Assessment of Liver Function and Diagnostic Studies

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Joseph Ahn, M.D., M.S.
Assistant Professor of Medicine
Medical Director, Liver Transplantation

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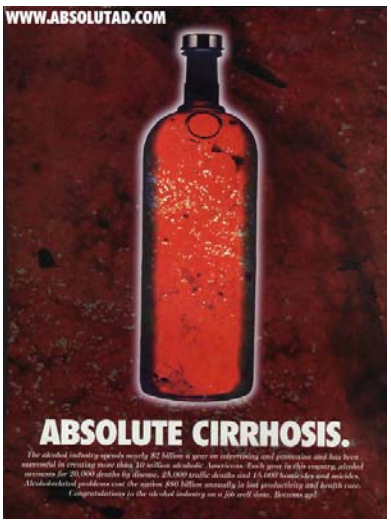
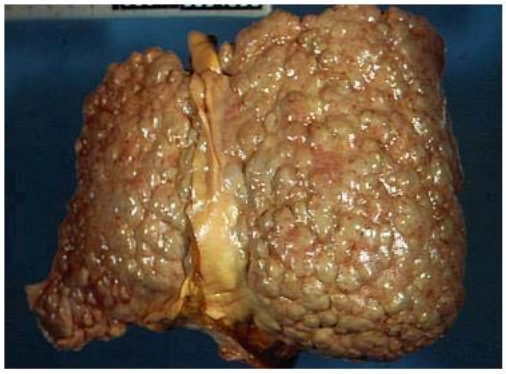
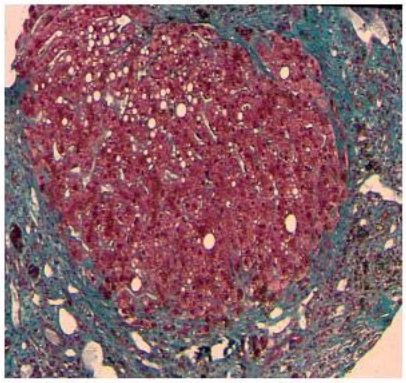


“Absolute” Autopsy





Key Points

1. Review the components of “Liver function tests” (LFTs)
2. Develop an understanding of diagnostic tests for liver disease
3. Formulate a diagnostic approach to assessing abnormal LFTs

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The Liver

•Largest internal organ

•Has more functions than any other organ

•Can sustain life even when only 10-20% of liver tissue is functioning

The Liver

- Weighs 1,200 to 1,500 grams.
- Dual blood supply: portal vein brings venous blood from the intestines and spleen (2/3)
- Hepatic artery rises from the celiac axis (1/3)
- General Clinical Definitions
  - Acute liver disease: Liver disease of 8 weeks duration or less.
  - Subacute liver disease: Liver disease 8 weeks - 6 months duration.
  - Chronic liver disease or chronic hepatitis: Abnormal liver chemistries > than six months.

Clinical Definitions-continued

- Liver failure-Failure of the liver to perform its biosynthetic functions.
- Fulminant hepatic failure- coagulopathy (elevated protime) with encephalopathy without a previous history of chronic liver disease
- Cirrhosis: fibrosis of the liver with regenerative nodules
  - Cirrhosis is typically a sequelae of chronic hepatitis.

Role of the Liver (brief review)

<u>Purification</u>

Potentially harmful chemicals are broken down into harmless chemicals or substances

(acetaminophen, alcohol, other drugs, herbs etc)

<u>Synthesis</u>

The liver makes most of the proteins found in blood including albumin and coagulation proteins

Synthesizes and excretes bile necessary for digestion and absorption of fats and vitamins

<u>Storage</u>

Sugars, fats, and vitamins all stored in the liver

Role of the Liver (brief review)

Transformation

- The liver uses enzymes and proteins synthesize proteins
  - (an excess of two of these enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in serum when liver cells have been damaged)
- The liver also inactivates hormones and regulates the amount of testosterone and estrogen in the blood
- The liver plays a major role in break down and synthesis of cholesterol

H&P

If all else fails

Take a history

And

Examine the patient

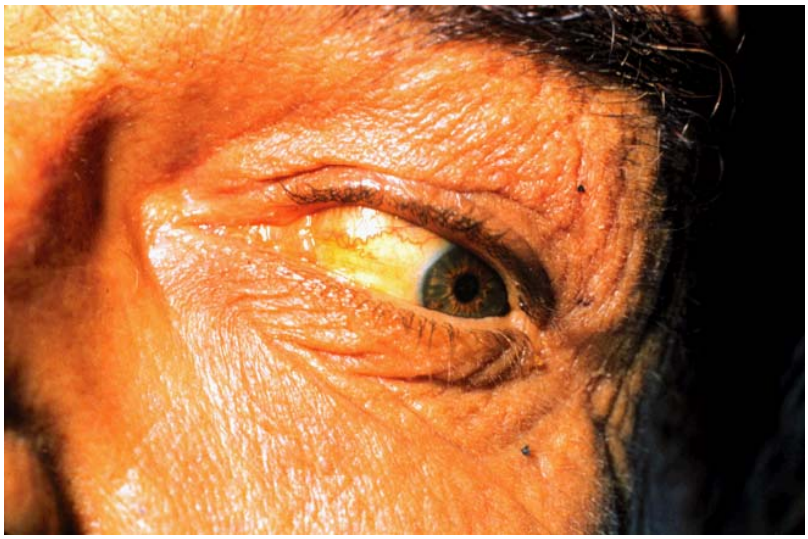
History

- Symptoms
- Duration of LFT abnormalities
- Risk factors:
  - Social history- ETOH, drug use, medications, chemical exposures, blood transfusions, sexual history, travel history
  - Medical, surgical history
  - Family history

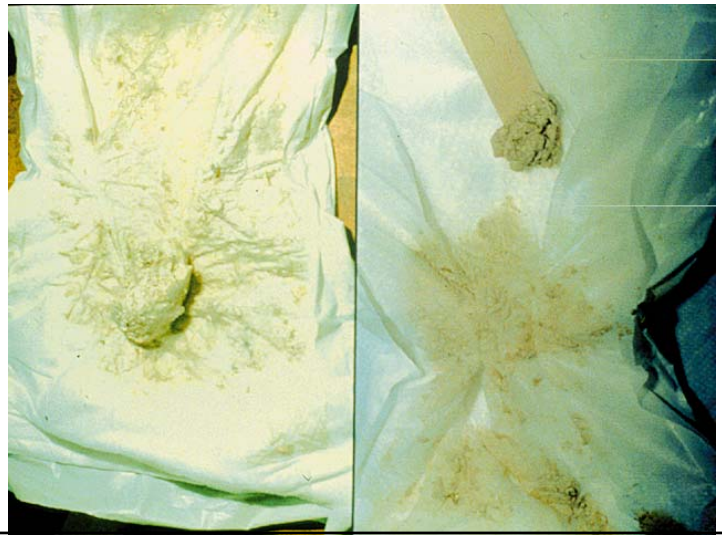
Symptoms of Liver Disease

- Fatigue
- Anorexia
- Malaise
- Weight loss, gain
- Fever
- Pruritis
- RUQ pain
- GI bleeding
- None

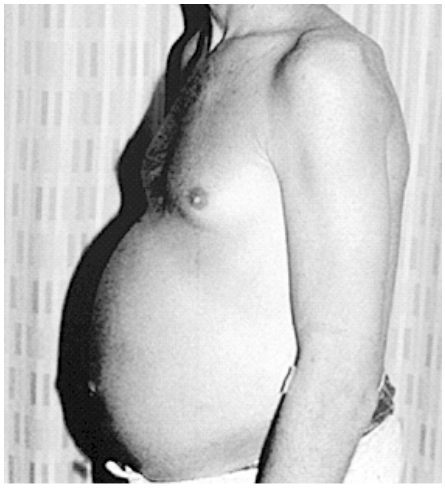
Scleral Icterus

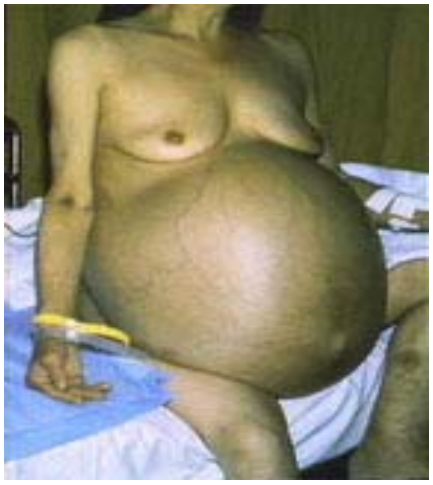


Acholic stools

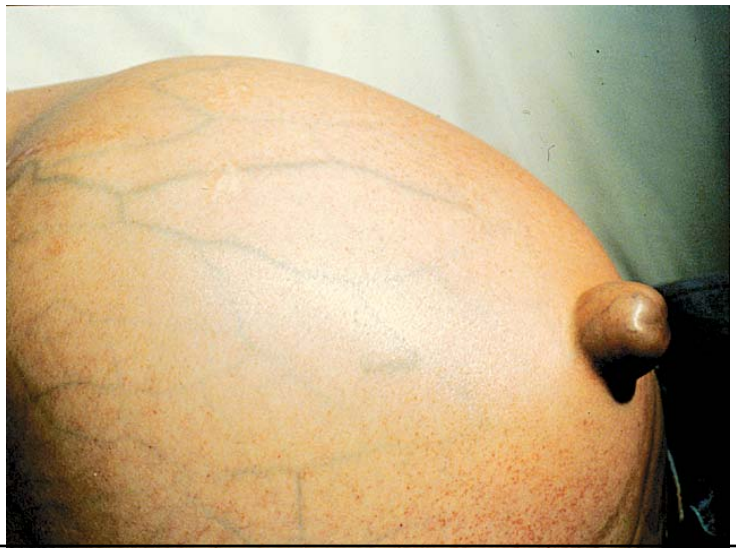


Ascites/Gynecomastia

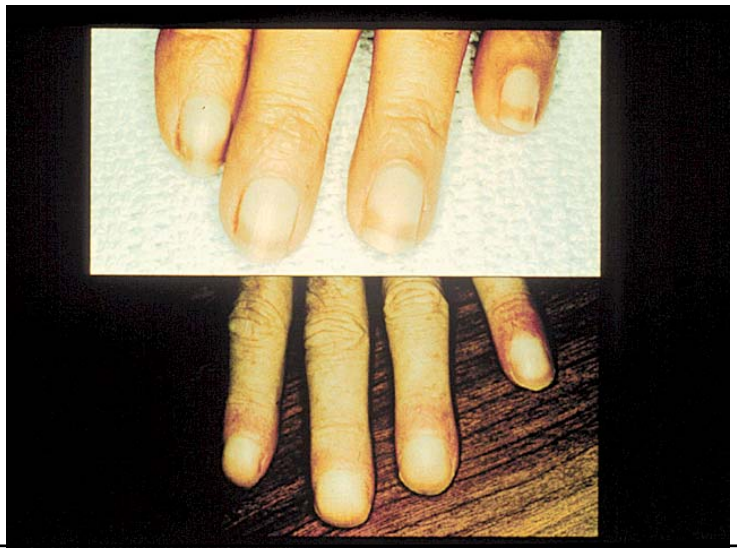




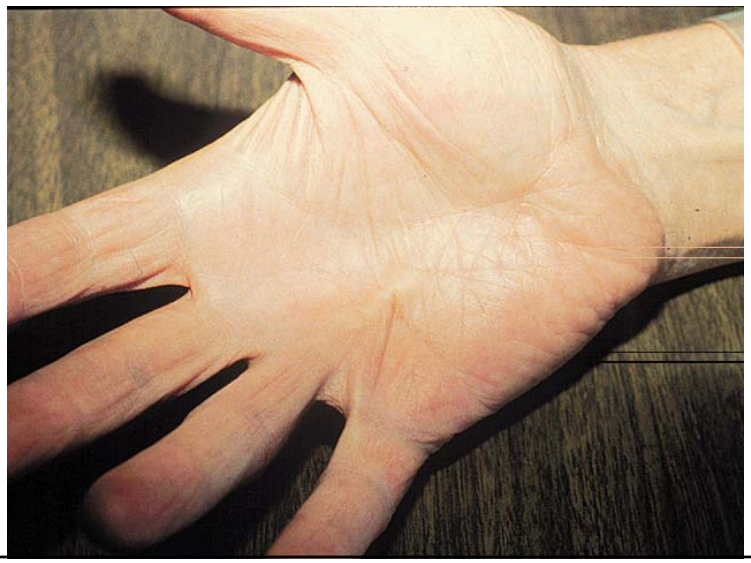
Ascites with Umbilical Hernia



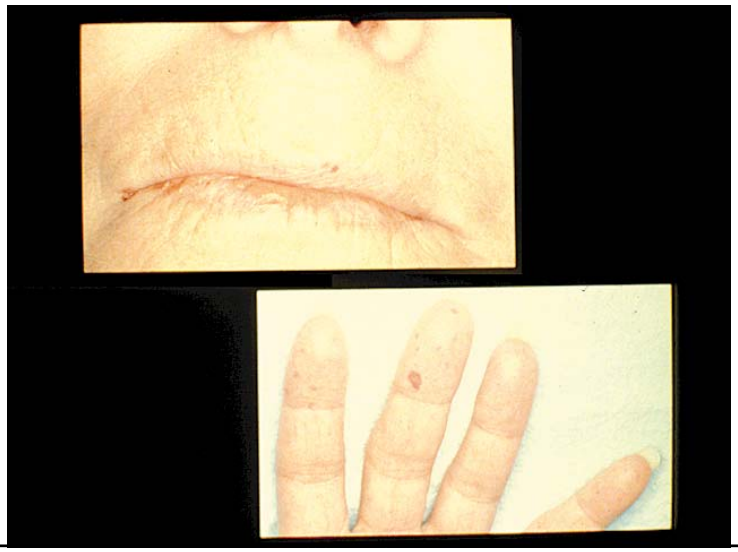
Leukonychia/Clubbing



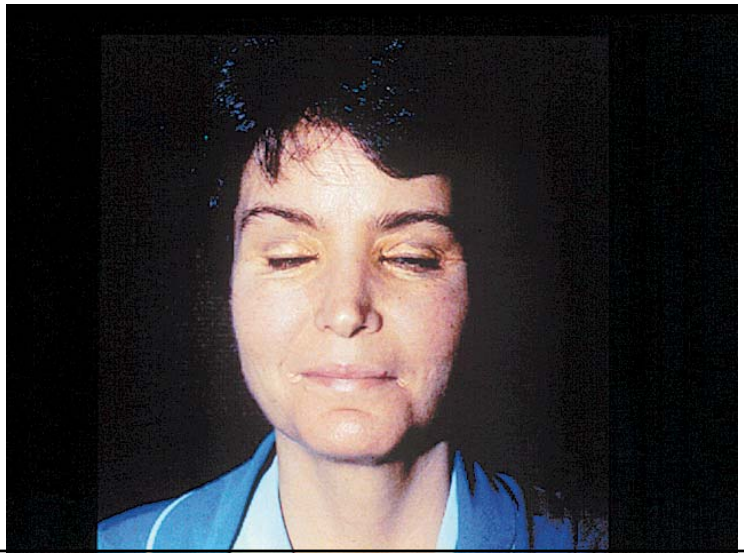
Palmar Erythema/Dupuytren's contracture



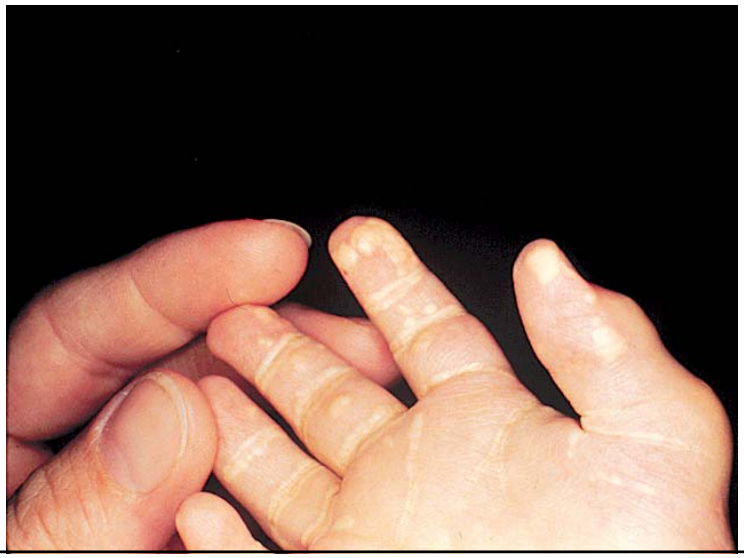
Telangiectasias



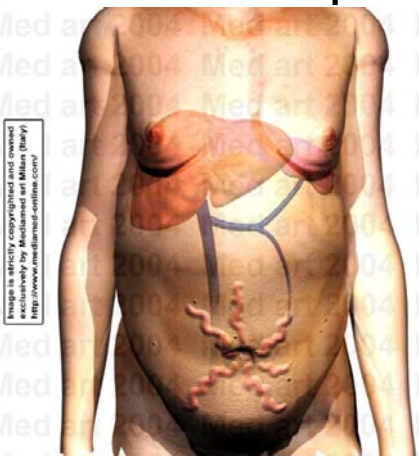
Xantholasma

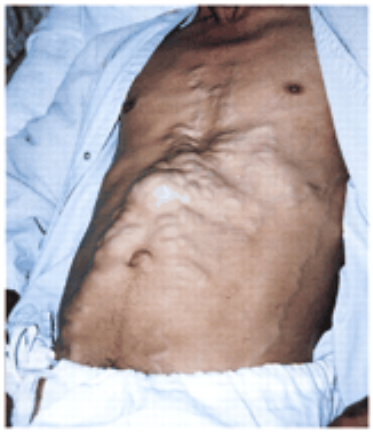


Xanthomata

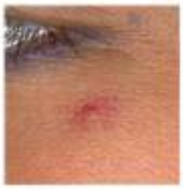


Caput Medusae

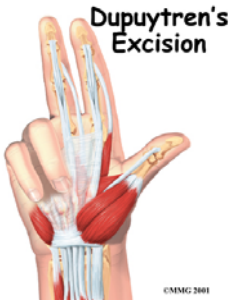


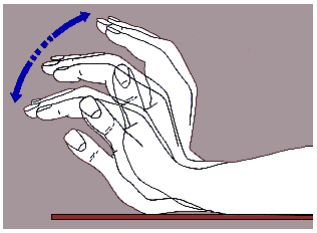


Shunting of blood through umbilical veins to systemic circulation



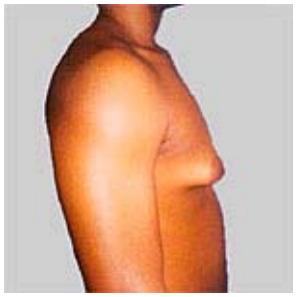
Spider angiomata



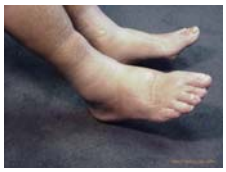


Asterixis

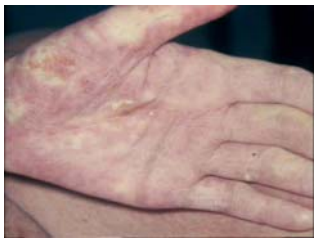
Estrogen & Steroid Binding Proteins



Gynecomastia



Edema

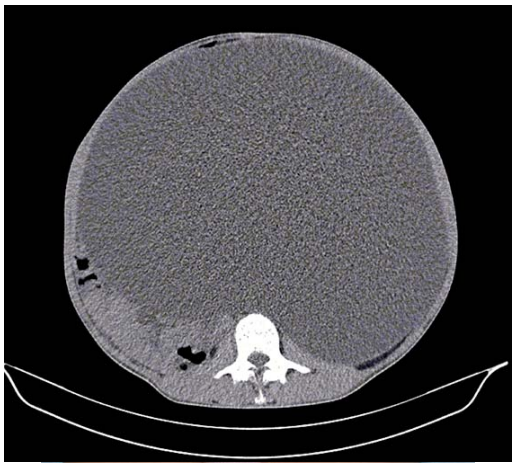


Palmar erythema

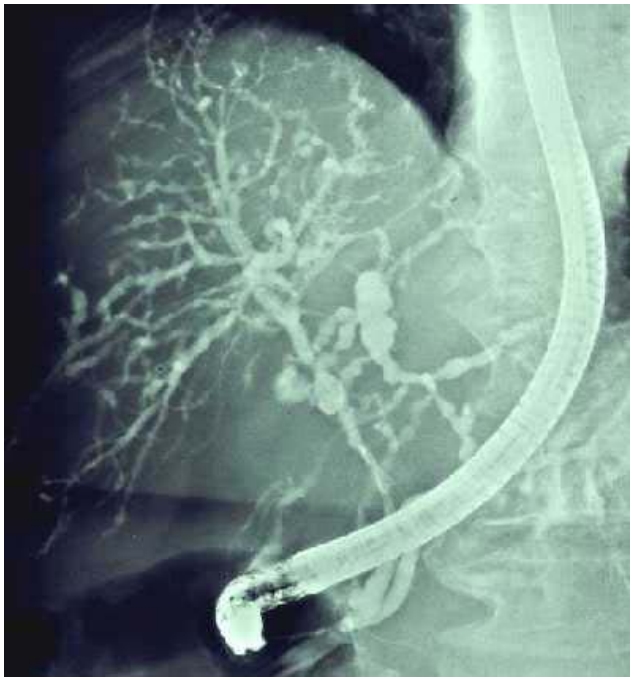
Diagnostic Studies

- Plain films/barium studies
- Ultrasound studies
- CT scans
- MRI
- Radioisotope scanning
- Upper GI endoscopy (EGD)
- Liver biopsy

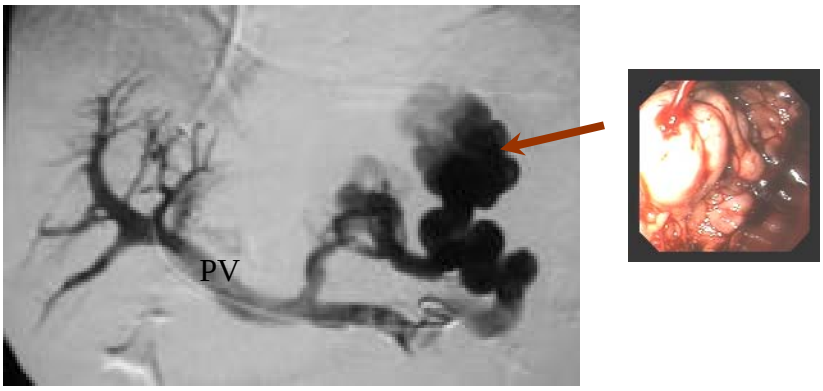
Imaging studies

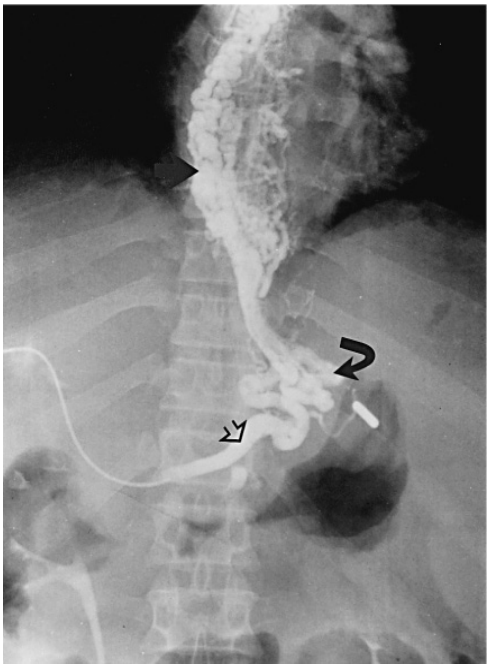


PSC

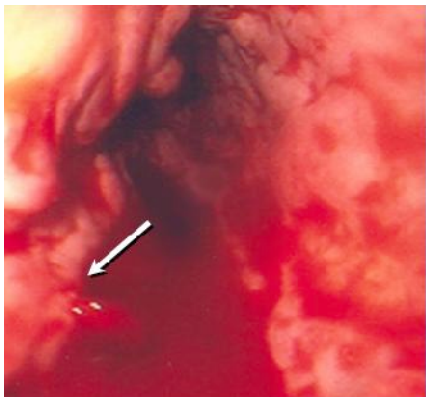


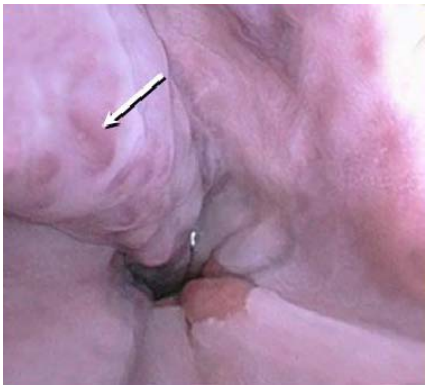
Interventional Radiology



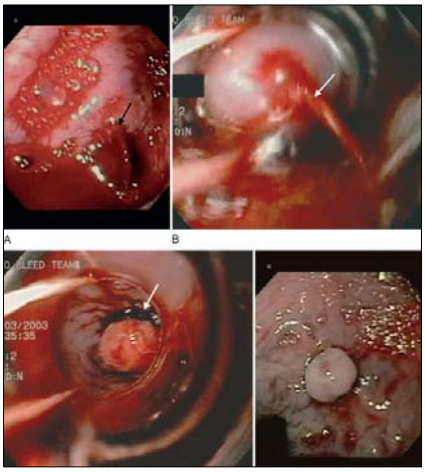


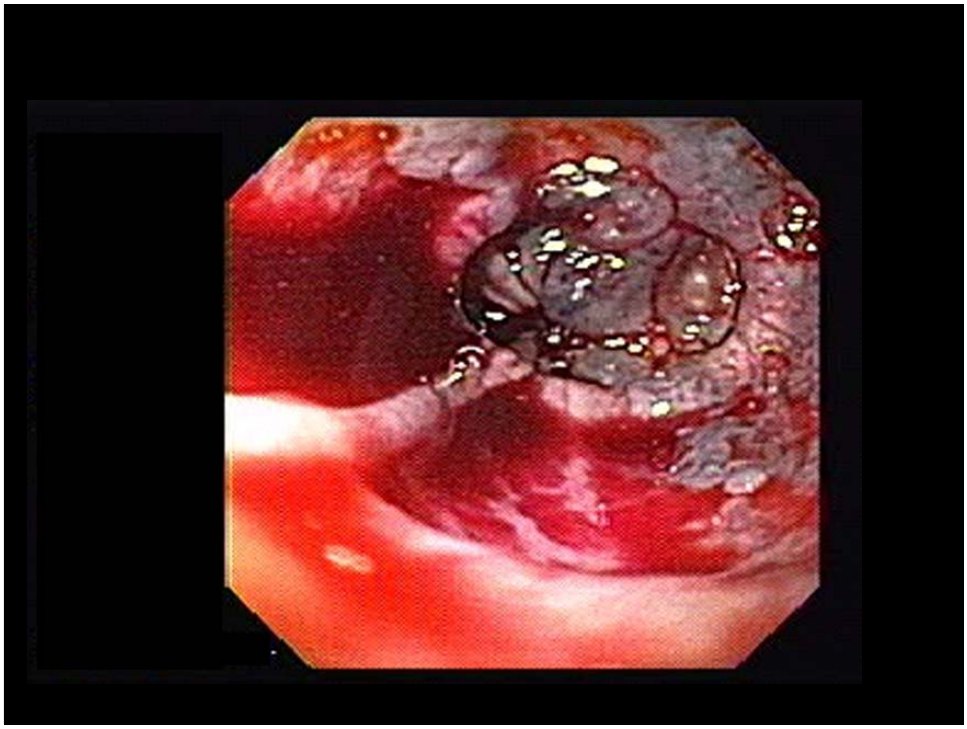
Endoscopy- Esophageal Varices

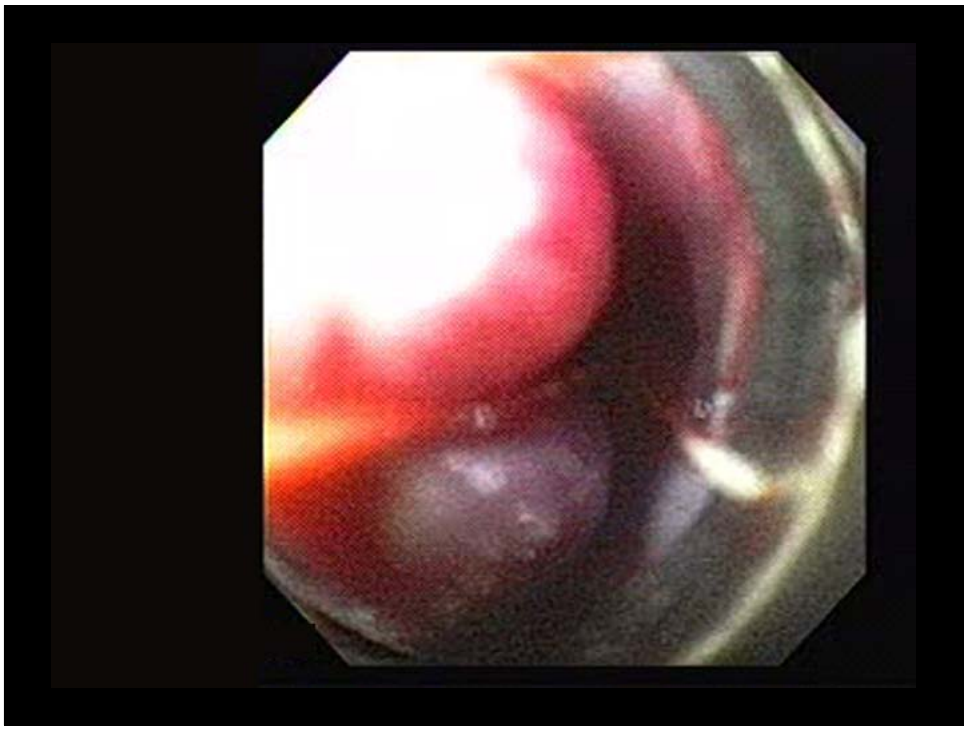




Variceal Band Ligation







Liver Biopsy

- Gold standard to assess:
  - Etiology of elevated LFTs or cirrhosis
  - Severity of liver disease
- Percutaneous or transjugular with pressure measurements
- Not necessary if obvious clinical, laboratory, imaging signs of hepatic decompensation and portal hypertension

Am J Gastro 1998;93(1):44-8

Introduction- Liver Tests

- Liver **"Function"** tests are a misnomer- not a true test of function
- Abnormal LFTs are often the first indication of underlying liver disease but normal results do not preclude significant liver disease
- Sequential testing may allow assessment of the effectiveness of therapy

Abnormal Liver Tests

- Laboratory determinations that reflect liver disease commonly termed liver function tests
  - Misnomer: elevated serum aminotransferase levels and alkaline phosphatase levels are markers of liver injury, not indices of degree of liver function.
- Measures of hepatic function: albumin, bilirubin, prothrombin time
  - can be affected by extrahepatic factors such as nutrition, hemolysis, antibiotic use, systemic illness
- Liver function tests are best referred to as liver tests or liver chemistries.

Abnormal Liver Tests

- True liver function tests are not widely used
  - galactose clearance, aminopyrine clearance tests.
- Abnormal liver chemistry results occur in as many as one-third of patients screened.
- Incidence of clinically significant unsuspected liver disease is approximately 1%.

Aminotransferases

- ALT and AST are the most widely ordered liver chemistries that reflect injury to the liver.
  - ALT localized in the liver
  - AST more widely distributed in liver (mainly) as well as cardiac, skeletal, kidney and brain tissue
    - ALT predominantly localizes to the cytosol
    - AST localizes to the mitochondria
- These levels increase in the serum with the death of hepatocytes
  - either by necrosis or apoptosis

Aminotransferases

- Degree of elevation of AST and ALT are useful in distinguishing acute and chronic liver diseases.
- Aminotransferase levels $\leq$ 300 IU/mL
  - alcoholic hepatitis, non-alcoholic fatty liver disease, chronic viral hepatitis (hepatitis B and C).
- Patients with levels between 500 IU/mL and 5,000 IU/mL
  - acute viral hepatitis, autoimmune hepatitis, drug reaction
  - Viral and drug induced hepatitis will raise aminotransferase levels steadily and peak in the low thousands within 7-14 days, return to normal over weeks
- High levels (greater than 5,000 IU/ml)
  - acetaminophen related liver failure, ischemia, or herpes simplex hepatitis

Aminotransferases

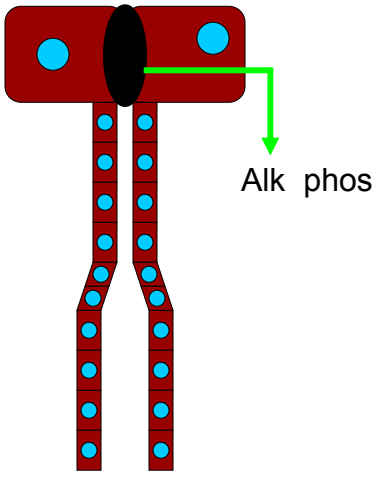
- AST to ALT ratio can be very useful.
  - When greater than 2.0, this typically suggests alcoholic liver disease
  - due to deficiency of pyridoxine seen in alcoholics
    - depresses ALT levels to a greater degree than AST ratios.
    - alcohol is a mitochondrial toxin as well.
- AST may also be higher in cirrhotic patients regardless of etiology of liver disease
- Non-hepatic causes of elevated AST/ALT should be considered if no other cause can be found

Cholestasis

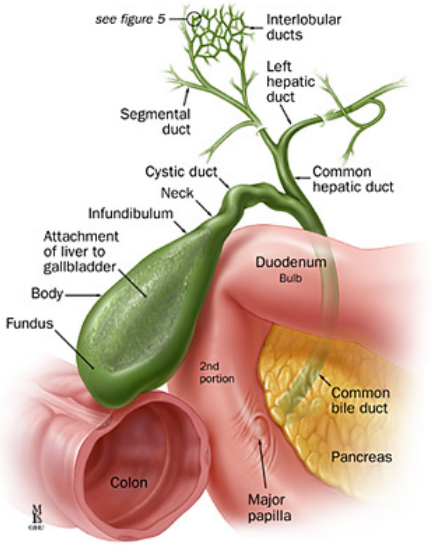
- Defined as an impairment in bile flow.
- Cholestatic liver profile is characterized by an elevation in alkaline phosphatase with or without an elevation in bilirubin.
- Alkaline phosphatase elevation seen in those who are less than 18 years old, or in women who are pregnant
  - In children, the alkaline phosphatase level is increased up to three times the upper limit of normal, and in pregnant patients it can be increased up to two times that of normal (placenta)
- Normal Alk phos level ~ 125 IU/ml

CHOLESTASIS

- Direct effect on cannalicular membrane by:
  - Toxins, metabolites
  - Drugs
  - Interleukins, TNF
  - EtOH
  - Obstruction (leads to bile salt accumulation)
- Alk Phos is synthesized and translocates to basolateral membrane of hepatocyte where it is lost to serum and hence it is raised in cholestasis when you measure the level



Cholestasis can be a microscopic or macroscopic problem



Cholestasis

•Alkaline phosphatase refers to a family of enzymes that catalyze hydrolysis of phosphate esters at an alkaline pH

- •Found in hepatocytes, not bile duct cells

•Present in bone, placenta, intestine, and kidney, as well as liver

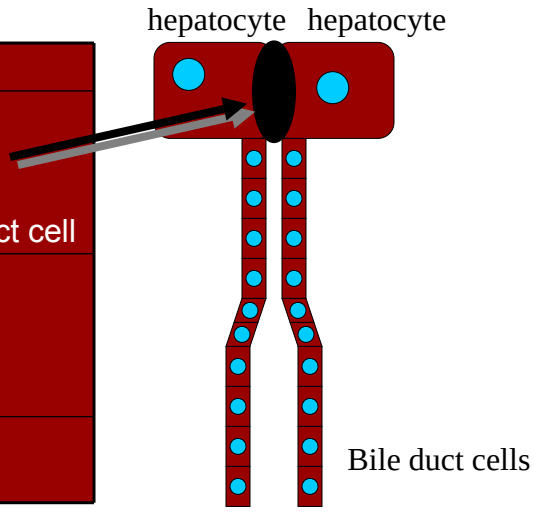
•Alkaline phosphatase increase disproportionate to bilirubin level (bilirubin <1.0 mg/dl, alkaline phosphatase >1,000 IU/mL) ,

- •granulomatous or infiltrative disease of the liver: sarcoid, fungal infections, TB and lymphoma
- •chronic cholestatic disorders including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)

•When alkaline phosphatase is elevated in conjunction with an elevated AST/ALT and bilirubin, this is termed a cholestatic hepatitic pattern

ALKALINE PHOSPHATASE
SITES OF PRODUCTION

	Site
Liver	Hepatocyte cannalicular membrane NOT bile duct cell
Bone Intestine Kidney Placenta	
Tumors	Lung Ovary



Jaundice: Clinical Presentation

- Infants: vast majority of cases of jaundice are physiologic
- In adolescence, Gilbert's represents half the cases of jaundice.
  - Also acute viral hepatitis
- Young adults: viral hepatitis followed by alcohol and biliary tract disease
- Elderly > 50% likely related to malignancy within the liver.

Total bilirubin

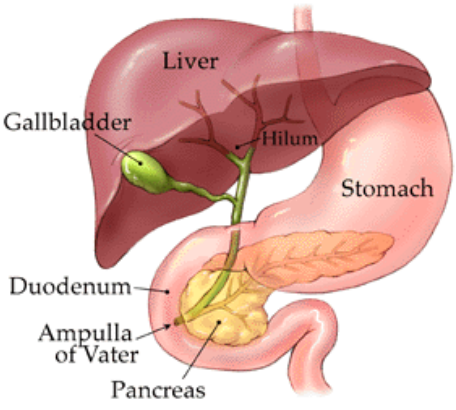
- Total Bilirubin (TB) = Unconjugated Bilirubin + Conjugated Bilirubin
  - Normal 0.2 to 1.3 mg/dl
  - Jaundice clinically apparent when bilirubin > 3mg/dL
- 95% derived from breakdown of senescent RBC's, 5% from heme-containing enzymes
- Terminology
  - Direct= conjugated bilirubin
  - Indirect= unconjugated bilirubin

Unconjugated Bilirubin

- Increased in:
  - Congenital disease- Gilbert's (defective uptake and storage)
  - Overproduction
    - Hemolysis
    - Hematoma resorption
    - Ineffective erythropoiesis
    - Transfusion
- Rarely rises > 5 if from isolated unconjugated bilirubin elevation

Conjugated Bilirubin

- Increased in:
  - Congenital disease- Dubin Johnson (black liver), Rotor's
  - Intrahepatic disease- cirrhosis, hepatitis, drug/toxin damage, liver failure
  - Extrahepatic- bile duct disease (stone, stricture, infection, cancer)



Very High Total Bilirubin

- >30 mg/dL indicates hemolysis plus parenchymal dysfunction or biliary obstruction
- >60 mg/dL seen in patients who have a hemoglobinopathy (sickle cell) who develop obstructive liver disease or acute hepatitis
- Urine bilirubin and urobilinogen add little diagnostic information about hepatic function

True Tests of Liver Function

•Albumin: plasma protein albumin is exclusively synthesized by the liver and has a circulating half life of approximately three weeks.

• Reduction in albumin (normal $\geq$ to 3.5 gm/dl) usually indicates liver disease of more than three weeks duration.

- •Caveat: any severe illness can decrease albumin due to cytokine effects if duration of disease is less than three weeks.

•Prothombin time: may be elevated if there is cholestasis, primary hepatocellular dysfunction, or antibiotic use

Ammonia

"Blood ammonia levels cause as much confusion in those requesting the measurement as in the patients in whom they are being measured"

Adrian Reuben
Hepatology 2002; 35:983

Diagnostic Thoughts

- ~ 9% of Americans have "abnormal" ALT
- Increasing incidence ~ obesity increase
- Up to 30% of abnormal tests are normal on repeat~ Fluctuations are common
- Cutoff values should be adjusted for gender and BMI

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Case 1

- 38 year old white male with ALT 65 on routine health insurance screen

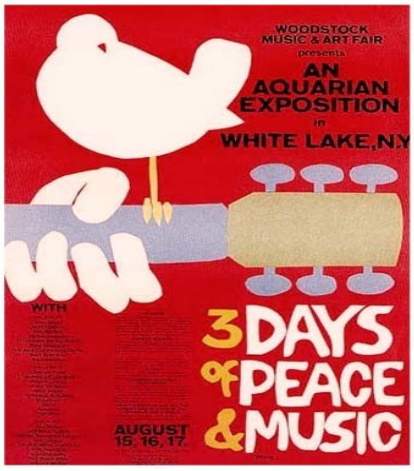
Abnormal Transaminases

- If < 3 x ULN, recheck in 1-3 months
- Two results elevated, investigate further
- Look at AST/ALT ratio
  - < 1 in most hepatocellular injury
  - >1 in alcoholic liver disease, drug induced, malignancy, cirrhosis

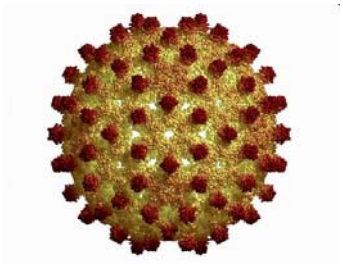
Asymptomatic Elevated Transaminases

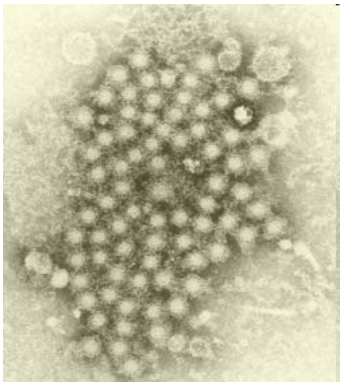
- NAFLD
  - DM, metabolic syndrome, hyperlipidemia
- ETOH
  - AST > ALT, ↑ MCV, ↑ GGT
- HBV
  - Immigration from endemic country; high risk sexual behavior
- HCV
  - IVDA, blood transfusions

Woodstock- 40 years later



Hepatitis B & Hepatitis C

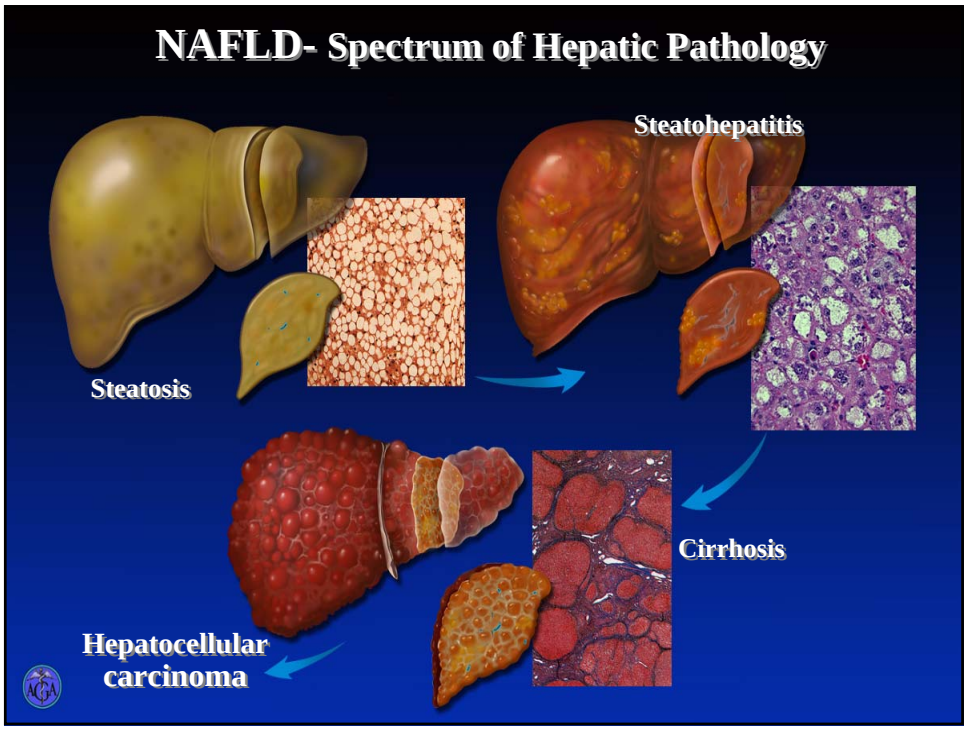




450
Million

170
Million

Annals Int Med 2006; 144:705
WHO. Hepatitis B. Fact Sheet # 2004.



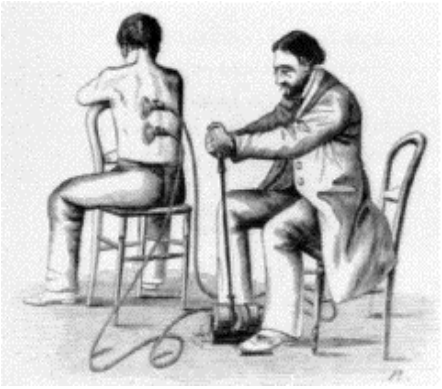
Initial Testing

- HBsAg, HBcAb, HBsAb
- HCV Ab
- ETOH level, GGT
- RUQ US with dopplers

Second Round Testing

- Autoimmune hepatitis
  - ANA, ASMA, SPEP, LKM
- Hemochromatosis
  - Fe, TIBC, Ferritin, HFE
- Alpha 1 antitrypsin deficiency
  - A1AT phenotype

Iron Men



Management

Third Round Testing

- Celiac sprue- serology
- Thyroid disease- TSH
- Muscle breakdown- creatine kinase, aldolase
- Adrenal insufficiency

Case 2

- 65 year old with AST 2000 and ALT 2200 after presenting unconscious to the ED

Transaminases in the Thousands

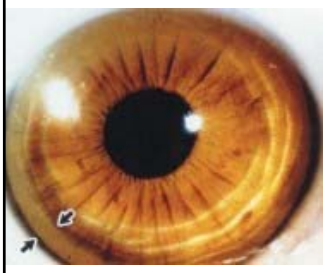
A- Autoimmune, acetaminophen, hepatitis A

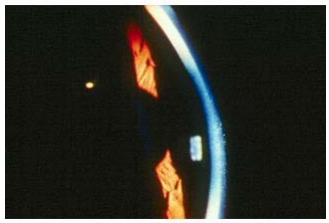
B- Hepatitis B

C- Cardiac (Shock), choledocholithiasis, Cocaine

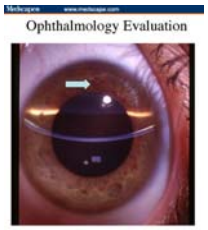
D- Drugs (Toxin)

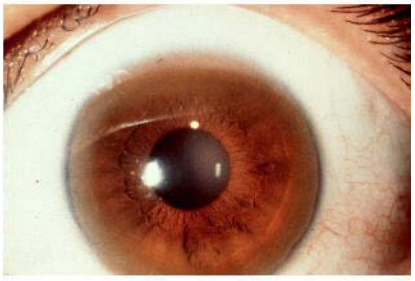
E- Esoterics: Wilson's





•< 50% have KFR- lack of KFR does NOT exclude WD





Case 3

- 50 year old with acute jaundice

Jaundice

- Increased heme breakdown
- Decreased hepatic ability for conjugation
- Impaired hepatic excretion
- Biliary obstruction

Increased Heme Breakdown

- Hematoma resorption
- Hemolysis
  - Sepsis, DIC
  - TTP, HUS
  - Autoimmune hemolytic anemia
  - Wilson's
  - Autoimmune hepatitis

Hepatic Causes of Jaundice

- Decreased hepatic ability for conjugation
  - Gilbert's
- Impaired hepatic function and excretion
  - Alcoholic hepatitis
  - Drug injury
  - Viral hepatitis- HAV, HBV, HCV, HDV, HEV, EBV
  - PSC, PBC
  - Cirrhosis

Extrahepatic Causes of Jaundice

- Stricture
- Stone
- Malignancy
  - Pancreatic cancer, cholangiocarcinoma, ampullary cancer, duodenal cancer

RUQ US → CT/MRI → EUS/ERCP

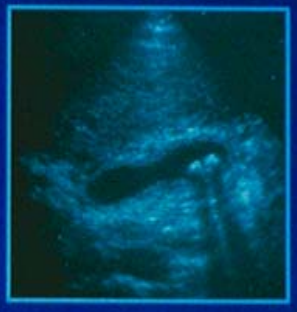
Tests in the Evaluation of jaundice

- Viral serologies
- Drug/toxin/ETOH history
- Ceruloplasmin
- AMA

Tools in the Evaluation of jaundice

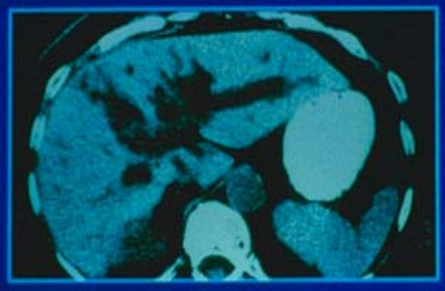
- Diagnostic imaging studies
  - ultrasound and CT scan
  - A liver/spleen scan can be ordered, but this has largely been replaced by ultrasound
- Magnetic resonance imaging
- A HIDA scan is useful to assess for cystic duct obstruction (acute cholecystitis)
- Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous cholangiography (PTC), Magnetic resonance cholangiopancreatography (MRCP)
- Liver biopsy

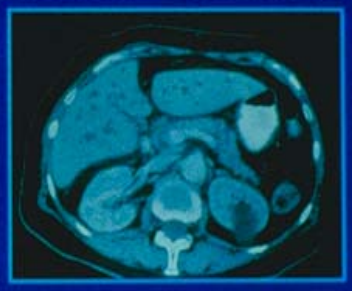
ULTRASONOGRAPHY

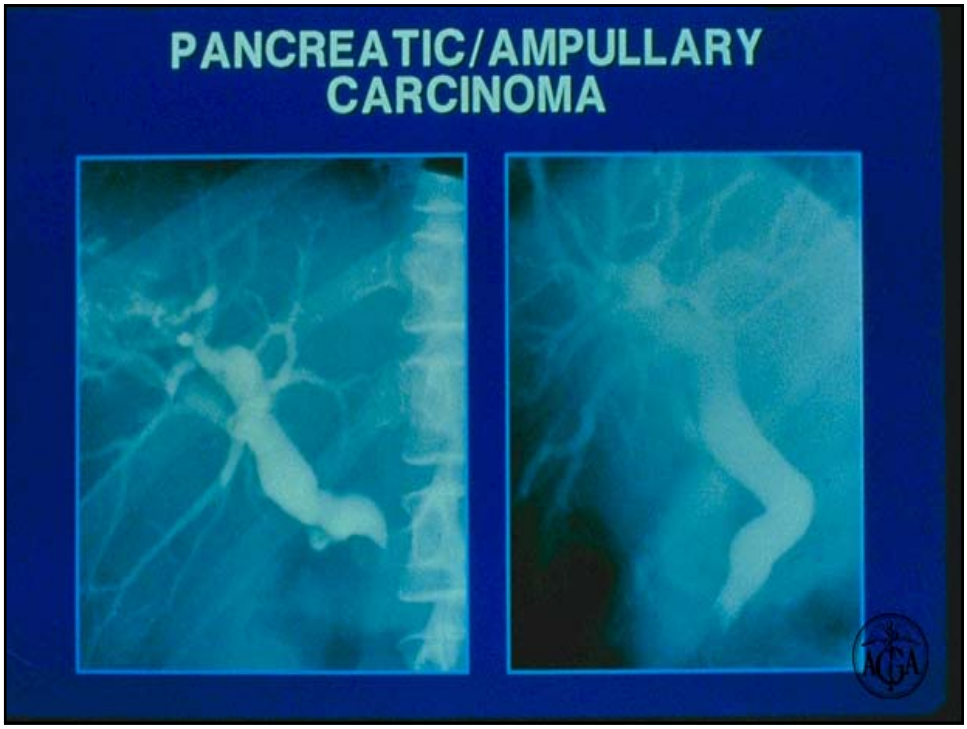


ADVANTAGES	LIMITATIONS
No ionizing radiation	Operator dependent
Portable	Patient dependent
Multiple planes	Interpretation subjective
Biopsy localization	Poor for intraductal stones

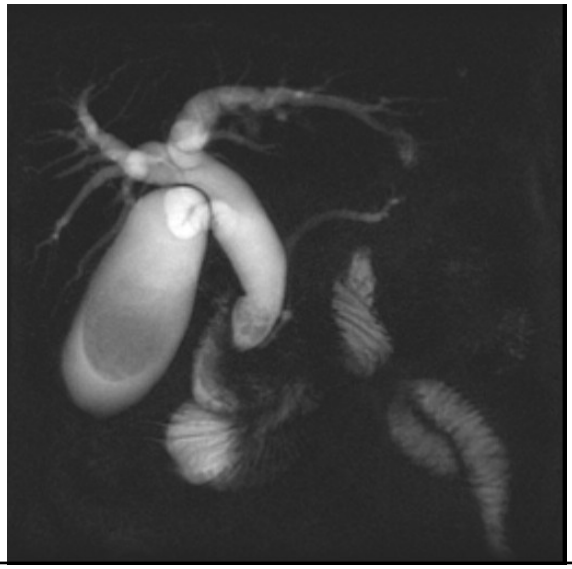
BILE DUCT DILATATION

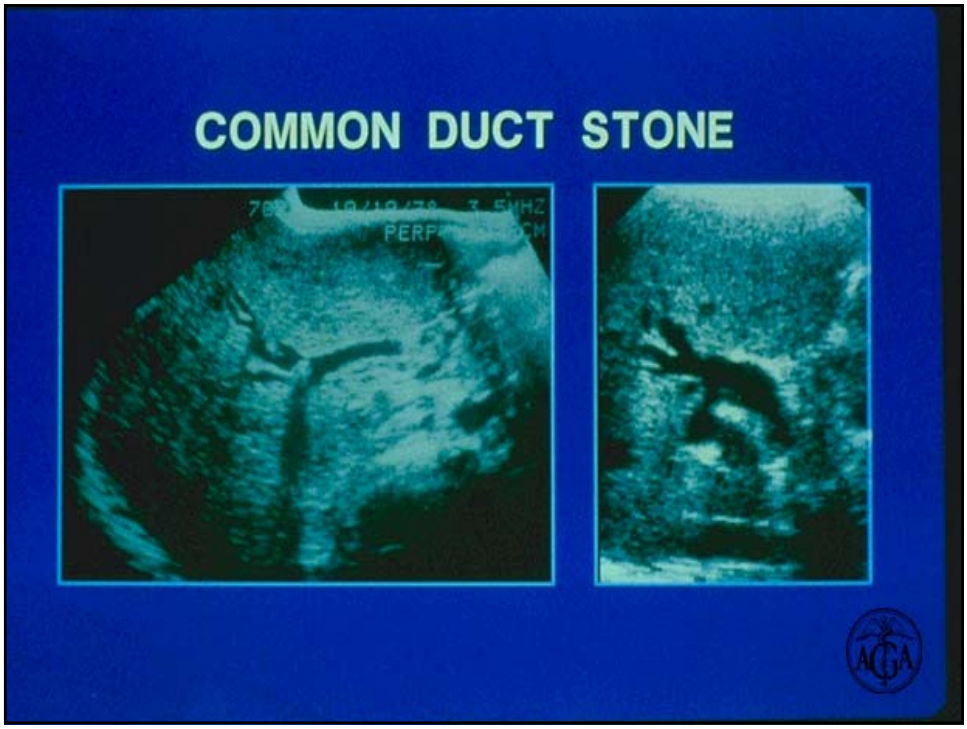






MRCP with large distal common bile duct stone





Case 4

- 49 year old AF with pruritus
- AP 300
- AST 40
- ALT 30
- TB 0.5

Elevated Alkaline Phosphatase

- Confirm liver origin
  - Bone, Placenta, Intestine
- Bony causes- metastases, hyperparathyroidism, CRF, Paget's
- CHF, hyperthyroidism
- Pregnancy

Elevated Alkaline Phosphatase

- AP isoenzymes
- GGT
- 5' NT
- Or other concomitant LFT increases suggests liver disease
- RUQ US

If from liver= Cholestasis

Elevated Alkaline Phosphatase

- PBC
  - AMA
- Drug, toxin history
  - Antibiotics, Seizure medications, Immunosuppressants
- Infiltrative disease
  - Sarcoid,
- Malignancy

Isolated GGT

This has limited use as primary liver test and there is no clear consensus on follow up. Suggestions are:

- Although nonspecfic, consider alcohol
- Review risk factors for non-alcoholic fatty liver disease.
- Consider ultrasound

Outpatient Hepatology Consultation

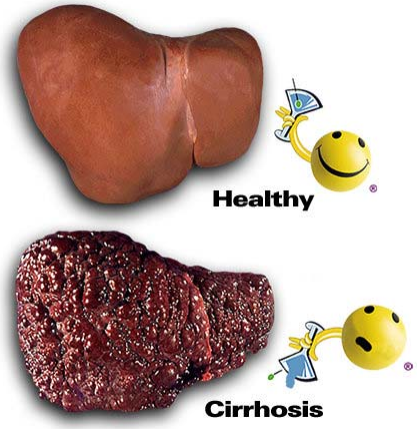
- HBsAg positive, ALT > ULN for at least 6 months.
- AFP is >100 = should be seen urgently.
- Hepatitis C positive
- Evidence of acute or chronic failure of liver synthetic function.
- Hemochromatosis positive with abnormal LFTs, hepatomegaly or untreated ferritin > 1000 μg/L.
- Anyone with persisting **unexplained** LFT abnormalities.

Inpatient Hepatology Consultation

- Jaundice + Hepatic encephalopathy = Acute Liver Failure
- New onset ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, jaundice = Decompensated cirrhosis
- Unexplained LFT abnormalities

Is it over yet?

Word from our sponsors…



Joseph Ahn, M.D., M.S.
Medical Director, Liver Transplant
Associate Chief, Section of Hepatology
Loyola University Medical Center
jahn2@lumc.edu
708-216-0464