Liver Cirrhosis

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Introduction

- The two most common causes in the United States are alcoholic liver disease and hepatitis C, which together account for almost one-half of those undergoing transplantation

Introduction

- 12th leading cause of death in the united states in 2002
- On average about 27,000 deaths per year
- Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced

Exactly How Much Do You Drink?

- Estimated that the development of cirrhosis requires, on average, the ingestion of 80 grams of ethanol daily for 10 to 20 years
- This corresponds to approximately one liter of wine, eight standard sized beers, or one half pint of hard liquor *each day*

Pathophysiology

- Irreversible chronic injury of the hepatic parenchyma
- Extensive fibrosis - distortion of the hepatic architecture
- Formation of regenerative nodules

Clinical Manifestations

- Spider angiomas
- Palmar erythema
- Nail changes
  - Muehrcke's nails
  - Terry’s nails
- Gynecomastia
- Testicular atrophy

Clinical Manifestations

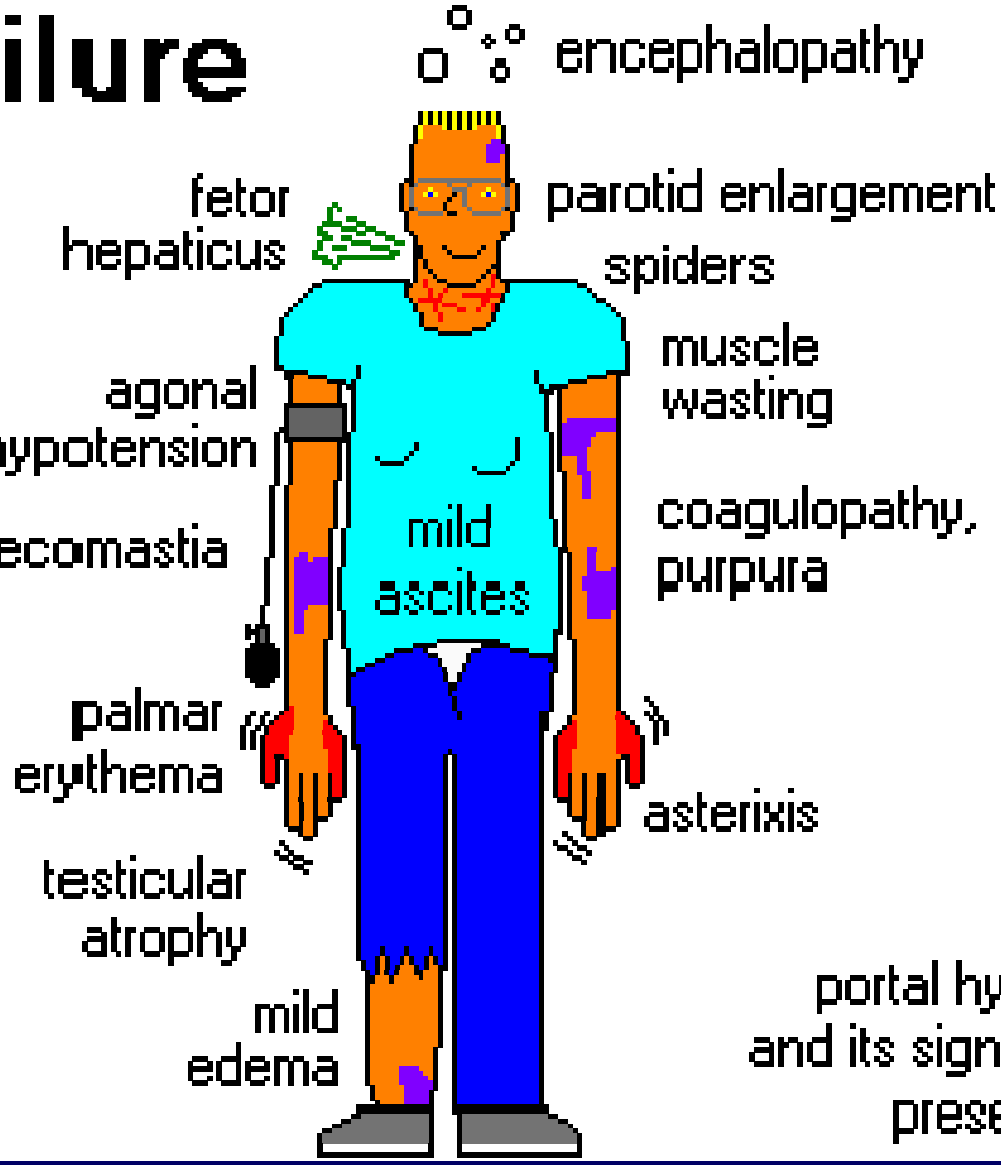
- Muehrcke's nails

- Terry’s nails

Clinical Manifestations

- Fetor hepaticus
- Jaundice
- Asterixis
- Pigment gallstones
- Parotid gland enlargement
- Cruveilhier-Baumgarten murmur
- Hepatomegaly
- Splenomegaly
- Caput medusa

Liver Failure

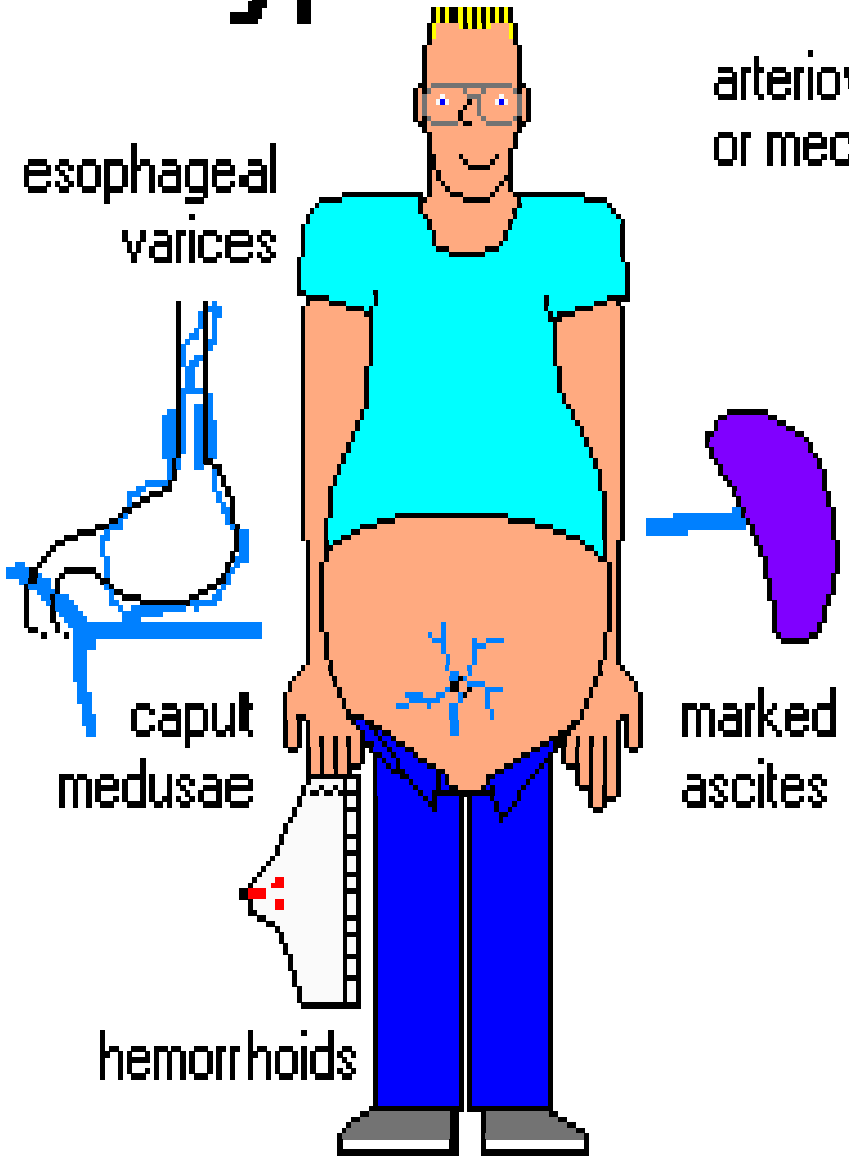


elevated urinary urobilinogen (why?)
elevated serum indirect bilirubin (why?)
most liver diseases also elevate direct bilirubin (why?)

hepatorenal syndrome?
hepatopulmonary syndrome?

Of course, portal hypertension and its signs are often present as well.

Portal Hypertension



arteriovenous shunting and/ or mechanical obstruction

hypersplenism:
-- moderate anemia
-- neutropenia
-- thrombocytopenia

Of course, liver failure and its signs are often present as well.

Laboratory Studies

- most common measured laboratory test classified as LFTs include
  - the **enzyme tests** (principally the serum aminotransferases, alkaline phosphatase, and gamma glutamyl transpeptidase), the serum bilirubin
  - **tests of synthetic function** (principally the serum albumin concentration and prothrombin time)

Radiologic Modalities

- Can occasionally suggest the presence of cirrhosis, they are not adequately sensitive or specific for use as a primary diagnostic modality
- Major utility of radiography in the evaluation of the cirrhotic patient is in its ability to detect complications of cirrhosis

Diagnosis

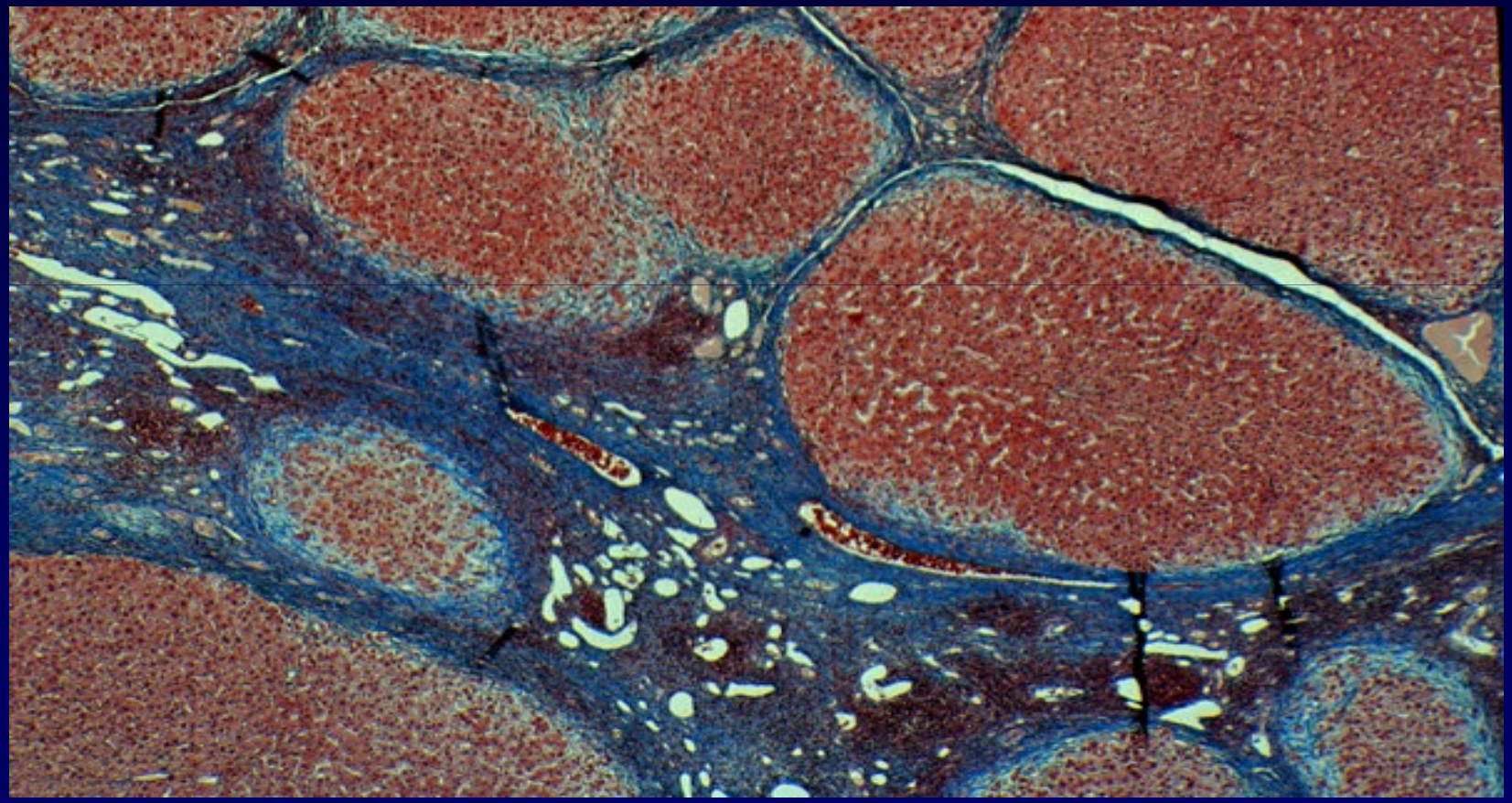
- Liver biopsy
  - Obtained by either a percutaneous, transjugular, laparoscopic, or radiographically-guided fine-needle approach
  - Sensitivity of a liver biopsy for cirrhosis is in the range of 80 to 100 percent depending upon the method used, and the size and number of specimens obtained

Diagnosis

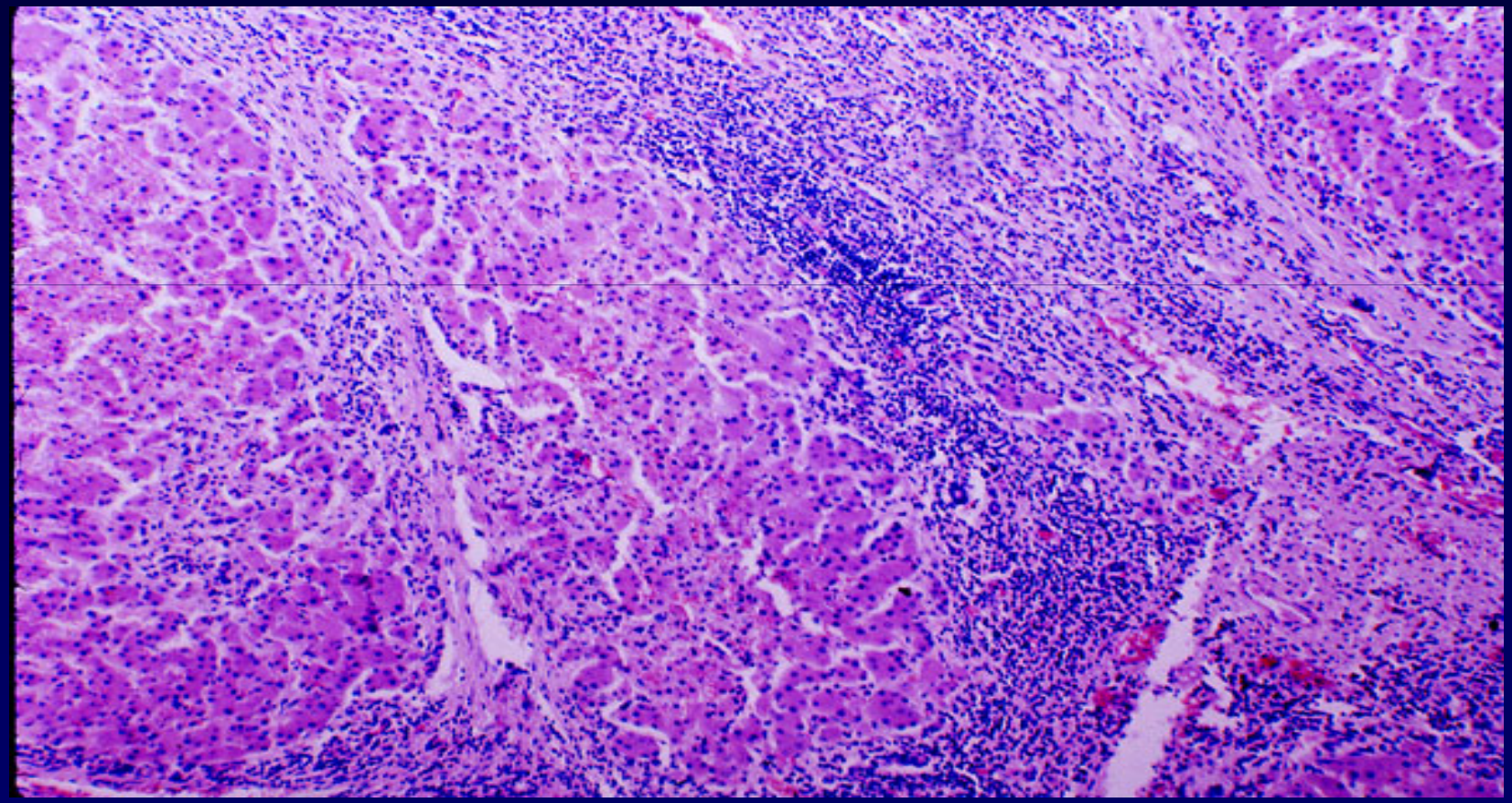
※ not necessary if the clinical, laboratory, and radiologic data strongly suggest the presence of cirrhosis

※ liver biopsy can reveal the underlying cause of cirrhosis

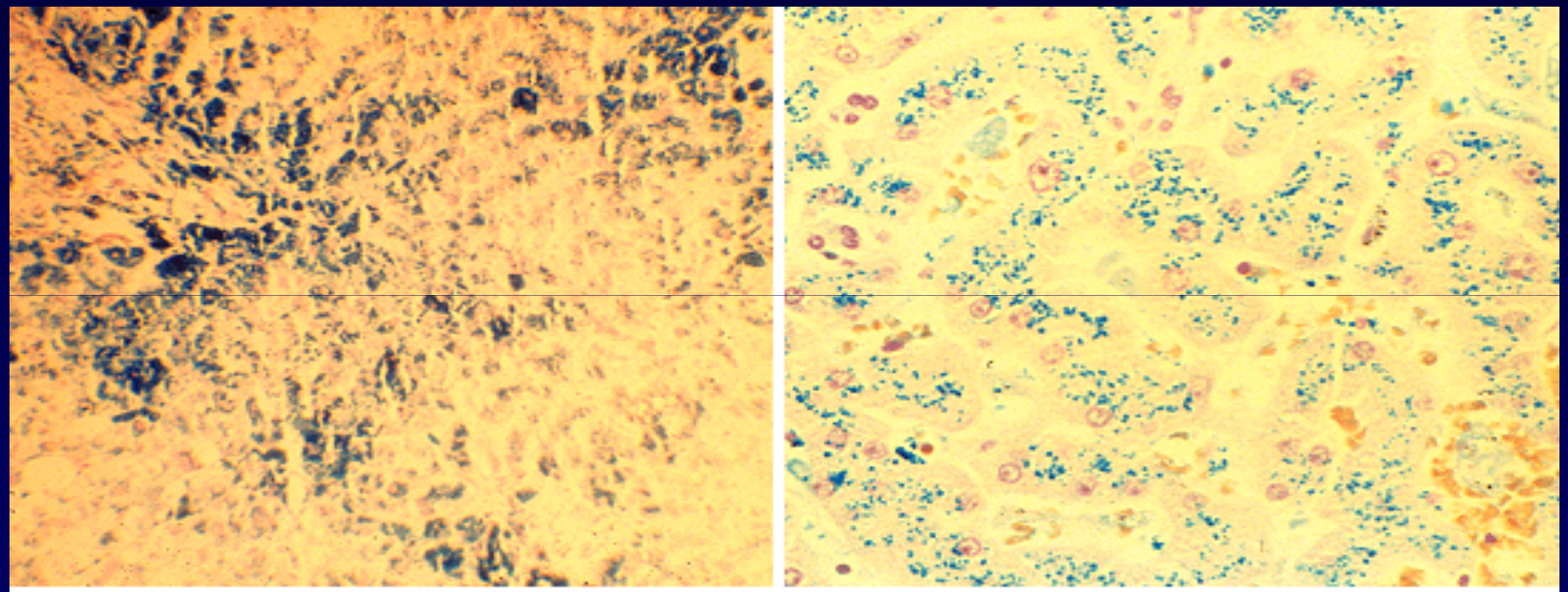
Histopathology



Histopathology

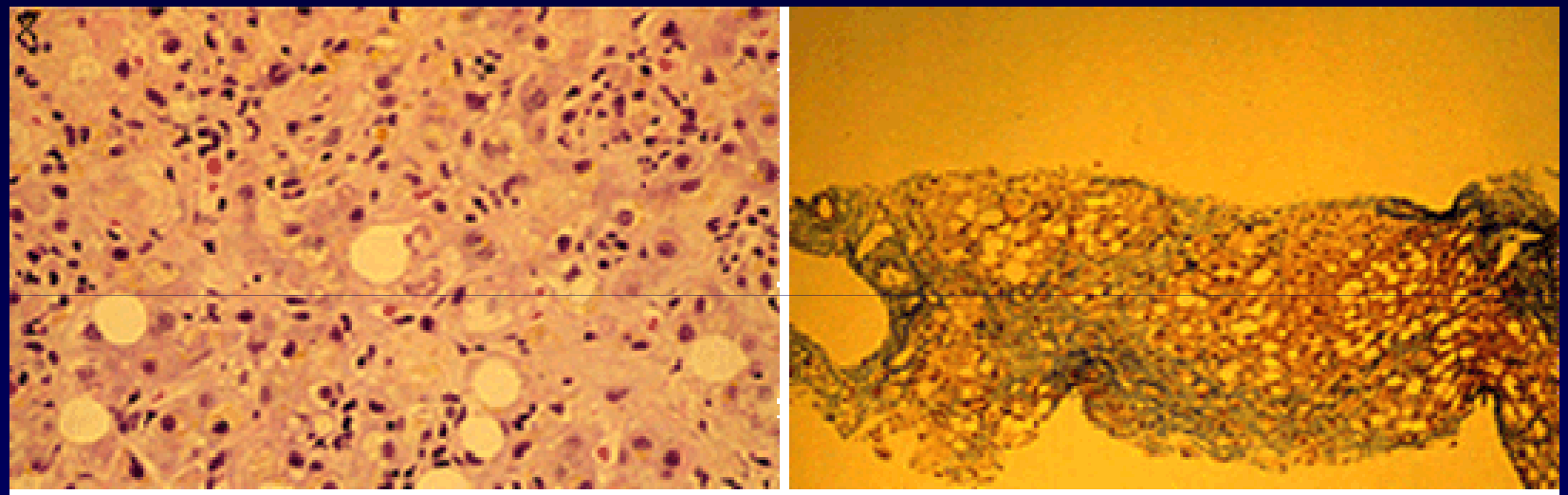


Histopathology

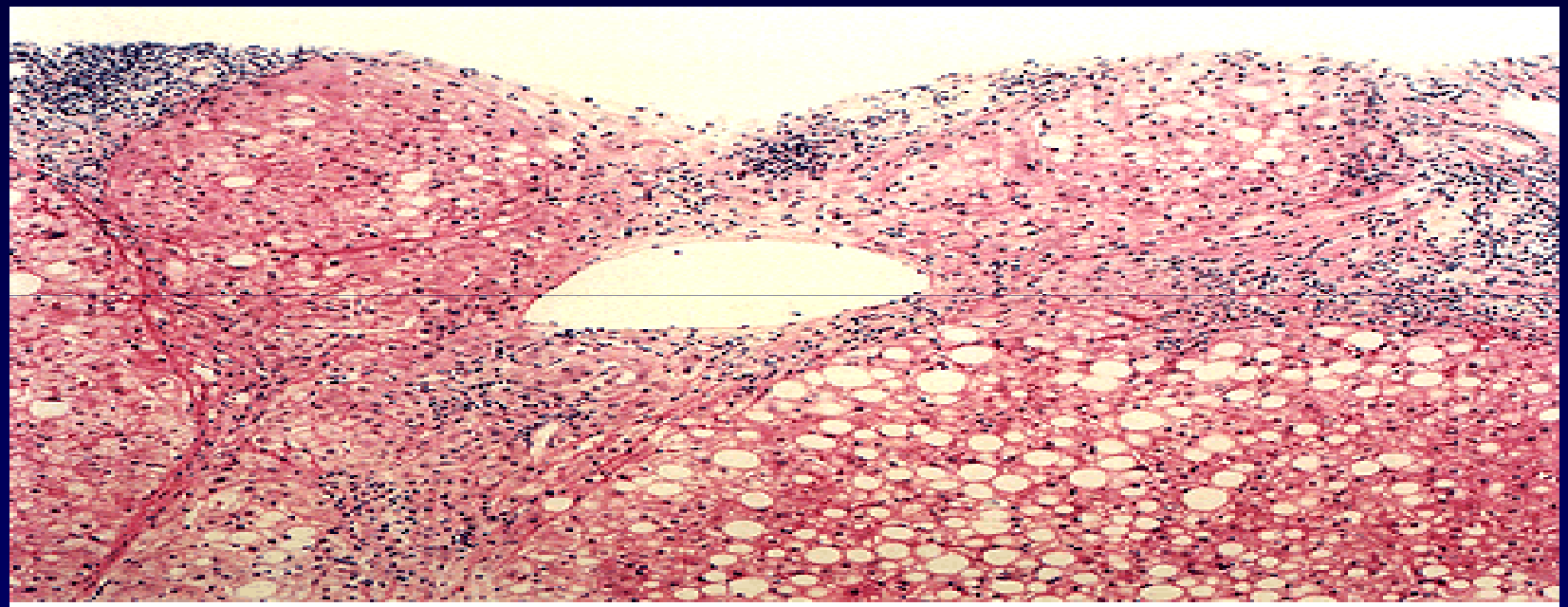


Iron overload in liver Perls' Prussian blue stain of a liver biopsy from a patient with hereditary hemochromatosis. Left panel: Low power view shows intense iron staining of hepatocytes. The blue-stained iron deposits typically start at the periphery of the liver lobule and extend centrally. Right panel: High power view shows intense iron staining (in blue) of hepatocytes. Courtesy of Stanley L Schrier, MD.

Histopathology



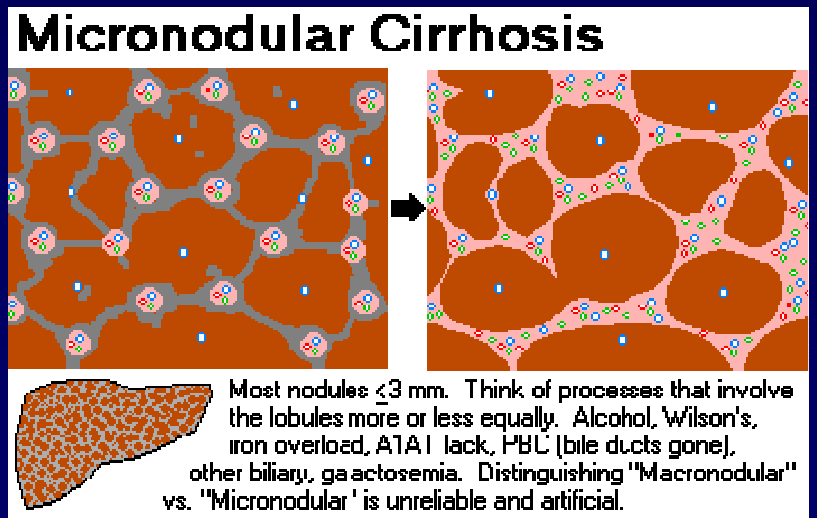
Nonalcoholic steatohepatitis Histologic changes in nonalcoholic steatohepatitis (NASH). Left panel: The hepatocyte in the center contains a large vacuole of fat and deeply staining eosinophilic strands of cytoplasmic hyalin. Numerous neutrophils and phagocytic cells containing golden brown pigmented material (bile components and cellular debris) are present in the sinusoids. Right panel: NASH with cirrhosis. Trichrome stain shows regenerating nodules with fat surrounded by fibrous tissue.



Hepatitis C and alcohol Needle biopsy of the liver (100x) of a 57 year old female with cirrhosis from both hepatitis C virus infection and chronic alcohol consumption. Hematoxylin and eosin stain demonstrates prominent steatosis as well as portal and peri-portal inflammation and fibrosis. Courtesy of Jeremy Ditelberg, MD.

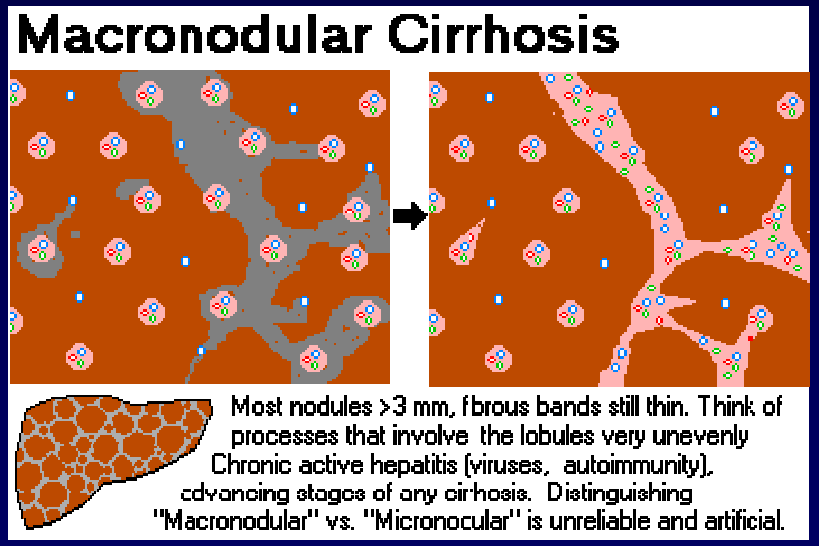
Morphologic Classification

- Micronodular cirrhosis
  - Nodules less than 3 mm in diameter
  - Believed to be caused by alcohol, hemochromatosis, cholestatic causes of cirrhosis, and hepatic venous outflow obstruction



Morphologic Classification

- Macronodular cirrhosis
  - Nodules larger than 3 mm
  - Believed to be secondary to chronic viral hepatitis



Morphologic Classification

- Relatively nonspecific with regard to etiology
- The morphologic appearance of the liver may change as the liver disease progresses
  - micronodular cirrhosis usually progresses to macronodular cirrhosis
- Serological markers available today are more specific than morphological appearance of the liver for determining the etiology of cirrhosis
- Accurate assessment of liver morphology may only be achieved at surgery, laparoscopy, or autopsy

Evaluation of Cirrhosis

Evaluation of the Patient with Cirrhosis

Disease	Tests and findings
Alcoholic liver disease	History of alcohol abuse AST/ALT >2 with both being less than 500 IU/mL if alcoholic hepatitis is present
Chronic hepatitis C	Second generation assay for anti-HCV PCR for HCV RNA if confirmatory test is necessary
Primary biliary cirrhosis	Antimitochondrial antibodies as an isolated finding
Primary sclerosing cholangitis	Strong association with inflammatory bowel disease Contrast cholangiography to establish the diagnosis Antinuclear and antismooth muscle antibodies and ANCA; these are not diagnostic
Autoimmune hepatitis	Hypergammaglobulinemia Antinuclear and antismooth muscle antibodies and ANCA in type 1; anti-LKM-1 in type 2
Chronic hepatitis B	HBsAg and HBeAg and, in some cases, HBV DNA by hybridization or bDNA assay
Hereditary hemochromatosis	Family history of cirrhosis Transferrin saturation and plasma ferritin should be performed but may be elevated by liver disease itself Diagnosis established by liver biopsy and calculation of hepatic iron index or by genetic testing
Wilson's disease	Family or personal history of cirrhosis at a young age Serum ceruloplasmin reduced in 95 percent of patients Liver biopsy shows increased copper content which may also be seen in cholestatic liver diseases
Alpha-1-antitrypsin deficiency	Family or personal history of cirrhosis at a young age Serum AAT; phenotyping if low or borderline values

Complications

- Ascites
- Spontaneous Bacterial Peritonitis
- Hepatorenal syndrome
- Variceal hemorrhage
- Hepatopulmonary syndrome

Complications

- Other Pulmonary syndromes
  - Hepatic hydrothorax
  - Portopulmonary HTN
- Hepatic Encephalopathy
- Hepatocellular carcinoma

Ascites

- Accumulation of fluid within the peritoneal cavity
- Most common complication of cirrhosis
- Two-year survival of patients with ascites is approximately 50 percent

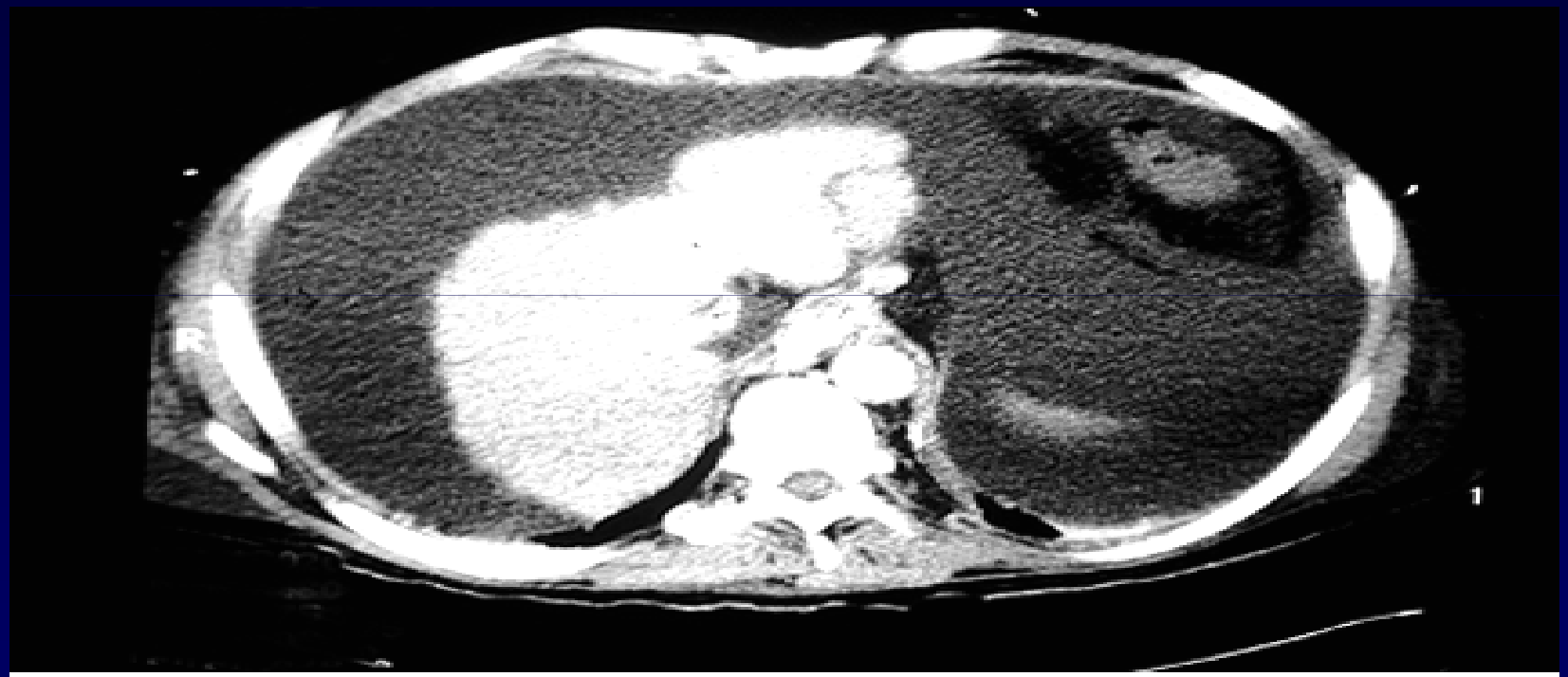
Ascites

- Assessment of ascites
  - Grading
    - Grade 1 — mild; Detectable only by US
    - Grade 2 — moderate; Moderate symmetrical distension of the abdomen
    - Grade 3 — large or gross asites with marked abdominal distension
  - Older system -subjective
    - 1+ minimal, barely detectable
    - 2+ moderate
    - 3+ massive, not tense
    - 4+massive and tense

Ascites

- Imaging studies for confirmation of ascites
  - Ultrasound is probably the most cost-effective modality

Ascites



Ascites CT scan shows a large volume of ascitic fluid surrounding a small shrunken cirrhotic liver. The fluid is of low attenuation and is free floating without septations or solid material. Courtesy of Jonathan Kruskal, MD.

Who gets a belly tap?

Indications for Abdominal Paracentesis in a Patient with Ascites

- New onset ascites
- At the time of each admission to the hospital
- Clinical deterioration, either inpatient or outpatient
  - Fever
  - Abdominal pain
  - Abdominal tenderness
  - Mental status change
  - Ileus
  - Hypotension
- Laboratory abnormalities that may indicate infection
  - Peripheral leukocytosis
  - Acidosis
  - Worsening of renal function
- Gastrointestinal bleeding (a high risk time for infection)

What do I want to order ?

Tests Performed on Ascitic Fluid

Routine tests	Optional tests	Unusual tests
Cell count and differential	Glucose concentration	Tuberculosis smear and culture
Albumin concentration	LDH concentration	Cytology
Total protein concentration	Gram stain	Triglyceride concentration
Culture in blood culture bottles	Amylase concentration	Bilirubin concentration

Ascites

- Treatment aimed at the underlying cause of the hepatic disease and at the ascitic fluid itself
- Dietary sodium restriction
  - Limiting sodium intake to 88 meq (2000 mg) per day

Ascites

- The most successful therapeutic regimen is the combination of single morning oral doses of Spironolactone and Furosemide, beginning with 100 mg and 40 mg
- Two major concerns with diuretic therapy for cirrhotic ascites:
  - Overly rapid removal of fluid
  - Progressive electrolyte imbalance

Spontaneous Bacterial Peritonitis

- Infection of ascitic fluid
- Almost always seen in the setting of end-stage liver disease
- The diagnosis is established by
  - A positive ascitic fluid bacterial culture
  - Elevated ascitic fluid absolute polymorphonuclear leukocyte (PMN) count (>250 cells/mm3)

Spontaneous Bacterial Peritonitis

- Clinical manifestations:
  - Fever
  - Abdominal pain
  - Abdominal tenderness
  - Altered mental status

Hepatorenal syndrome

- acute renal failure coupled with advanced hepatic disease (due to cirrhosis or less often metastatic tumor or severe alcoholic hepatitis)
- characterized by:
  - Oliguria
  - benign urine sediment
  - very low rate of sodium excretion
  - progressive rise in the plasma creatinine concentration

Hepatorenal Syndrome

- Reduction in GFR often clinically masked
- Prognosis is poor unless hepatic function improves
- Nephrotoxic agents and overdiuresis can precipitate HRS

Variceal hemorrhage

- Occurs in 25 to 40 percent of patients with cirrhosis
- Prophylactic measures
- Screening EGD recommended for all cirrhotic patients

Hepatopulmonary syndrome

- Hepatopulmonary syndrome
  - Liver disease
  - Increased alveolar-arterial gradient while breathing room air
  - Evidence for intrapulmonary vascular abnormalities, referred to as intrapulmonary vascular dilatations (IPVDs)

Hepatic Hydrothorax

- Pleural effusion in a patient with cirrhosis and no evidence of underlying cardiopulmonary disease
- Movement of ascitic fluid into the pleural space through defects in the diaphragm, and is usually right-sided
- Diagnosis -pleural fluid analysis
  - reveals a transudative fluid
  - serum to fluid albumin gradient greater than 1.1

Hepatic hydrothorax

- Confirmatory study:
  - Scintigraphic studies demonstrate tracer in the chest cavity after injection into the peritoneal cavity
- Treatment options:
  - diuretic therapy
  - periodic thoracentesis
  - TIPS

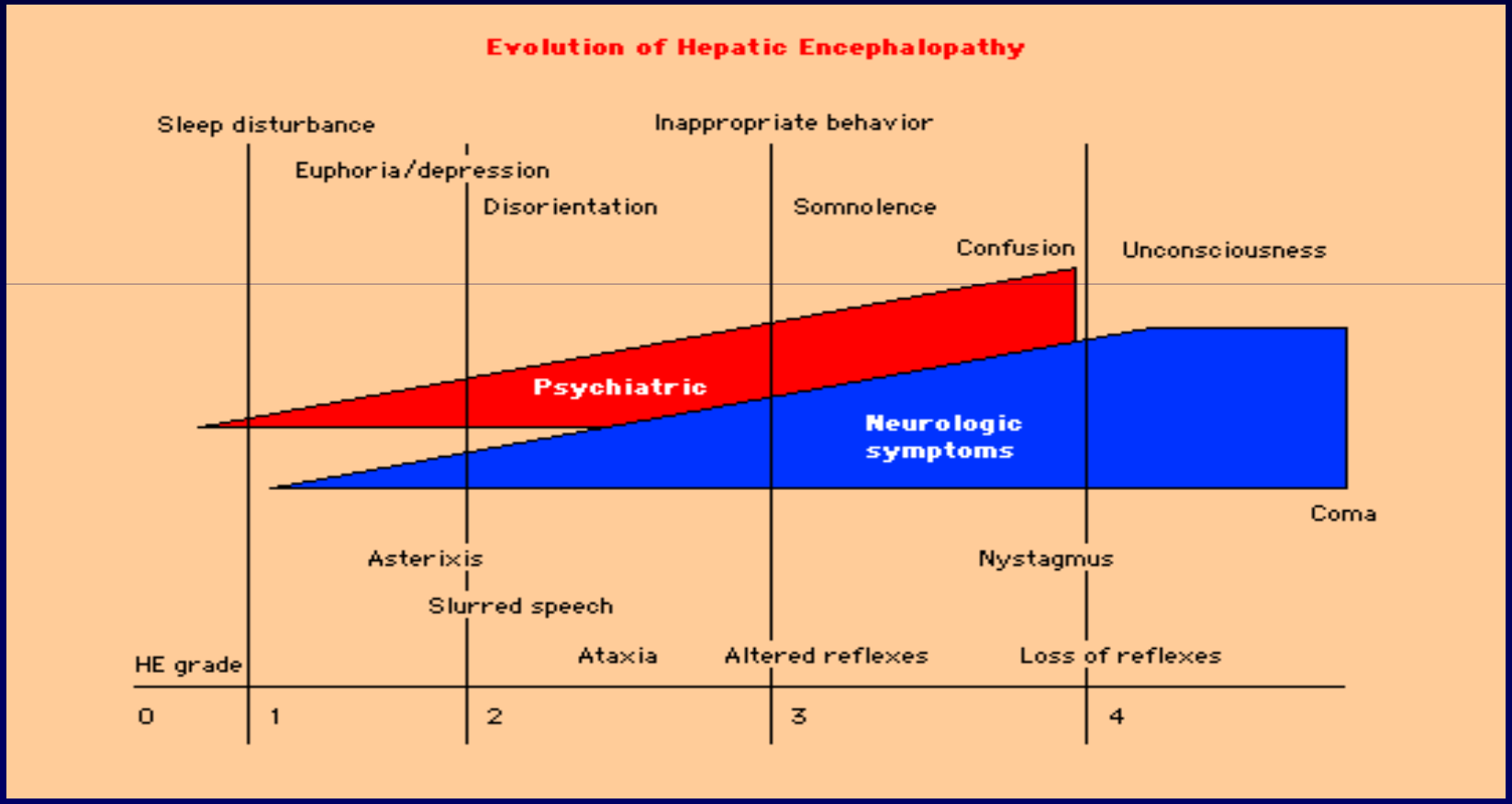
Portopulmonary HTN

- Refers to the presence of pulmonary hypertension in the coexistent portal hypertension
- Prevalence in cirrhotic patients is approximately 2 percent
- Diagnosis:
  - Suggested by echocardiography
  - Confirmed by right heart catheterization

Hepatic Encephalopathy

- Spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction
  - Diurnal sleep pattern pertubation
  - Asterixis
  - Hyperactive deep tendon reflexes
  - Transient decerebrate posturing

Hepatic Encephalopathy



Hepatic Encephalopathy

- Monitoring for events likely to precipitate HE [i.E.- variceal bleeding, infection (such as SBP), the administration of sedatives, hypokalemia, and hyponatremia]
- Reduction of ammoniagenic substrates
  - Lactulose / lactitol
  - Dietary restriction of protein
  - Zinc and melatonin

Hepatocellular Carcinoma

- Patients with cirrhosis have a markedly increased risk of developing hepatocellular carcinoma
- Incidence in well compensated cirrhosis is approximately 3 percent per year

Hepatocellular Carcinoma

- Symptoms are largely due to mass effect from the tumor
  - Pain, early satiety, obstructive jaundice, and a palpable mass
- Serum AFP greater than 500 micrograms/l in a patient with cirrhosis are virtually diagnostic
- Median survival following diagnosis is approximately 6 to 20 months

Prognostic Tools

- MELD (model for end-stage liver disease)
  - Identify patients whose predicted survival post-procedure would be three months or less

- MELD = 3.8[serum bilirubin (mg/dL)] + 11.2[INR] + 9.6[serum creatinine (mg/dL)] + 6.4

Prognostic Tools

- Child-Turcotte-Pugh (CTP) score
  - initially designed to stratify the risk of portacaval shunt surgery in cirrhotic patients
  - based upon five parameters: serum bilirubin, serum albumin, prothrombin time, ascites and encephalopathy
  - good predictor of outcome in patients with complications of portal hypertension

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤ 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds over control	1-3	4-6	>6
INR	<1.7	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child-Pugh classification of severity of liver disease Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C – 45 and 35 percent.

Prognostic Tools

- APACHE III (acute physiology and chronic health evaluation system)
  - Designed to predict an individual's risk of dying in the hospital

Treatment Options

- The major goals of treating the cirrhotic patient include:
  - Slowing or reversing the progression of liver disease
  - Preventing superimposed insults to the liver
  - Preventing and treating the complications
  - Determining the appropriateness and optimal timing for liver transplantation

Liver Transplantation

- Liver transplantation is the definitive treatment for patients with decompensated cirrhosis
- Depends upon the severity of disease, quality of life and the absence of contraindications

Liver Transplantation

- Minimal criteria for listing cirrhotic patients on the liver transplantation list include
  - A child-Pugh score 7
  - Less than 90 percent chance of surviving one year without a transplant
  - An episode of gastrointestinal hemorrhage related to portal hypertension
  - An episode of spontaneous bacterial peritonitis

Vaccinations

- Hepatitis A and B
- Pneumococcal vaccine
- Influenza vaccination

Surveillance

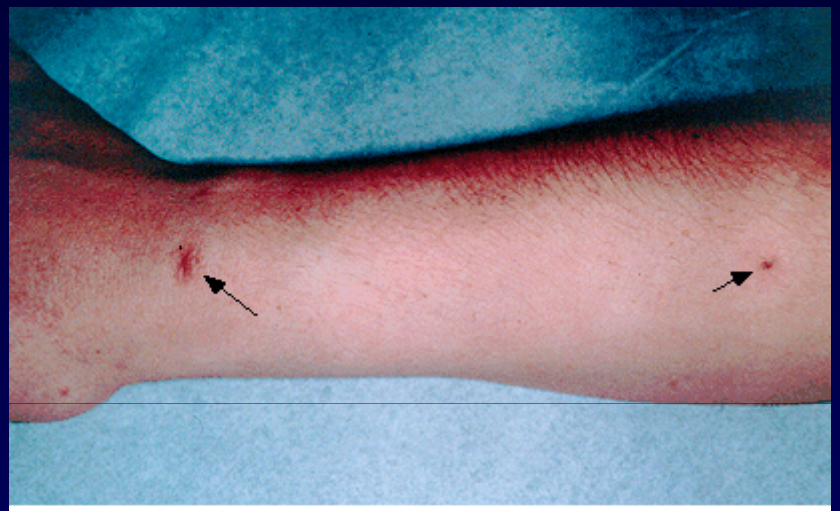
- Screening recommendations:
  - serum AFP determinations and ultrasonography every six months

Avoidance of Superimposed Insults

- Avoidance of:
  - Alcohol
  - Acetaminophen
  - Herbal medications

References

- Up to Date
- Harrison's
- New England Journal
- http://www.openclinical.org/aisp_apache.html
- **Nail abnormalities: clues to systemic disease, American Family Physician, March 15, 2004** Robert Fawcett



Spider angiomas This photograph shows two spider angiomas (spider telangiectasias) on the arm of a pregnant woman. A central feeding vessel, most easily seen in the lesion on the right, leads to other telangiectatic vessels, arranged in the shape of a spider, best appreciated in the lesion on the left. Pressure over the central vessel with the end of a paper clip or a glass slide causes the entire lesion to blanch. Similar lesions can be seen in patients with cirrhosis, and are most commonly seen on the upper chest, face, and back.