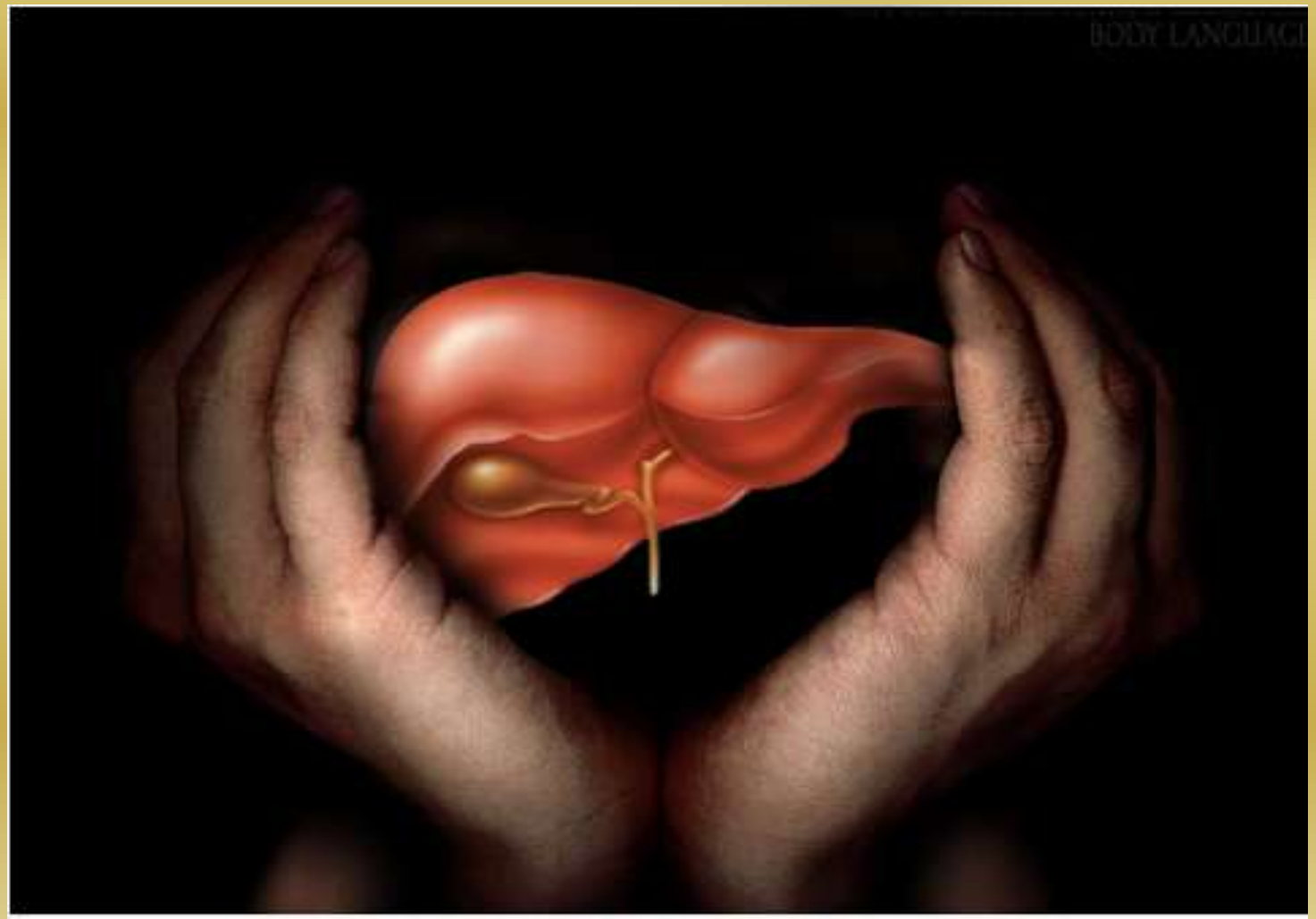
Liver Function Test



Overview

- ***Basics of Liver***

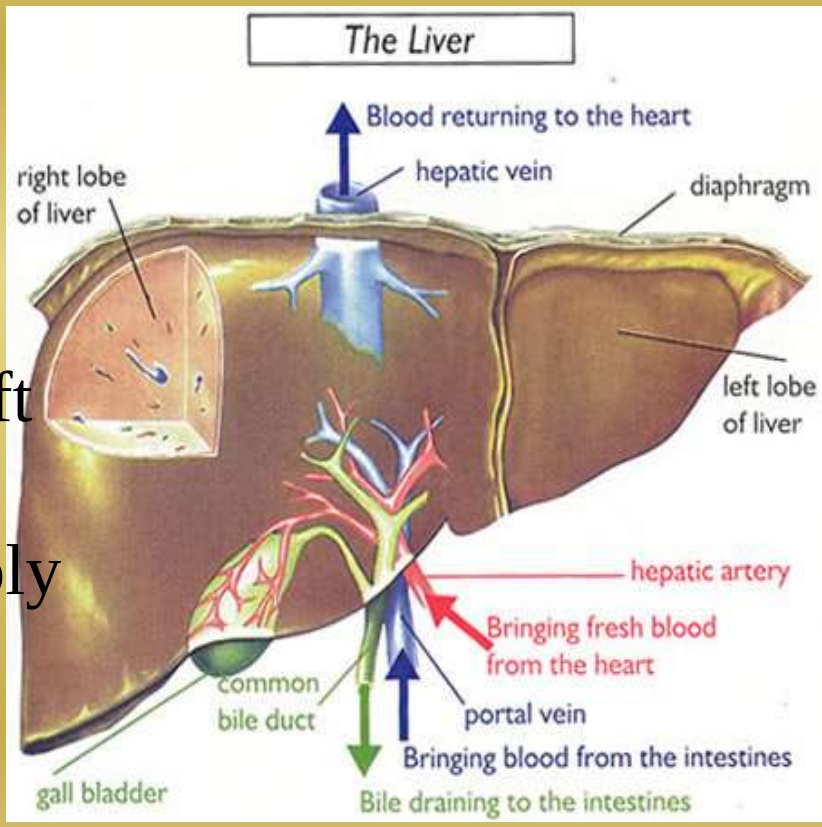
➢ Location.
➢ Wieght ,Shape.
➢ Vascular and nerveous supply .
➢ Summary of Normal Liver function.

- ***Liver function tests***

➢ Significance .
➢ Classification.
➢ Brief details of each LFT.
➢ Liver disease.
➢ Common laboratory tests in liver disease.

Liver

- ✓Largest parenchymal organ
- ✓Essential and has central role in metabolisms
- ✓Weight-1-1.5Kg,Wedge shaped
- ✓Location-Right upper quadrant below diaphragm extending upto left upper quadrant.
- ✓Vascular supply and nervous supply
- ➢Daul blood supply-20%-hepatic artery and 80% portal vein.
- ➢Nerve supply-Vagus ans phrenic nerve.



Summary of Normal Liver function

The Liver as Digestive organ

a) Processing and storage of Carbohydrate, Protien, lipid.

b) Processing and storage of vitamins and minerals.

The liver as Endocrine organ

a) Metabolism of glucocorticoids,mineralocorticoids and sex hormones.

b) Regulation of metabolisms

The liver as Heamatologic organ

a) Temprory storage of blood

b)Synthesis of bilirubin from blood breakdown products.

c) Synthesis of blood clotting factors

The liver as Excreatory organ.

a) Excreation of bile pigment.

b) Excreation of Cholesterol via bile

c) Urea synthesis

d) Detoxification of drugs and other foriegn substances

LIVER TEST

Significance-Laboratory tests are effective method for screening for

- ✓ Presence of the hepatic dysfunction
- ✓ Directing furthur diagnostic evaluation of identified abnormalities
- ✓ Assesing severity of the liver disease
- ✓ Broadly can also be classified in 3 groups
  - •Synthetic function : albumin, PT
  - •Hepatocyte injury : AST, ALT
  - •Cholestasis : bilirubin, ALP, GGT

Classification

Broadly can also be classified in 3 groups

- Synthetic function : albumin, PT
- Hepatocyte injury : AST, ALT
- Cholestasis : bilirubin, ALP, GGT.

Specifically classified on basis of Laboratory findings

Group 1 :Tests on hepatic excreatory function.

1. Serum –Bilirubin ;Total,conjugated and unconjugated.
2. Urine –Bile pigments,bile salts and urobilinogen.

Group 2 :Liver enzyme panel

1. Alanine amino transferase.
2. Aspartate amino transferase.

Classification

Group 3 :Plasma protiens

1. Total protiens
2. Serum albumin ,globulins,A/G ratio.
3. Prothrombin Time.

Group 4 : Special tests

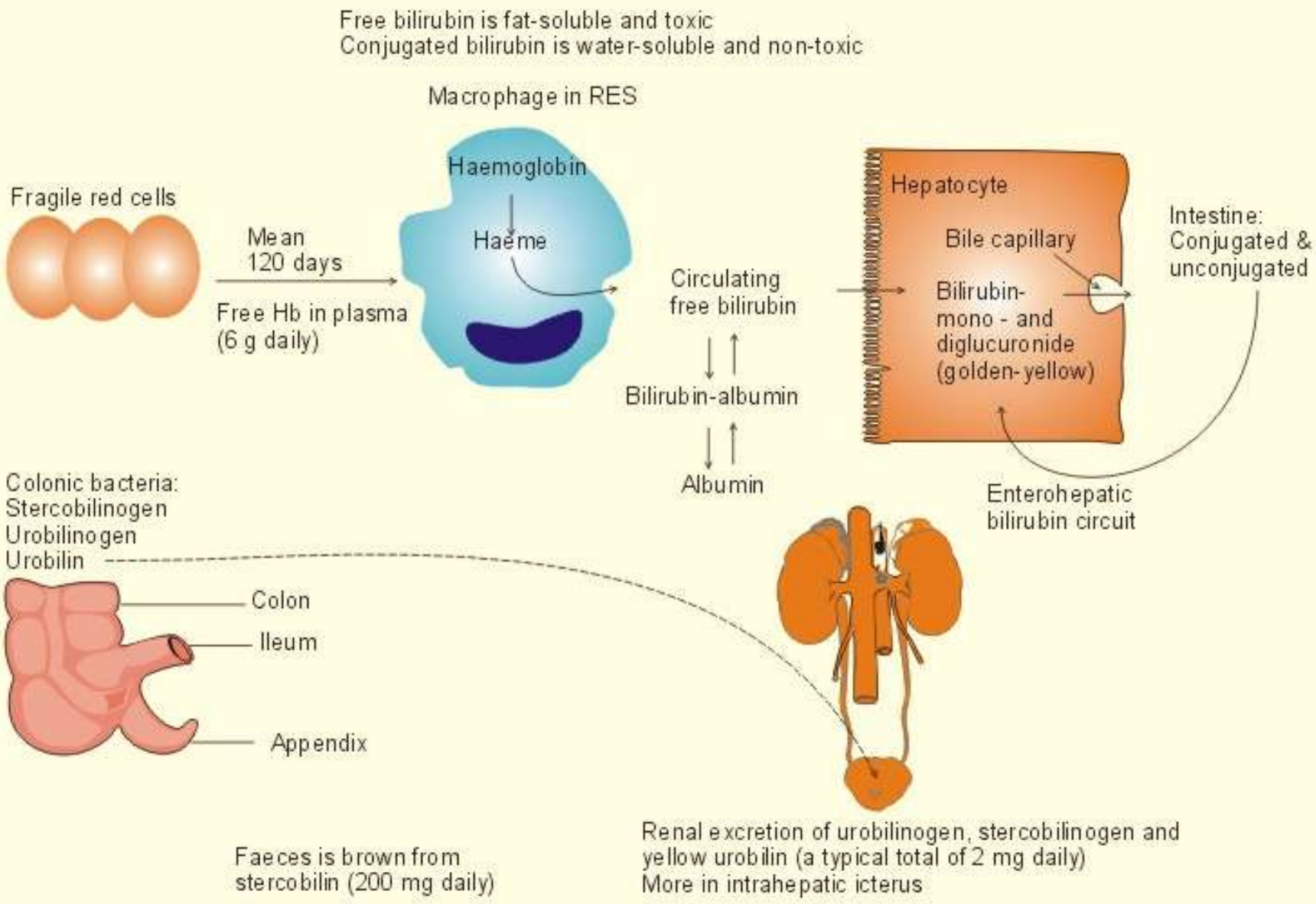
1. Ceruloplasmin
2. Ferritin
3. Alpha -1-antitrysin
4. Alpha –feto protien

Bilirubin

- endogenous anion
- a Tetrapyrrole pigment
- a breakdown product of heme
- 6-6.5 g of hemoglobulin in RBCs broken down daily in adult.
- Forms 220mg of bilirubin per day
- another 50- 60mg from other sources.

- Site of metabolism -Reticuloendothelial cells of liver and spleen.
- Heme →Biliverdin + CO-> Bilirubin.

Bilirubin Metabolism



Tests based on Bilirubin Metabolism

Van den Bergh's method

Total serum Normal level Bilirubin -0.2-1mg /dl.

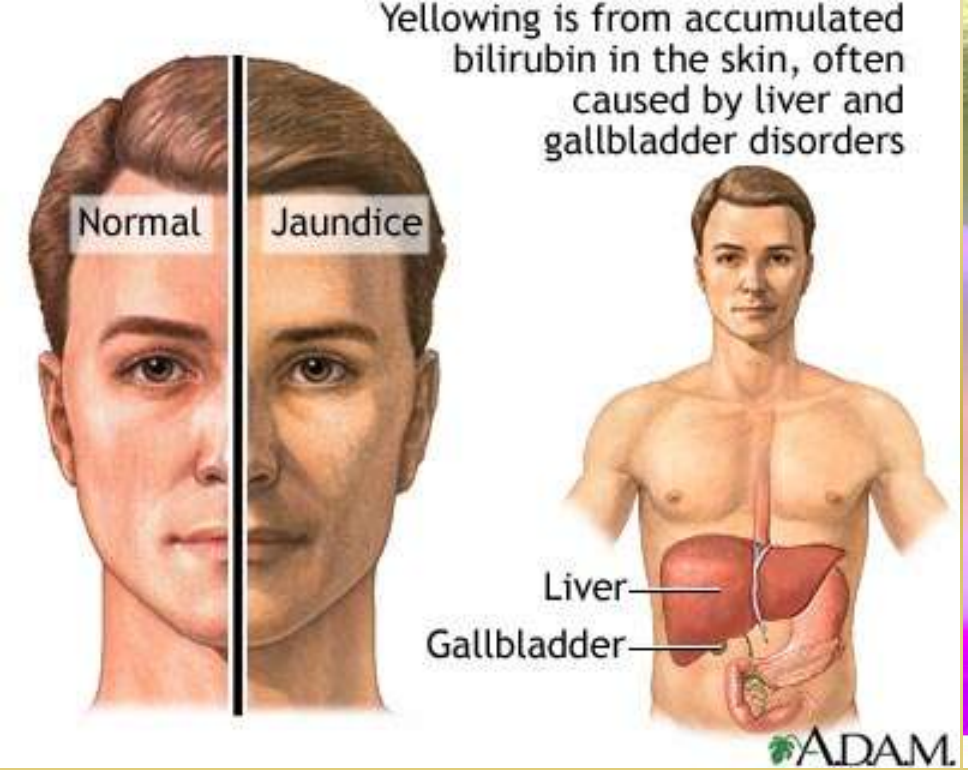
- Conjugated Bilirubin - 0- 0.2mg/dl.
- Unconjugated Bilirubin- 0.2-0.6mg/dl.

Assays based on dry reagent chemistry

❖Ektachem dry chemistry slides

Clinical interpretations

In Serum	Van der Bergh's test	Type of jaundice
↑ Unconjugated Bilirubin	Indirect +	Hemolytic jaundice / Prehepatic
↑Both Unconjugated Bilirubin and Conjugated Bilirubin	Biphasic	Hepatocellular jaundice/ Hepatic
↑ Conjugated Bilirubin	Indirect +	Obstructive Jaundice / Post Hepatic


Yellowing is from accumulated bilirubin in the skin, often caused by liver and gallbladder disorders
Normal
Jaundice
Liver
Gallbladder
A.D.A.M.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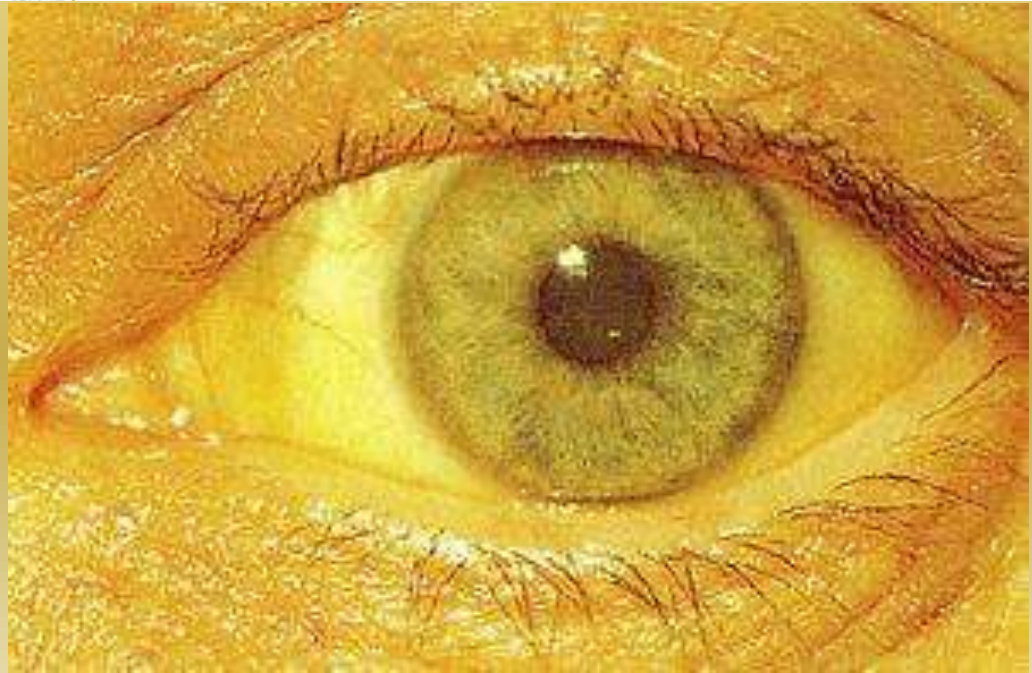


Hemolytic jaundice / Prehepatic-

Total bilirubin - 5mg/dl

a)Congenital abnormalities of RBCs.

b)Hemolytic disease of newborn.

c)Effect of chemicals or organisms.

d)Ineffective erythropoises

Hepatocellular jaundice/ Hepatic

Total bilirubin -10-30mg/dl

a) Impaired uptake of bilirubin by hepatocytes-

Non Hemolytic jaundice like Gilberts, Crigler-Najjar syndromes.

b) Ineffective transport within the cell -

Dubin johnson and Rotors syndrome

c) Defective conjugation within microsomes-

Toxic hepatitis (Drugs & Poison) , Viral hepatitis,liver cell necrosis.

- Obstructive Jaundice /Post Hepatic –

Total bilirubin 10-60mg/dl

Here cholestasis is extrahepatic

Tests based on detoxification

- Potentially hazardous substances from body.
- Endogeneous substances -NH_3 ,bilirubin,active hormones chemicals and drugs
- Metabolic changes oxidation,conjugation to produce more polar water soluble derivative,for excretion in urine and bile.
- Function is depended on the functional mass of liver cells
- Assesed earlier by Hippuric acid test

Currently

✓ Blood NH_3

✓ Aminopyrine breath test .

Blood NH_3

- Blood NH_3 –Normal level -40-70µg/100ml.
- Liver detoxifies NH_3 to form urea.
- Method of analysis-Diffusion(Conway ,Seligson), ion exchange NH_3 selective electrode enzymatic
- Interpretation In Liver disease the ability to remove NH_3 may be impaired.
- ↑ levels of NH_3 seen in Acute hepatitis, Cirrhosis and hepatic coma.

Tests based on synthetic function

- All proteins except immunoglobulinseg-albumin,globulin,clotting factors (Fibrinogen,prothrombin,factors V,VII,IX,X)
- ↓protien synthesis –Impaired hepatocellular function or decreased functional mass of liver.
- Total serum protien-6-8g/dl
- Serum Albumin-3.5-5.5g/dl
- Serum Globulin-2-3.5g/dl
- A/G ratio -1.2-1.5
- Total protiens-biuret method
- Fractionation into Albumin/globulin
  - Automated dye binding methods.
  - Paper /cellulose acetate electrophosesis.

Tests based on synthetic function contd…

Clinical interpretations

Albumin

- Synthesized in Liver
- Albumin half life -20 day
- 4% degraded each day
- Albumin synthesis depend on nutrition, volume status, vascular integrity, catabolism, hormone, systemic inflammation, loss in stool and urine.
- Good indicator of chronic hepatocellular damage.
- Normal in case of

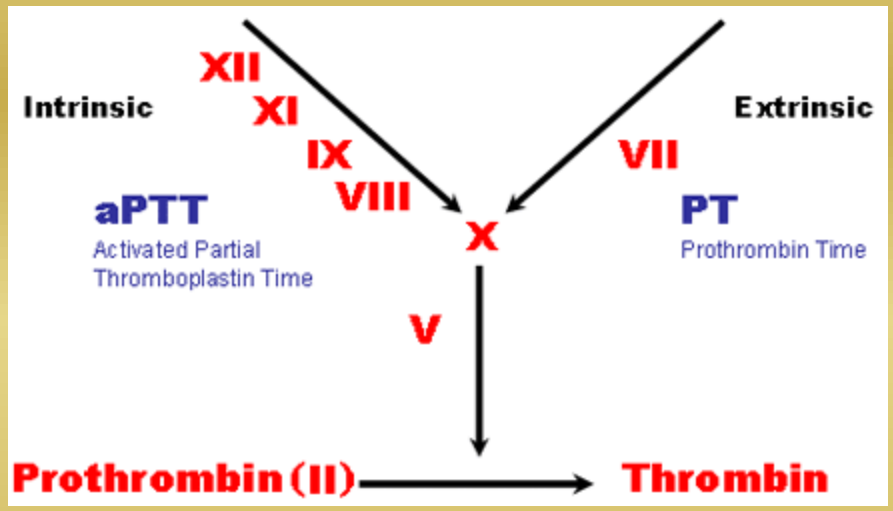
Acute viral hepatitis, drug related hepatotoxicity and obstructive jaundice.

- Less than 3g/dl-chronic hepatitis ,cirrhosis more common

Heavy ingestion of alcohol ,chronic inflammation inhibits protien synthesis.

In advanced stages Albumin is ↓ and globulin ↑. A/G ratio may be reversed.

Determination of prothrombin time



- Hepatic synthetic function assesed by simple coagulation test
- Factors I,II,V,VII,IX,X.
- First stage plasma Prothrombin time requires presence of prothrombin ,V,VII,X.
- Prothrombin time is depended
  - vitamin K defeciency
  - hepatocellular function

Interpretations

PT Long / aPTT Nl.	PT Nl. / aPTT Long	PT Long / aPTT Long
Low factor VII	Low factor VIII, IX, XI, or XII	Low factor V or X Liver disease
Vitamin K deficiency	Lupus anticoagulant	Low fibrinogen or prothrombin
Warfarin therapy	Heparin therapy	High hematocrit
Liver disease	Low prekallikrein (PK) or high molecular weight kininogen (HMWK)	Vitamin K deficiency Warfarin therapy Liver disease

Enzymes in diagnosis of liver disease

1)AMINOTRANSFERASES

- Alanine amino transferase
- Aspartate amino Transferase

2) ALKALINE PHOSPHATASE

3) Isocitrate dehydrogenase

4) Glutamate dehydrogenase

5) 5'Nucleotidase

AMINOTRANSFERASES

Alanine amino transferase(ALT) SGPT

- L-Alanine + α-ketogluterate ↔ Pyruvate + L-Glutamate
- Reference values-5.0-35.0 IU/L
- Method of determination

Coupled Enzymatic method

- ALT reversibly transfers amino group from alanine to α-ketogluterate
- the rate of formation of pyruvate is determined by coupling the ALT reaction with LD ,which converts pyruvate to lactate the decrease in absorbance at 340nm is measured as NADH is oxidized to NAD^{+}.

Aspartate amino Transferase(AST) SGOT.

- Aspartate + α-ketogluterate ↔ Pyruvate + oxaloacetate
- Reference values 5.0-35.0 IU/L
- Method of determination

Coupled Enzymatic method

Reaction is coupled with Malate dehydrogenase ,oxaloacetate is reduced to Malate as NADH is oxidized to NAD^+ the decrease in absorbance at 340nm is measured.

Clinical interpretations

- Alanine amino transferase(ALT)

Highest concentration in liver then any other tissues in body.

Cytosol

$T_{1/2}$ -47 hr

- Aspartate amino Transferase(AST)
- Present in liver,cardiac muscle,skeletal muscle kidneys,brain pancrease ,lungs ,leukocytes and erythrocytes in decreasing order of concentration.

cytosol (20%) and mitochondria (80%)

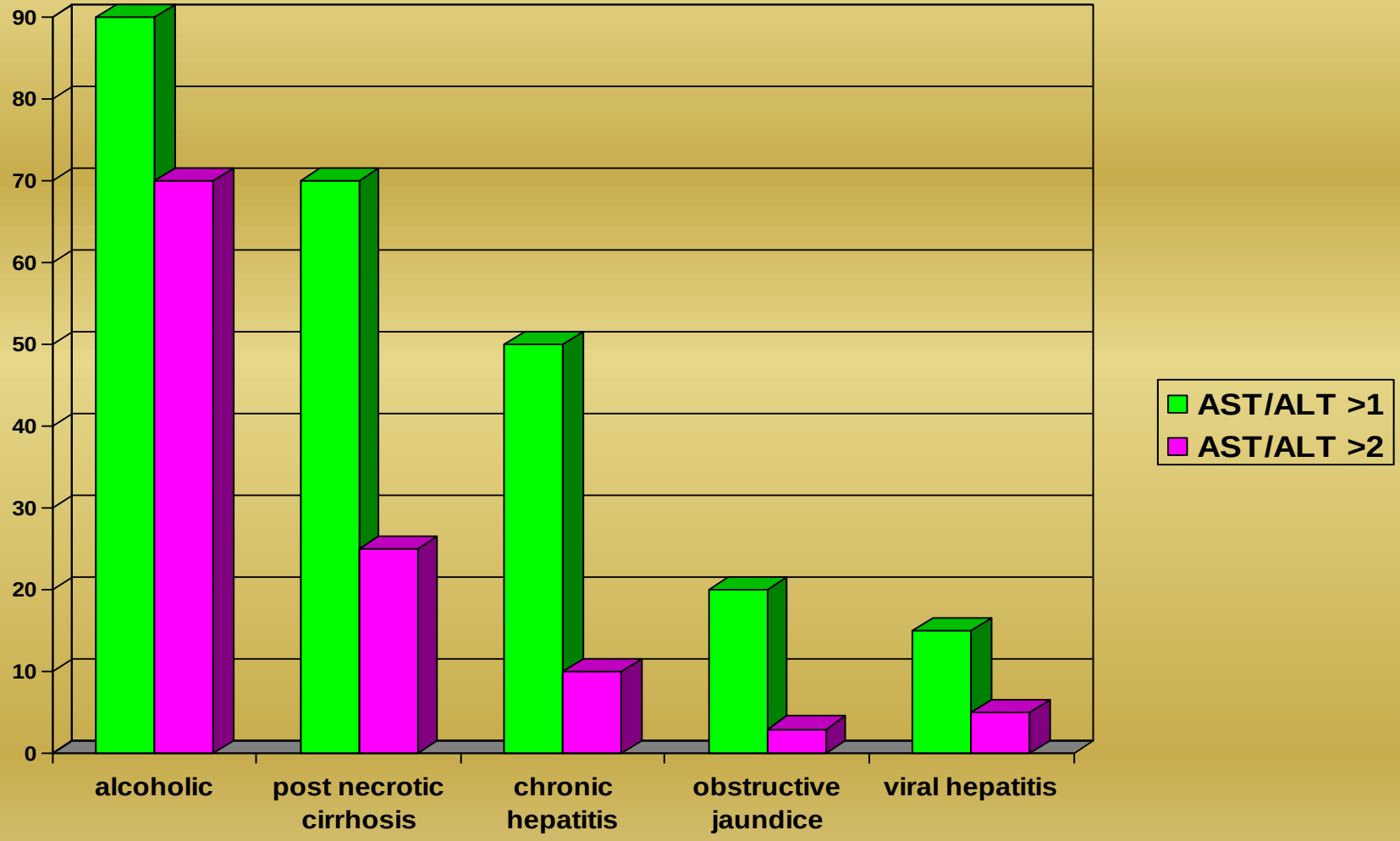
$T_{1/2}$ -17 hr. (cytosol)

87 hr. (mitochondria)

AST/ALT ratio

- More clinical utility
- >1 shows advanced liver fibrosis and chronic hepatitis C infection
- >2 Alcoholic hepatitis
- 0.9 for nonalcoholic steatohepatitis (NASH),
- 2.6 in alcoholic liver disease
- 1.4 in cirrhosis related to NASH
- 4.5 Wilson’s disease

AST/ALT ratio contd…



In Alcoholic hepatitis -AST/ALT >1 in 92%, >2 in 70%

Alcoholic hepatitis

- appropriate history of alcoholic consumption, serologic exclusion of other liver disease
- ♂ 40-80 g/D, ♀ 20-40 g/D 10-12 yrs.
- characteristic pattern
  - AST rarely exceeds 300 IU/dl
  - AST/ALT >1 in 92%, >2 in 70%
    - pyridoxine deficiency
    - alcohol induces release of mitochondrial AST
  - GGT/ALP >2.5

ALT and AST < 5 times

ALT predominant

- Chronic hepatitis B, C
- Acute hepatitis (A-E, EBV, CMV)
- Steatohepatitis
- Hemochromatosis
- Medications/toxins
- Autoimmune hepatitis
- Alpha1-antitrypsin deficiency
- Wilson's disease
- Celiac disease

AST predominant

- Alcohol-related liver injury
- Steatohepatitis
- Cirrhosis
- Drug
- Nonhepatic
  - Hemolysis
  - Myopathy
  - Thyroid disease
  - Strenuous exercise
- Macro AST

ALT and AST > 15 times

- **Autoimmune hepatitis**
- **Wilson's disease**
- **Acute Budd-Chiari syndrome**
- **Hepatic artery ligation**
- **Heat stroke**
- **Acute viral hepatitis (A-E, herpes)**
- **Medications/toxins**
- **Ischemic hepatitis**
- **Acute bile duct obstruction**

- AST predominate : medication/toxin, ischemic
- >75 times : ischemic, toxic, viral (less common)

Alkaline phosphatase

- Reference values- 35-150U/ml
- Group of enzymes that split off a terminal phosphate group from organic phosphate ester in alkaline medium at optimal pH 10
- membranes and cell surfaces located in brush border of mucosal cells of small intestine ,PCT of kidney, placenta, WBCs, and bone osteoblasts, canalicular membrane of hepatocytes .
- ↑ in serum ALP activity originates from one or both of 2 sources: liver and bone
- Isoenzymes of ALP separated by agarose gel electrophoresis.

Alkaline phosphatase

- Elevated in cholestasis,infilterative liver disease(cancer,granulomas)
- ALP > 1000 : malignant biliary obstruction, sepsis, AIDS with systemic infection
- decrease : hypothyroidism, pernicious anemia, Zn deficiency, congenital, Wilson’s disease, severe hepatic insufficiency

Glutamate dehydrogenase

- Found in liver ,heart muscle, kidneys, brain, skeletal muscle leukocytes.
- Zinc containing mitochondrial enzyme
- Reference values- upper reference limits are 6U/L in women and 8U/L in men.
- In liver highest concentration,in centrilobular hepatocytes elevated disease that affect centrilobular zone as alcoholic hepatitis.
- An initial report this can be sensitive and realatively specific marker for alcoholic hepatitis.

5'Nucleotidase

- Primarily cannalicular sinusidal ,microsomal cytoplasmic membrane.
- Reference values-1-7 IU/L
- Specifically catalysis hydrolyses of nucleotides as adenosine 5'phosphate and inosine 5' phosphate.
- Elevated in hepatobiliary disease more specific obstruction of liver disease.

γ-Glutamyl transpeptidase

- Reference values-10-48 U/ml
- catalyzed transfer of γ-glutamyl groups of peptides to other amino acid
- abundant in liver, kidney, pancreas, intestine, and prostate, spleen, heart, brain but not in bone
- $T_{1/2}$
  - 7-10 days
  - 28 days in alcohol-associated liver injury

- Elevated in cholestasis and hepatocellular disease
- Used to confirm that elevated alkaline phosphatase is of hepatic origin
- Disproportionately elevated in alcoholic liver disease.
- Elevated in hepatic metastasis

Specific tests

Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Heptitis E
Acute infectious disease Transmitted by ecteric route Lab finding –IgM antiHAV antibody in serum	Serum Hepatitis sexual intercourse/ parental route Lab finding HbsAg (Surface antigen) and HbcAg(core antigen). Detectable ↑ Serum ALP	Lab findings IgM anti HCV	RNA virus require HbV to be infective	HEV RNA by PCR

Common medication

- **Acetaminophen overdose**
- **Statins**
- **Antibiotics**
- **Antiepileptics**
- **Antituberculosis drugs**
- **Herbal remedies, alternative medications and substance abuse**


Thank you