or SGPT) < 45 units per liter (U/L)

- • Alkaline phosphatase (ALP) 40 to 125 U/L
- • Albumin. 3.5 to 5.0 grams per deciliter (g/dL)
- • Total protein 6.3 to 7.9 g/dL

Common LIVER FUNCTION TEST Reference VALUES

- Total Bilirubin. 0.1 to 1.2 mg/dL
- • Unconjugated (Indirect)-0.1 to1mg/dL
- • Conjugated (Direct) < 0.3 mg/dL
- • γ-Glutamyl transferase (GGT) <55 U/L
- • Lactate Dehydrogenase 180 to 360 U/L
- • Prothrombin time (PT) 11 to 16 seconds
- OTHER blood TESTS:
- Reticulocyte count: 0.5-2.5%

CASE BASED DISCUSSION CHARTS

LIVER FUNCTION TEST CHART A

- A four-year-old male child presents with tiredness. Physical Exam revealed pallor (+), scleral icterus (+) and splenomegaly (+). Lab investigations are given below.
- • Hemoglobin- 6.3 g/dL
- • Reticulocyte count –10%
- • Platelet count 200 x 103 cells/μL [200,000 cells/μL]
- • Total bilirubin - 4.1mg/dL
- • Unconjugated (Indirect) bilirubin - 3.8 mg/dL,
- • Conjugated(Direct) bilirubin - 0.2 mg/dL.
- • Alkaline phosphatase (ALP) -66 U/L
- • Aspartate amino transferase (AST or SGOT) -30 U/L
- • γ-Glutamyl transferase (GGT) -40 U/L
- • Ultrasound abdomen – gallstones
- • Urine analysis for bilirubin was negative.

Answers

- 1) List the abnormal test findings ? (1mark)
- a. Hemoglobin – reduced; Reticulocyte count- increased; Unconjugated bilirubin -increased; USG- gall bladder stones

- 2) What is the type of jaundice? Give possible reason. (1mark)
- a. Unconjugated hyperbilirubinemia; Hemolysis/Haemolytic anemia

- 3) Mention any two diseases which can cause these set of findings? (1mark)
- a. Hereditary spherocytosis, sickle cell anemia, Thalassemia

- 4) Name some tests which are useful for definitive diagnosis? (1mark)
- a. Peripheral smear , osmotic fragility test, haemoglobin electrophoresis

- 5) What could be the reason for absence of bilirubin in urine analysis in this case? (1mark)
- a. Unconjugated bilirubin is water insoluble and is tightly bound to serum albumin and so it cannot be filtered by kidney even when blood level is high.

- LIVER FUNCTION TEST CHART B
- A 21year old male presented with history of jaundice and yellow-brown coloured urine for the past one week. He had history of travel one week back after which he developed flu like symptoms, low grade fever, nausea, loss of appetite and malaise. Following are the results of liver function tests (LFT).

- Hemoglobin 15.5 g/dL
- Albumin – 3.7 mg/dL
- Protein – 7.2 mg/dL
- Total bilirubin – 3.8 mg/dL
- Conjugated(Direct) bilirubin-2.2mg/dL
- Unconjugated (Indirect) bilirubin -1.8mg/dL
- γ-Glutamyl transferase (GGT) - 46 U/L
- Alkaline phosphatase (ALP) - 200 U/L
- Alanine amino transferase (ALT or SGPT) - 356 U/L
- Aspartate amino transferase (AST or SGOT) - 322 U/L
- Anti HAV IgM antibody – Positive
- HBsAg- Negative
- Anti HCV antibody – Negative

Answers

- 1) What is your diagnosis? (1 mark)
- a. Acute Viral hepatitis , hepatitis A / Combined conjugated & unconjugated hyperbilirubinemia

Answers

- 2) List out the abnormal findings in LFT & give reasons (3 marks)
- a. Conjugated Bilirubin -elevated due to blockage of bile canaliculi secondary to the inflammatory process, preventing excretion of conjugated Bilirubin
- b. Unconjugated Bilirubin -elevated due to inability of injured hepatocytes to conjugate bilirubin;
- c. Transaminases are elevated (ALT >AST) due to liver cell injury,
- d. Alkaline phosphatase elevated due to block in bile canaliculi,
- e. Anti HAV IgM Positive – due to infection with Hepatitis A virus

- 3) Mention the reason for yellow-brown coloured urine. (1 mark)
- a. Due to excretion of conjugated bilirubin (unbound to albumin) in urine.

- LIVER FUNCTION TEST CHART C
- A 72-year-old male patient present with progressive jaundice, itching and loss of weight. He gives history of passing green-brown colour urine and passage of clay color (pale) stools in the past 2 months. Routine blood investigations show

- Hemoglobin -14.7gm/dL
- Total protein -6.5 g/dL
- Serum ALBUMIN 3.9 g/dL
- Total bilurubin-20 mg/dL
- Unconjugated (Indirect) bilirubin -0.4 mg/dL
- Conjugated(Direct) -19.6 mg/dL
- Alanine amino transferase (ALT or SGPT) – 58 U/L
- Aspartate amino transferase (AST or SGOT) - 67 U/L
- Alkaline phosphatase (ALP) -990 U/L
- γ-Glutamyl transferase (GGT) -85 U/L
- Lactate Dehydrogenase -200 U/L

Answers

- 1) What is your diagnosis? (1mark)
- a. Obstructive jaundice/ conjugated hyperbilirubinemia

- 2) List out the abnormal test findings. (1mark)
- a. ALP markedly elevated;
- b. Conjugated Bilirubin markedly elevated

- 3) Mention any two possible causes for your diagnosis? (1mark)
- a. Bile duct obstruction by: gallstones,
- b. Bile duct obstruction by Malignancy of bile duct or
- c. Bile duct obstruction by Malignancy of head of pancreas;
- d. Bile duct stricture

- 4) What are the normal total, conjugated and unconjugated bilirubin levels? (1mark)
- a. Total Bilirubin. 0.1 to 1.2 mg/dL
- b. Conjugated (Direct) < 0.3 mg/dL
- c. Unconjugated (Indirect)-0.1 to 1mg/dL

- 5) What is the reason for clay color (pale) stools and pruritis? (1mark)
- a. Due to blockage of bile duct, conjugated bilirubin cannot be excreted into the intestine & be converted into stercobilin which gives the stools its normal color. So, the absence of stercobilin in faeces gives clay color to stools.
- b. Pruritis is due to Elevated serum bile acids.