Pathology of Liver, Part IV

Intrahepatic Biliary Tract Disease

Circulatory Disorders

Pregnancy-Associated Disorders

Neoplasms and Tumor-Like Masses

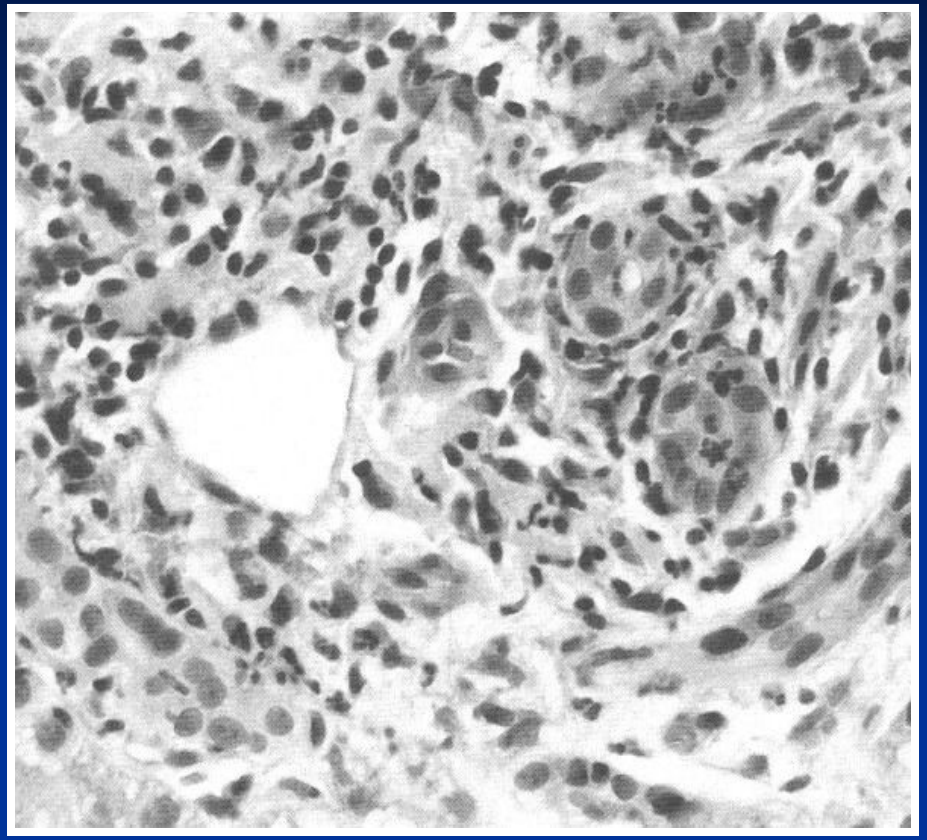
Intrahepatic biliary tract diseases

- **Big 3**
  - Secondary Biliary Cirrhosis
  - Primary Biliary Cirrhosis
  - Primary Sclerosing Cholangitis
- **Clinical presentations similar for all 3**
  - Malaise, jaundice, pruritus, hepatomegaly
  - Conjugated hyperbilirubinemia, elevated serum alkaline phosphatase and GGT
- **All 3 diseases progress toward cirrhosis**

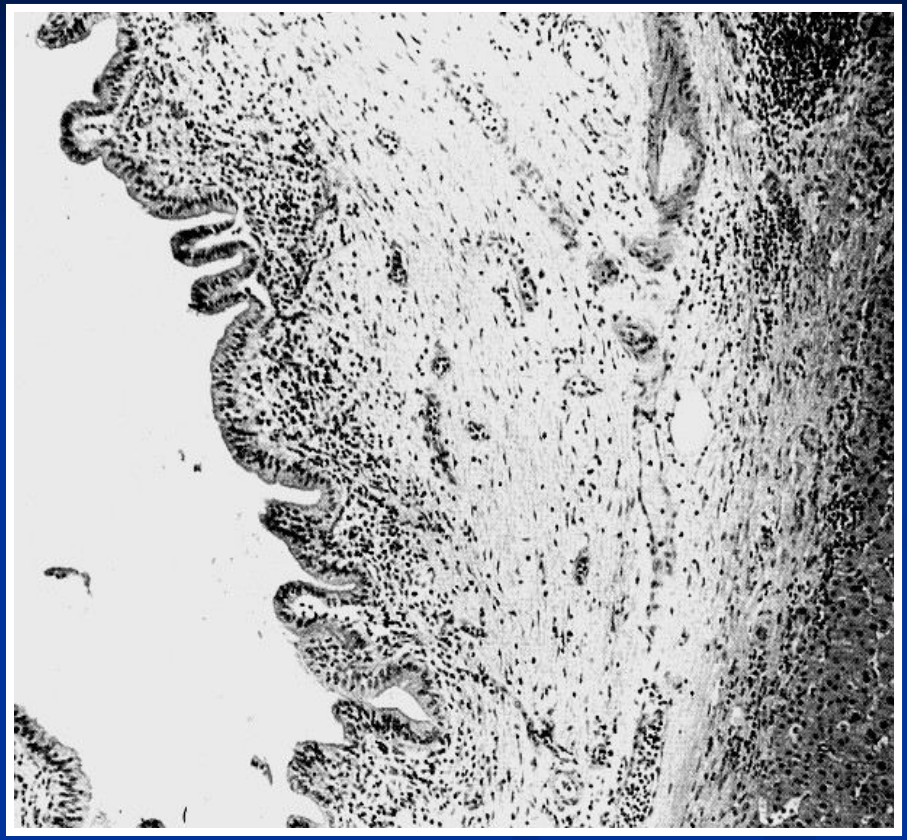
Secondary biliary cirrhosis: overview

- **Cause: any disease producing prolonged obstruction of extrahepatic biliary tree**
  - **Gallstones in bile ducts**
  - **Malignant neoplasms in bile ducts/pancreas**
  - **Strictures (scarring) of biliary tree (previous surgery)**
- **Pathologic progression in liver:**
  - **Cholestasis (reversible if obstruction relieved)**
  - **Secondary inflammation ⇒ portal fibrosis**
  - **Portal fibrosis ⇒ bridging fibrosis ⇒ cirrhosis**
- **Dangerous complication of untreated obstruction: ascending cholangitis (bacterial infection involving extrahepatic bile ducts): high mortality, especially in elderly patients**

Secondary biliary cirrhosis: early and late histopathologic changes



EARLY: Portal edema with neutrophils in bile duct epithelium (due to tumor obstructing common bile duct)



LATE: Periductal fibrosis and mononuclear portal infiltrate (after prolonged common bile duct obstruction by tumor)

Secondary biliary cirrhosis: endstage

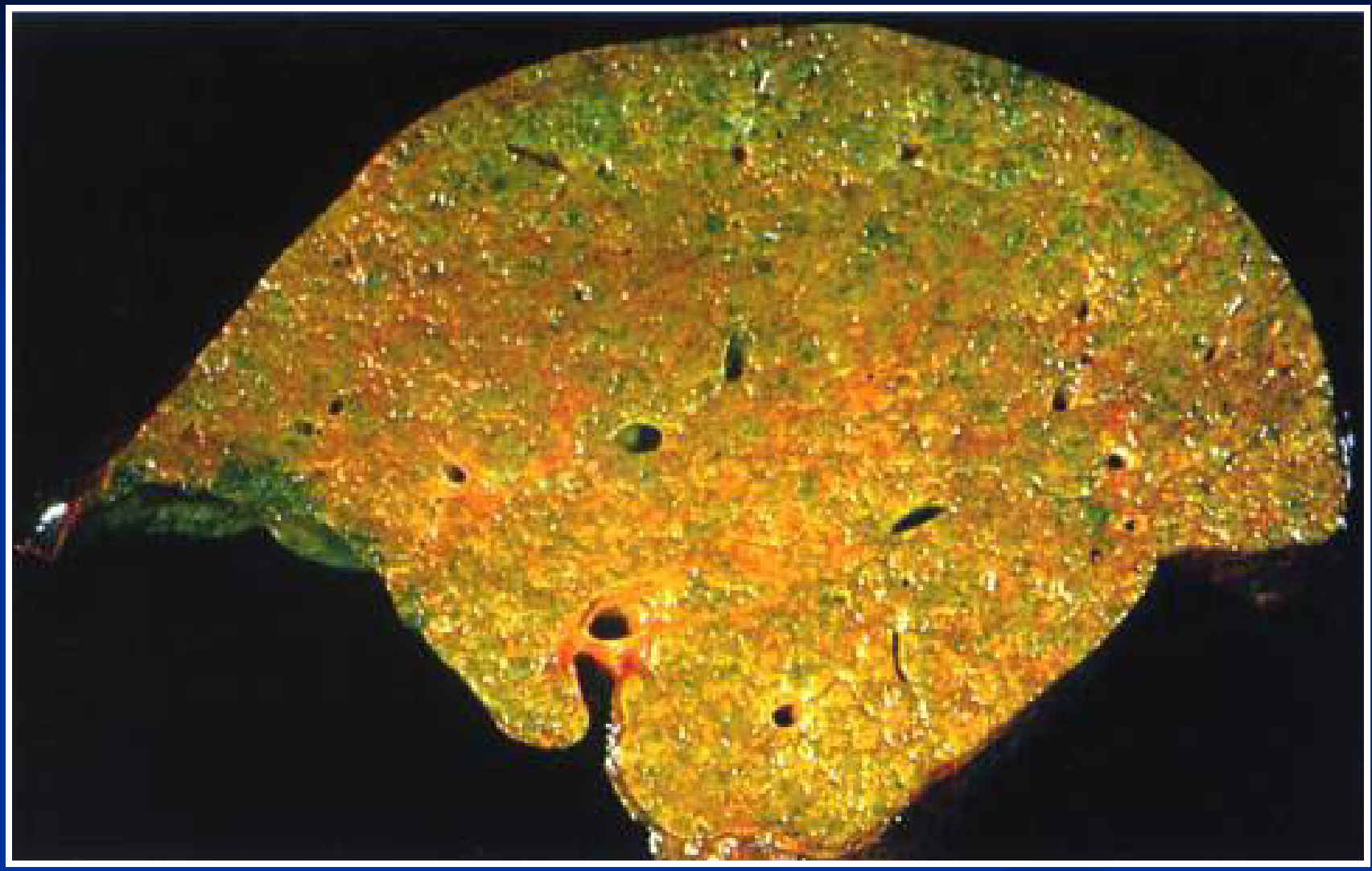


Fig. 18-30, Pathologic Basis of Disease, 7th ed, Elsevier 2005

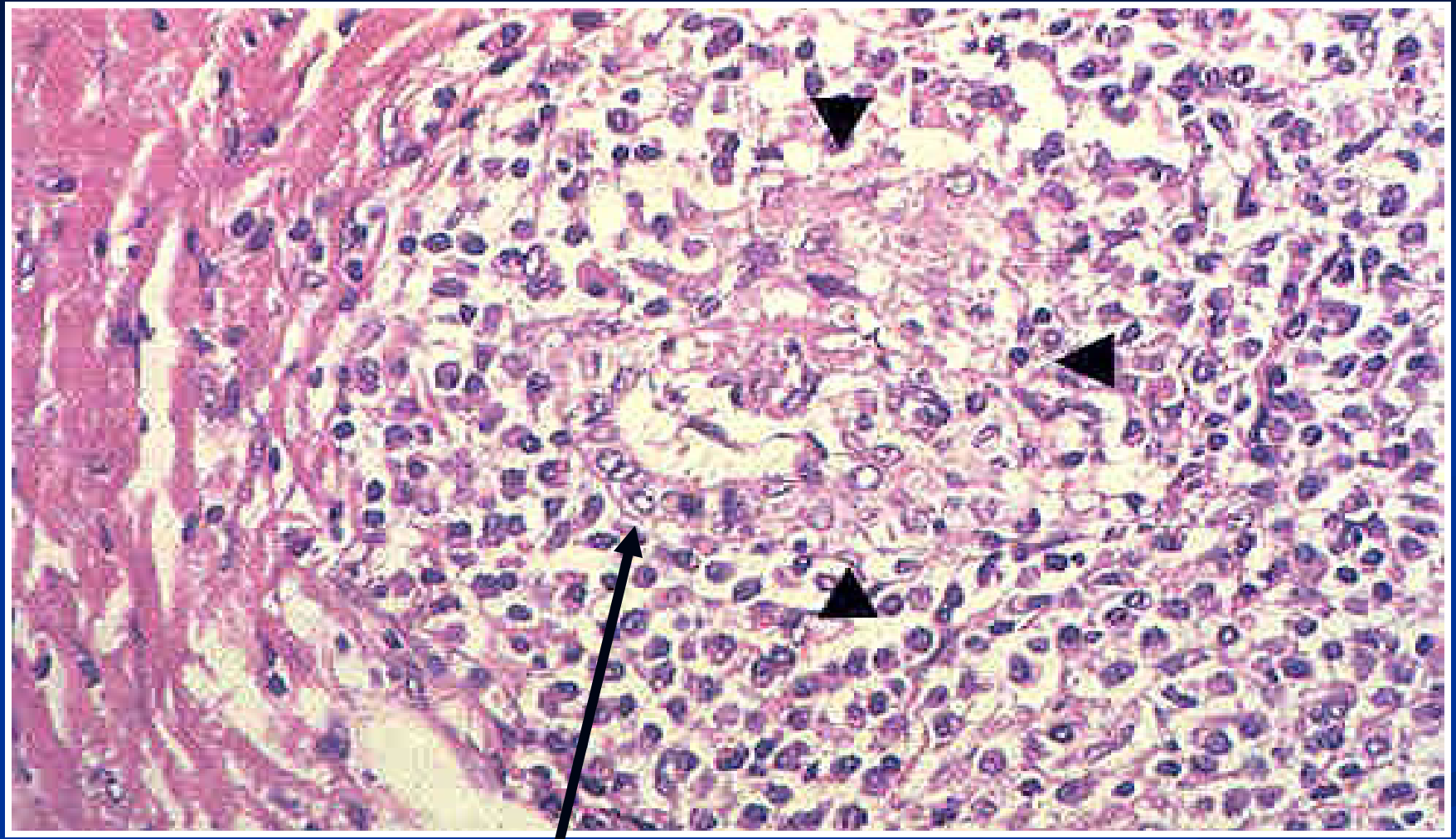
Primary biliary cirrhosis: overview

- **Chronic disease** showing non-suppurative slowly progressive destruction of intrahepatic bile ducts
- Primarily middle-aged women (F:M = 6:1)
- **Autoimmune etiology:** > 90% have circulating anti-mitochondrial antibodies

Primary Biliary Cirrhosis: pathogenesis

- **Evidence for autoimmune etiology**
  - Aberrant expression MHC class II molecules on bile duct epithelial cells
  - Autoreactive T cells around bile ducts
  - Hypergammaglobulinemia with complement activation and circulating immune complexes
- **Associated extrahepatic autoimmune diseases**
  - Sjogren syndrome, scleroderma, thyroiditis, rheumatoid arthritis, membranous glomerulonephritis
- ??? Why are anti-mitochondrial Abs associated with chronic granulomatous inflammation in bile ducts?

PBC: early histopathology



Early stage PBC (florid duct lesion): portal mononuclear inflammation destroying a bile duct with granulomatous response (arrowheads)

PBC: later histopathology

- Progressive destruction/disappearance of bile ducts < 70 microns diameter
- Progressive appearance of fibrosis: portal, bridging, eventual cirrhosis. **Strongest prognostic indicator is degree of fibrosis**.
- Problems for biopsy interpretation:
  - After the early florid bile duct lesion with granulomatous inflammation, histologic changes resemble chronic viral hepatitis (need clinical & lab)
  - As cirrhosis develops, distinctive features mostly obliterated, except for absent bile ducts <70 microns

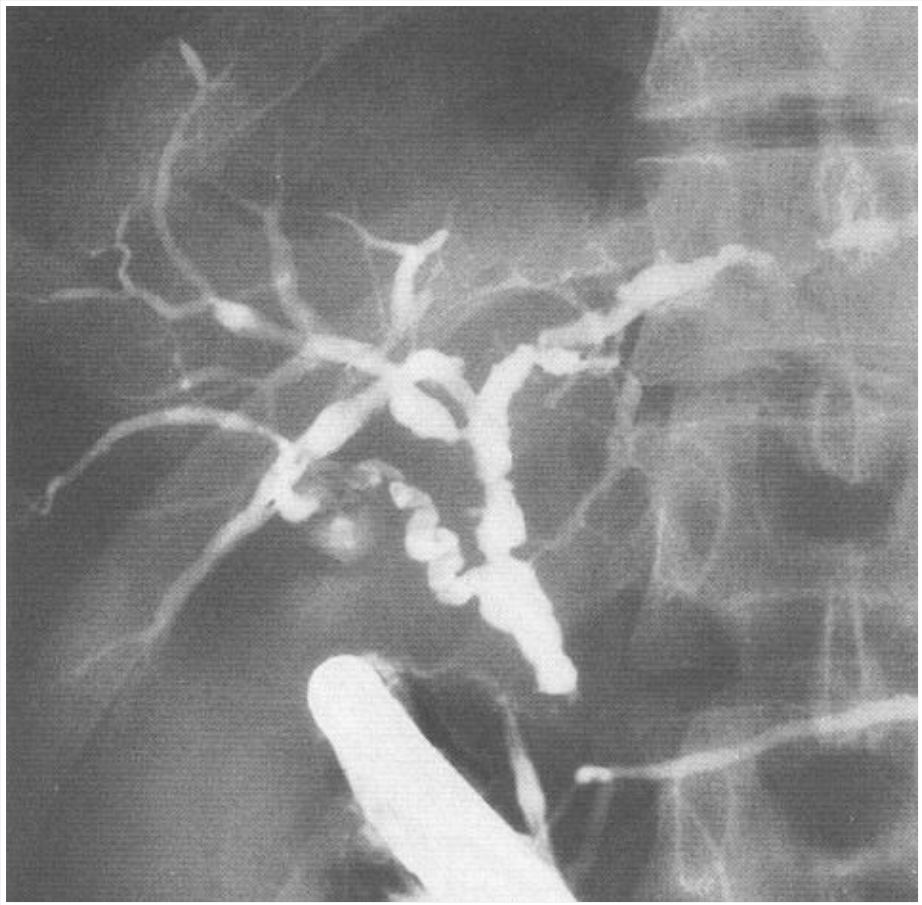
PBC: clinical diagnosis & management

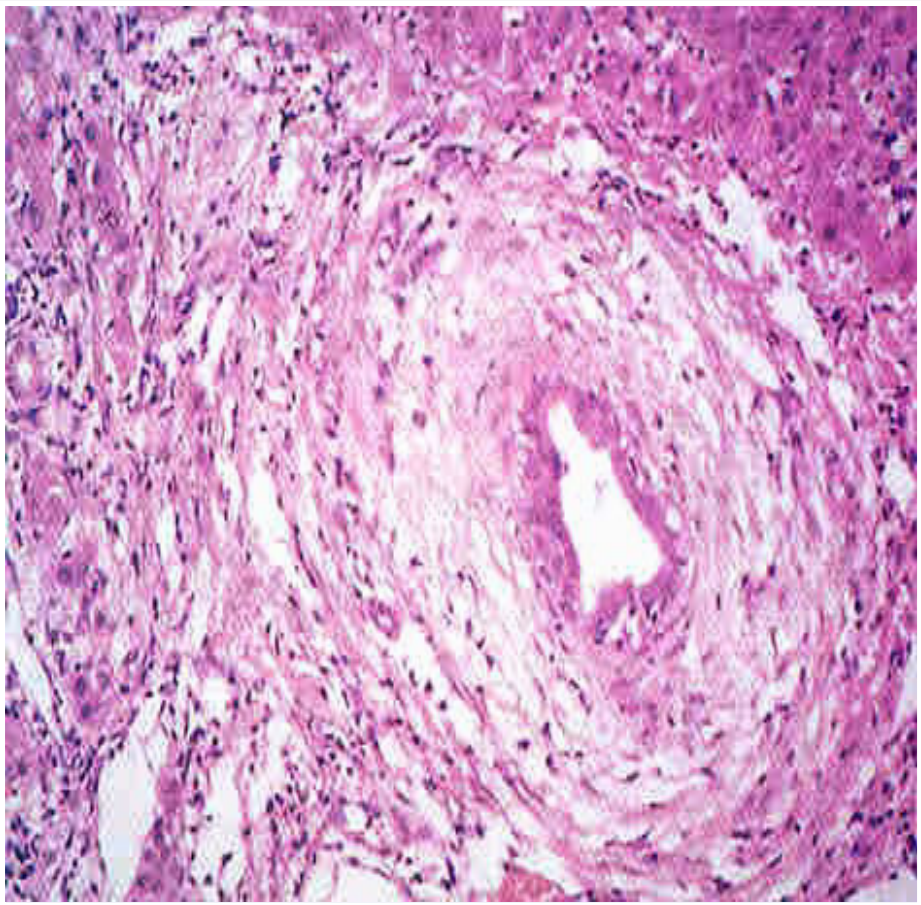
- Insidious onset pruritus, +/- jaundice
- Lab data and biopsy complementary:
  - Elevated serum alkaline phosphatase & GGT
  - Serum anti-mitochondrial antibodies present
  - Biopsy: compatible with PBC? Degree of fibrosis? Is cirrhosis present?
- Treatment: supportive until liver failure demands transplantation

Primary sclerosing cholangitis: overview

- Chronic disease with inflammation, obliterative fibrosis, and segmental constriction of intra- and extra-hepatic bile ducts
- **X-ray findings are distinctive!** (cholangiogram)
- 70% patients with PSC have chronic ulcerative colitis; 4% with chronic ulcerative colitis have PSC.
- Pathogenesis unclear (? cause inflammation)

PSC: cholangiogram & pathology





Endoscopic retrograde cholangiogram: beaded bile ducts with strictures

Bile duct with “onion-skin” periductal fibrosis and mononuclear inflammation

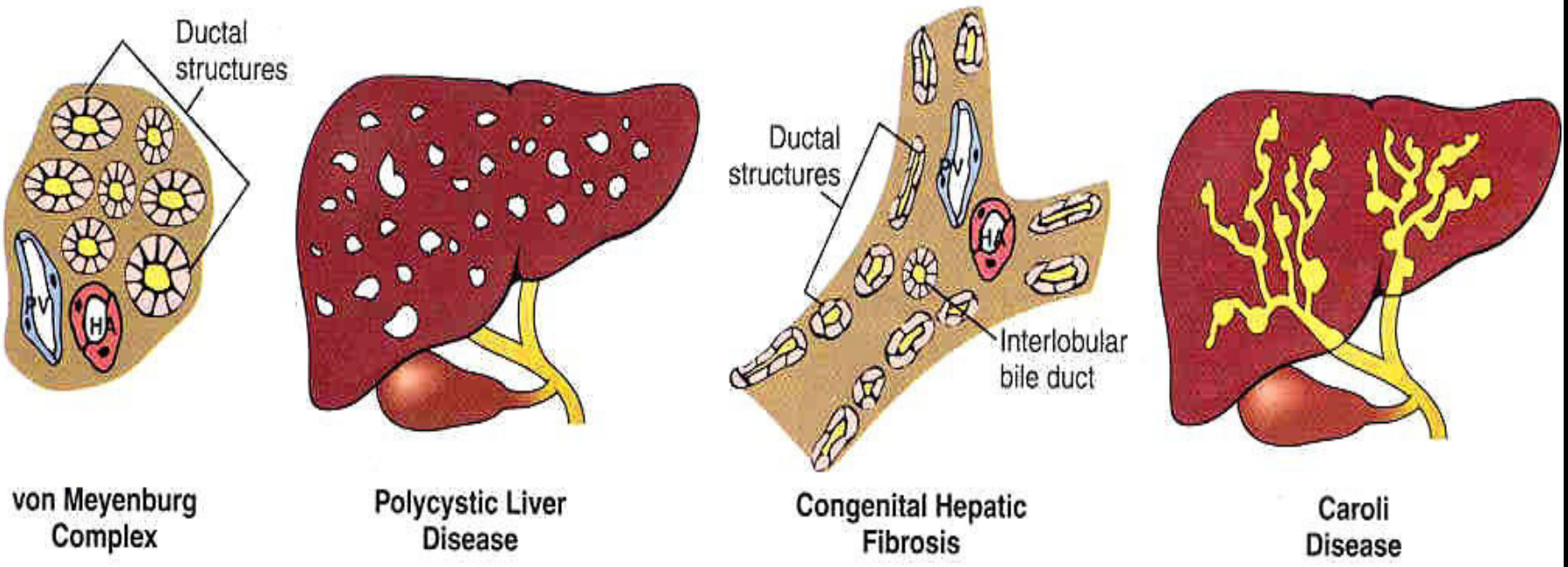
Primary sclerosing cholangitis: Clinical diagnosis and management

- Symptoms of ulcerative colitis may overshadow liver disease
- Fatigue, pruritus, jaundice early; signs of cirrhosis and liver failure late
- Rx: liver transplantation
- Diagnostic studies
  - Consistent: elevated alkaline phosphatase
  - Negative for serum autoantibodies
  - **Cholangiogram is most specific test**

Architectural anomalies of intrahepatic biliary tree

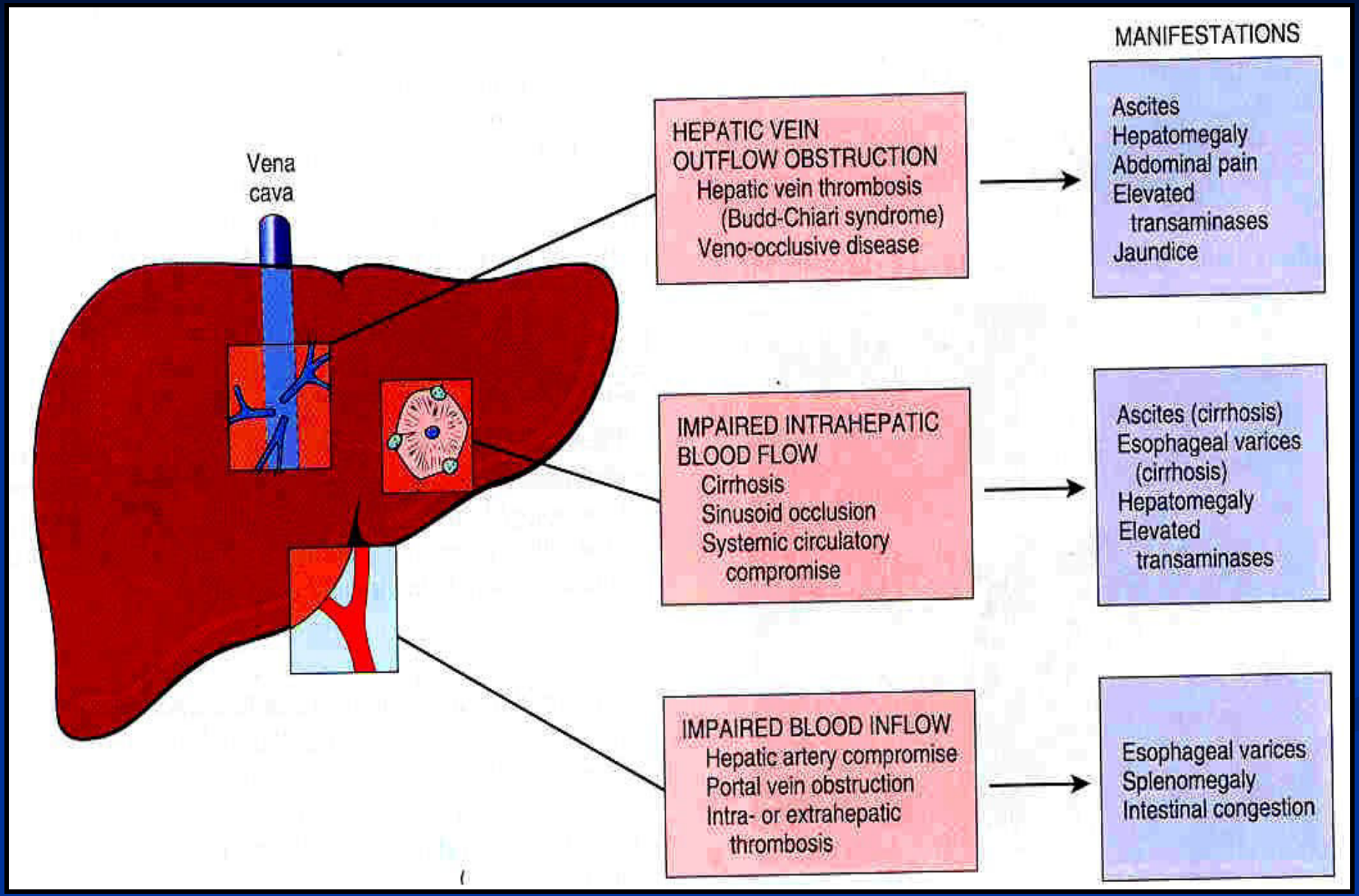
- Often incidental findings in asymptomatic patients
- **Big 4**
  - **Von Meyenburg complexes:** clusters of dilated bile ducts in/near portal tracts
  - **Polycystic liver disease:** multiple diffuse simple cysts detached from biliary tree
  - **Congenital hepatic fibrosis:** extensive portal fibrosis with abnormally shaped bile ducts
  - **Caroli disease:** larger bile ducts segmentally dilated with inspissated bile; often seen with congenital hepatic fibrosis

Anomalies of intrahepatic bile ducts



	von Meyenburg Complex	Polycystic Liver Disease	Congenital Hepatic Fibrosis	Caroli Disease
INHERITANCE:	Sporadic	Autosomal Dominant	Autosomal Recessive	Autosomal Recessive
ASSOCIATION WITH POLYCYSTIC KIDNEY DISEASE (PKD)				
Autosomal dominant PKD:	+	+ + +	+	+
Autosomal recessive PKD:	-	-	+ + +	+

Circulatory disorders of liver: 3 mechanisms



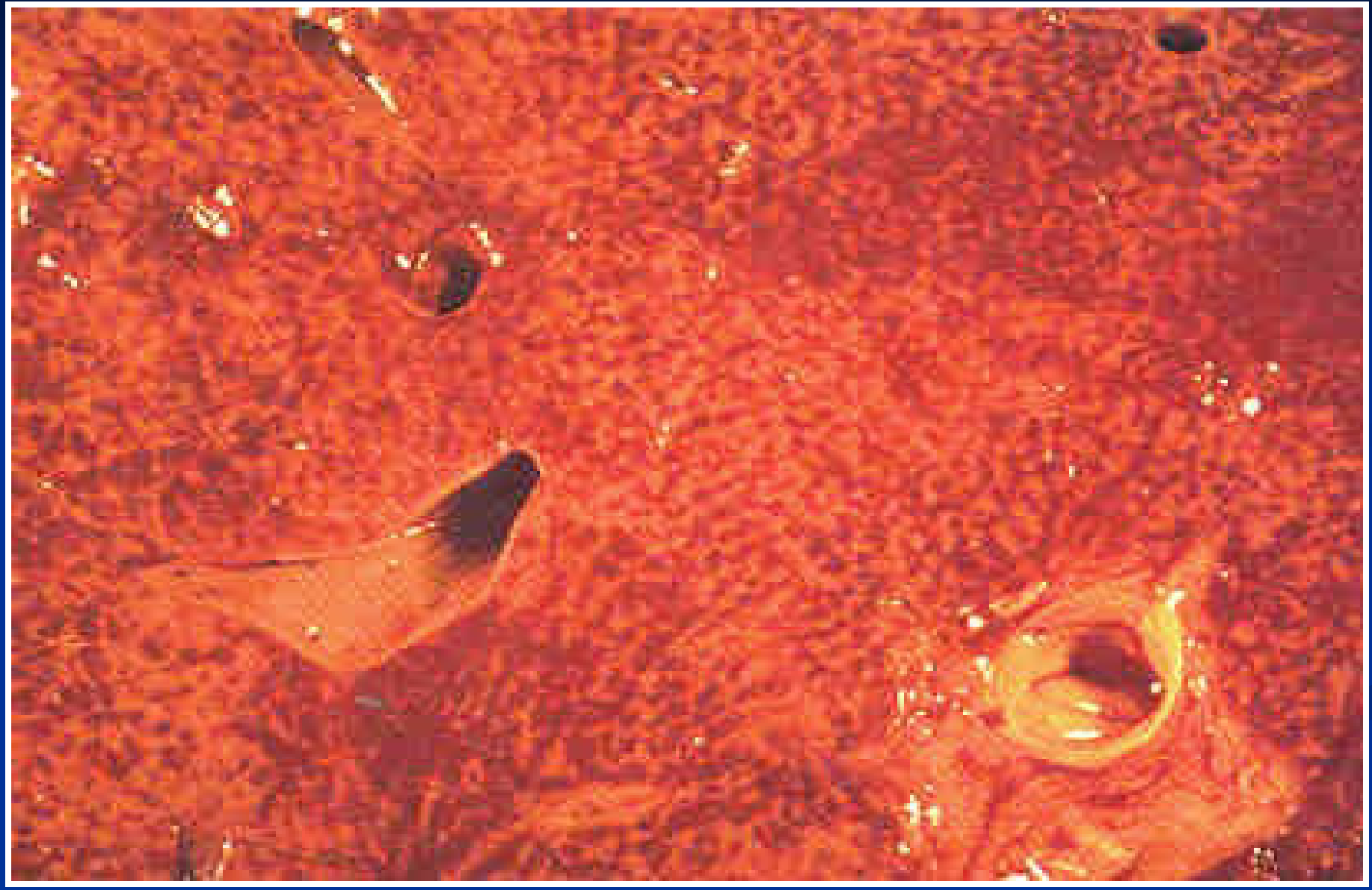
Mechanism 1: Impaired blood inflow

- **Portal vein thrombosis or obstruction**
  - Symptoms & signs: abdominal pain, portal hypertension with esophageal varices, ascites, venous congestion, intestinal infarction
  - Causes: peritonitis, metastatic neoplasm in lymph nodes, pancreatitis ⇒ splenic vein thrombosis ⇒ propagation of thrombus into portal vein, post-surgical fibrous strictures
- **Hepatic artery compromise**
  - Thrombosis or compression of intrahepatic branch ⇒ localized infarction
  - Thrombosis or compression of main hepatic artery ⇒ variable ischemic necrosis, tempered by portal vein inflow and collateral circulation
  - Causes: embolism, neoplasm, vasculitis

Mechanism 2: Impaired blood flow through liver

- **Signs:** portal hypertension, ascites, hepatomegaly, elevated transaminases
- **Causes**
  - Cirrhosis (*most common by far*)
  - Occlusion sinusoids: sickle cell anemia, DIC, eclampsia, metastatic neoplasm
  - Right heart failure: central lobular congestion, producing "nutmeg" liver
  - Left heart failure or shock: ischemic necrosis of central lobular hepatocytes

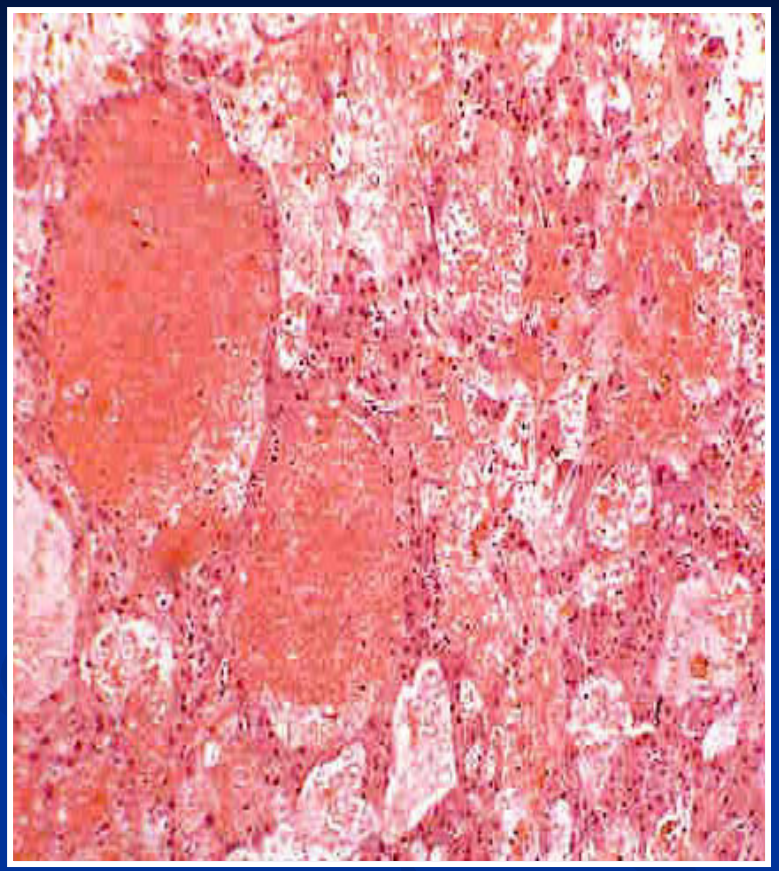
Nutmeg Liver (marked centrilobular congestion)



Mechanism 2: Impaired blood flow through liver: Peliosis Hepatis

- Definition: primary diffuse dilation of sinusoids
- Settings
  - Anabolic steroids, estrogens, azathioprine
  - HIV (secondary to bacillary angiomatosis)
- Signs: asymptomatic, intra-abdominal hemorrhage
- Pathology
  - Unevenly distributed cysts (0.1 – 4 cm)
  - Cysts are dilated hepatic sinusoids containing blood

Peliosis Hepatis: pathology

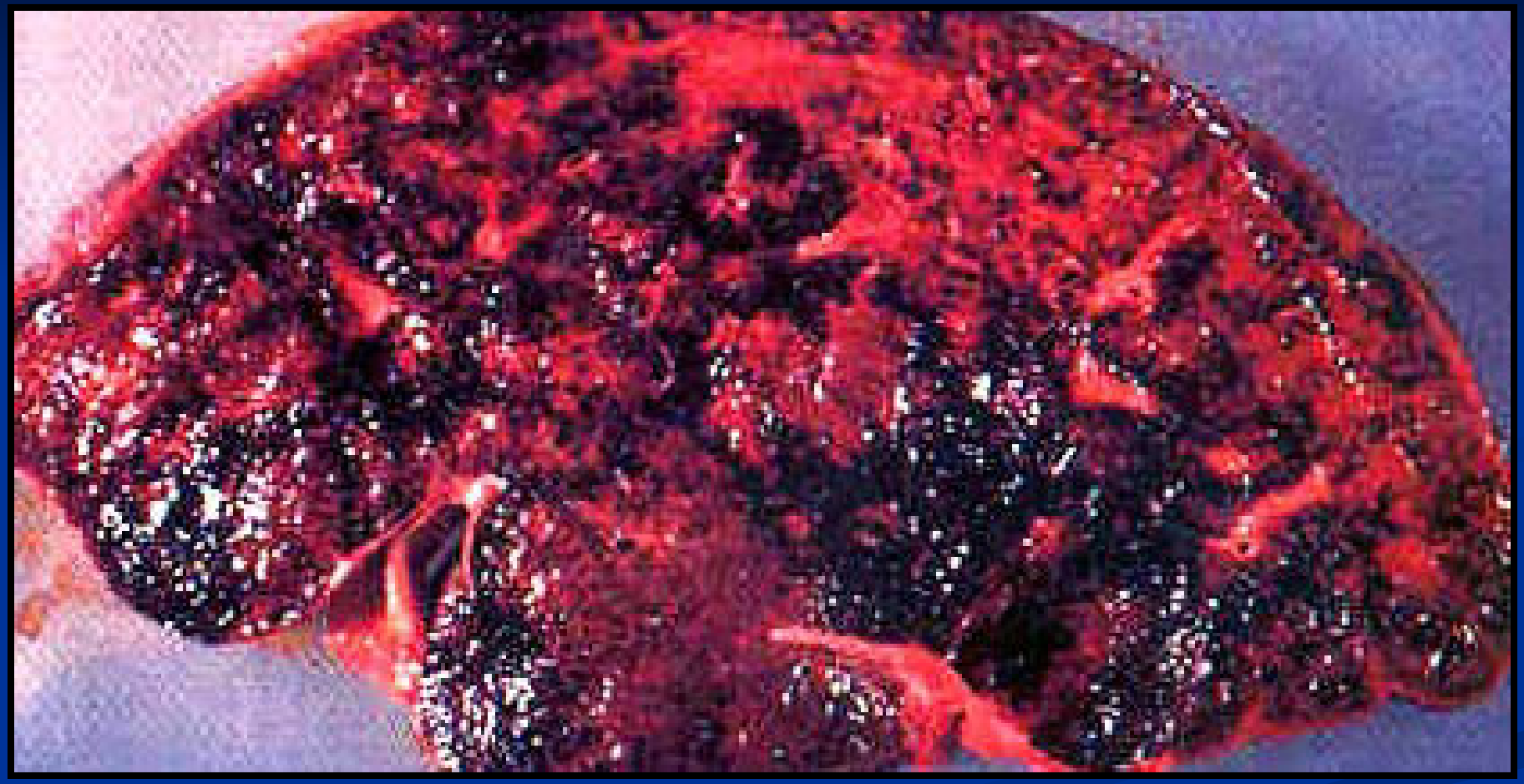


H&E: blood-filled spaces, incompletely lined by endothelial cells

Mechanism 3: Hepatic vein outflow obstruction: hepatic vein thrombosis (Budd-Chiari syndrome)

- Original description: fatal acute thrombosis
- Expanded definition: acute, subacute, or chronic occlusions of hepatic vein
- Signs/symptoms: hepatomegaly, pain, ascites
- Causes (most frequent to less frequent)
  - Polycythemia vera (myeloproliferative diseases)
  - Pregnancy or post-partum state
  - Oral contraceptives
  - Paroxysmal nocturnal hemoglobinuria
  - Cancers, especially hepatocellular carcinoma
  - Idiopathic (10%, presumably undiagnosed thrombogenic disorder)

Budd-Chiari syndrome: pathology



Severe centrilobular congestion & necrosis; degree of necrosis depends on degree of hepatic outflow occlusion

Budd-Chiari syndrome: treatment

- Address underlying cause; high mortality without treatment
- Acute interventions:
  - Surgical creation of portal-systemic shunt (portal vein to systemic circulation), which allows reverse flow through portal vein, but hepatic artery inflow preserved to prevent infarction
  - Angiographic thrombectomy and/or dilation of hepatic vein

Pregnancy-associated disease

- Approximately 1 in 1000 pregnancies develop new liver disease while pregnant
- Major disorders
  - **Preeclampsia & eclampsia**
  - **Acute fatty liver of pregnancy**
  - **Intrahepatic cholestasis of pregnancy**

Preeclampsia-eclampsia

- **HELLP syndrome in preeclampsia**
  - *H*: ***h***emolysis
  - *E L*: ***e***levated ***l***iver enzymes
  - *L P*: ***l***ow ***p***latelets
- Pathology: patchy hemorrhage, infarction, hematomas (risk of massive bleeding if hematoma is subcapsular)
- Treatment: supportive, according to liver function; terminate pregnancy if life-threatening changes or coagulopathy seen

Acute fatty liver of pregnancy

- Huge spectrum: subclinical ⇔ lethal
- Usually third trimester; symptoms related to hepatic insufficiency: nausea/vomiting, jaundice, bleeding, encephalopathy
- Biopsy: microvesicular steatosis (reverses with termination of pregnancy)
- Management:
  - Supportive with fresh frozen plasma
  - Terminate pregnancy if liver failure

Intrahepatic cholestasis of pregnancy

- Pruritus and jaundice in 3rd trimester
- Diagnostic evaluation
  - Lab: mildly elevated conjugated bilirubin, alkaline phosphatase
  - Biopsy: mild cholestasis; no necrosis
- Pathogenesis: ? estrogens inhibiting bile secretion
- Management: conservative, resolves after pregnancy

Neoplasms & tumor-like masses

- **What you see depends on where you are**
  - U.S.: metastases to liver > primary neoplasms
  - Asia & Africa: hepatocellular carcinoma is the most common malignant neoplasm !
- **History very important !**
  - History of previously diagnosed malignancy suggests metastatic disease is most likely
  - Risk factors for cirrhosis increase risk of hepatocellular carcinoma
  - Drugs associated with specific neoplasms
- **Diagnostic modalities**
  - Imaging (ultrasound, CT, angiography)
  - Fine needle aspiration; core & wedge biopsy

Biggest picture: revised World Health Organization classification

Table 10.1 An abbreviated classification of primary tumors of the liver

	Benign	Malignant
Epithelial tumors	Liver cell adenoma Bile duct adenoma Bile duct cystadenoma Biliary papillomatosis	Liver cell (hepatocellular) carcinoma Bile duct carcinoma (cholangiocarcinoma) Bile duct cystadenocarcinoma Combined and mixed carcinomas Hepatoblastoma Carcinoid tumor
Non-epithelial tumors	Hemangioma Angiomyolipoma Other benign tumors	Angiosarcoma Epithelioid hemangioendothelioma Embryonal sarcoma Rhabdomyosarcoma Other sarcomas, lymphoma, germ cell tumors
Tumor-like lesions	Cysts Mesenchymal hamartoma Focal nodular hyperplasia Nodular regenerative hyperplasia Peliosis Inflammatory pseudotumor	

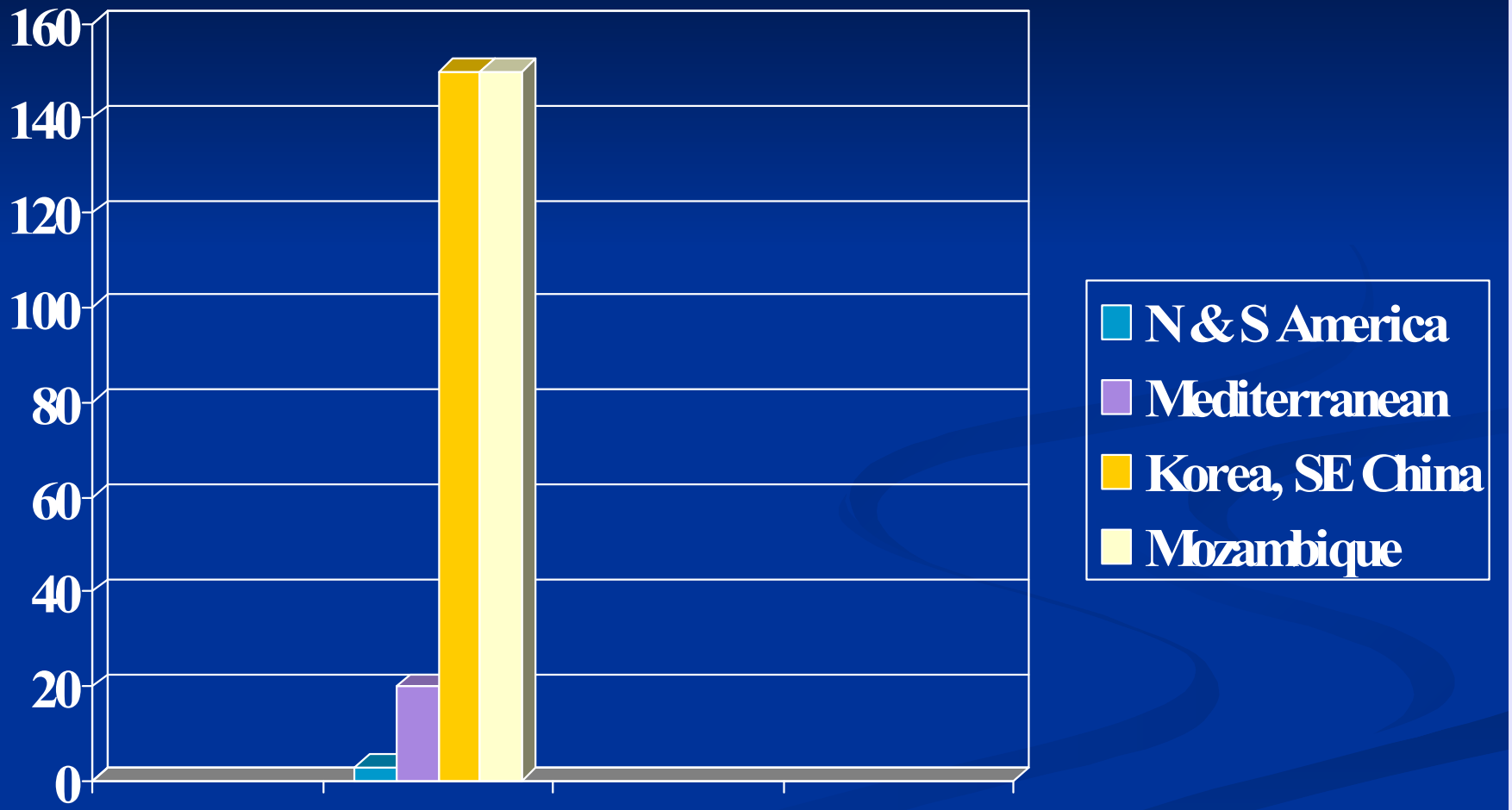
Selected tumors: only the 6 best !

- **Malignant Neoplasms**
  - Hepatocellular carcinoma = liver cell carcinoma
  - Bile duct carcinoma = cholangiocarcinoma
- **Benign Neoplasms**
  - Liver cell adenoma
  - Hemangioma
- **Tumor-like masses**
  - Focal nodular hyperplasia
  - Nodular regenerative hyperplasia

Hepatocellular carcinoma (HCC)

- >95% of primary malignant neoplasms in liver
- Erroneously called "hepatoma" (not by us!)
- Global incidence and distribution strongly correlated with prevalence of HBV infection
  - Endemic regions (Asia/Africa): HBV carriers from infancy; HCC often occurs in persons ages 20-40
  - Western societies: cirrhosis precedes HCC in 80-90%; risk factors include ethanol, HCV, HBV

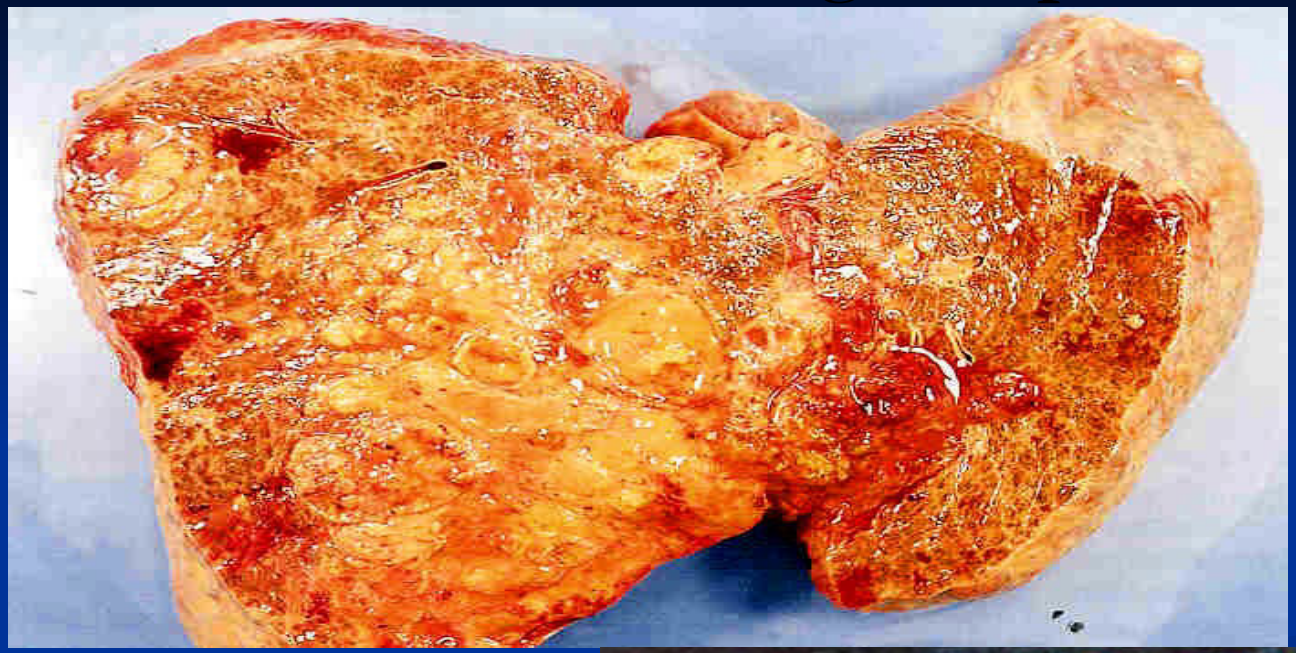
Geographic Incidence HCC per 100,000 persons



Pathogenesis of HCC

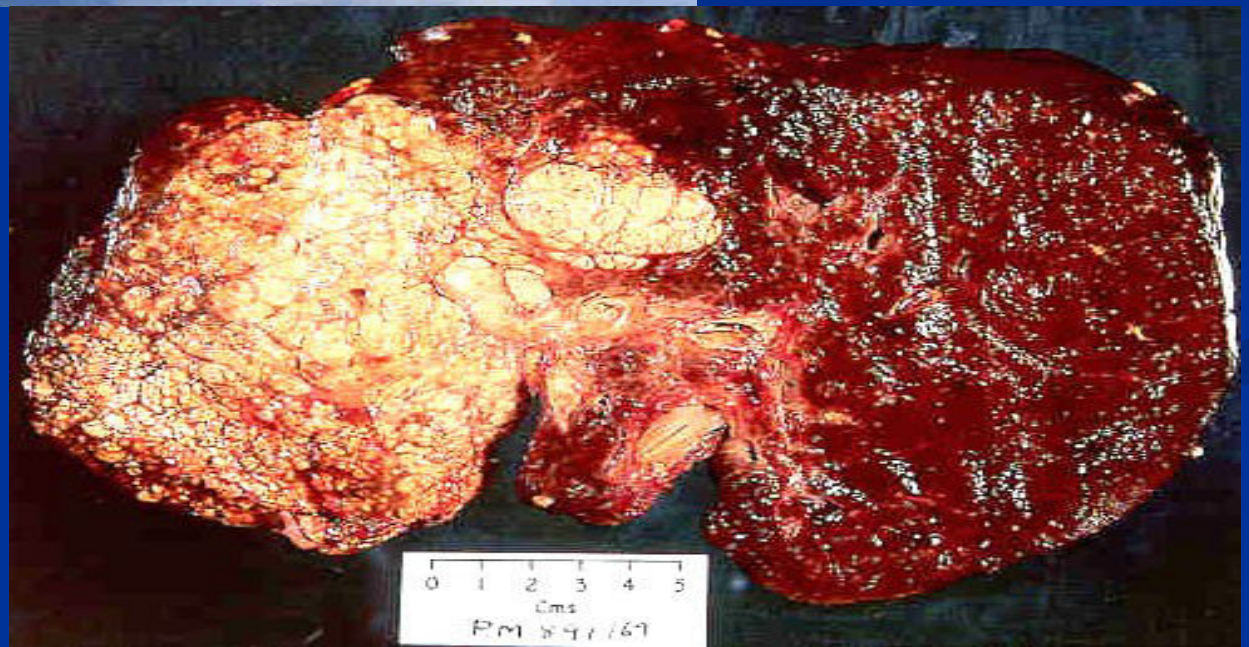
- Repeated cycles of liver cell death/regeneration increase opportunity for genetic mutations
- HBV-associated HCC: viral DNA integrated into cancer cell genome
- HBV "X protein": proposed transactivator of cell promoters, disrupting growth control
- Aflatoxins (food spoilage molds) present in endemic areas, show mutagenic activity in liver cell DNA
- HBV vaccination of children in Taiwan since 1984: infection rate decreased 10% to 1.3% in 10 years, with anticipated corresponding decrease in incidence of HCC in adult years

HCC: gross pathology



Multinodular HCC arising in a cirrhotic liver

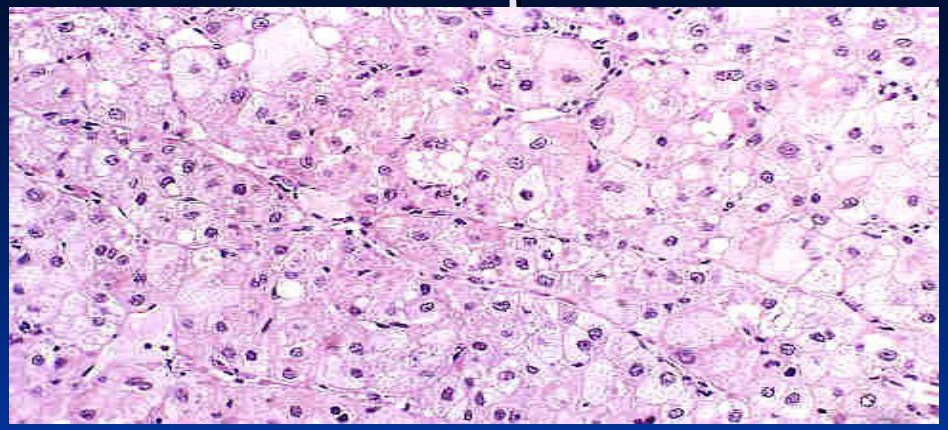
Solitary mass of HCC arising in right lobe of non-cirrhotic liver



HCC: histopathologic features

- **Cardinal feature:** disorganized growth of hepatocytes without portal tracts or central veins
- **Classification**
  - Well-differentiated (like hepatocytes)
  - Moderately differentiated
  - Poorly differentiated (pleomorphic)
  - Fibrolamellar variant
    - Better prognosis, often resectable
    - Ages 20-40***, not associated with HBV or cirrhosis***

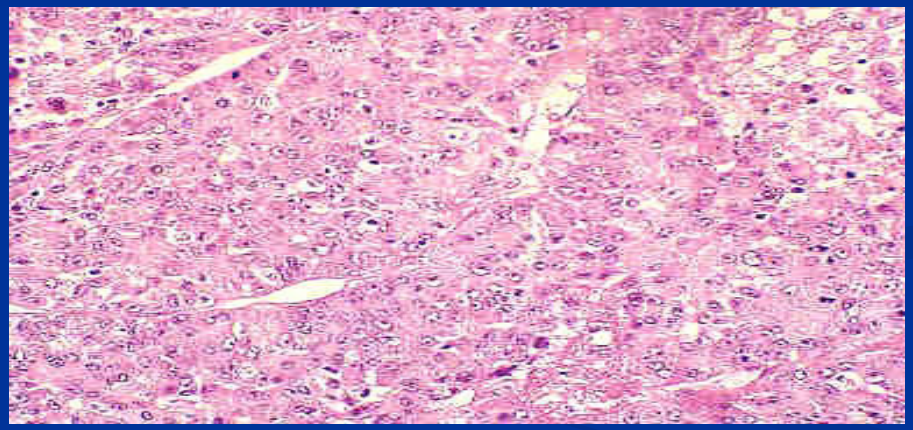
HCC: spectrum histopathology

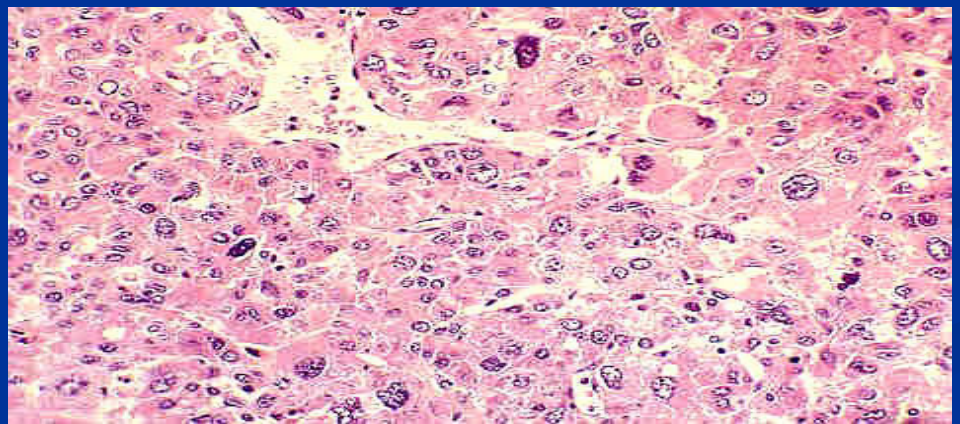


Well-differentiated

(like hepatocytes)

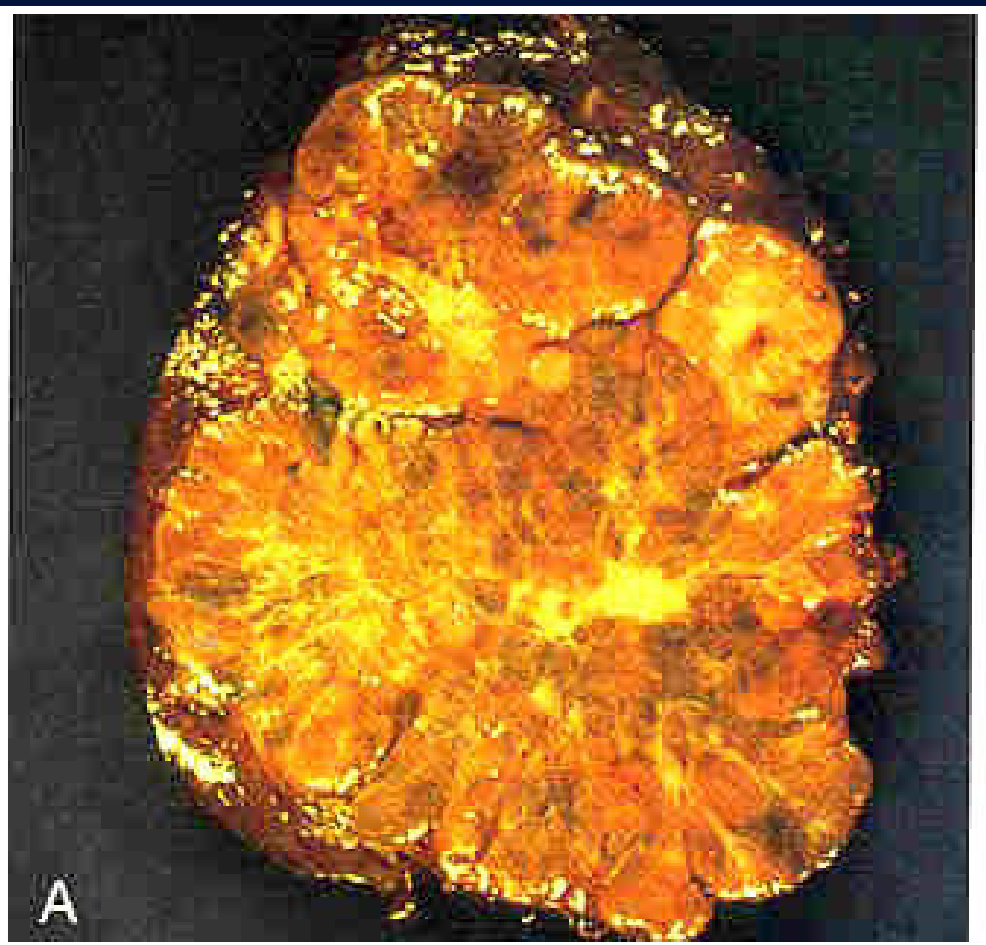
Moderately differentiated

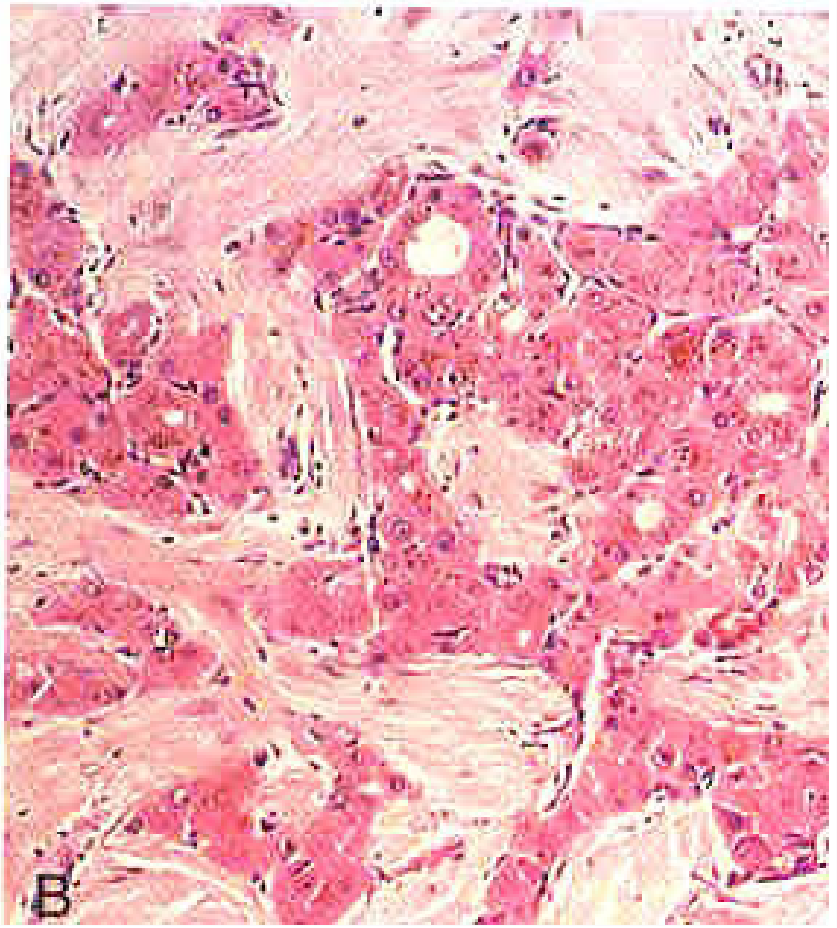




Poorly differentiated (pleomorphic)

HCC: fibrolamellar variant





Hard, fibrous, circumscribed tumor excised surgically

Well-differentiated cells separated by dense collagen

Fig. 18-44, Pathologic Basis of Disease, 7th ed, Elsevier 2004

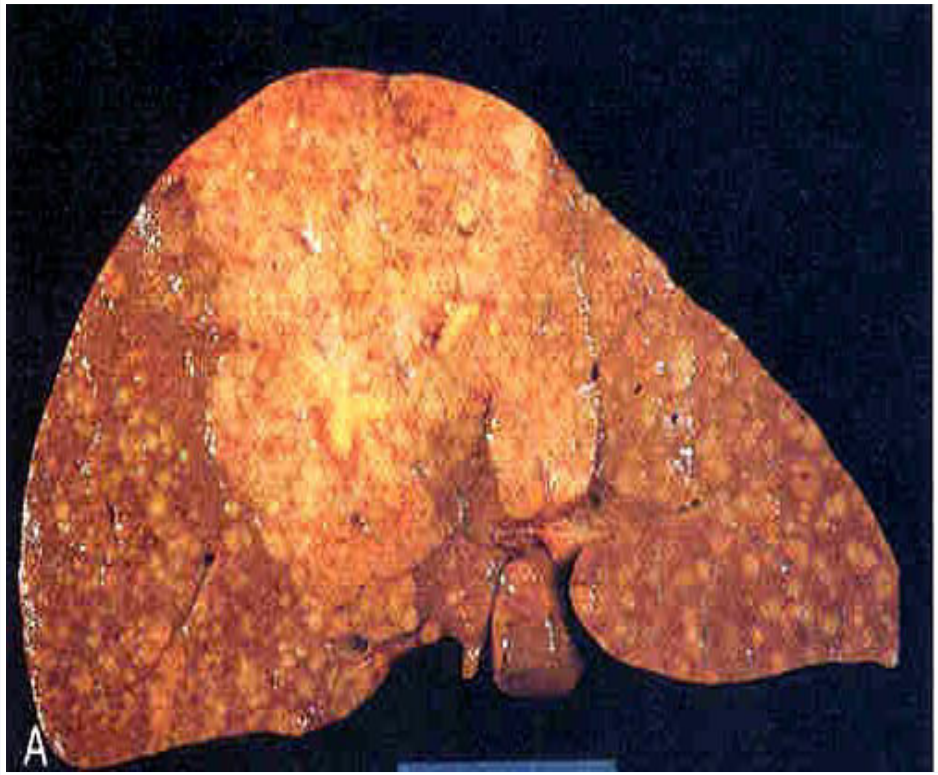
HCC: Clinical Features

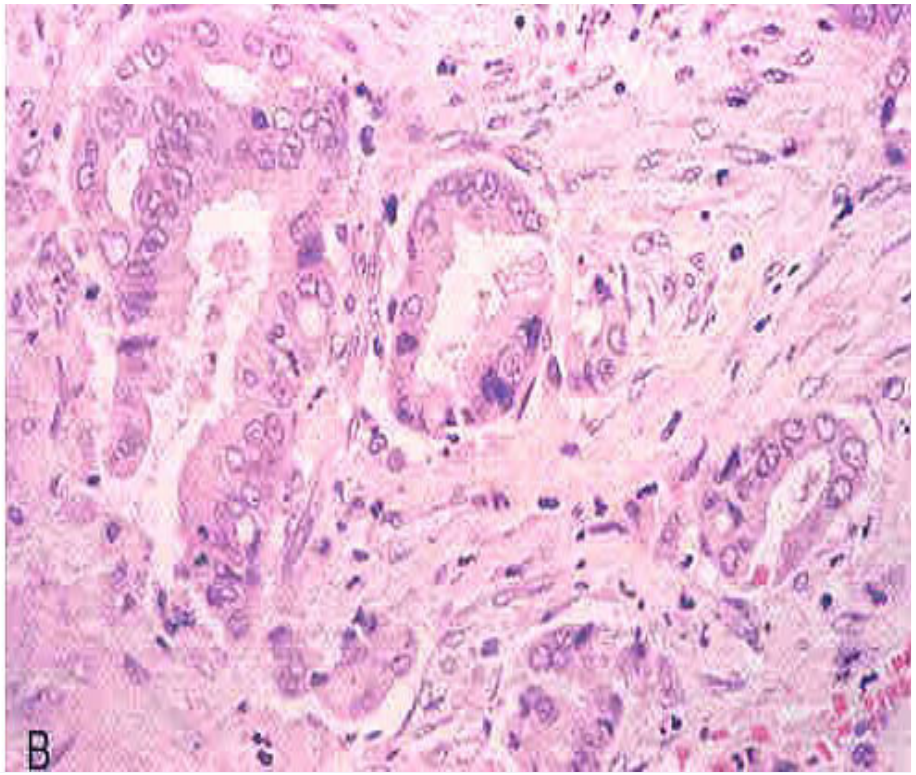
- **Often masked by cirrhosis**; weight loss, malaise, abdominal pain/fullness, hepatomegaly
- **Serum alpha-fetoprotein**: elevated in 50-70% cases (also elevated in chronic hepatitis, liver necrosis, cirrhosis, gonadal germ cell tumors)
- Imaging: ultrasound, CT, MRI, angiography if surgical resection is considered
- Treatment: complete surgical excision (before lung and nodal metastases) is only hope of cure
- 5 year survival all HCC: 5% (dismal)
- 5 year survival HCC, fibrolamellar variant: 60%

Bile Duct Carcinoma (cholangiocarcinoma)

- Arise from intrahepatic or extrahepatic ducts
- Identified risk factors
  - *Opisthorchis sinensis* in biliary tract
  - Exposure to Thorotrast (obsolete imaging dye)
- Pathologic features
  - Adenocarcinomas with prominent sclerotic stroma (must differentiate from more common metastatic adenocarcinoma)
  - Widespread hematogenous metastases
- 5 year survival: < 5%; most die 6-12 months

Bile Duct Carcinoma: pathology





Primary mass (yellow central superior) with innumerable intrahepatic satellite tumors (smaller yellow lesions)

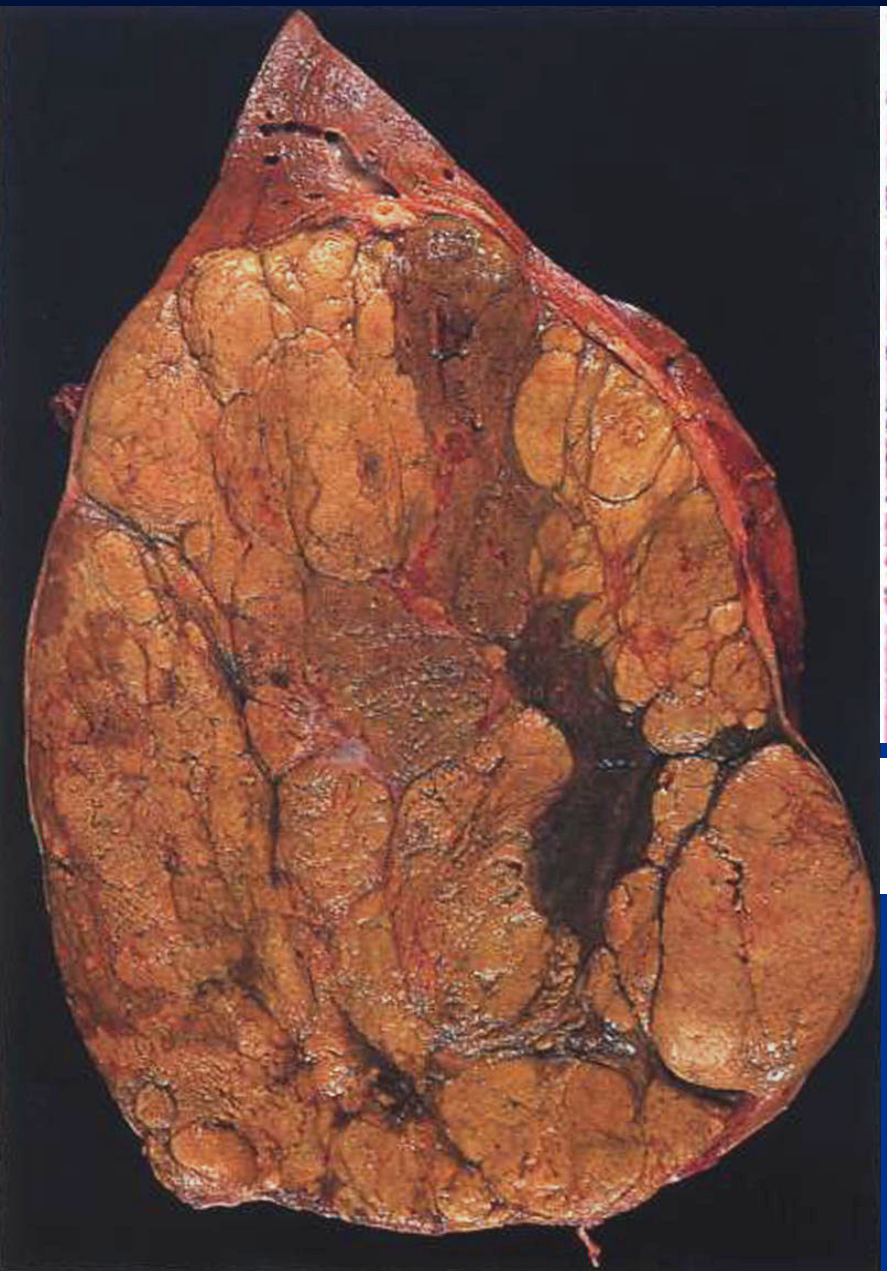
Moderately differentiated adenocarcinoma forming distorted ducts within prominent sclerotic stroma

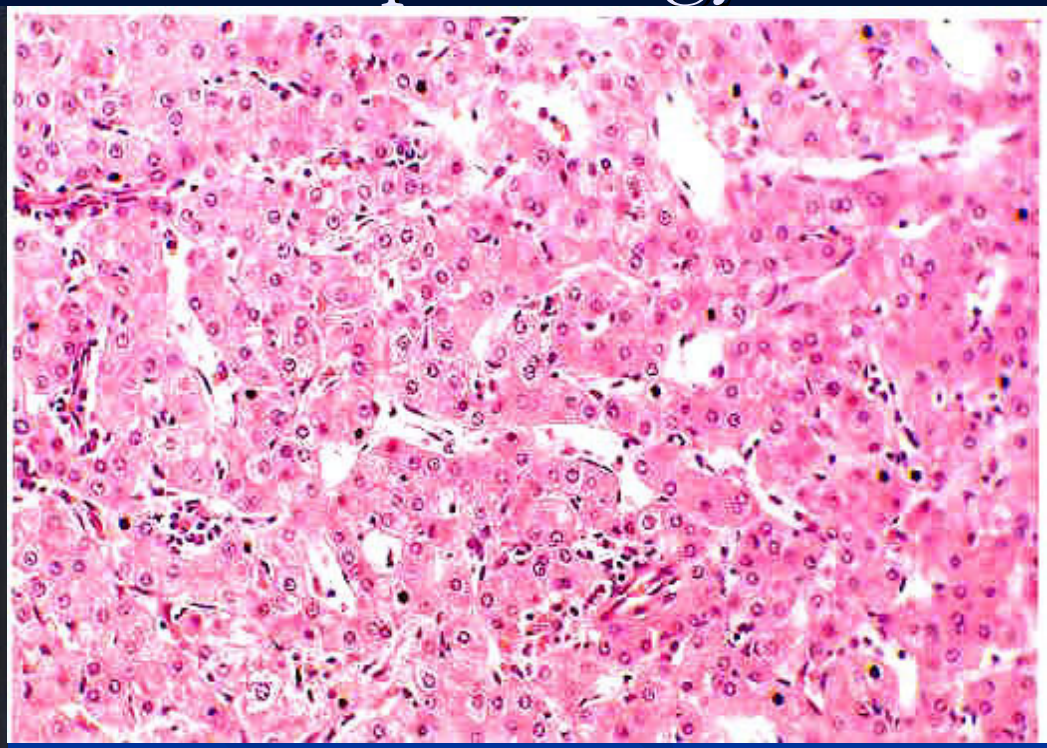
Fig. 18-45, Pathologic Basis of Disease, 7th ed, Elsevier 2004

Liver Cell Adenoma

- Benign neoplasm composed of hepatocytes
- Risk factors
  - Females, mostly reproductive years
  - Long-term oral contraceptives (progesterone)
- Complications
  - Subcapsular tumor may rupture, especially during pregnancy $\Rightarrow$ intraperitoneal hemorrhage
- Pathology: must differentiate from HCC
- Treatment: surgical resection is curative

Liver Cell Adenoma: pathology





Disorganized cords of well-differentiated hepatocytes without bile ducts or portal tracts

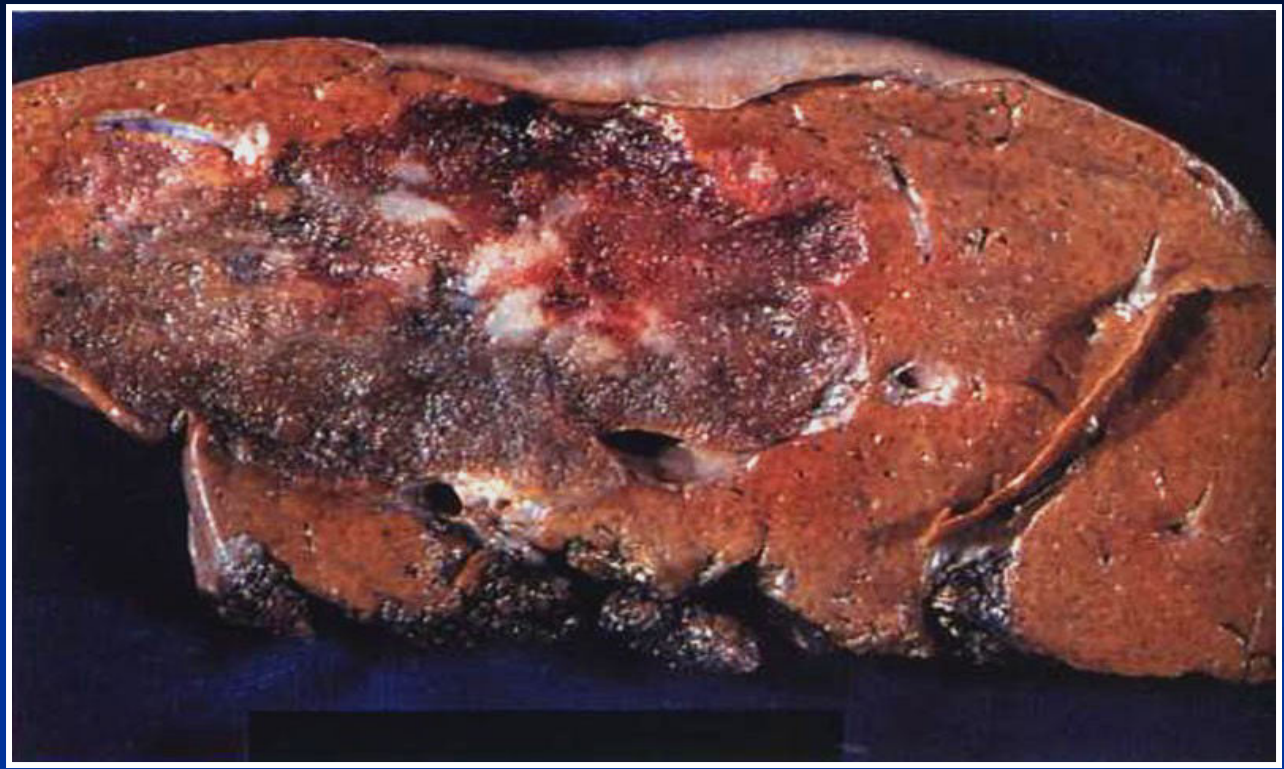
Figs. 37-6, A&B, Sternberg's Diagnostic Surgical Pathology, 4th edition, Lippincott 2004.

Well-circumscribed, encapsulated mass, homogeneous, no central scar

Hemangioma

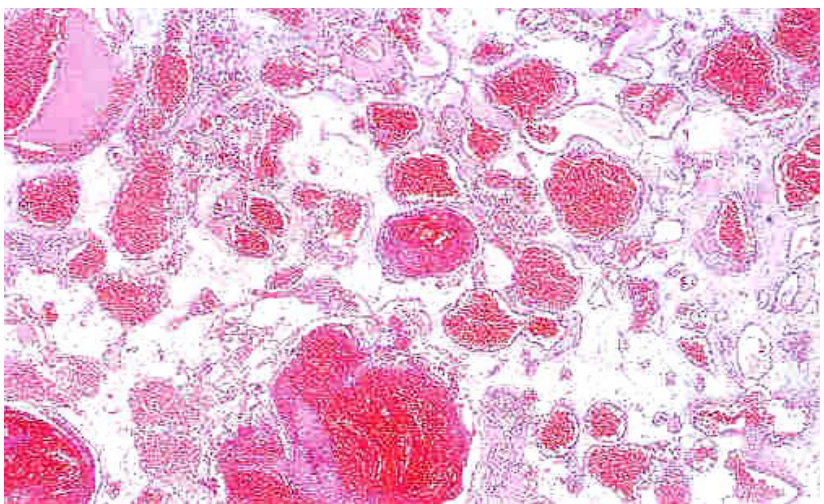
- Benign neoplasm of endothelial cells forming vascular channels; usually solitary and < 5 cm; surgeon may discover at laparotomy if subcapsular
- **Most common benign neoplasm of liver;** a common incidental finding at autopsy
- Imaging appearance distinctive
- Avoid biopsy/excision (risk of hemorrhage)
- ***LEAVE IT ALONE*** (it doesn't hurt anyone)

Hemangioma: pathology



Spongy, red-purple nodule with variable hemorrhage & fibrosis

Fig. 37-21A, Sternberg's Diagnostic Surgical Pathology, 4th ed, Lippincott, 2004.

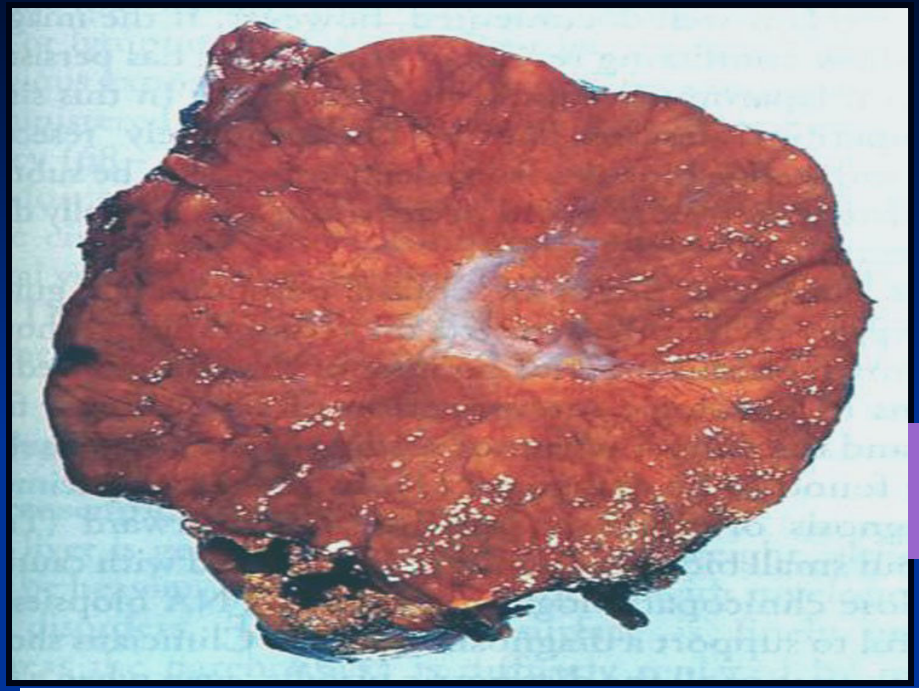


Dilated vessels lined by single layer endothelial cells

Tumor-like mass: focal nodular hyperplasia

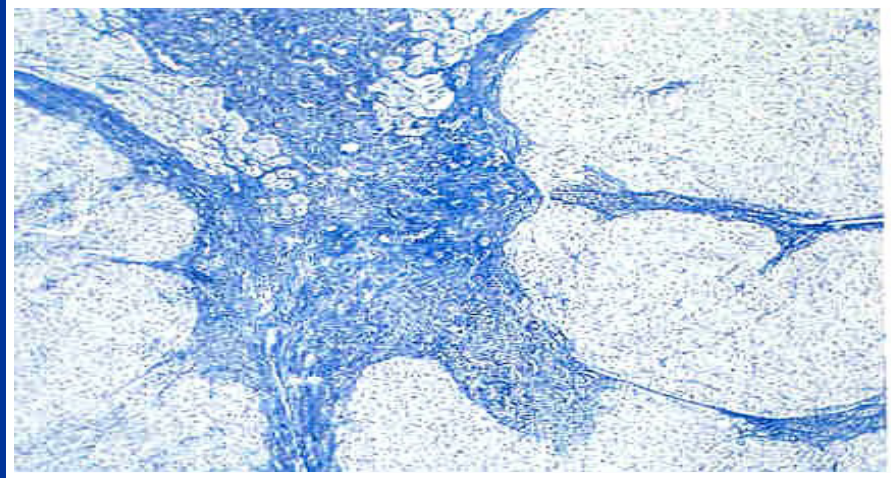
- Solitary nodule of hyperplastic liver parenchyma arising in non-cirrhotic liver (not a neoplasm)
- Most asymptomatic; discovered incidentally
- 85% in females (all ages, mostly adults)
- Low risk of hemoperitoneum (1%)
- Distinctive arteriography: centrifugal filling with dense capillary blush
- Surgical resection curative

Focal nodular hyperplasia: pathology

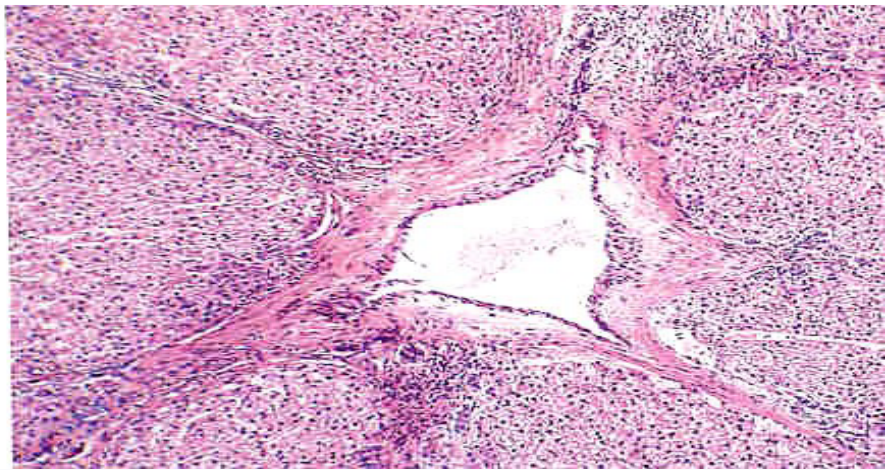


Well-demarcated nodule, 1-10 cm diameter, with typical central stellate scar

Fig. 37-7A, Sternberg's Diagnostic Surgical Pathology, 4th ed, Lippincott, 2004.



Trichrome stain, central scar (dark blue)



H&E, all normal components of liver present

Tumor-like mass: Nodular regenerative hyperplasia

- Diffuse spherical nodules of regenerating hepatocytes, arising in non-cirrhotic liver (***key difference from cirrhosis***: nodules are **not** separated by fibrous septae)
- Both sexes equally, all ages
- Wide variety clinical settings, common denominator: altered circulation in liver with multifocal obliteration of portal vein radicles
- Potential complication: portal hypertension

Nodular regenerative hyperplasia: pathology

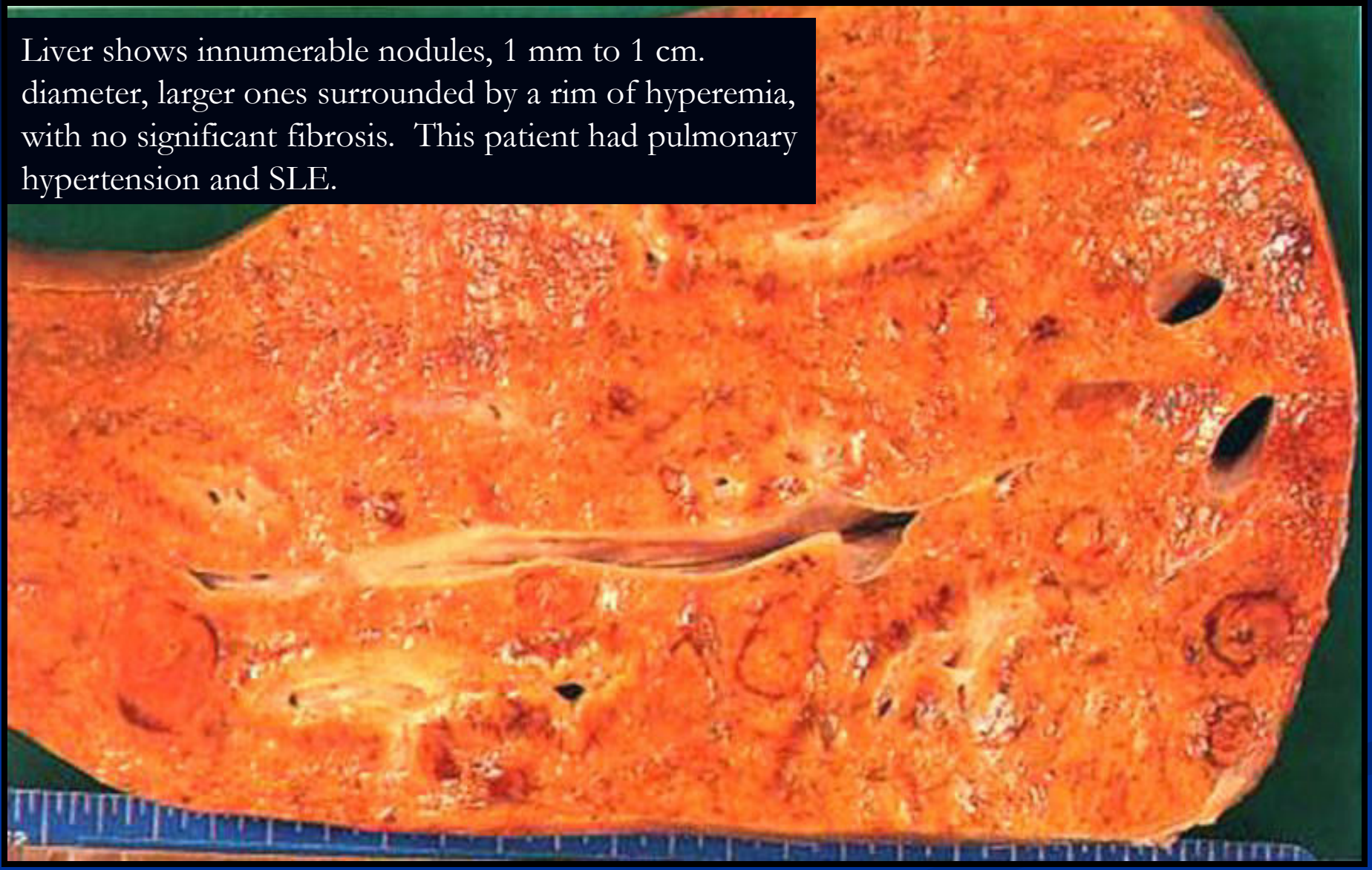


Fig. 37-8A, Sternberg's Diagnostic Surgical Pathology,4th edition, Lippincott, 2004.

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