Charles Lombard, M.D.

Department

of

Pathology

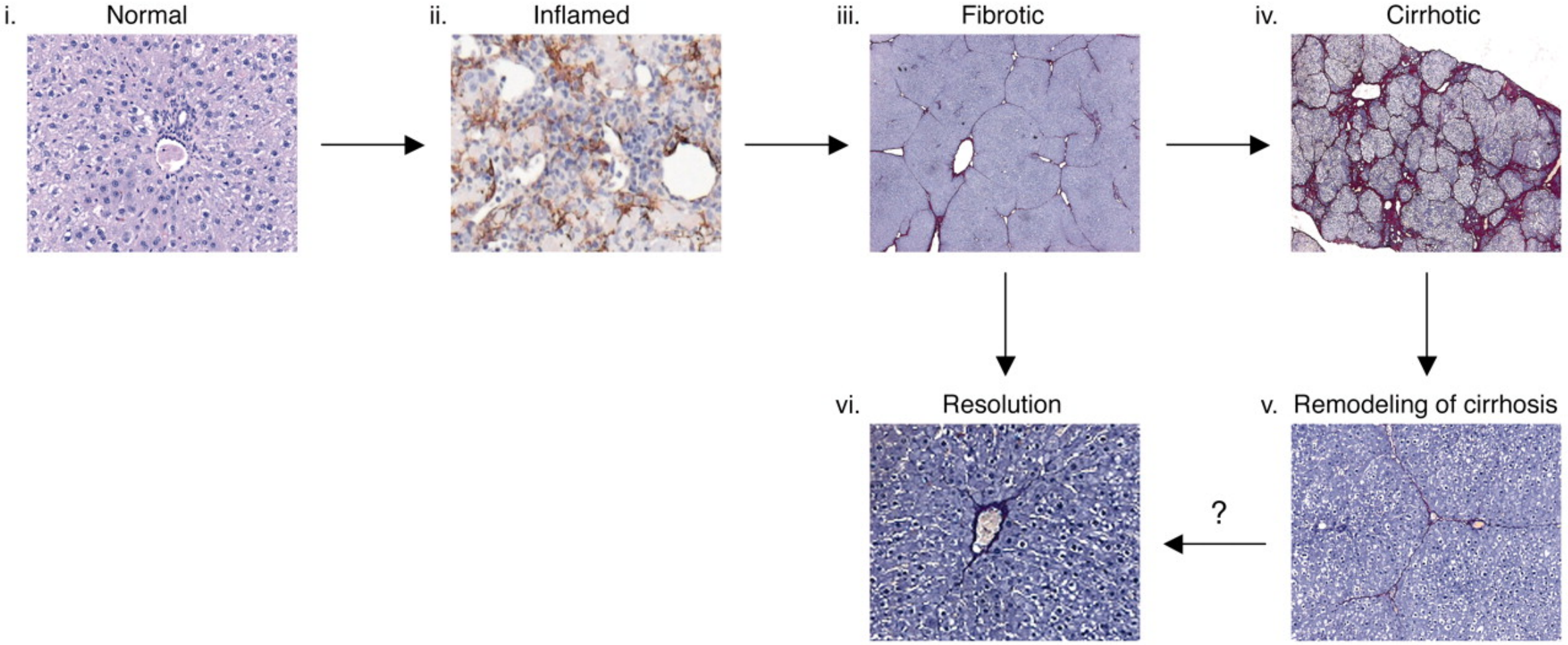
# Pathology of Cirrhosis


STANFORD
UNIVERSITY

# CIRRHOSIS

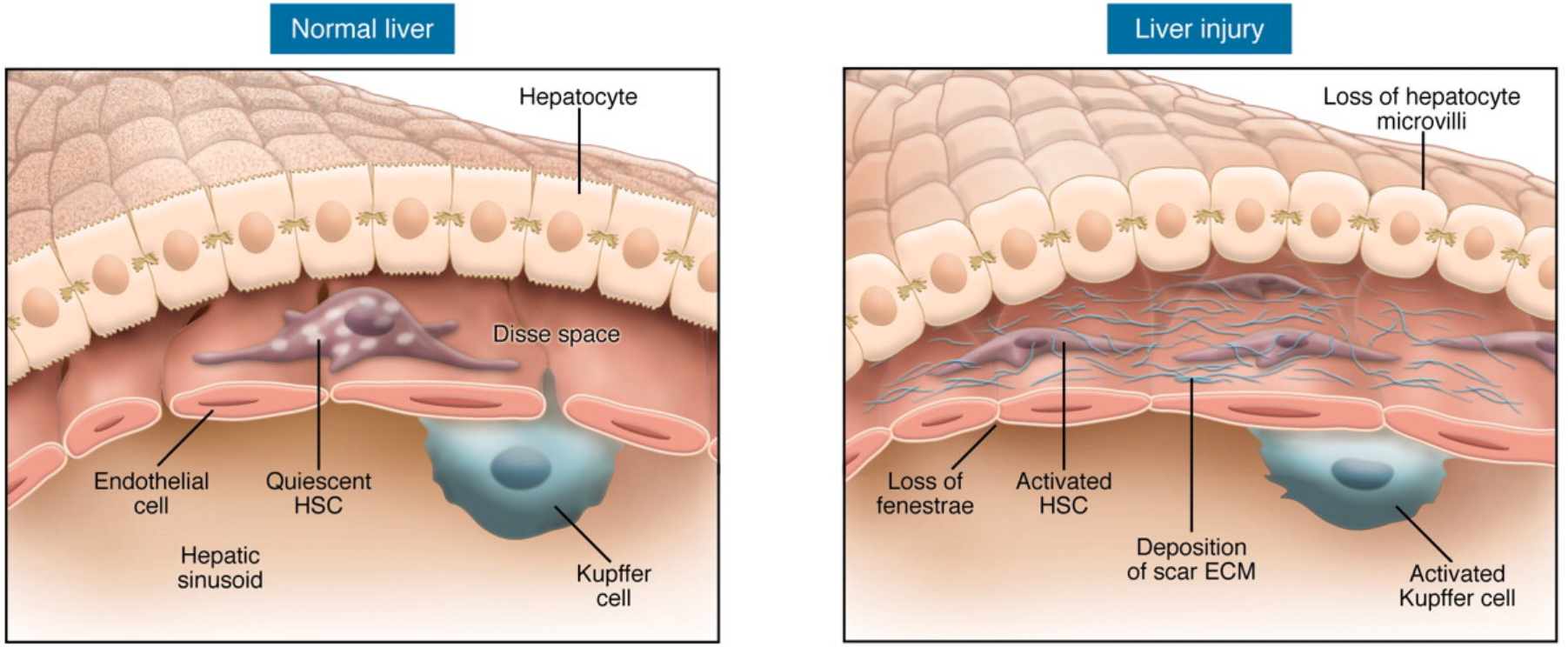
- The result of a variety of liver diseases
- Cell Death
- Fibrosis (ECM deposition) in the liver
- Abnormal arrangement of hepatocytes in nodules with “twinning” of plates
- Anastamoses (HA-PV) develop
- Portal hypertension ensues

# Model of liver cirrhosis as wound healing:



Injury→cell death→inflammation→ release of proinflammatory cytokines

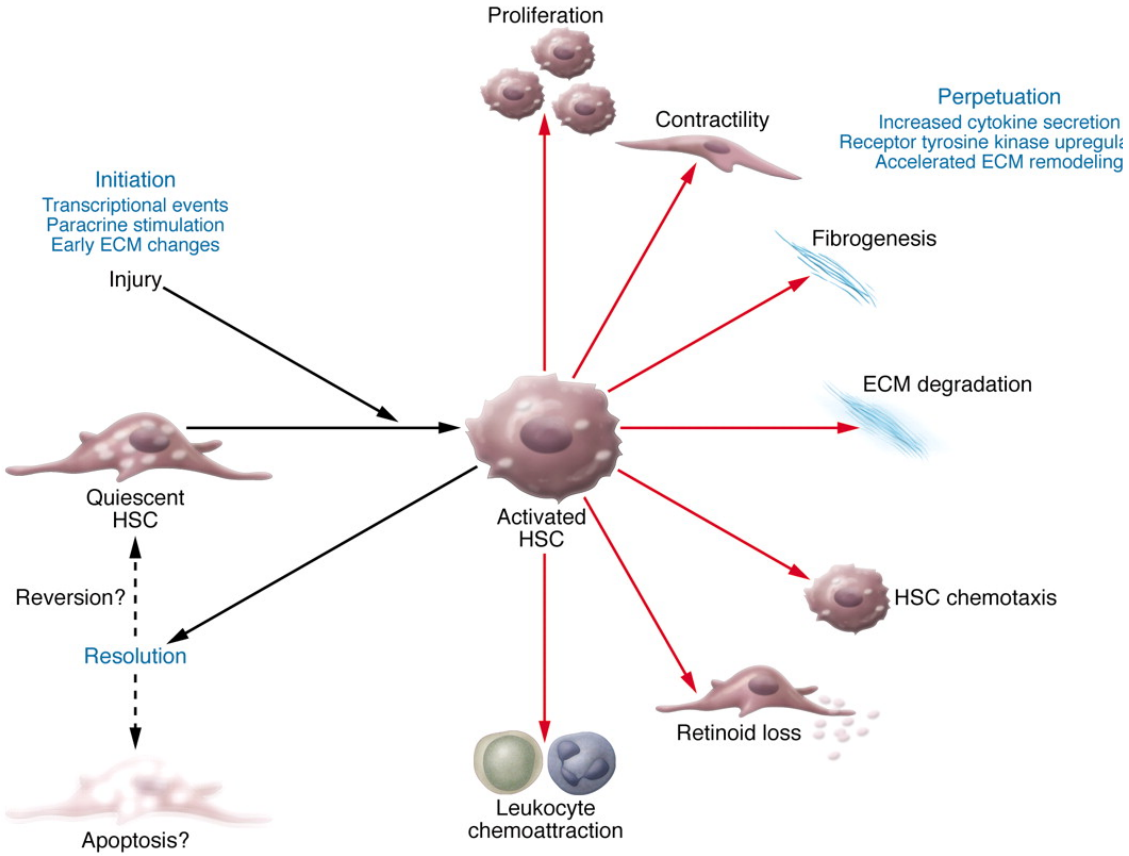
↓



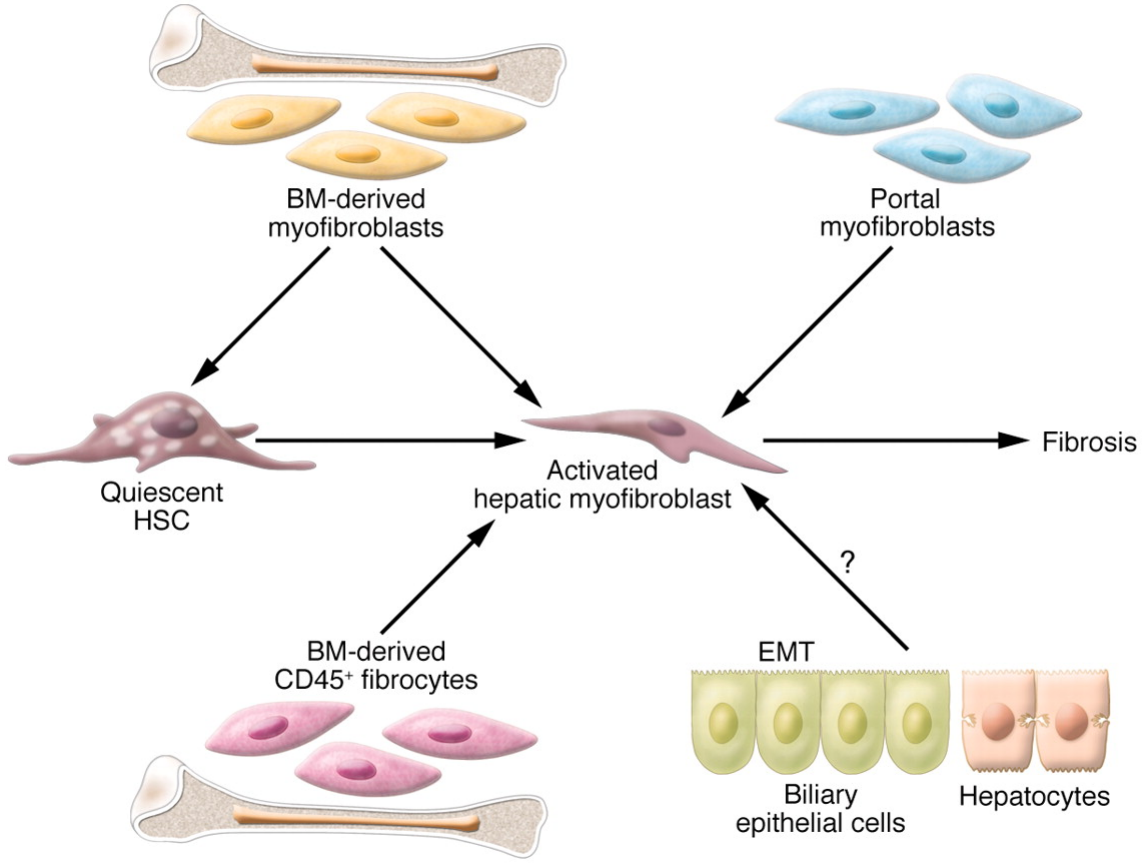

Iredale, J. P. J. Clin. Invest. 2007;117:539-548

# Hepatic stellate cells in cirrhosis

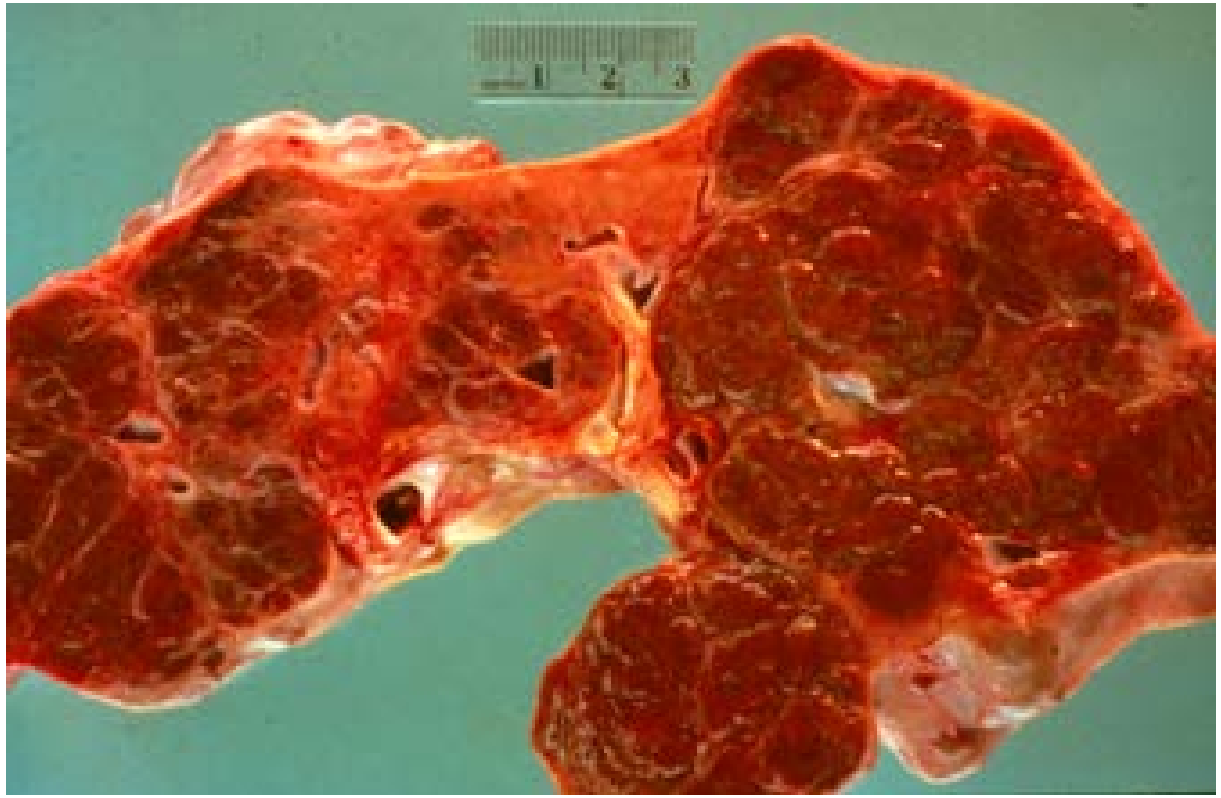
## ACTIVATION

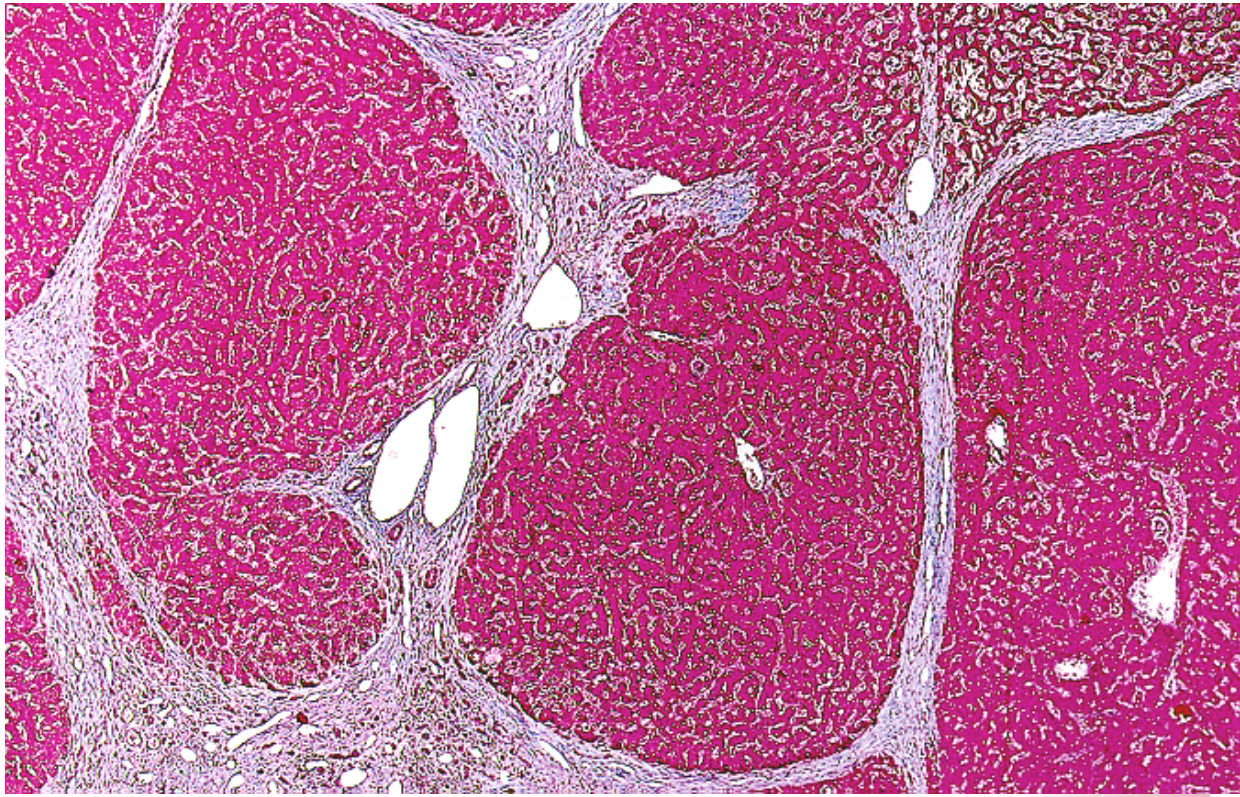



## FIBROSIS

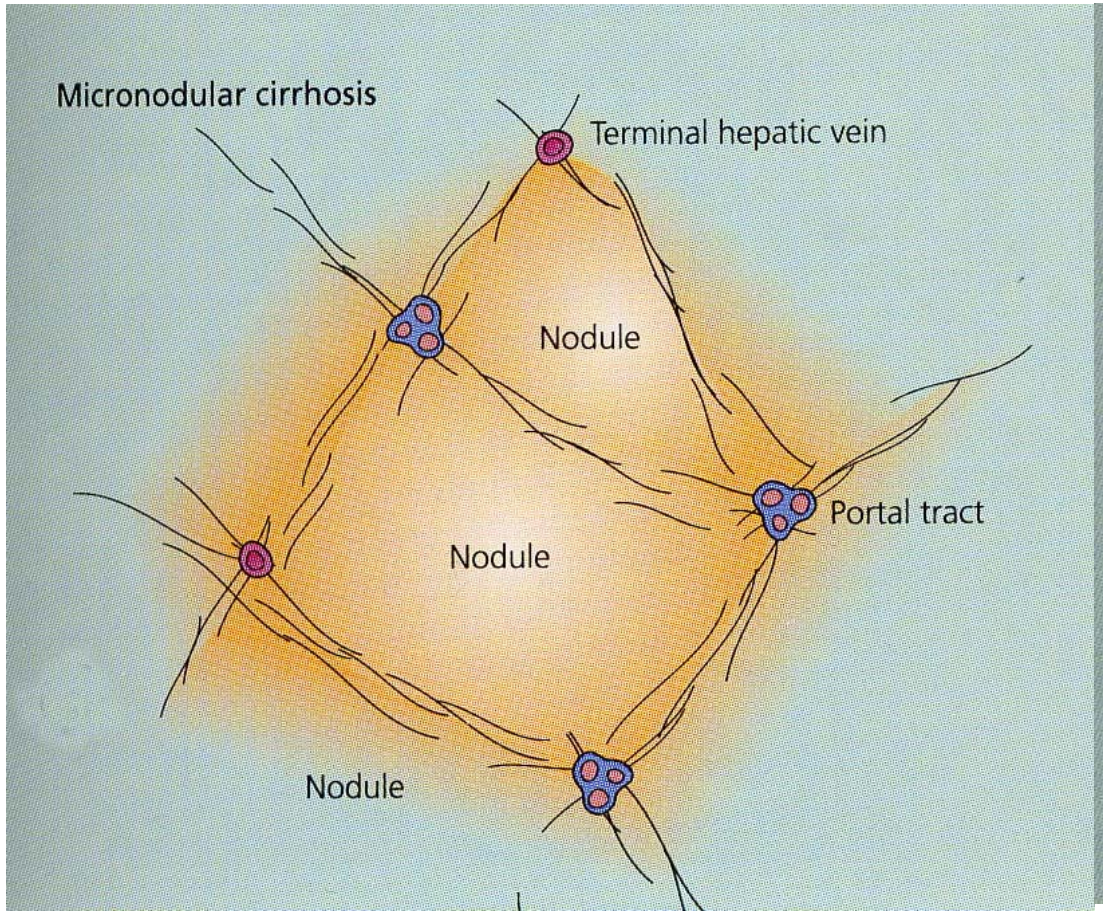


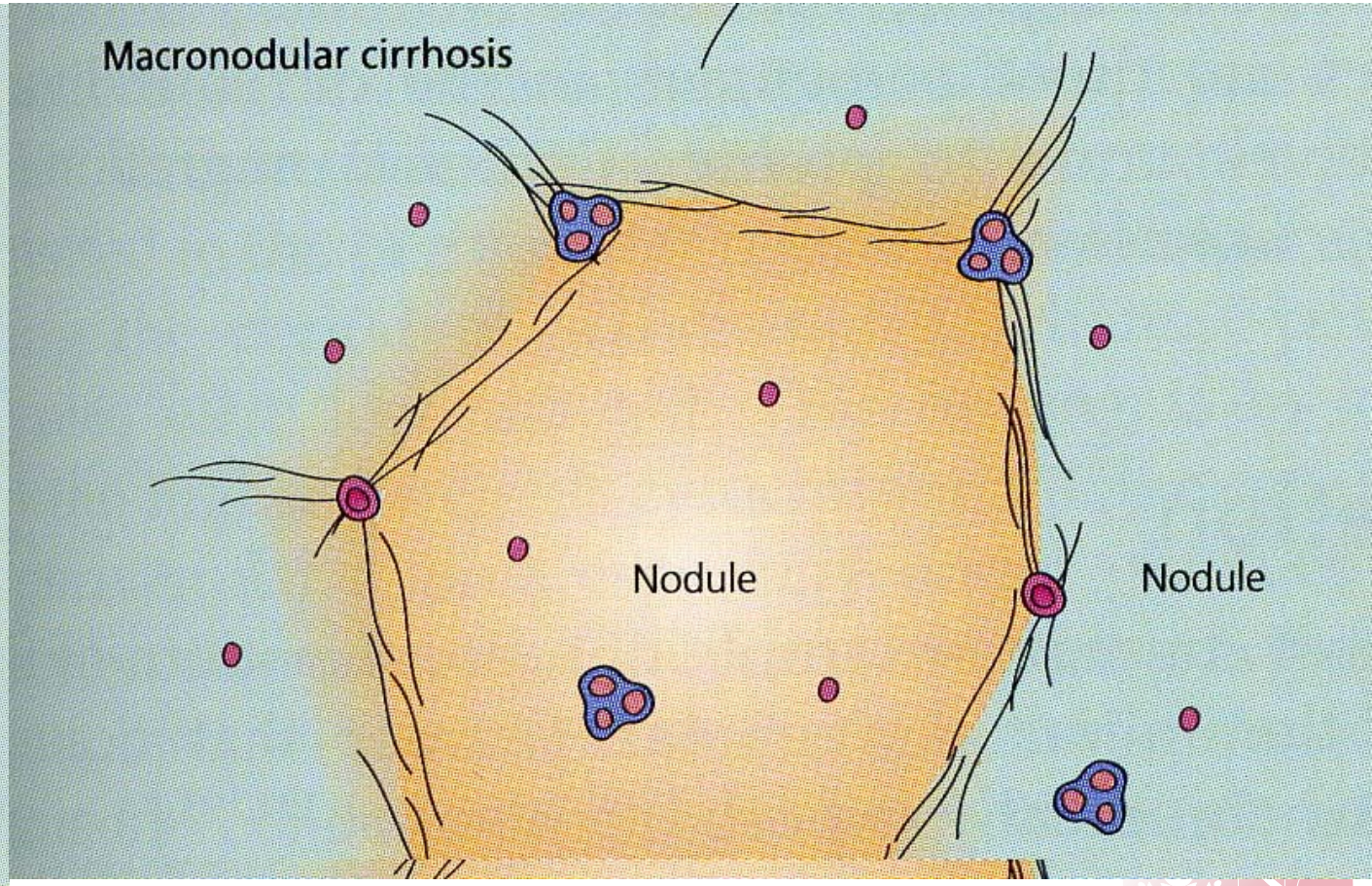
# Cirrhosis of the liver





# Anatomic classification of cirrhosis



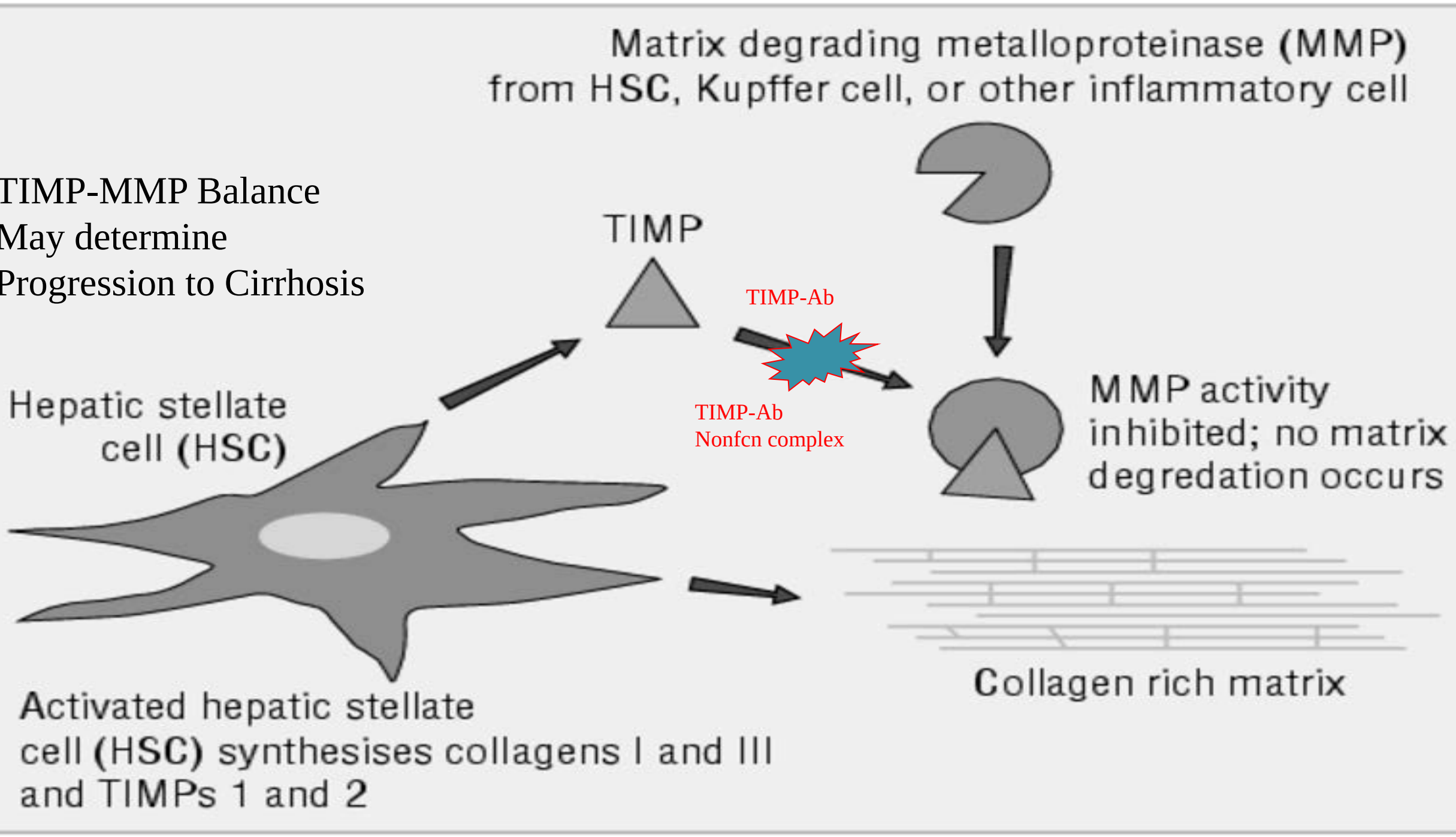



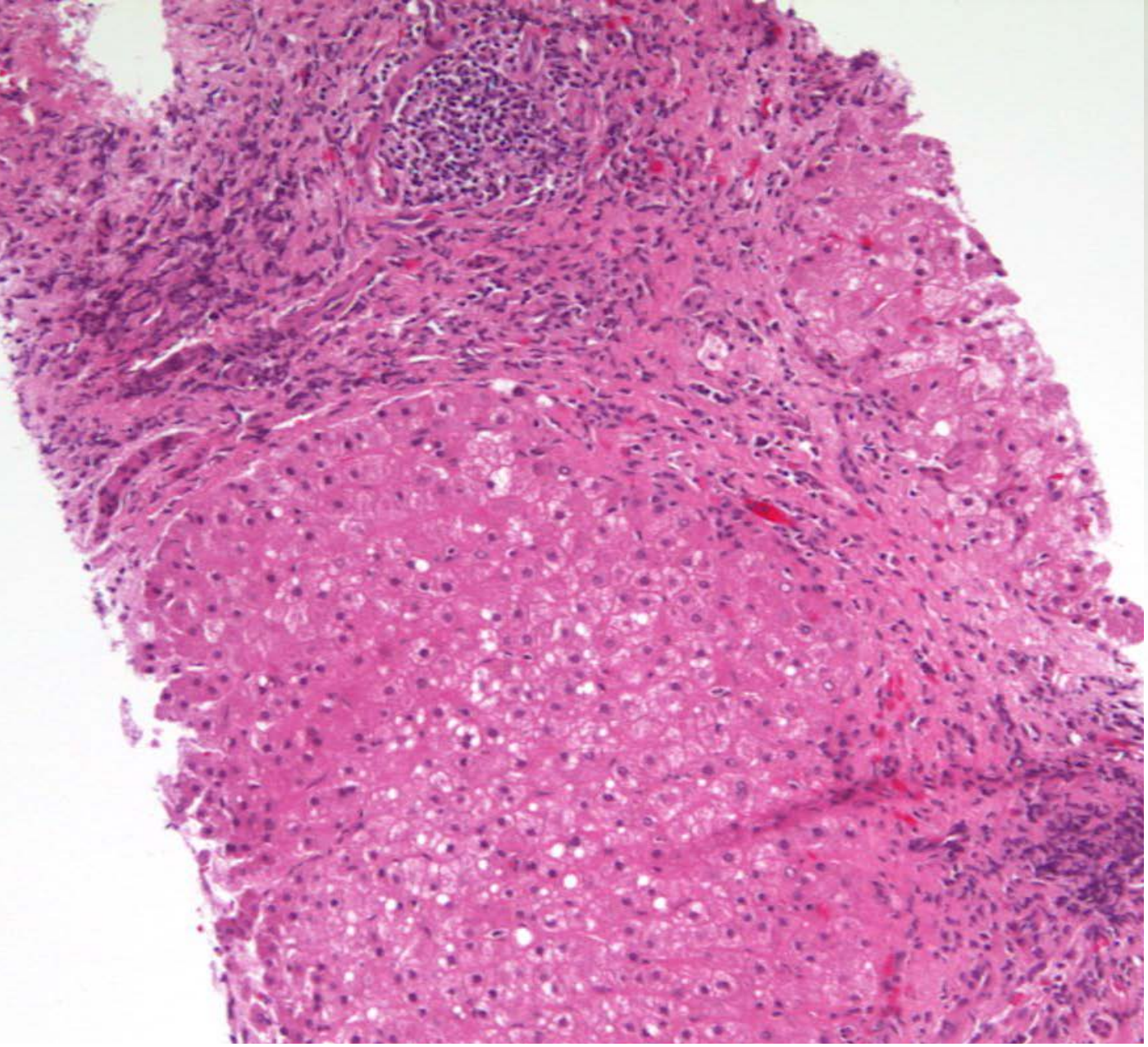

INHIBITED REGENERATION

LARGE REGENERATIVE NODULES

# Is Cirrhosis Reversible???

TIMP-MMP Balance
May determine
Progression to Cirrhosis

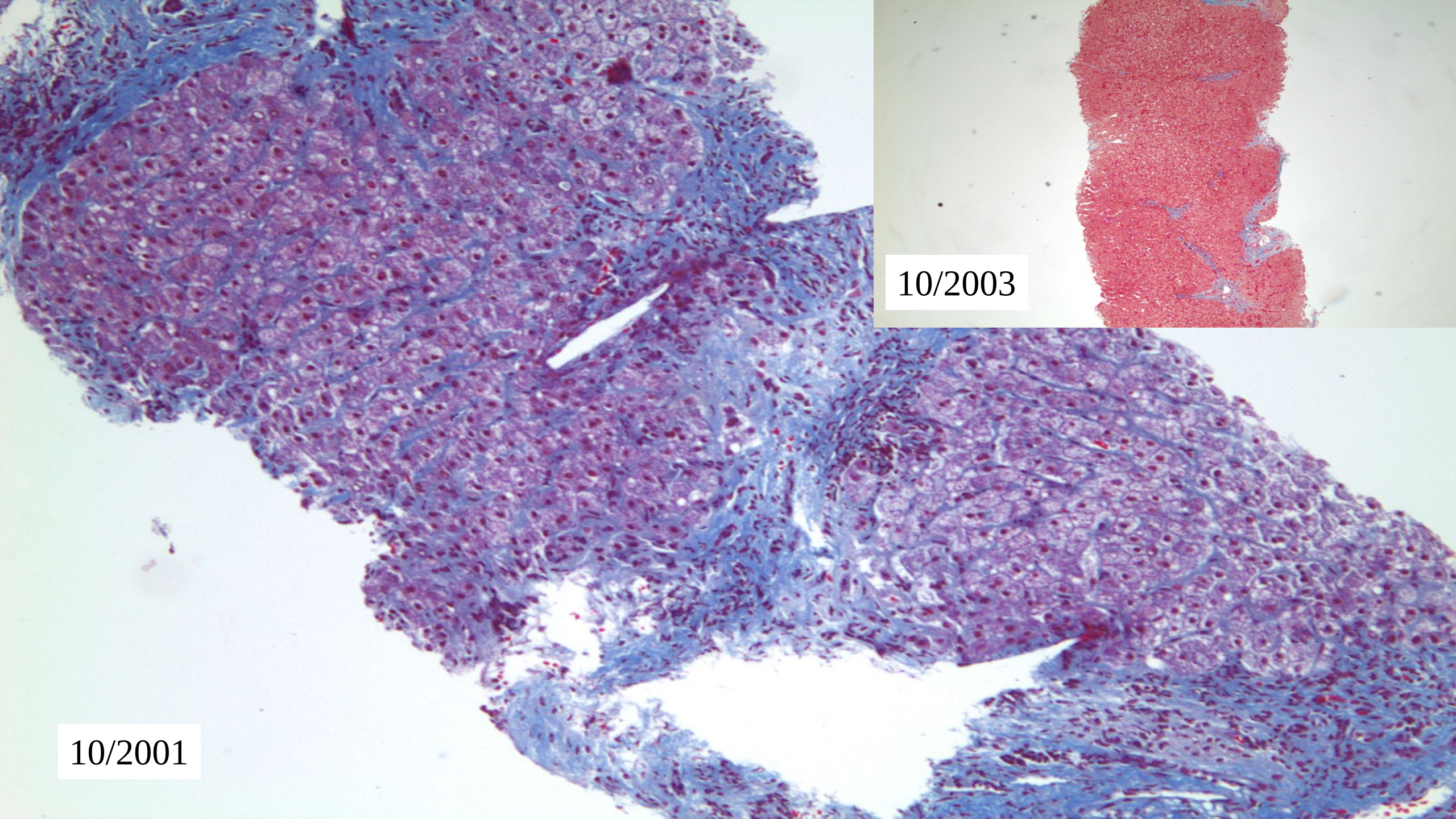




10/2001 at diagnosis: Chronic HCV infection with cirrhosis



10/2003 after Rx


10/2003
10/2001

# Etiologies of Cirrhosis

- Alcohol
- Viral
- Metabolic
- Biliary
- Hepatic vein obstruction
- Drugs and toxins
- Miscellaneous

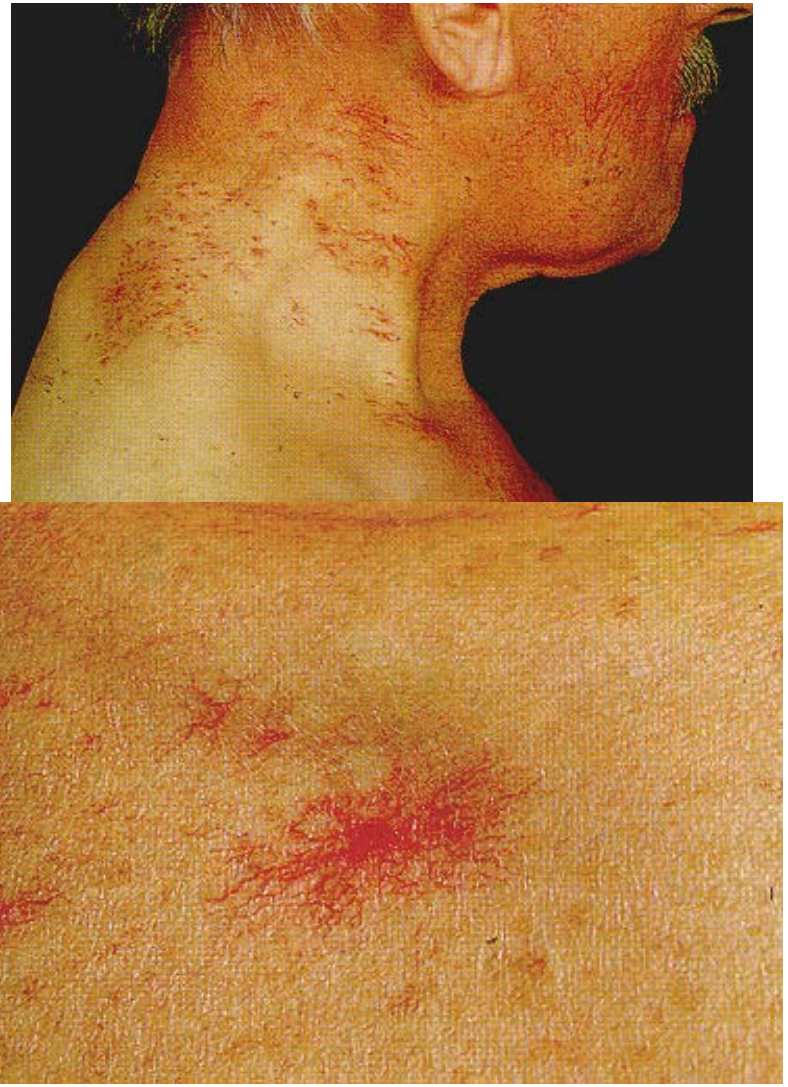
# Cirrhosis:  Symptoms

- Anorexia
- Nausea
- Abdominal pain
- Weakness
- Hematemesis
- Encephalopathy

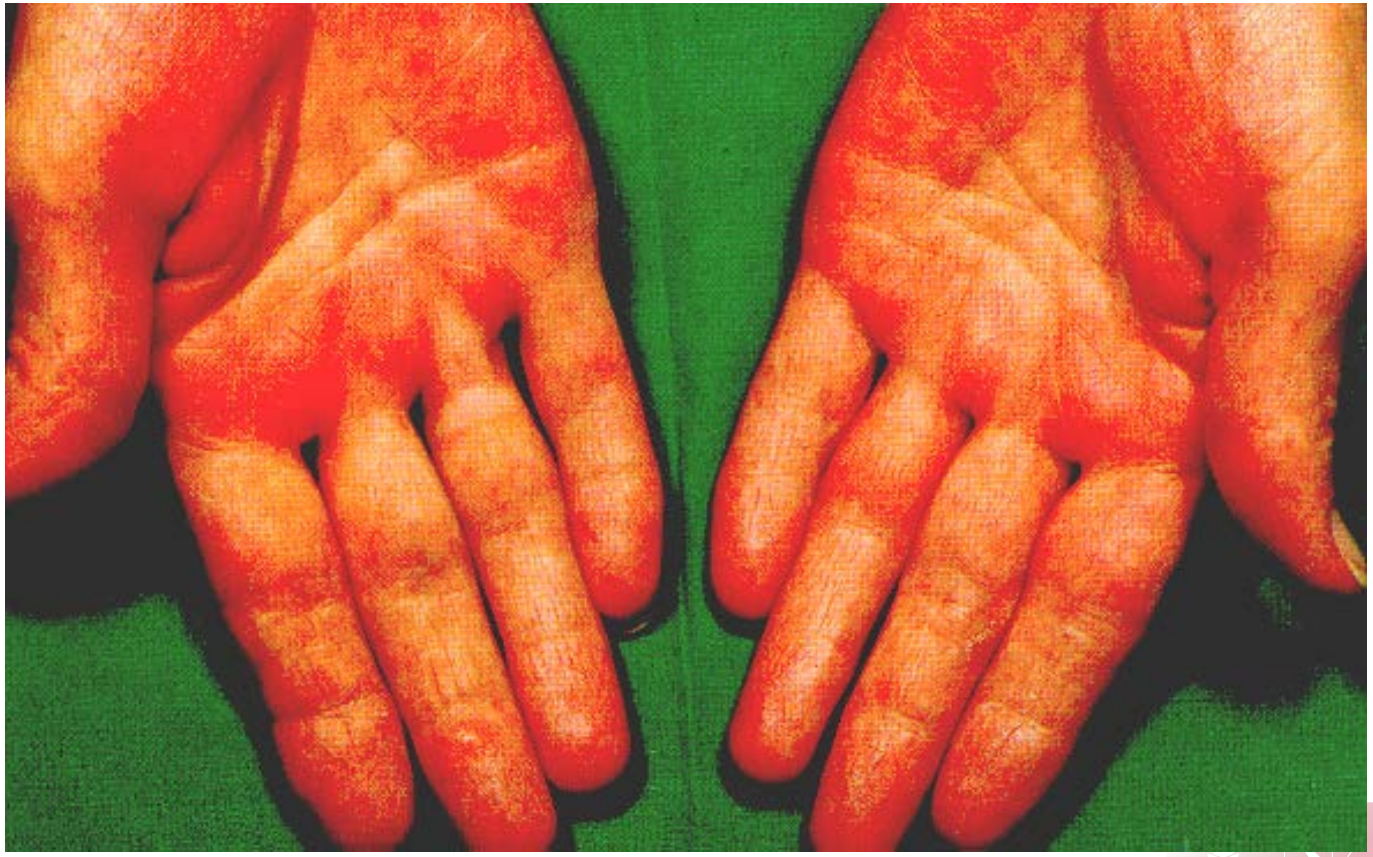
# Cirrhosis:  Signs

- Varices
- Jaundice
- Ascites
- Spider Angiomas
- Hepatomegaly
- Splenomegaly

# Clinical signs of cirrhosis

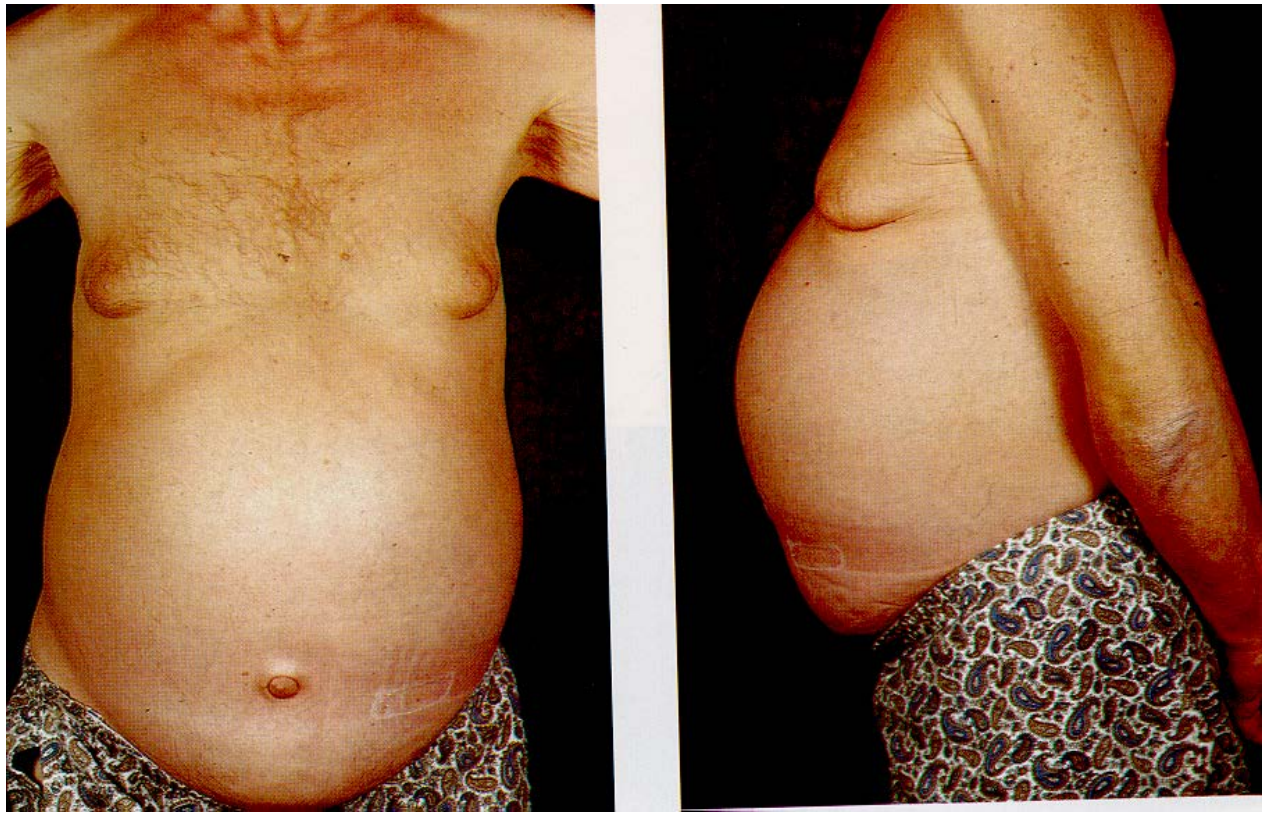


Spider hemangiomas

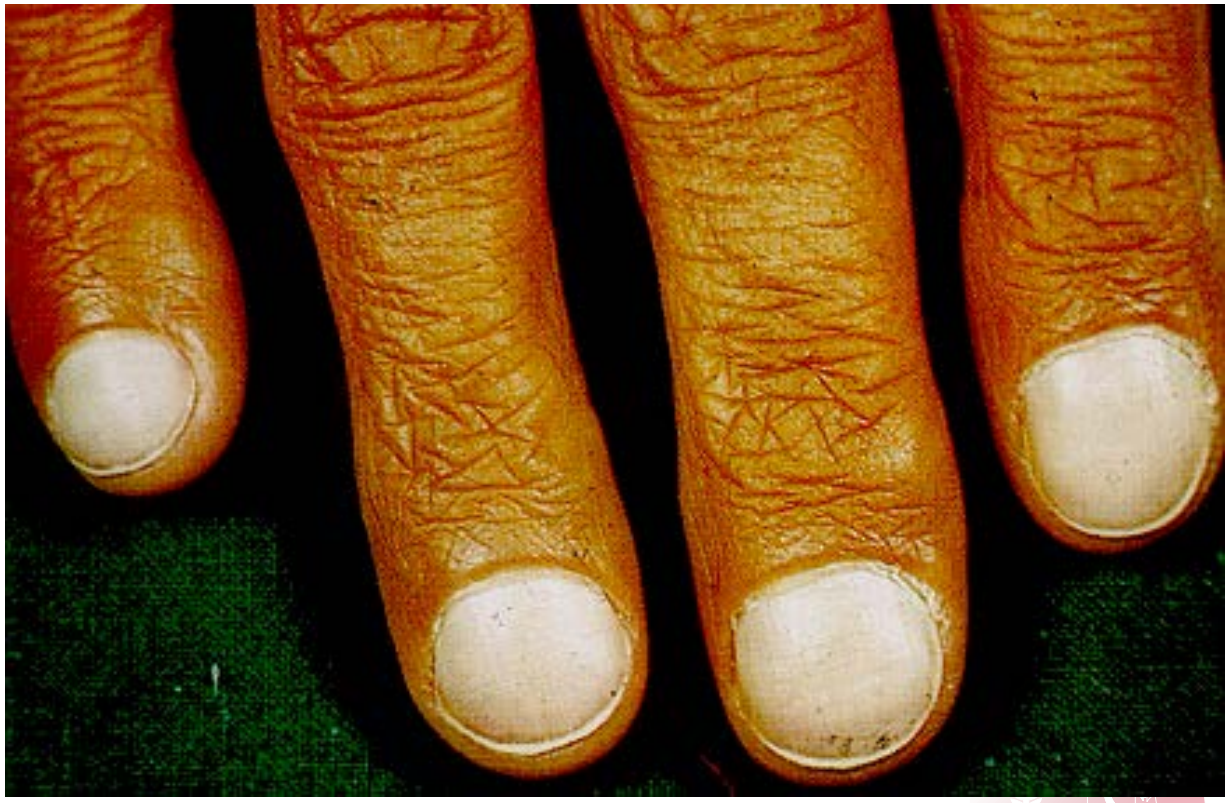


Palmar erythema

# Clinical signs of cirrhosis



Ascites



Clubbing of fingers

# Sequela of Cirrhosis

- Portal Hypertension
  - Varices
  - Splenomegaly
  - Ascites
  - Encephalopathy
- Coagulopathy
  - Decreased Factors 2,7,9,10
  - DIC
  - Splenic Sequestration
- Hepatorenal Syndrome

# Survival in Cirrhosis

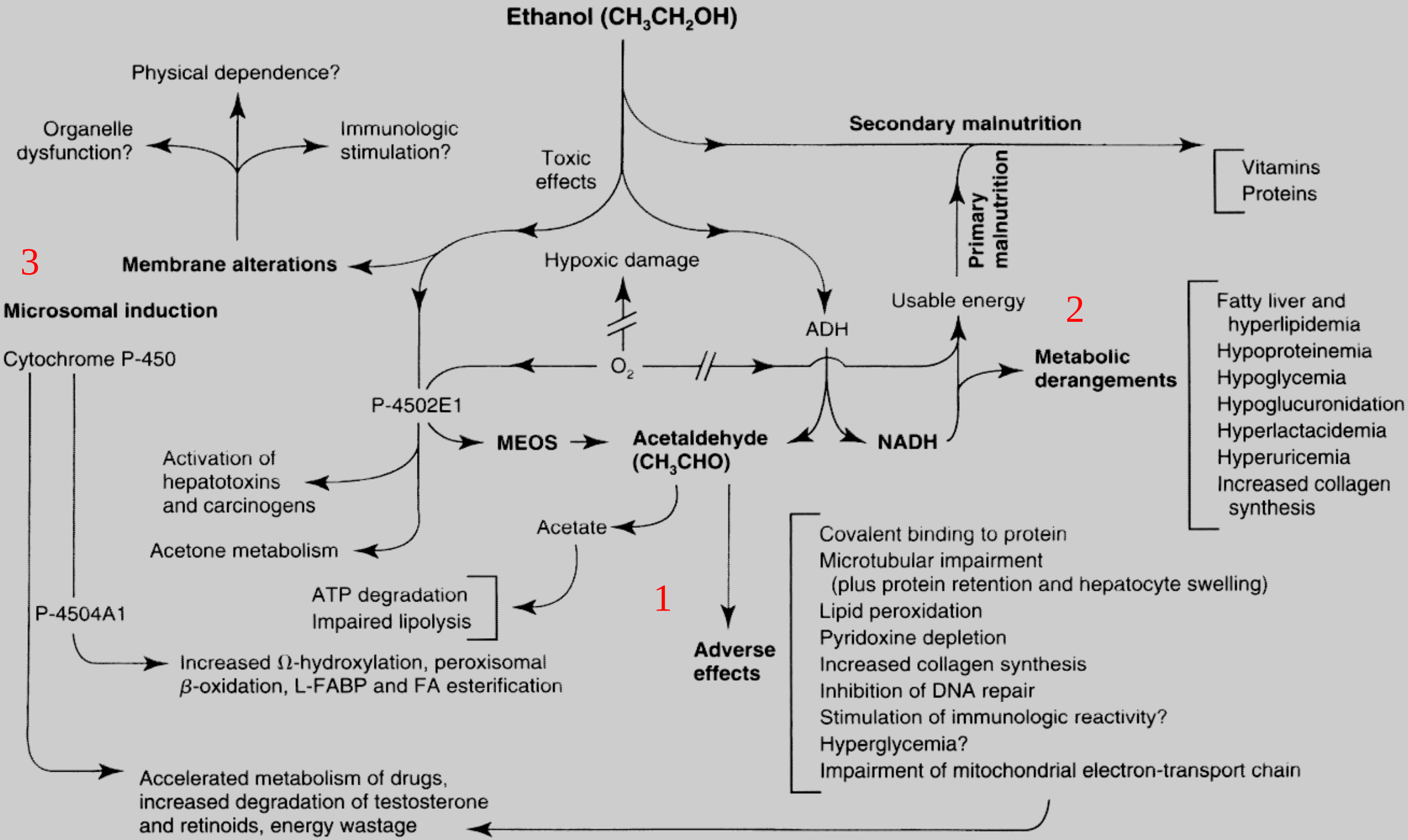
- Compensated Cirrhosis:  85 % at 5 years
- Decompensated Cirrhosis:  15% at 5 years
- 10 % develop Hepatocellular Carcinoma

# Alcoholic Liver Disease

- Fatty Liver
- Alcoholic Hepatitis
- Perivenular Sclerosis
- Chronic Active Hepatitis
- Micronodular (Laennec's) Cirrhosis

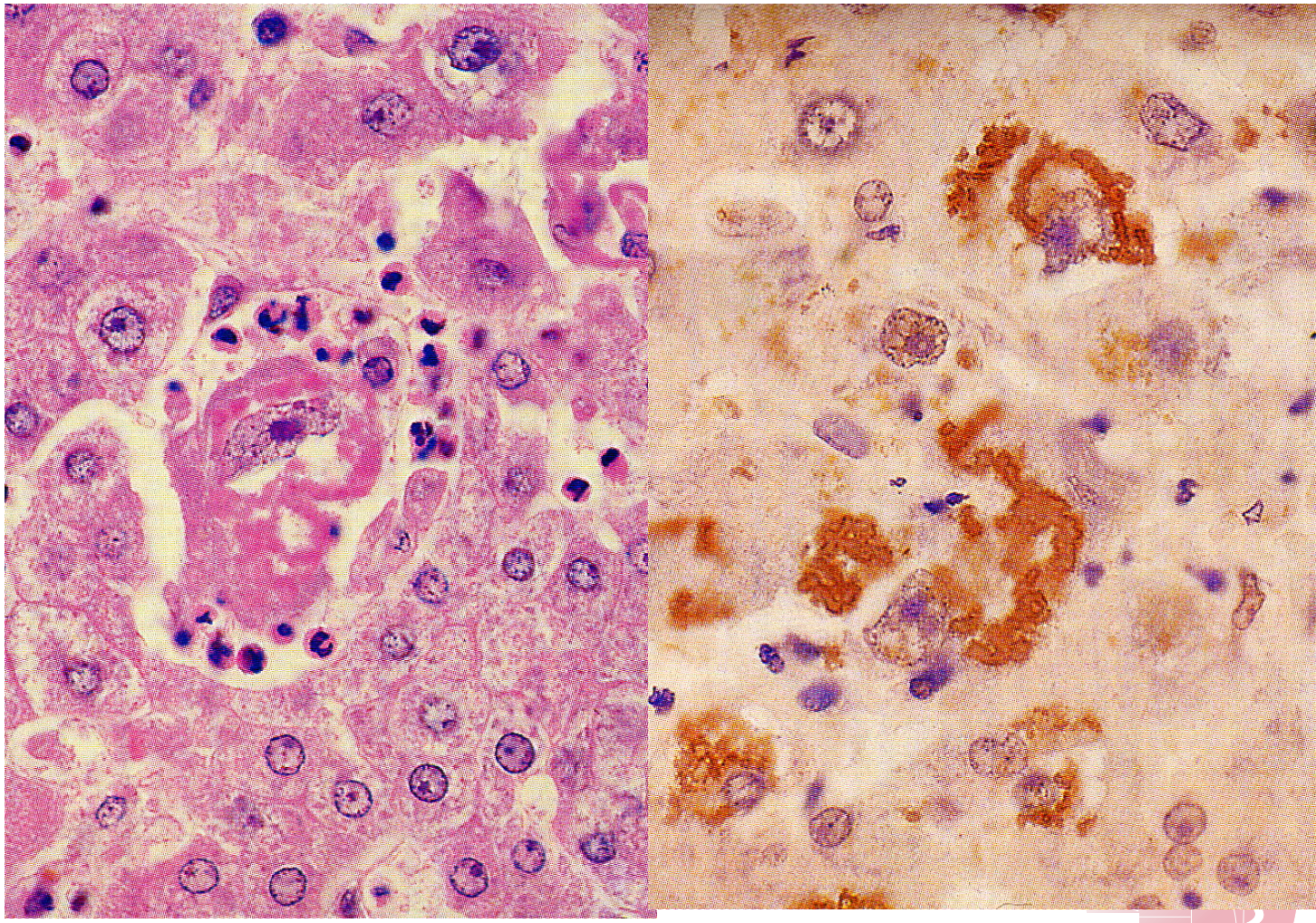
# Pathogenesis of ALD

- Metabolic injury
  - Acetaldehyde
  - Excess reducing equivalents (NADH)
  - Hyperactivity of MEOS (chronic ALD)
- Inflammatory injury
  - Kupffer cell activation
  - Mallory bodies


Ethanol ($CH_3CH_2OH$)
Physical dependence?
Organelle dysfunction?
Immunologic stimulation?
Toxic effects
Secondary malnutrition
Vitamins
Proteins
Primary malnutrition
3
Membrane alterations
Hypoxic damage
Microsomal induction
Cytochrome P-450
$O_2$
ADH
Usable energy
2
Metabolic derangements
Fatty liver and hyperlipidemia
Hypoproteinemia
Hypoglycemia
Hypoglucuronidation
Hyperlactacidemia
Hyperuricemia
Increased collagen synthesis
P-4502E1
MEOS
Acetaldehyde ($CH_3CHO$)
NADH
Activation of hepatotoxins and carcinogens
Acetone metabolism
Acetate
ATP degradation
Impaired lipolysis
1
P-4504A1
Adverse effects
Covalent binding to protein
Microtubular impairment (plus protein retention and hepatocyte swelling)
Lipid peroxidation
Pyridoxine depletion
Increased collagen synthesis
Inhibition of DNA repair
Stimulation of immunologic reactivity?
Hyperglycemia?
Impairment of mitochondrial electron-transport chain
Increased Ω-hydroxylation, peroxisomal β-oxidation, L-FABP and FA esterification
Accelerated metabolism of drugs, increased degradation of testosterone and retinoids, energy wastage

# Mallory Bodies

- Deranged cytoskeletal proteins
  - Alter shape and stability of cell membranes
  - Neutrophil Chemotaxis
  - Stimulates Fibroplasia
- Not Specific for Alcoholic Liver Disease

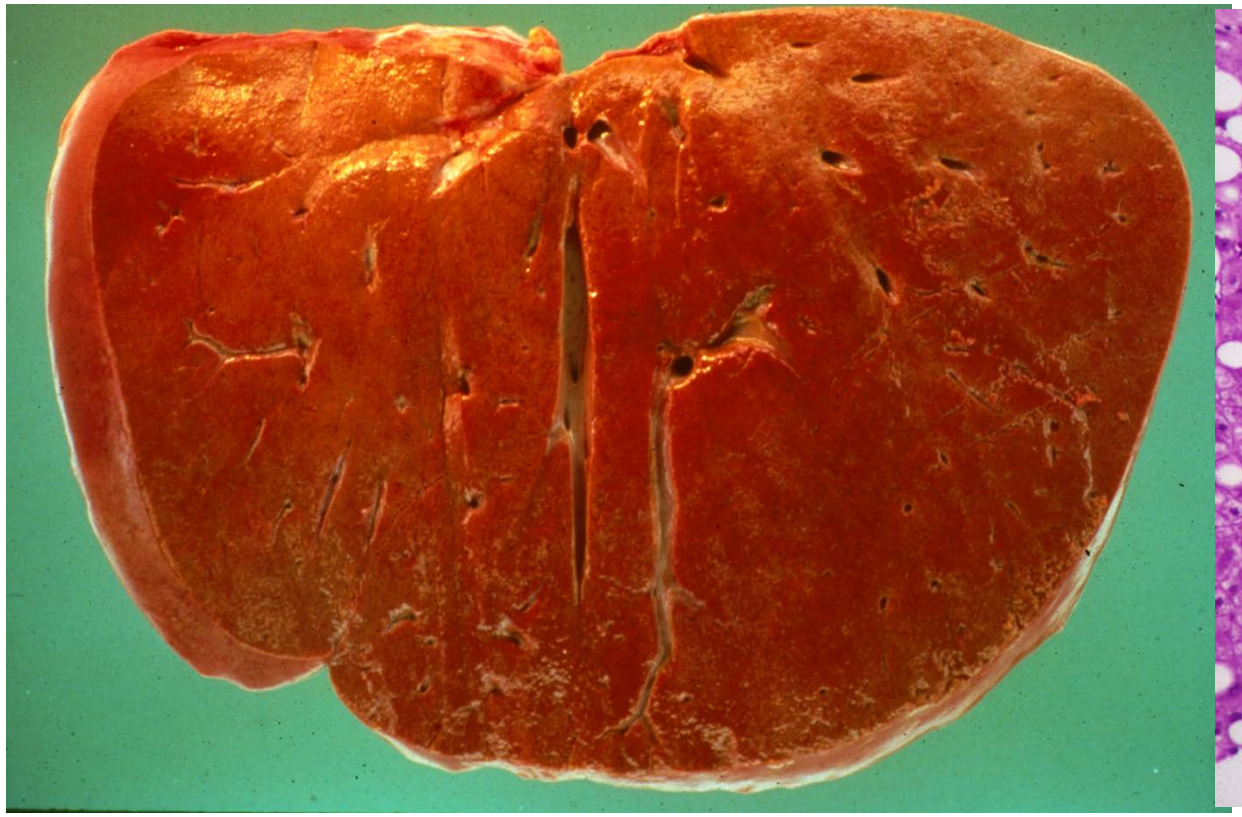


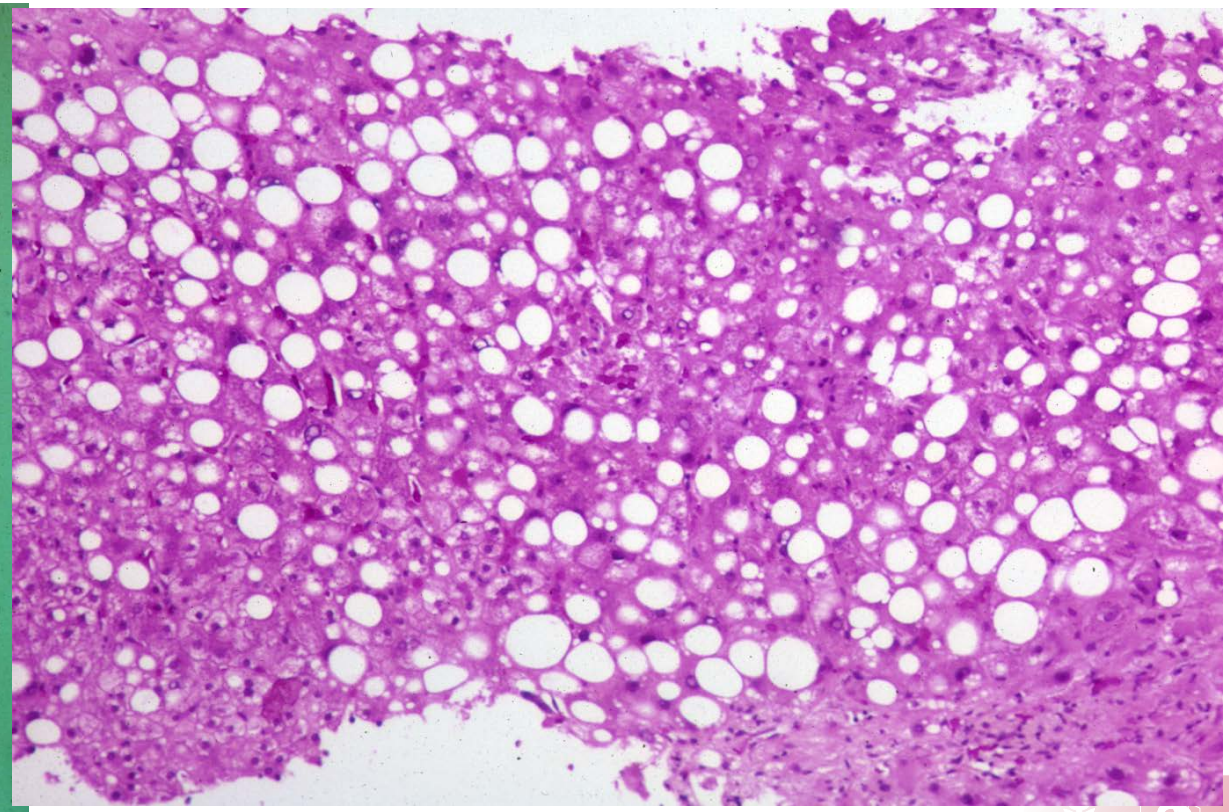
IPOX: Ubiquitin

# Alcohol-induced Fatty Liver

- Most common change in ALD
- Reversible in 4-6 weeks
- Centrilobular in location
- Macrovesicular
- No significant associated inflammation

# Fatty Liver

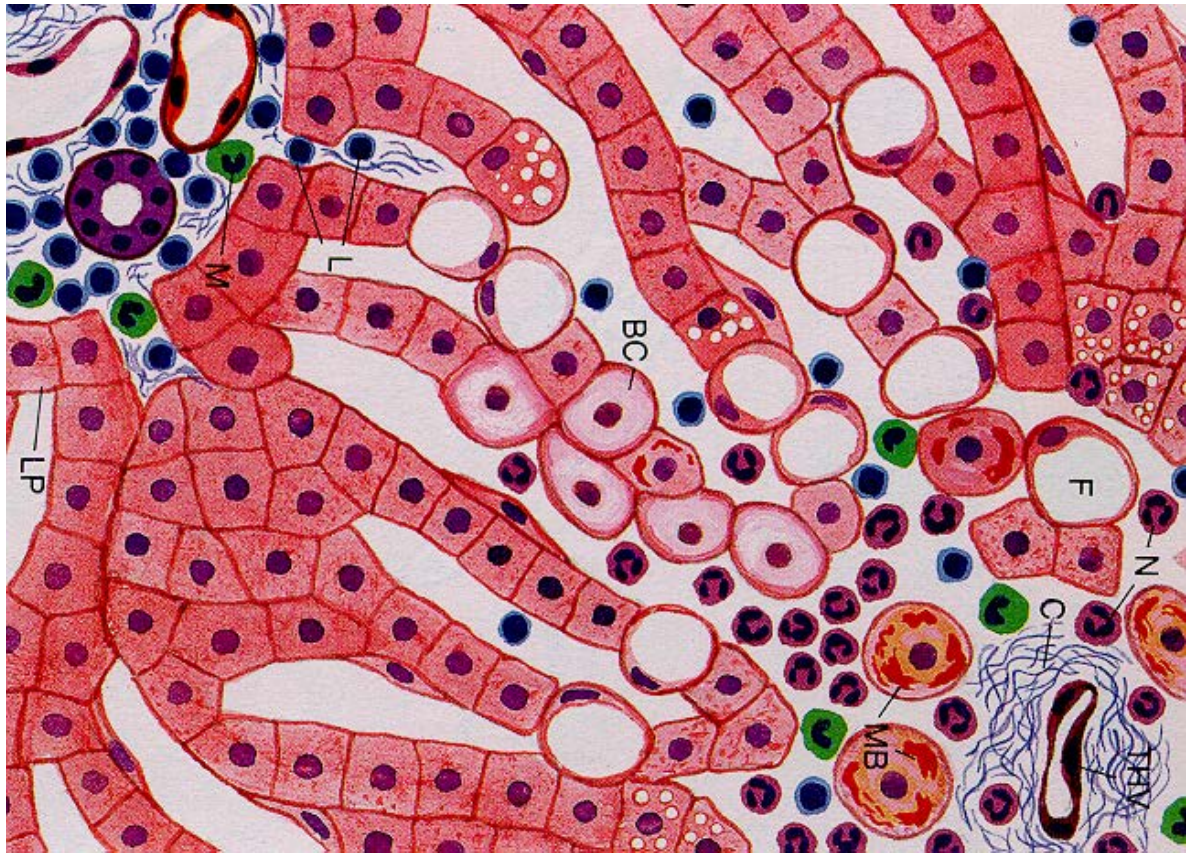


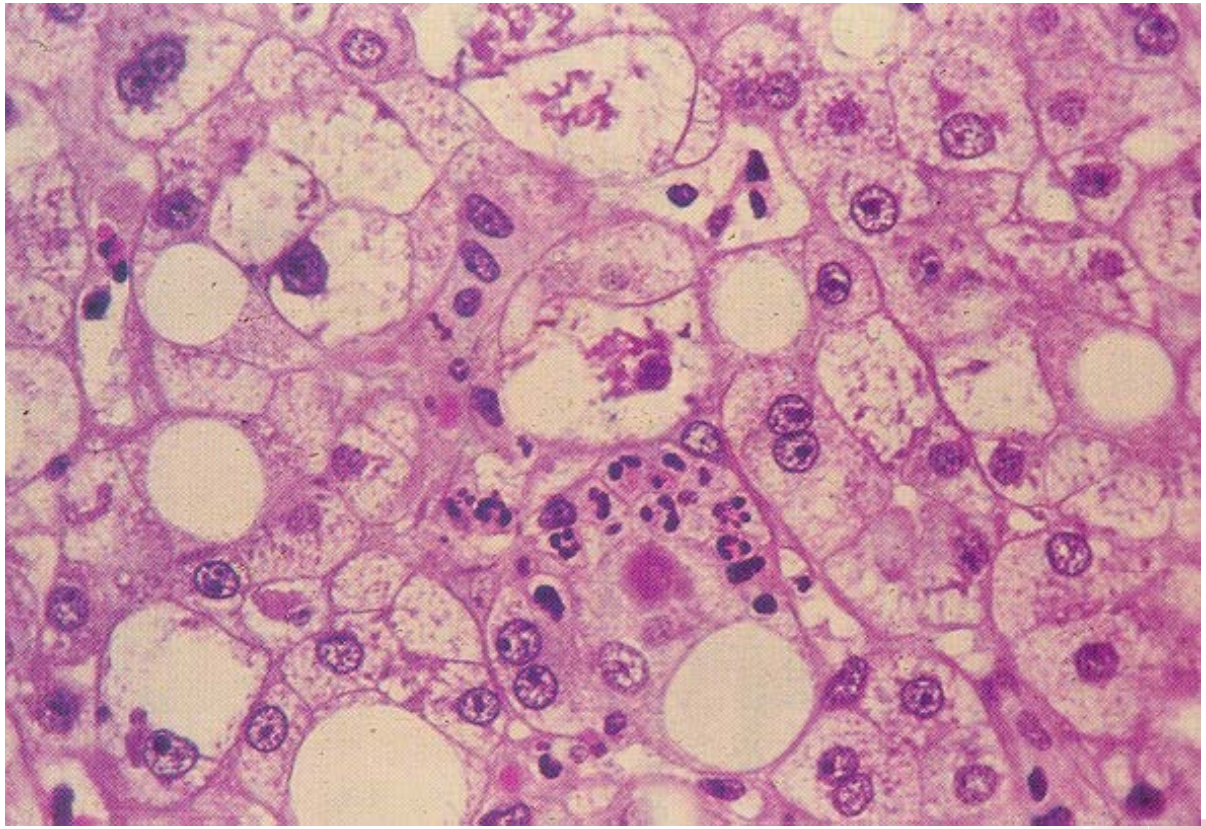


# Alcoholic Hepatitis

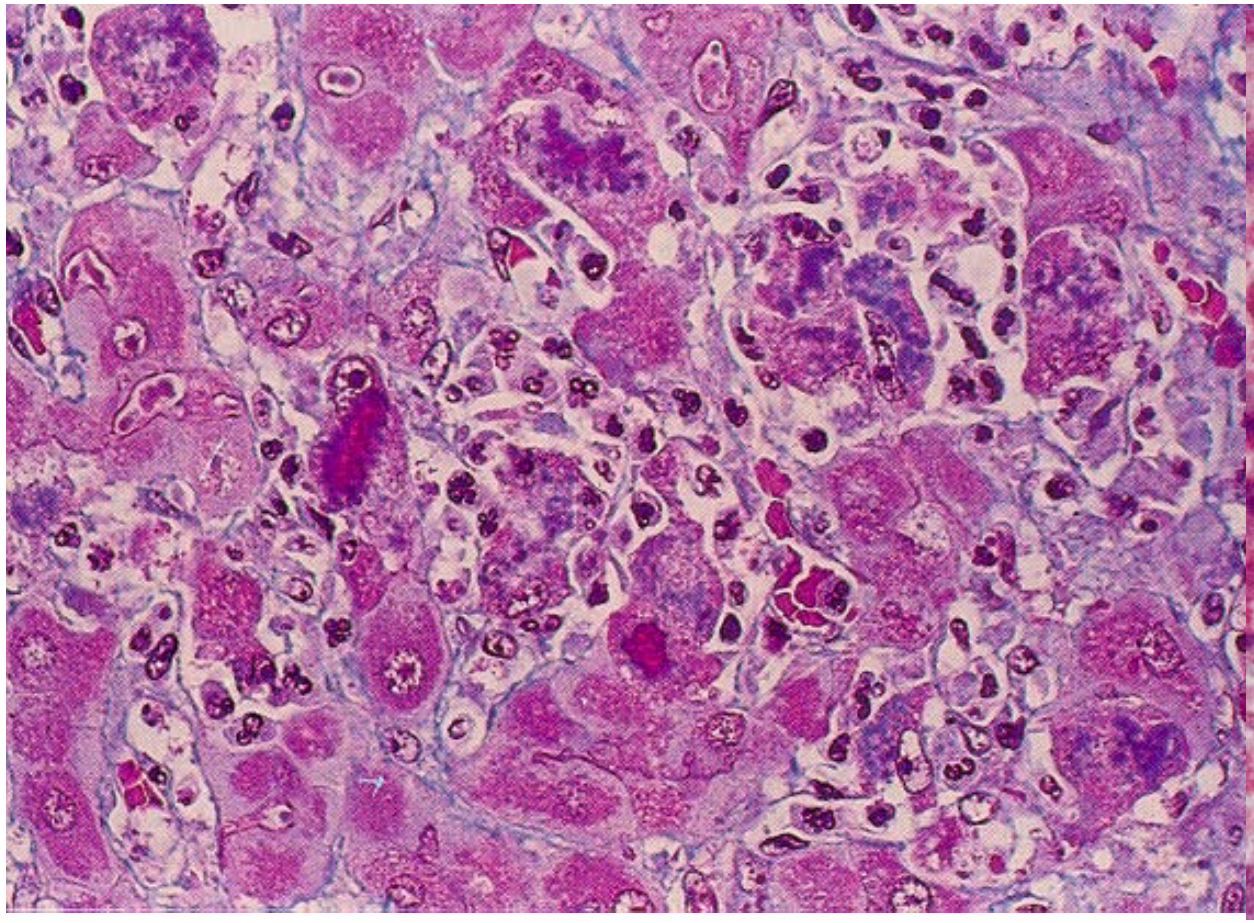
- Clinical Features:
  - Fever
  - Leukocytosis
  - Tender Hepatomegaly
- Pathology:
  - Fatty change
  - Neutrophilic inflammation
  - Hepatocyte degeneration
  - Mallory's Hyaline
- Laboratory
  - AST>ALT (levels less than 500 mg/dl)

# Alcoholic Hepatitis:  Pathology

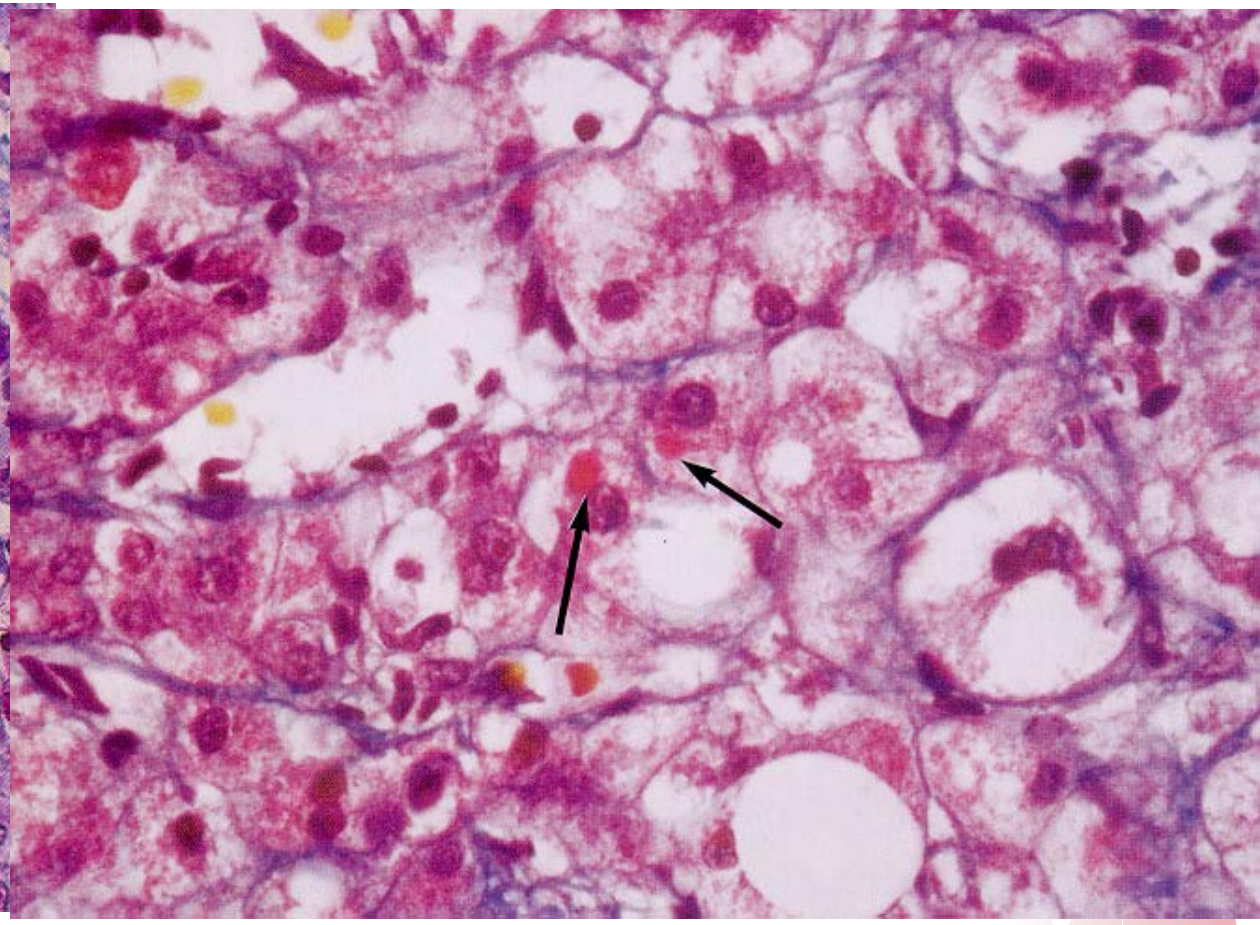


# Alcoholic Hepatitis:  Pathology



**Mallory's Hyaline**



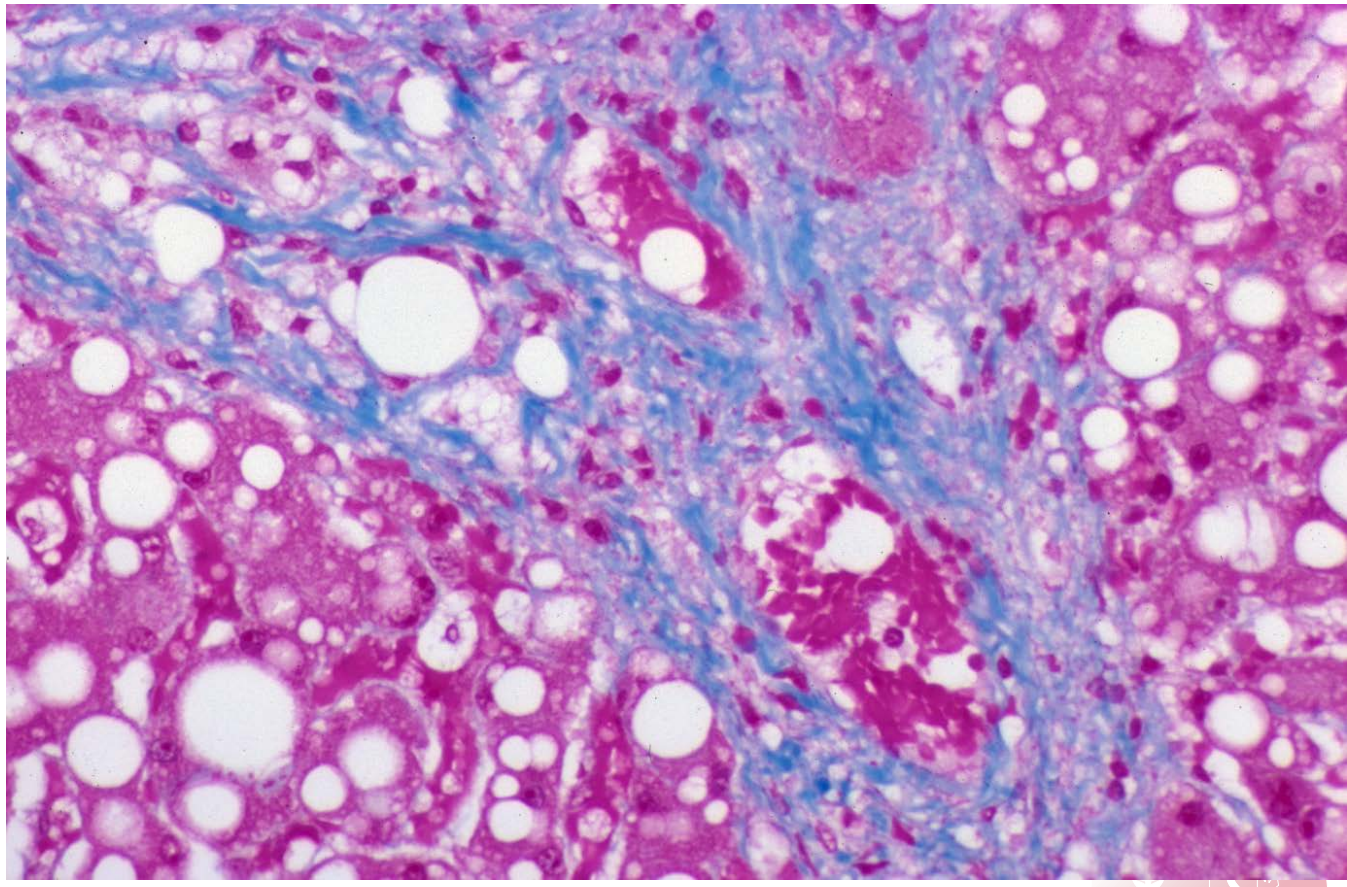
**Giant Mitochondria**

# Alcoholic Hepatitis:  Outcome

- Occurs in 20-40 % of chronic alcoholics
- Outcome determined by subsequent ingestion of alcohol:
  - 10 % abstained:  normal liver
  - 52 % imbibed: persistant hepatitis
  - 38 % imbibed: cirrhosis

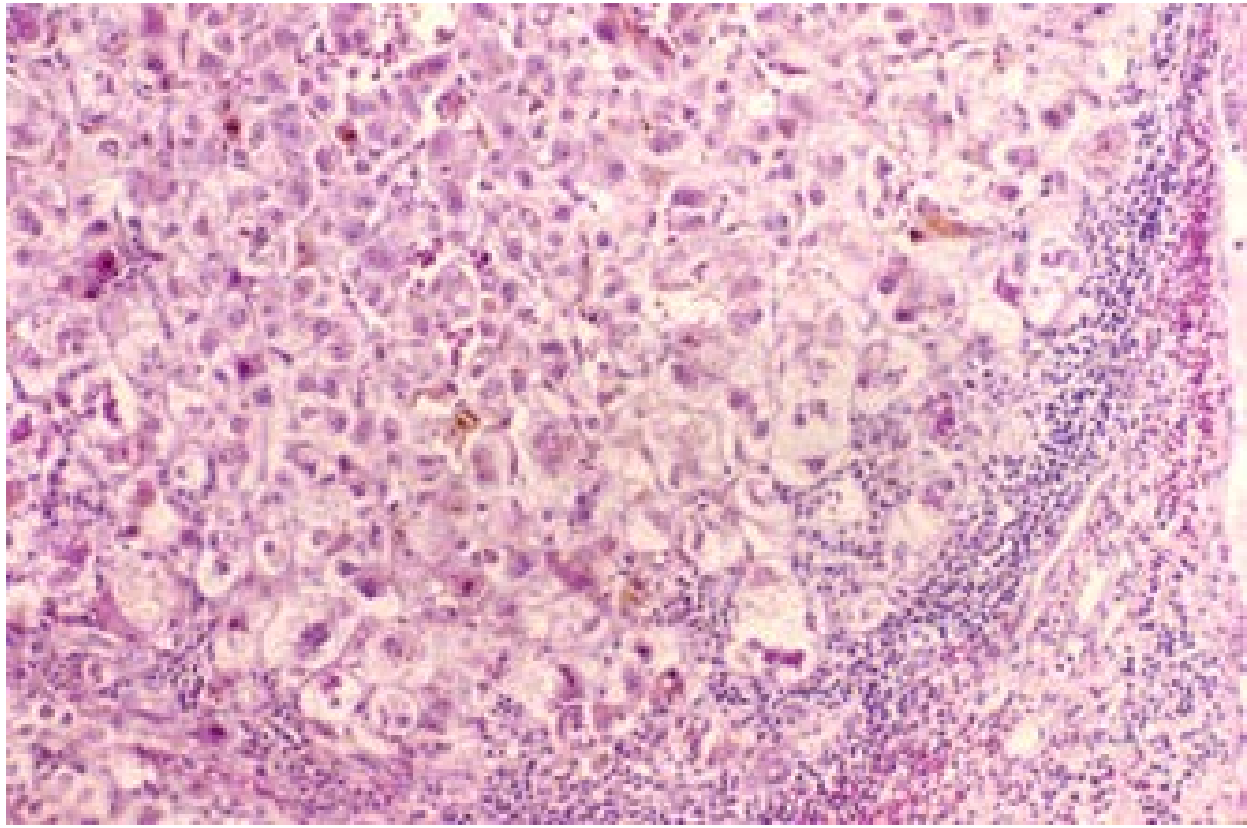
# Perivenular sclerosis in ALD

- Predictive of prolonged, heavy alcohol consumption
- Predictive of progressive ALD
- ? Precursor to cirrhosis in absence of alcoholic hepatitis
- Rarely lesions become occlusive



# Chronic Hepatitis in Alcoholic Liver Disease

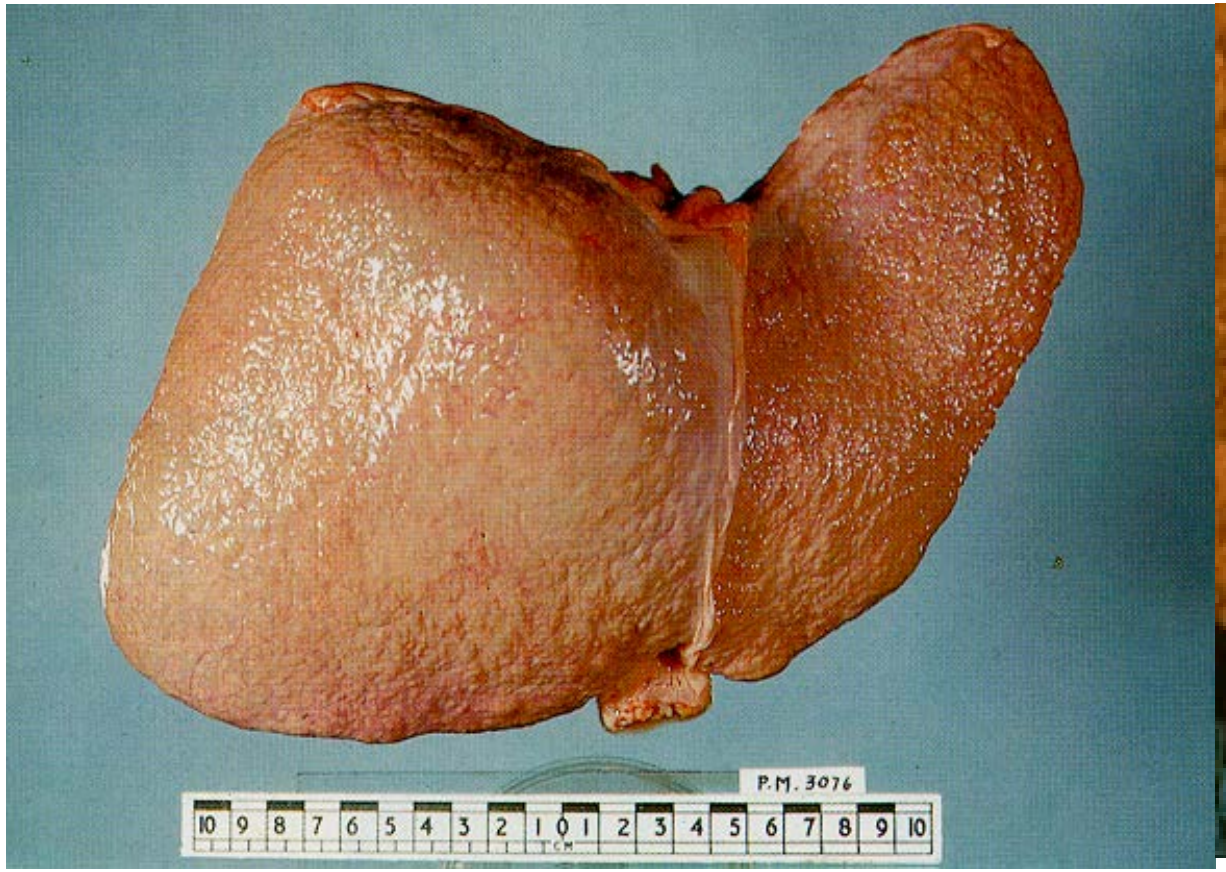
- CH is observed in chronic alcoholic patients with and without prior viral hepatitis
- Hypothesized role of immune-mediated damage
- Alcohol and HBV appear to work synergistically increasing the risk of both cirrhosis and hepatocellular carcinoma



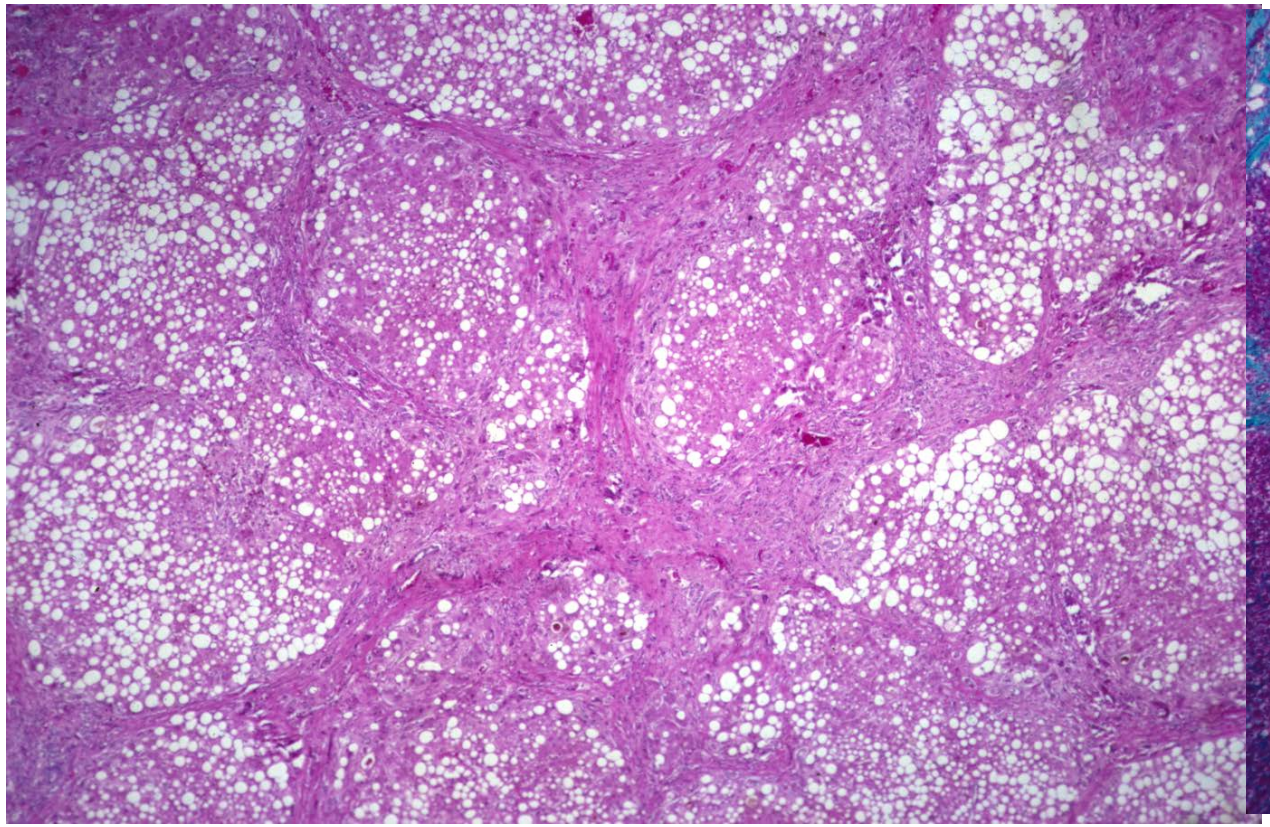
# Alcoholic Cirrhosis

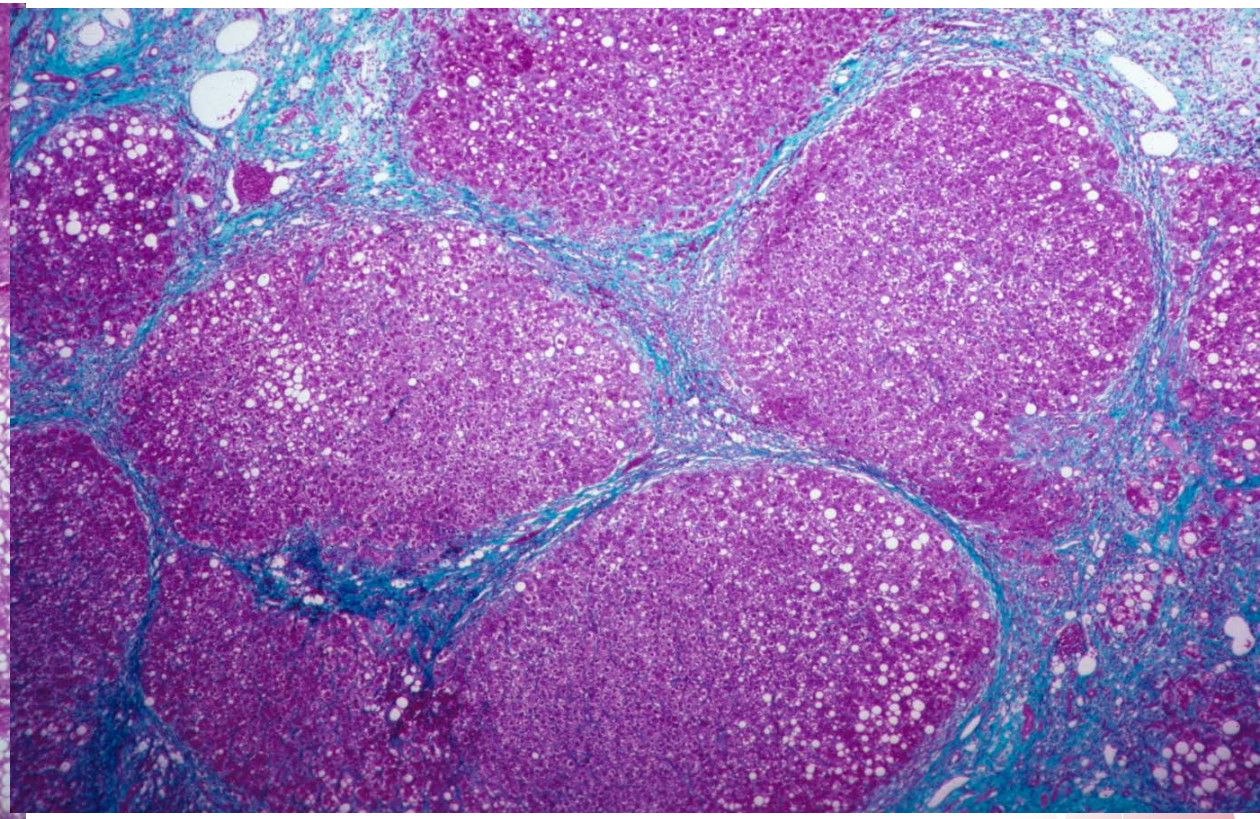
- 10-15 % of chronic alcoholic patients
- Generally Micronodular in type
- Hepatocellular Carcinoma develops in 10-15 %

# Alcoholic Cirrhosis



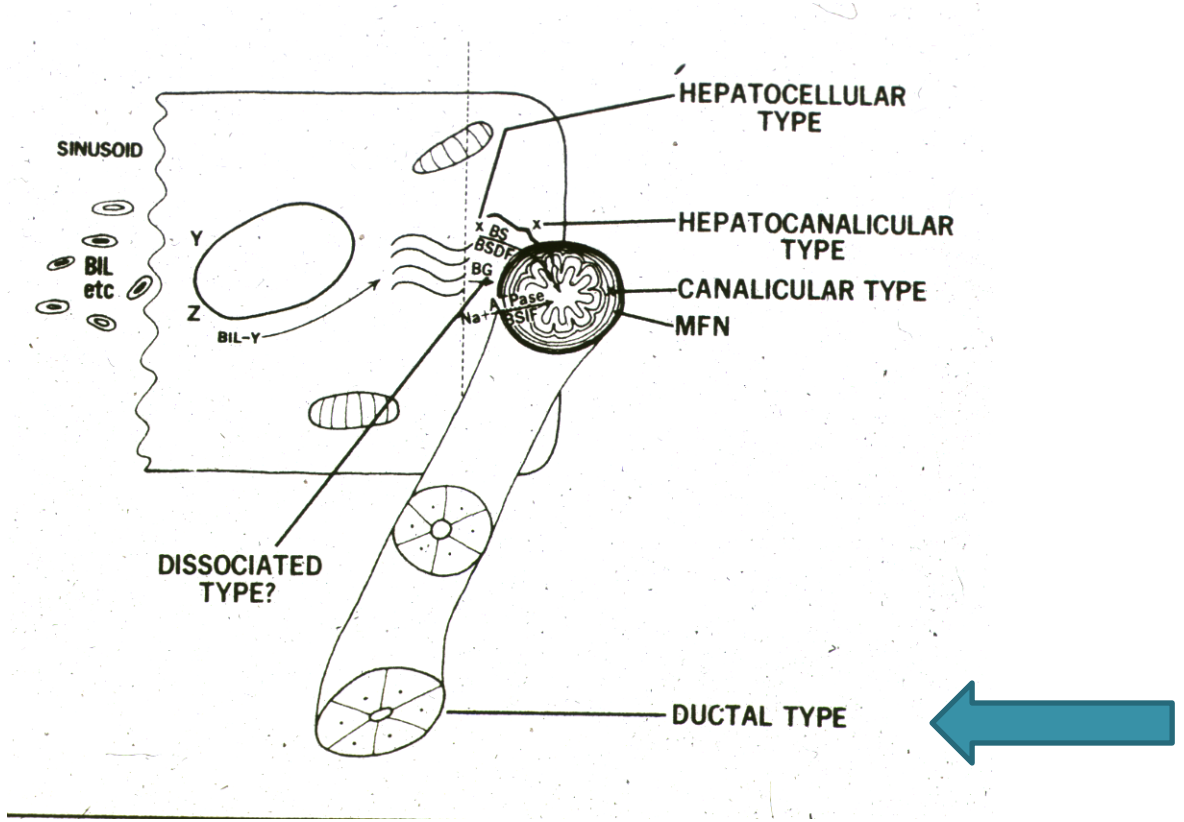

# Alcoholic Cirrhosis





**Trichrome Stain**

# Intrahepatic cholestasis



# Primary Biliary Cirrhosis

Females: 90 % Age: 30-60

75 % asymptomatic at presentation

Symptoms: Fatigue, Pruritus, Jaundice

Outcome: Cirrhosis

Lab: Increased Alkaline Phosphatase,

Cholesterol (esp. HDL-cholesterol)

Positive Anti-Mitochondrial Antibody Test

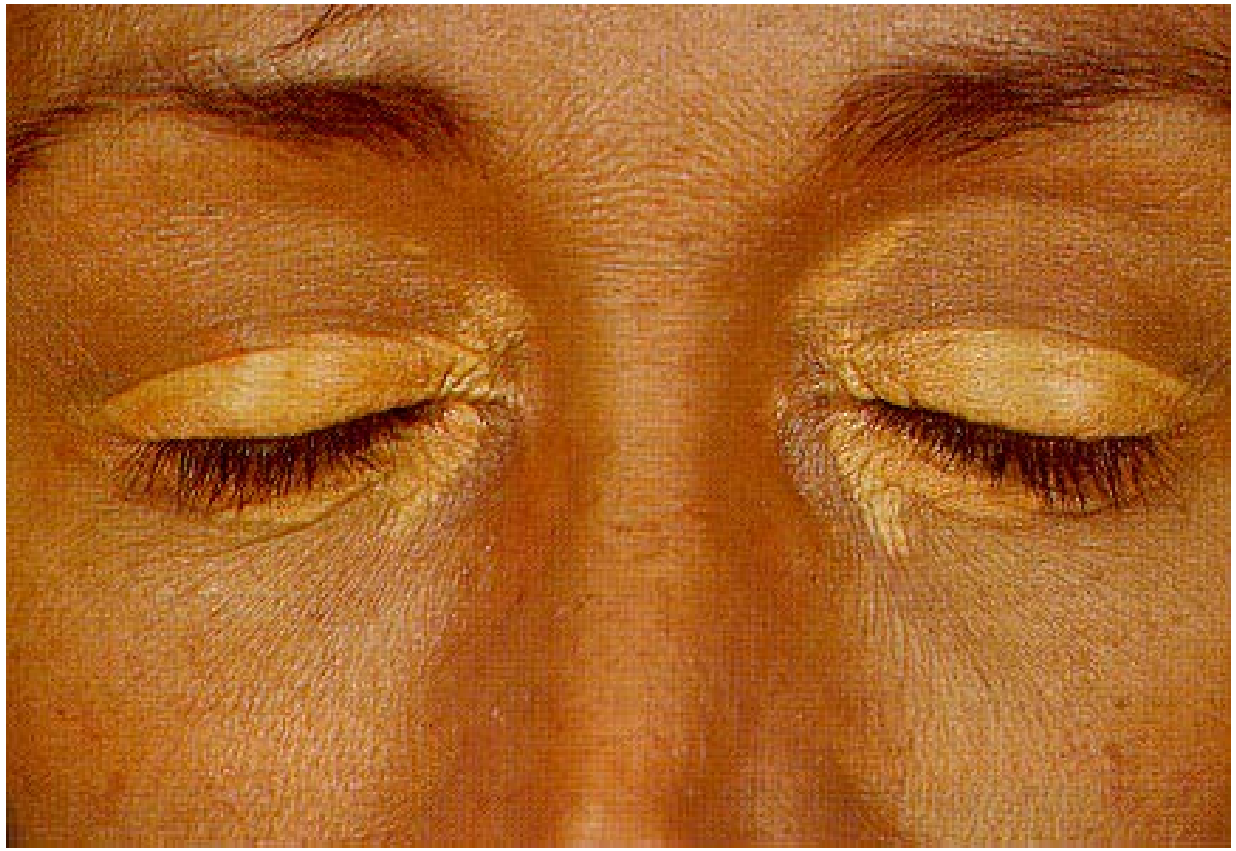
# Primary Biliary Cirrhosis

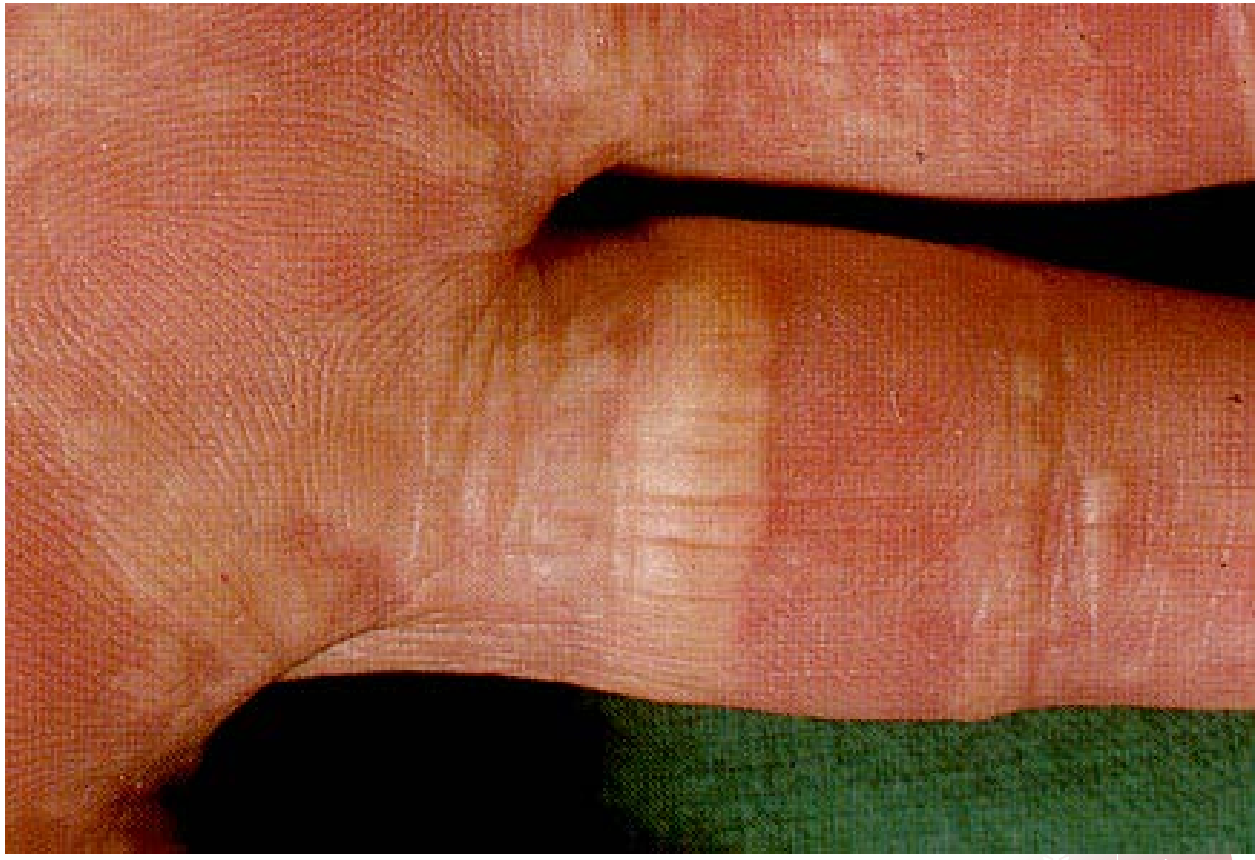
- Prevalence:  20-150/million population
- 1000x increase risk if +family history
- Rare case where only 1 of 2 identical twins developed the disease
  - Suggests need for “triggering factor/event” in a genetically susceptible patient
- Weak association with HLA DR8
  - Other HLA allelles appear “protective” HLA DR11/13

# PBC:  Natural History

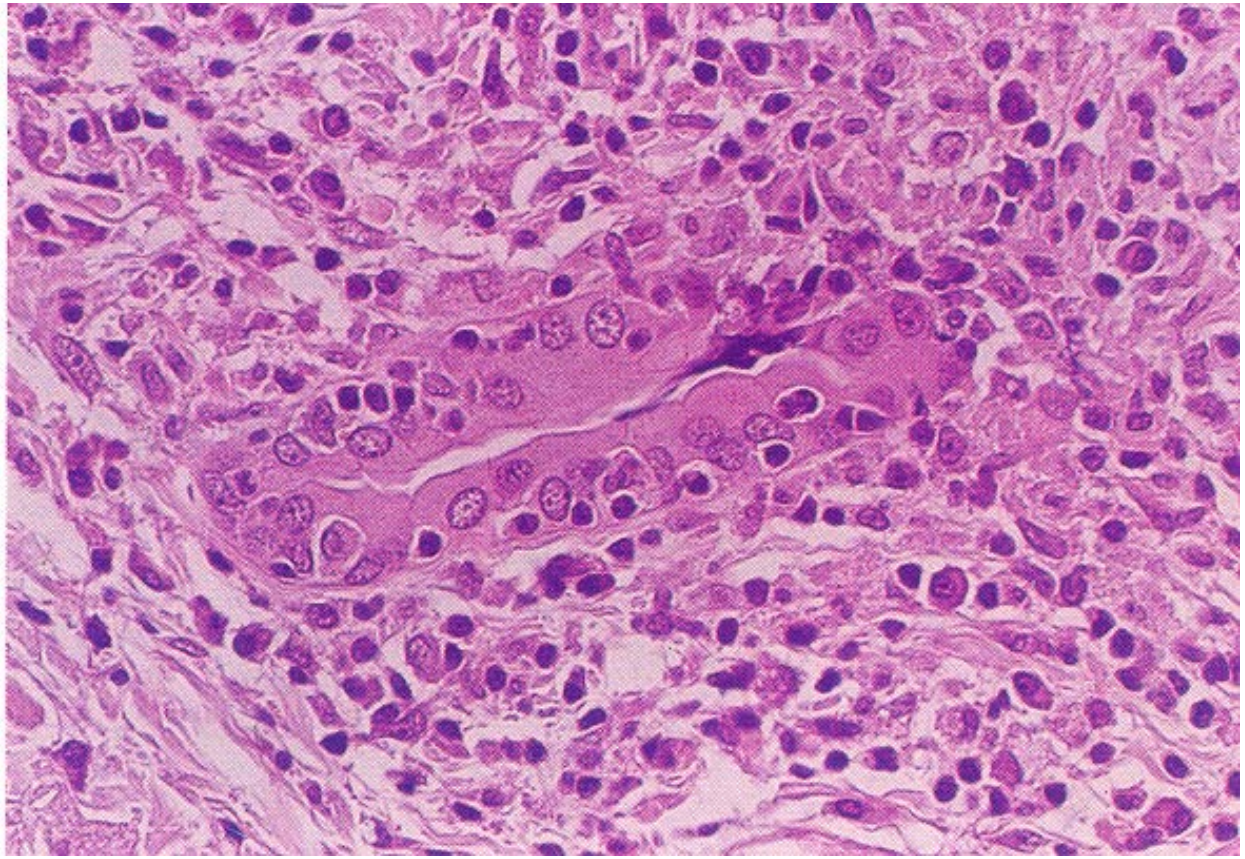
- Inexorably progressive
- Median survival for symptomatic: 10 years
- Asymptomatic patients develop symptoms usually within 2-4 years after diagnosis
  - Only 20 % symptom free at 10 years
- Treatment:  Cholestyramine for pruritus
- Treatment of underlying disease:
  - Ursodiol, Methotrexate, Liver transplant

# Xanthomas in Primary Biliary Cirrhosis

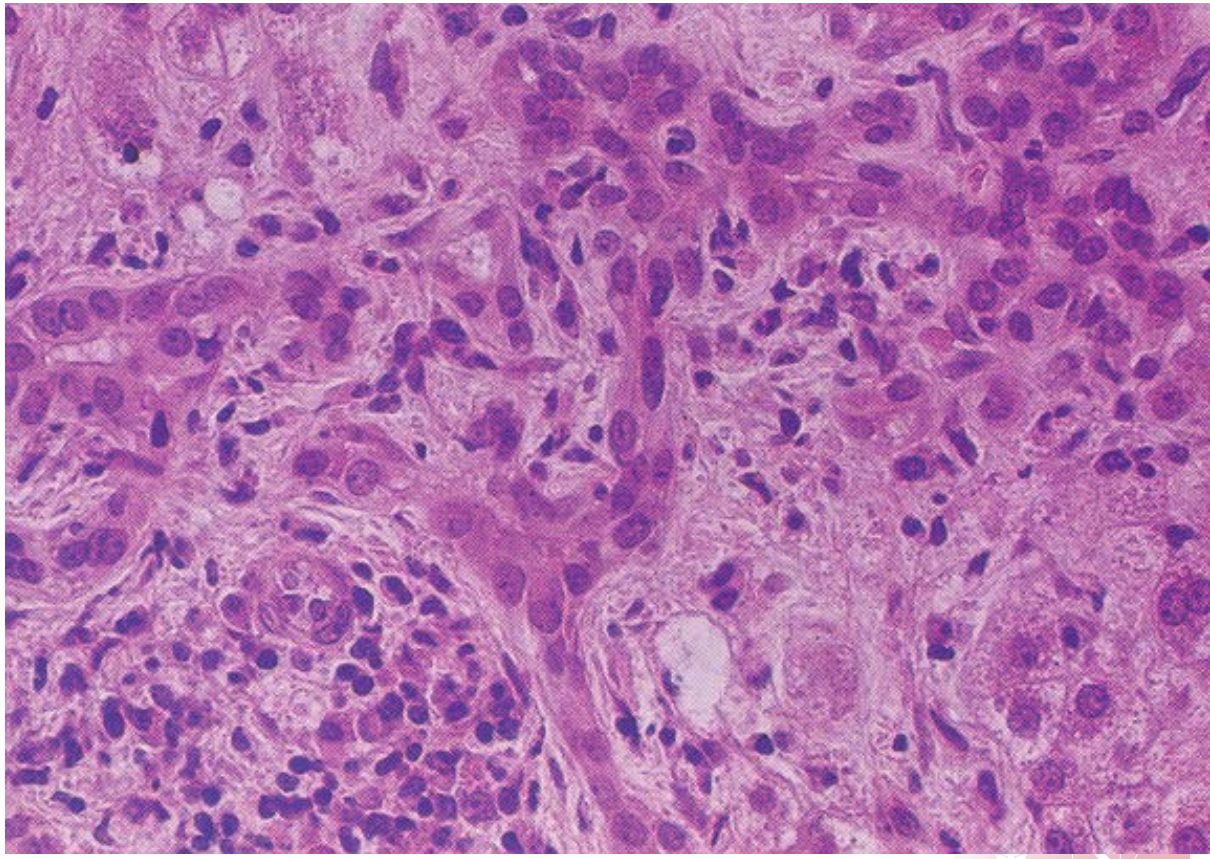




# Pathology of Primary Biliary Cirrhosis

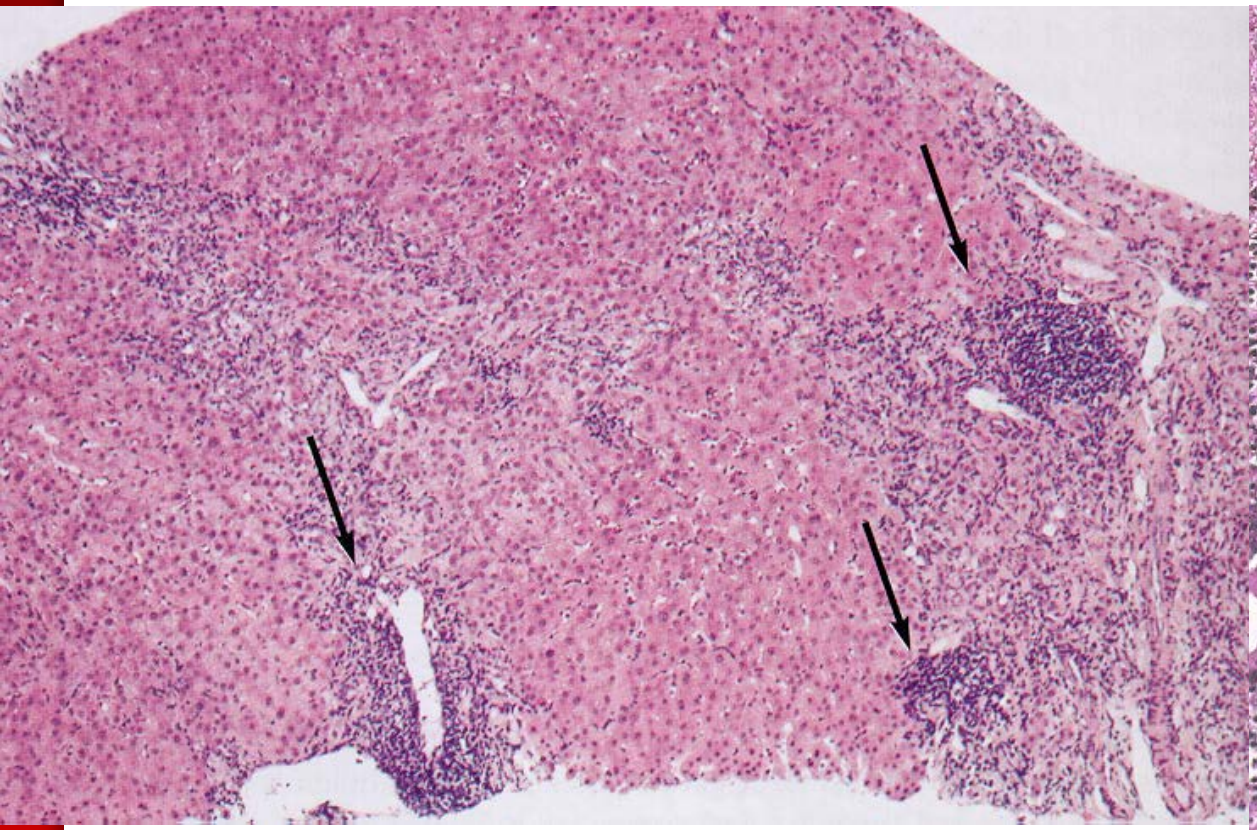


**Bile duct infiltration by lymphocytes**

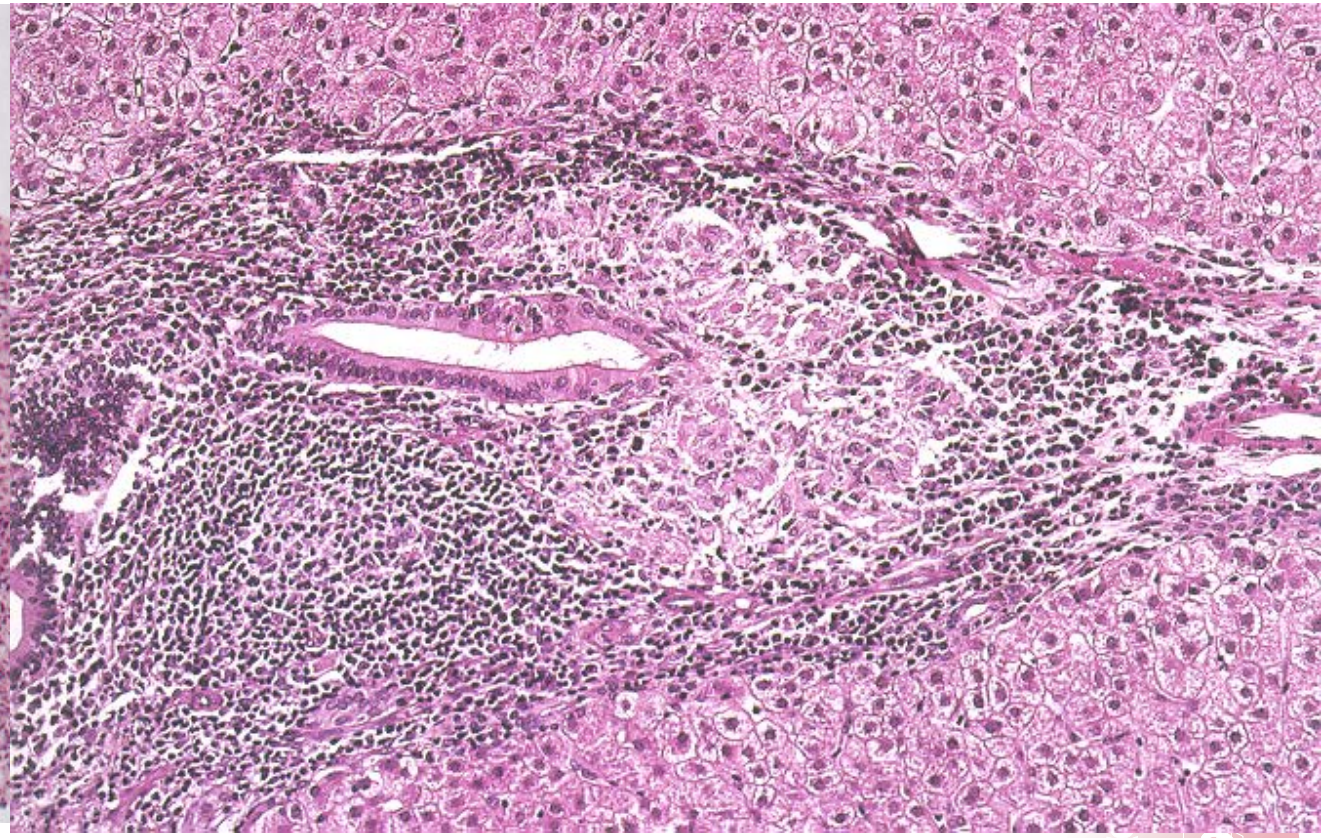


**Bile duct proliferative phase**

# Pathology of Primary Biliary Cirrhosis

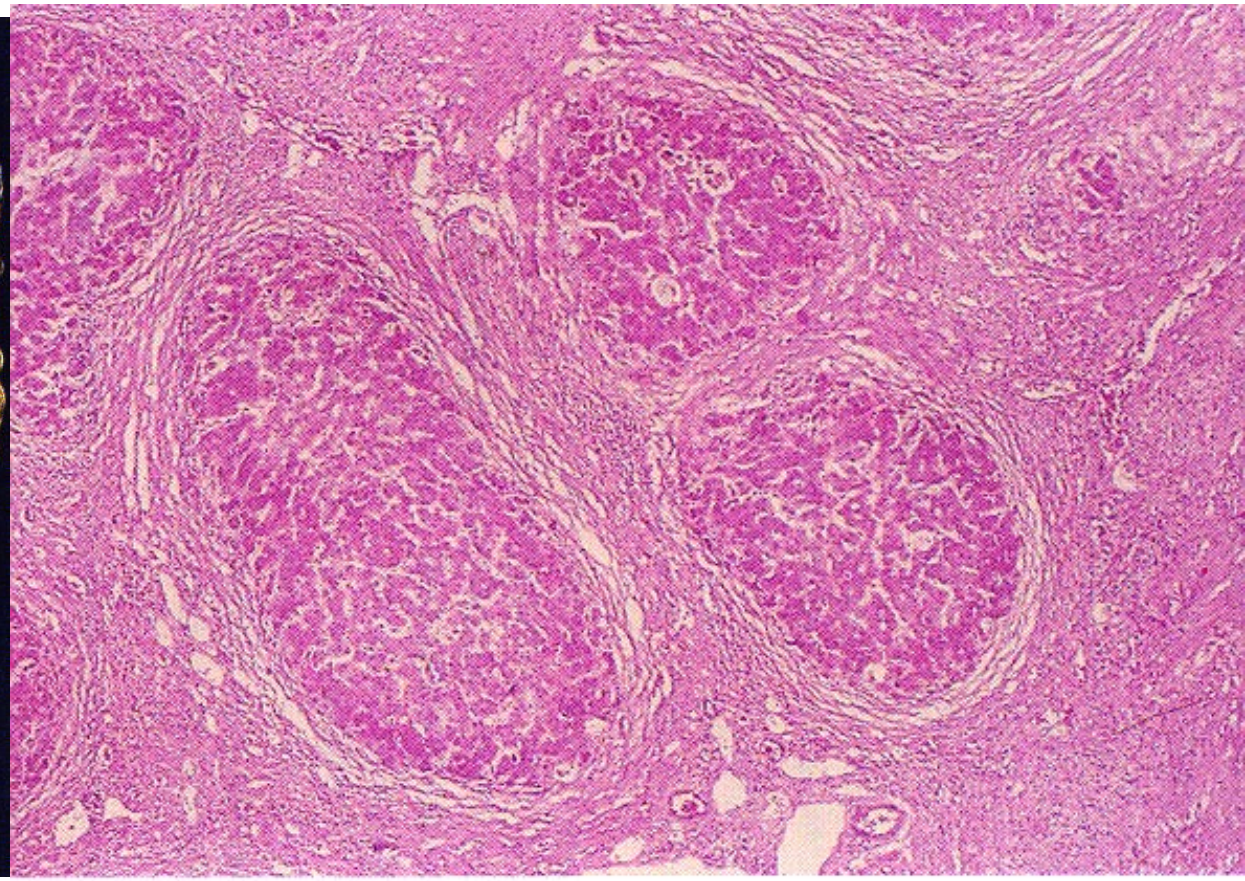


**CAH-like picture with absence/paucity of bile ducts**



**Granuloma centered on bile duct**

# End-stage Primary Biliary Cirrhosis



# Pathogenesis of PBC

- Unknown, although there are many theories
  - Increased/aberrant expression of antigens on Biliary epithelial cells
  - Aberrant trafficking of IgA auto-Antibodies
  - Stimulation of cytotoxic CD8 + T cells
  - Bacterial role:  “Molecular Mimicry”
  - Other…

# Primary Sclerosing Cholangitis

M:F 2:1 Associated with HLA type: DRw52a

50-75 % of cases associated with IBD Mostly U.C. (90%)

Less than 5 % of patients with UC develop PSC

Symptoms: RUQ pain, Jaundice, Pruritus

Outcome: May progress to cirrhosis

Lab: Increased alk phos, bili, transaminases,

AMA negative, ANCA positive

# Primary Sclerosing Cholangitis

Radiology: Beaded Strictures in Biliary Tree

20 % extrahepatic ducts

80 % both extrahepatic and intrahepatic ducts

Pathology: Variable features (none pathognomonic)

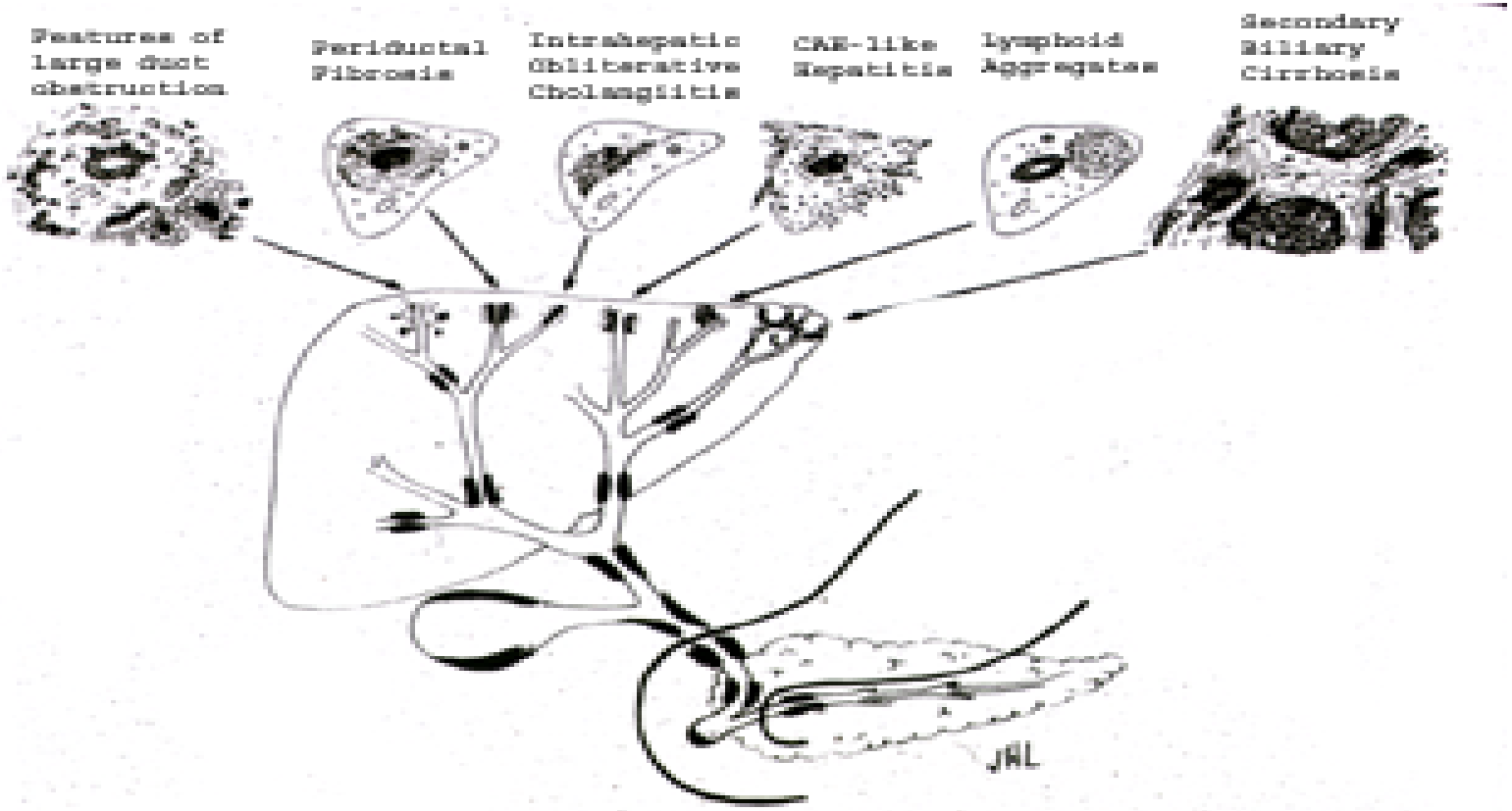
Diagnosis requires exclusion of:

Choledocholithiasis

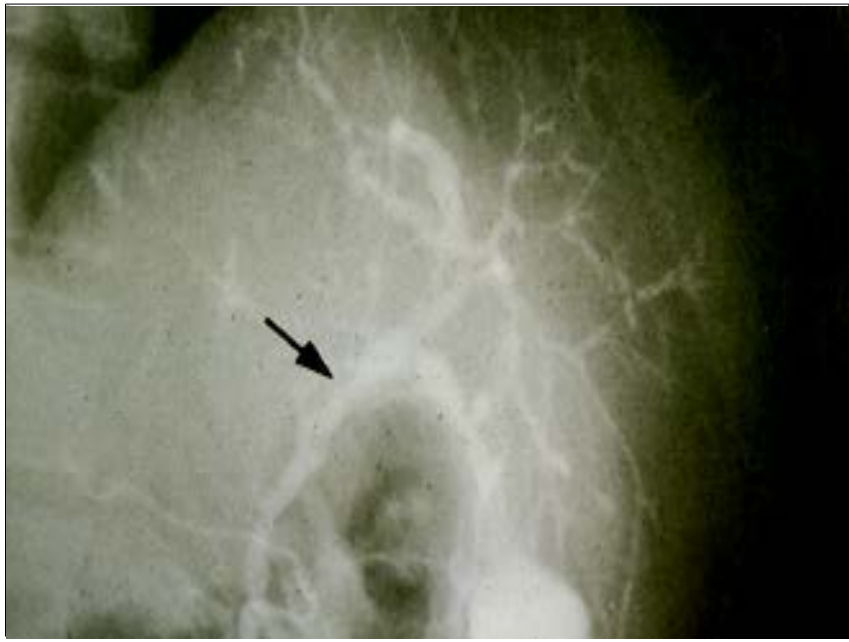
Prior Biliary Surgery

Bile Duct Carcinoma

# Diagnosis of Primary Sclerosing Cholangitis

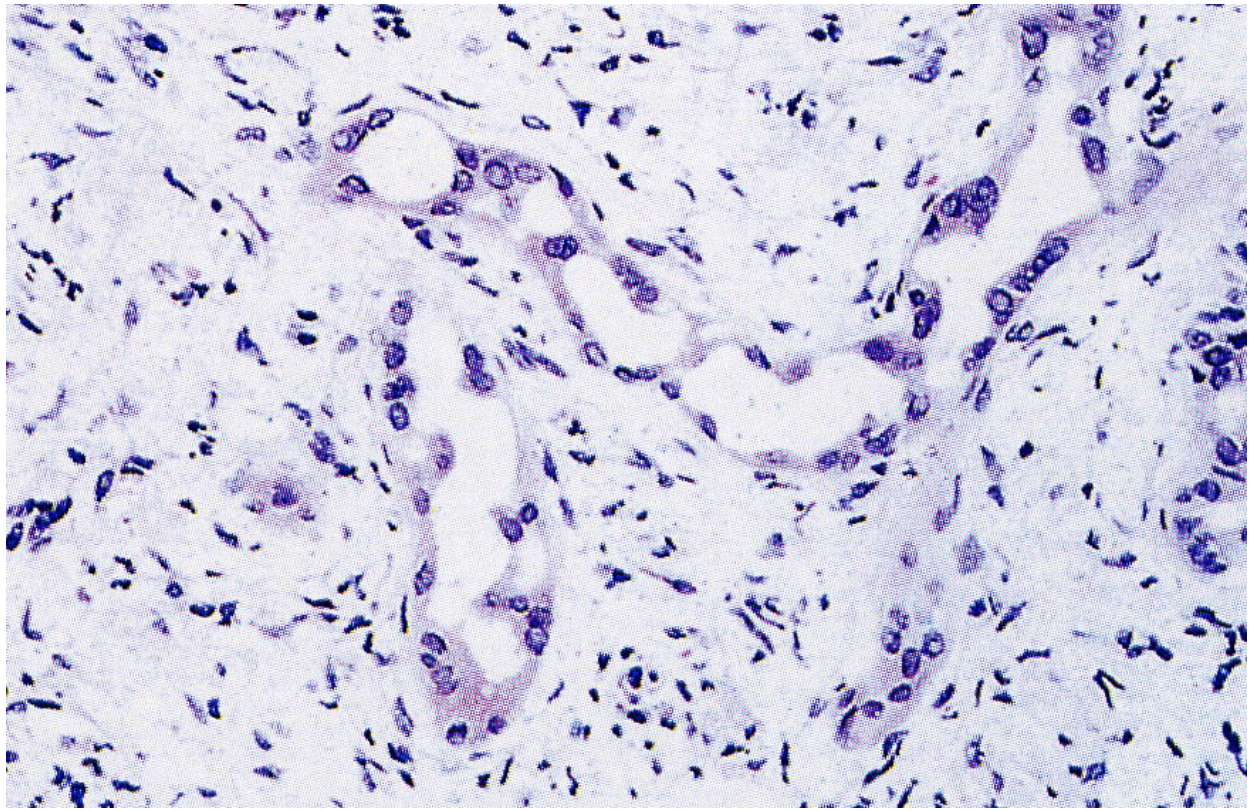



**Spectrum of Pathologic Findings in PSC**

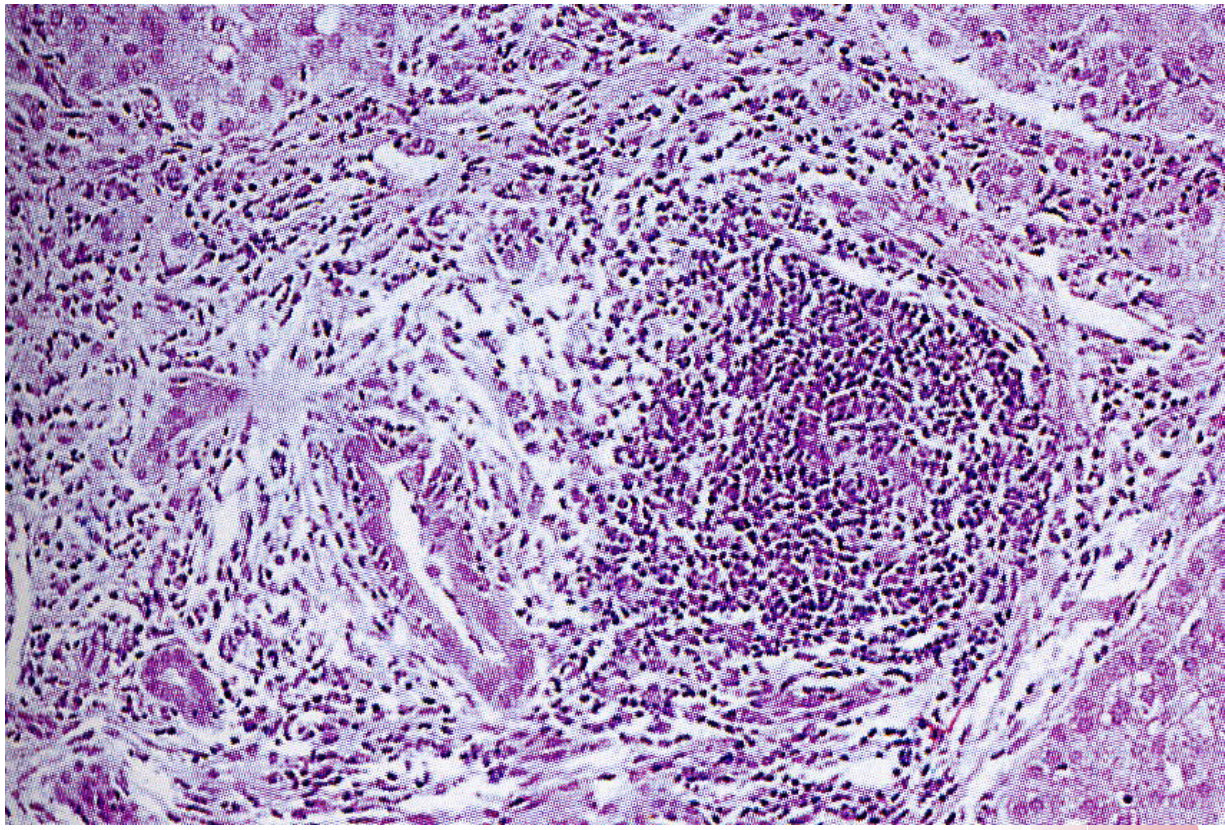


**ERCP**

# Pathology of Primary Sclerosing Cholangitis

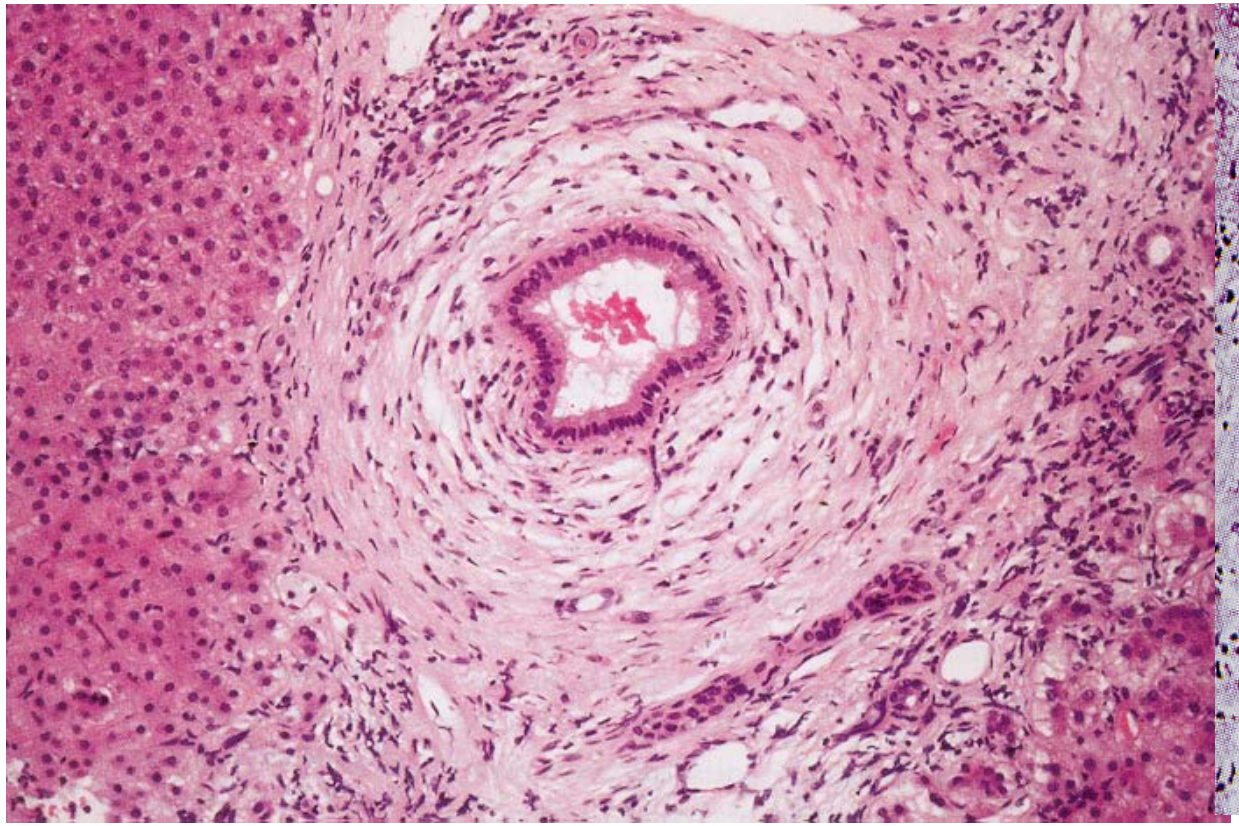


**Extra-hepatic obstructive-like changes**

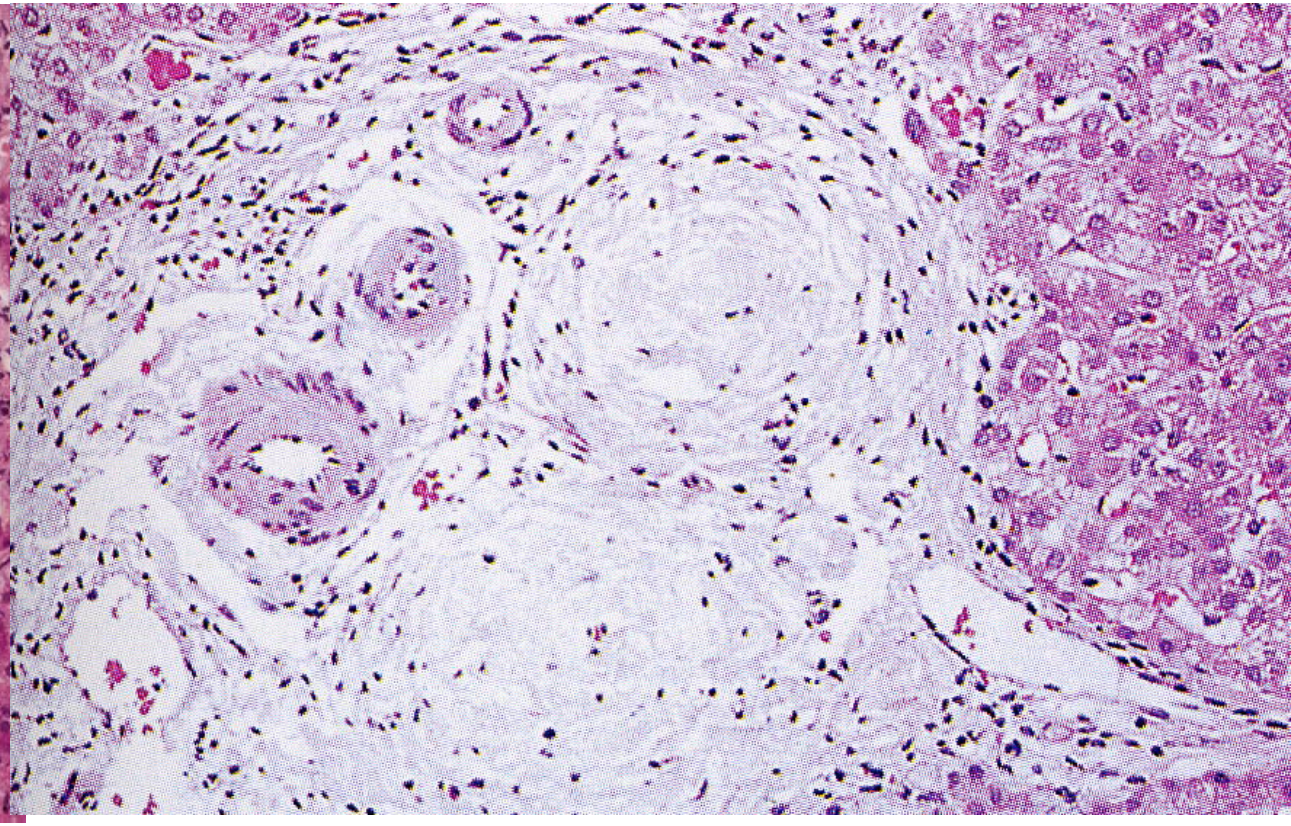


**Chronic Active Hepatitis-like changes**

# Pathology of Primary Sclerosing Cholangitis

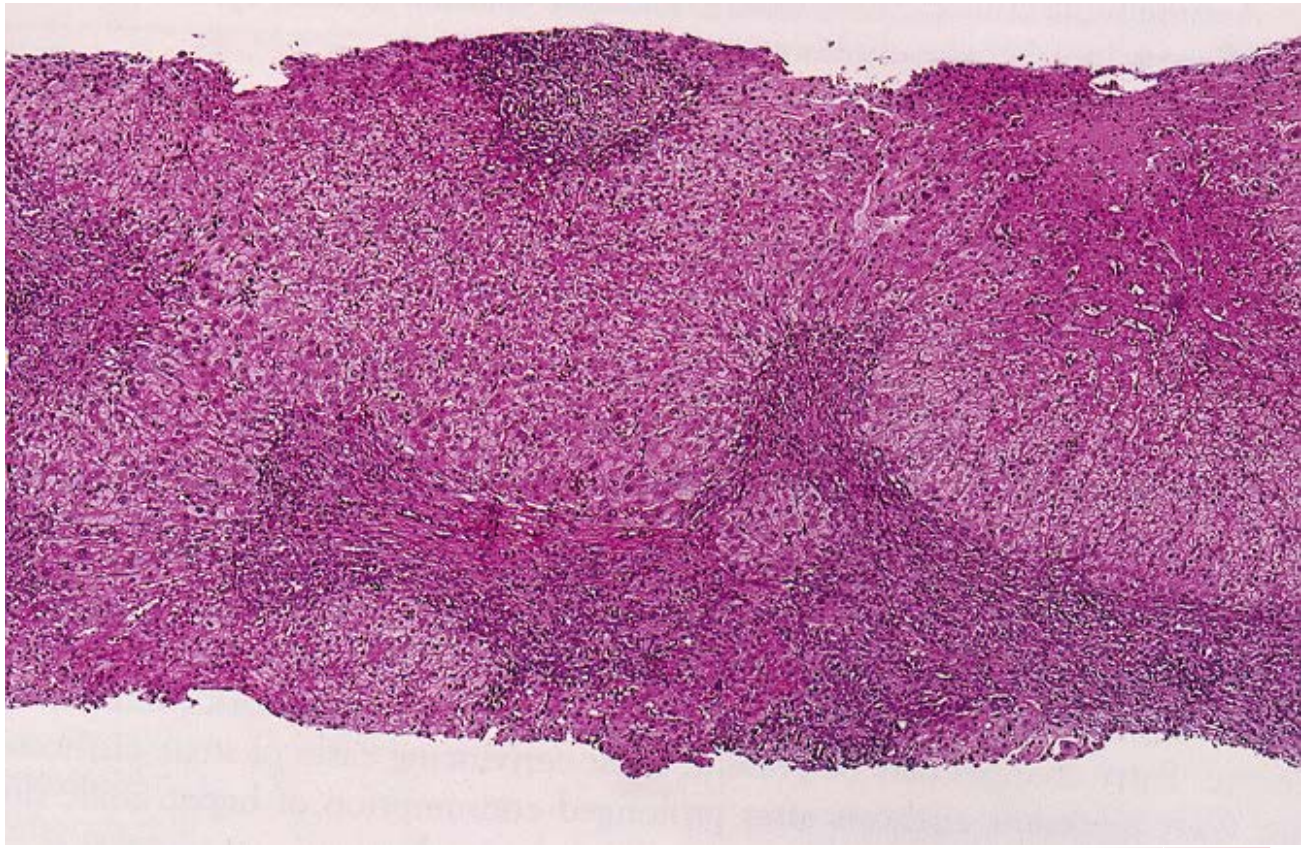


**Concentric periductal fibrosis**



**Sclerosed obsolescent bile ducts**

# Pathology of Primary Sclerosing Cholangitis



**CIRRHOSIS**

# PSC:  Natural History

- Mean age at diagnosis:  40 years old
- Median length of survival:  12 years
- PSC oftens occurs or worsens as IBD becomes quiescent
- Treatment:
  - Similar to PBC but less effective

# Primary Hemochromatosis

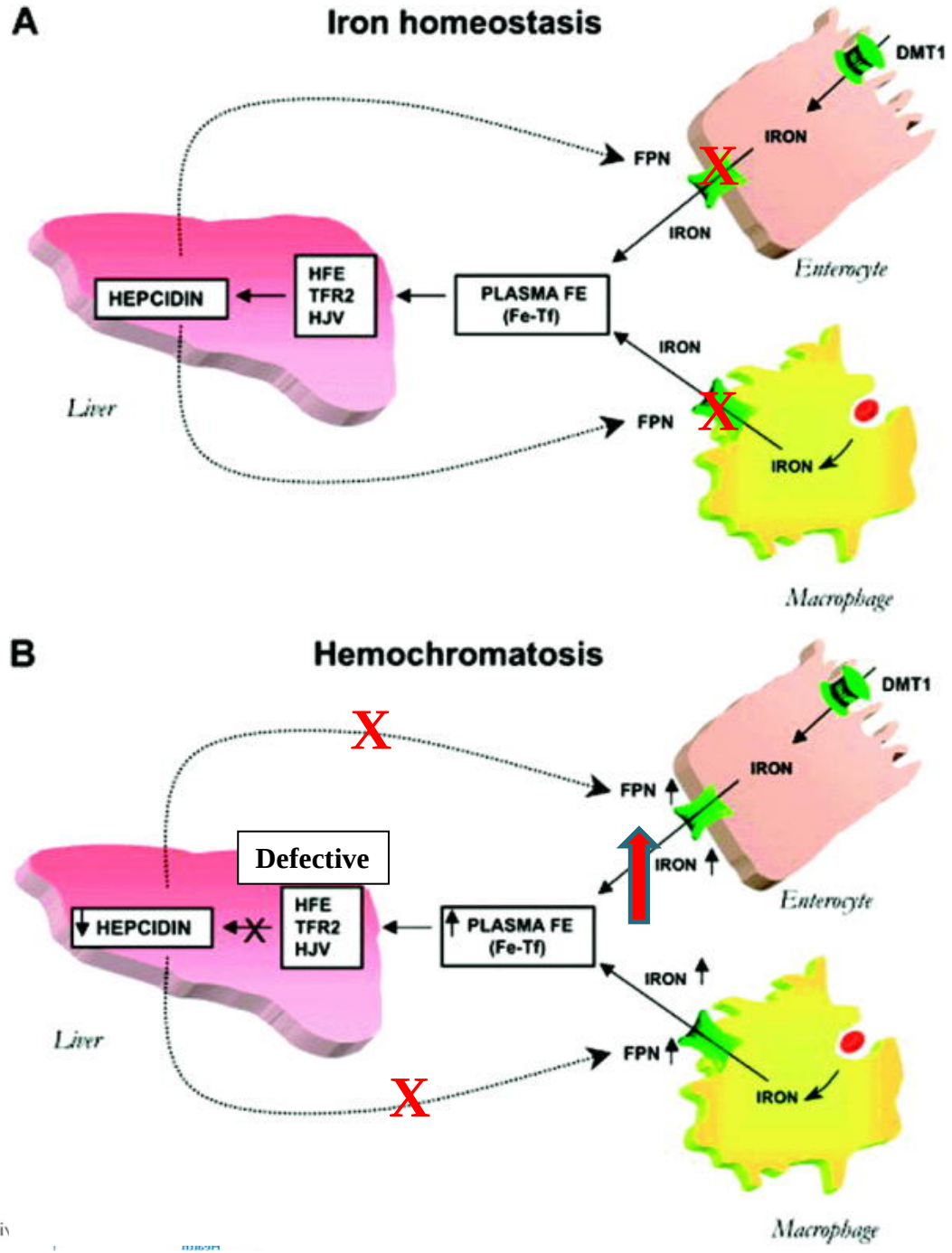
- Abnormality in iron metabolism
- Autosomal Recessive
- Chromosome 6 close to HLA (70 % have HLA subtype A3)
- Intestinal hyperabsorption of iron
- Homozygous prevalence:  1:200
- Clinical disease frequency:  1:5,000

# Primary Hemochromatosis

- Iron accumulates over many years
- Age range at presentation: 40-60
- Variable clinical expression
- Clinical disease is 10x more common in men
- Heterozygotes are clinically normal
- Increased se iron,transferrin saturation, ferritin
- Increased Hepatic iron index
- Clinical disease rare if ferritin < 1,000µg/L

# Hemochromatosis

- 1996 the gene for Hemochromatosis discovered:  HFE
- Membrane bound protein binds TfR and defective binding results in ↓hepcidin synthesis
- Responsible for negative feedback regulation of iron absorption
- Absence leads to hyperabsorption of iron by cells


A
Iron homeostasis
DMT1
IRON
FPN
X
IRON
Enterocyte
HEPCIDIN
HFE
TFR2
HJV
PLASMA FE
(Fe-Tf)
IRON
Liver
FPN
X
IRON
Macrophage
B
Hemochromatosis
X
DMT1
FPN
IRON
Defective
IRON
Enterocyte
HEPCIDIN
HFE
TFR2
HJV
PLASMA FE
(Fe-Tf)
IRON
Liver
FPN
X
IRON
Macrophage

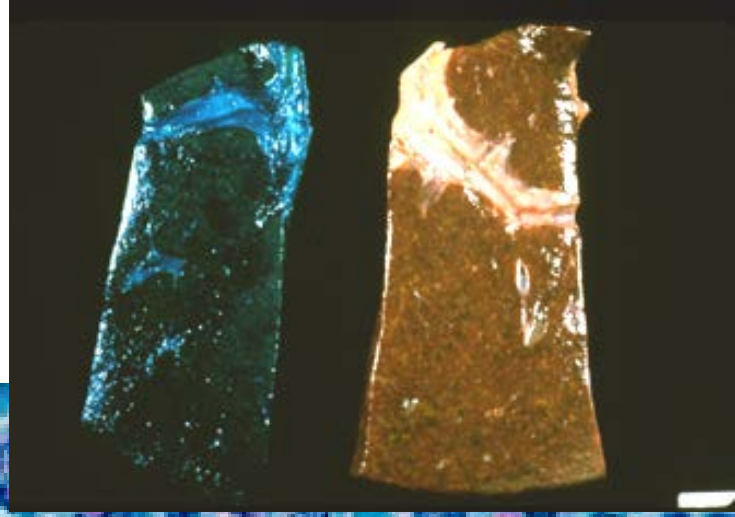
# Hemochromatosis: Genetics

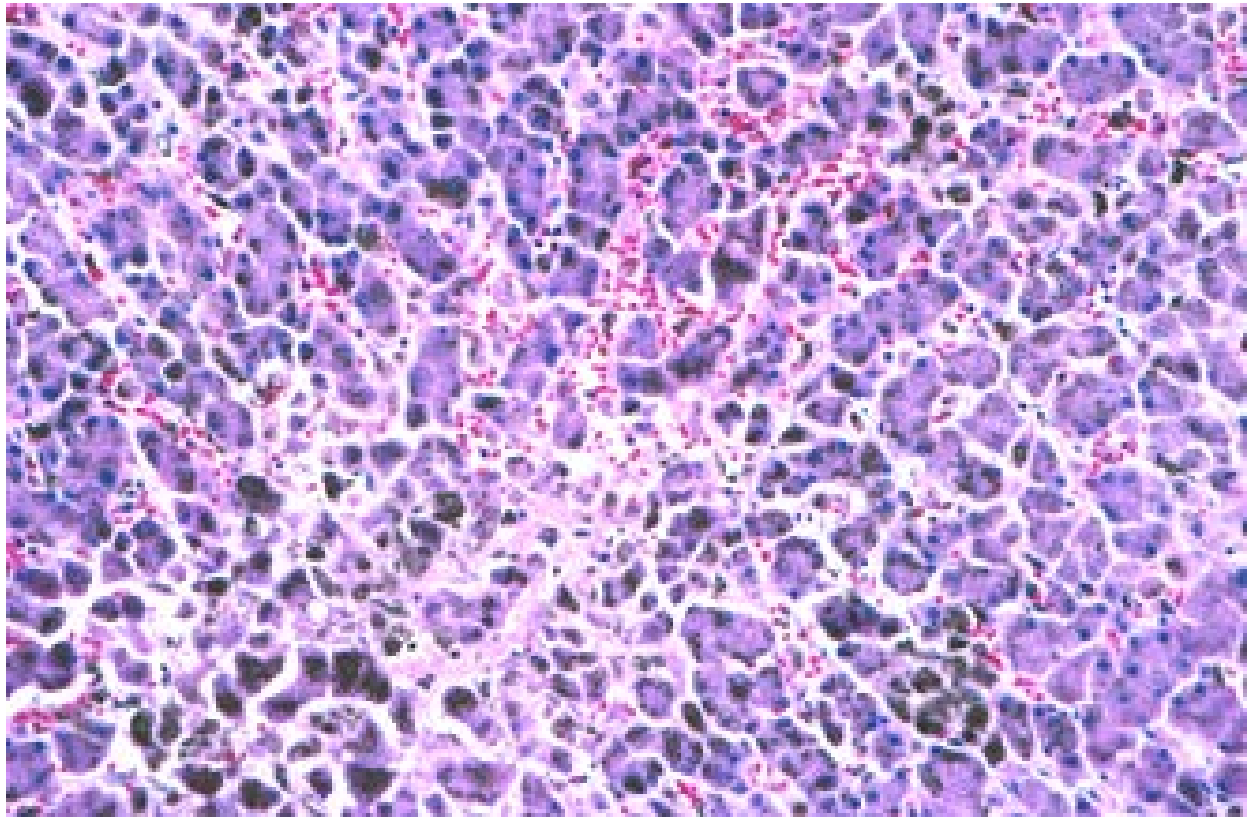
- About 80 % of patients have HFE mutation C282Y
- About 20 % of patients have HFE mutation H63D
- High frequency of these mutations makes genetic testing feasible
- Clinical disease occurs in ~2-25% of homozygotes
- No test available to predict which homozygotes will develop clinical disease

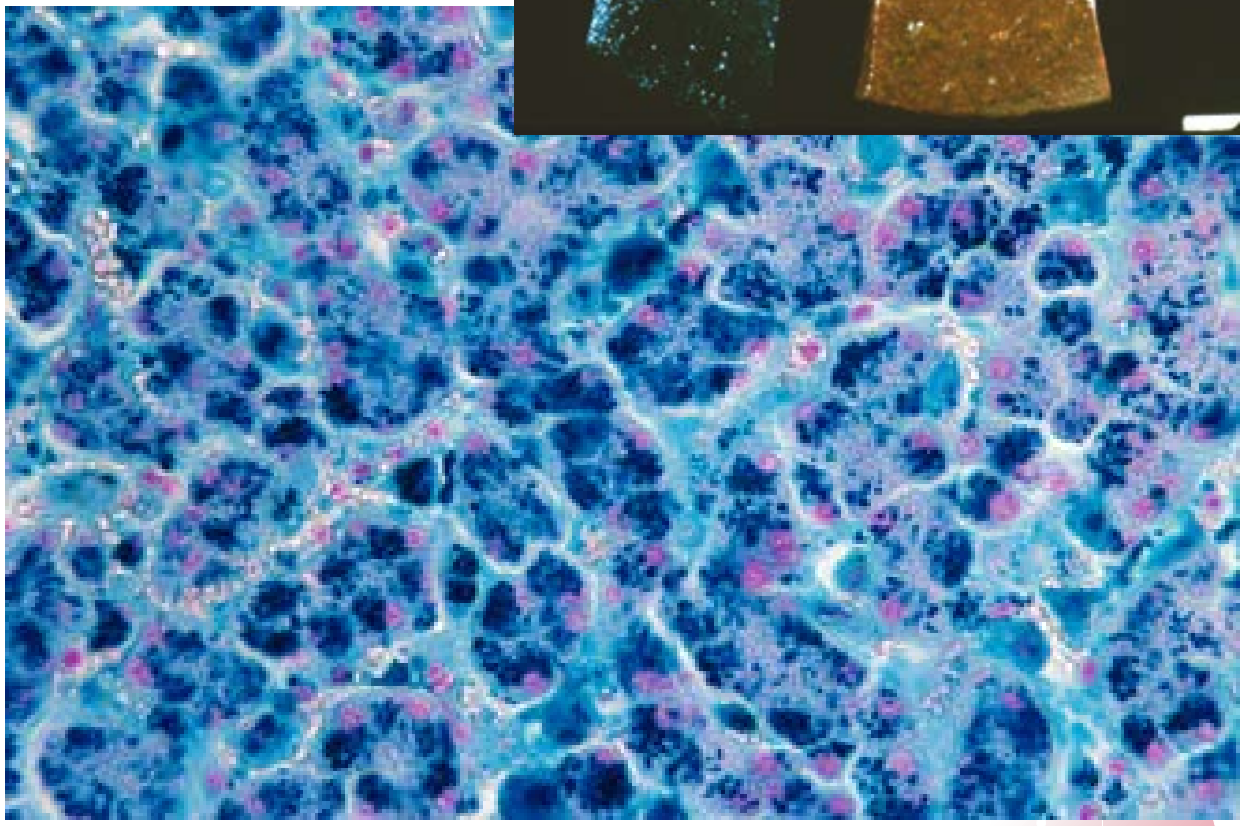
# Primary Hemochromatosis

- Cutaneous hyperpigmentation
- Diabetes Mellitus
- Hepatic abnormalities
  - Chronic hepatitis
  - Cirrhosis
  - Hepatocellular Carcinoma
- Cardiomyopathy
- Arthralgias/arthritis (pseudo-gout)

# Pathology of hemochromatosis

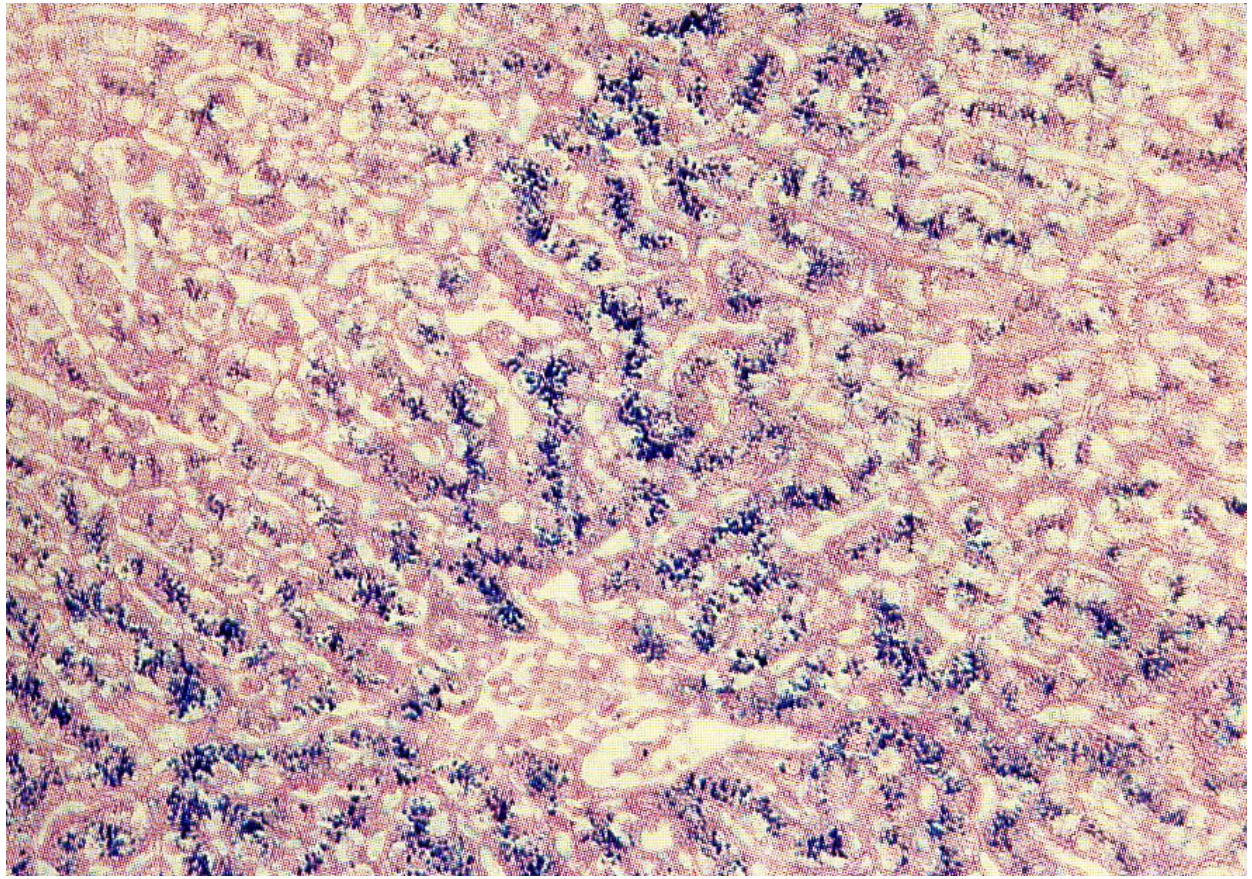




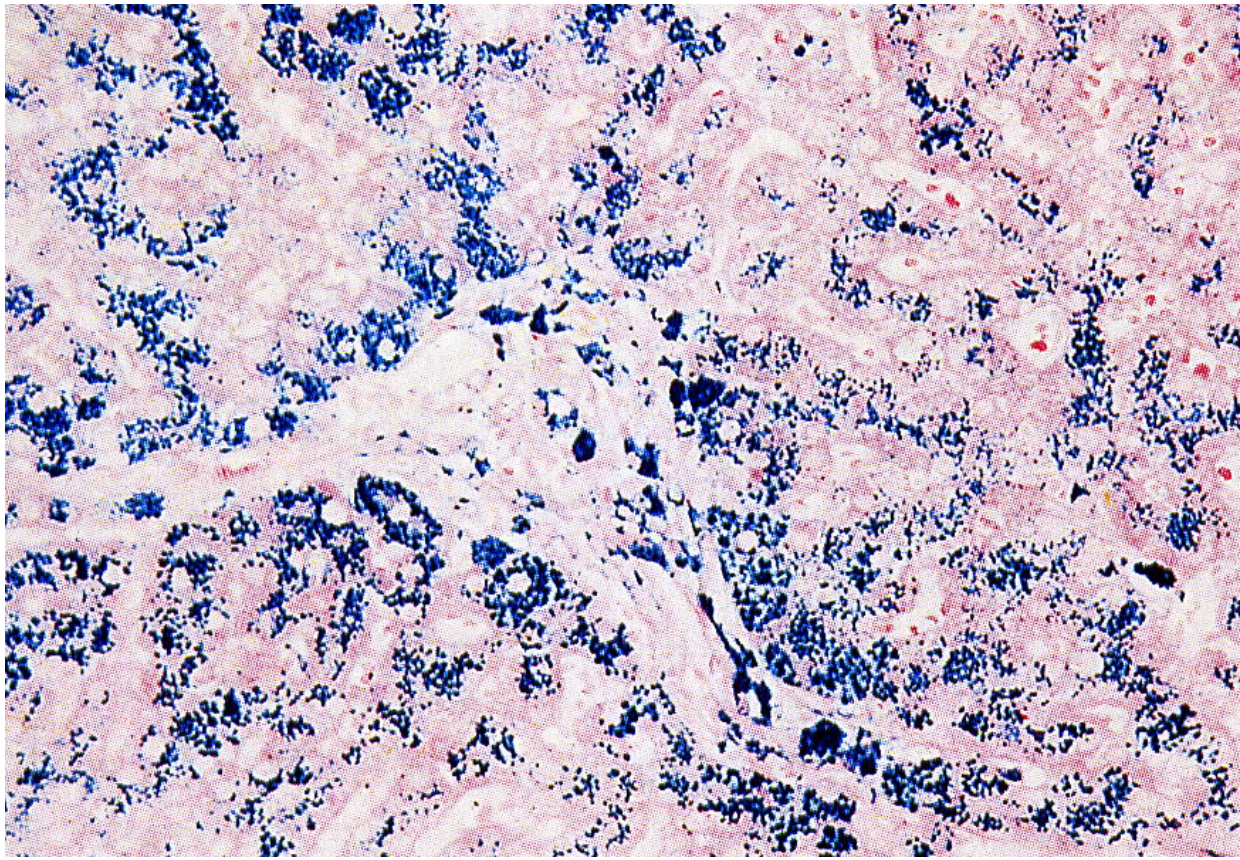


**Prussian Blue stain for iron**

# Progressive accumulation of iron in hemochromatosis

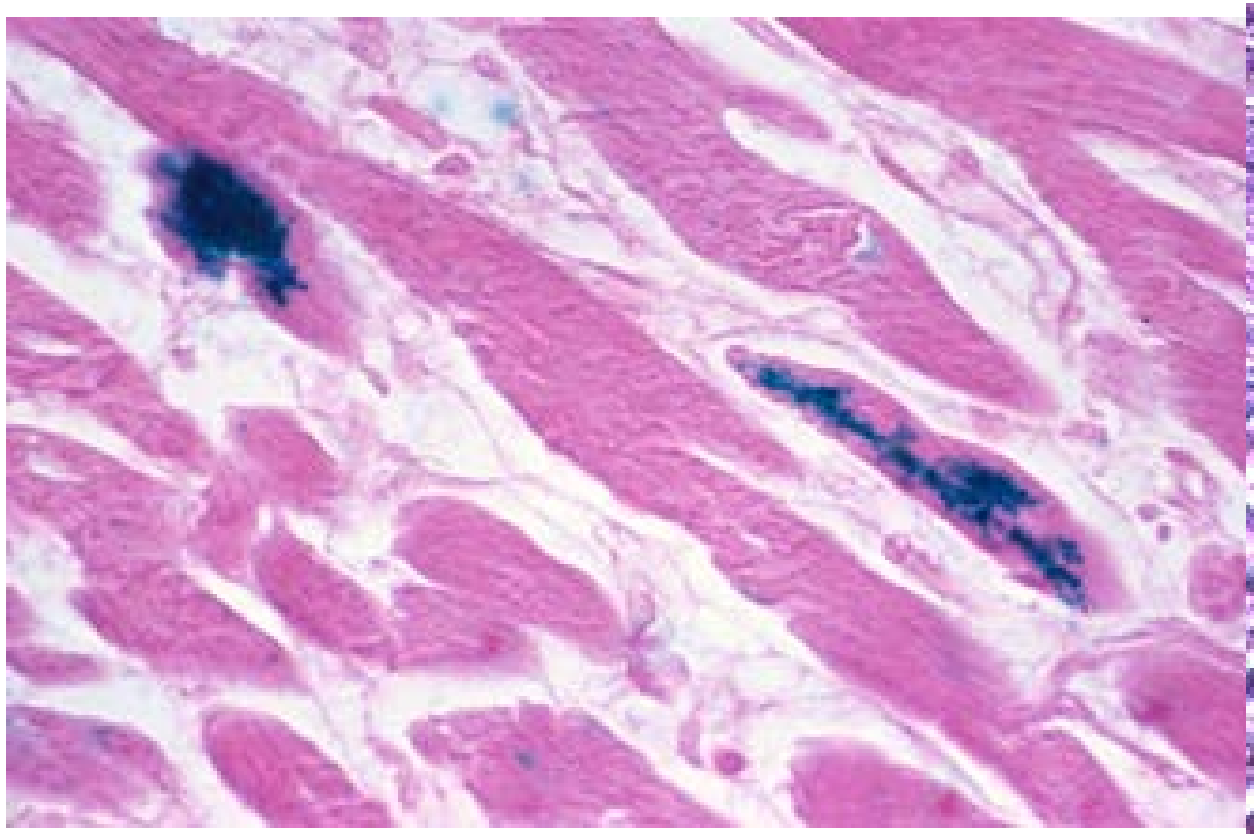


15 yo boy homozygous for C282Y mutation:
2+ iron in liver

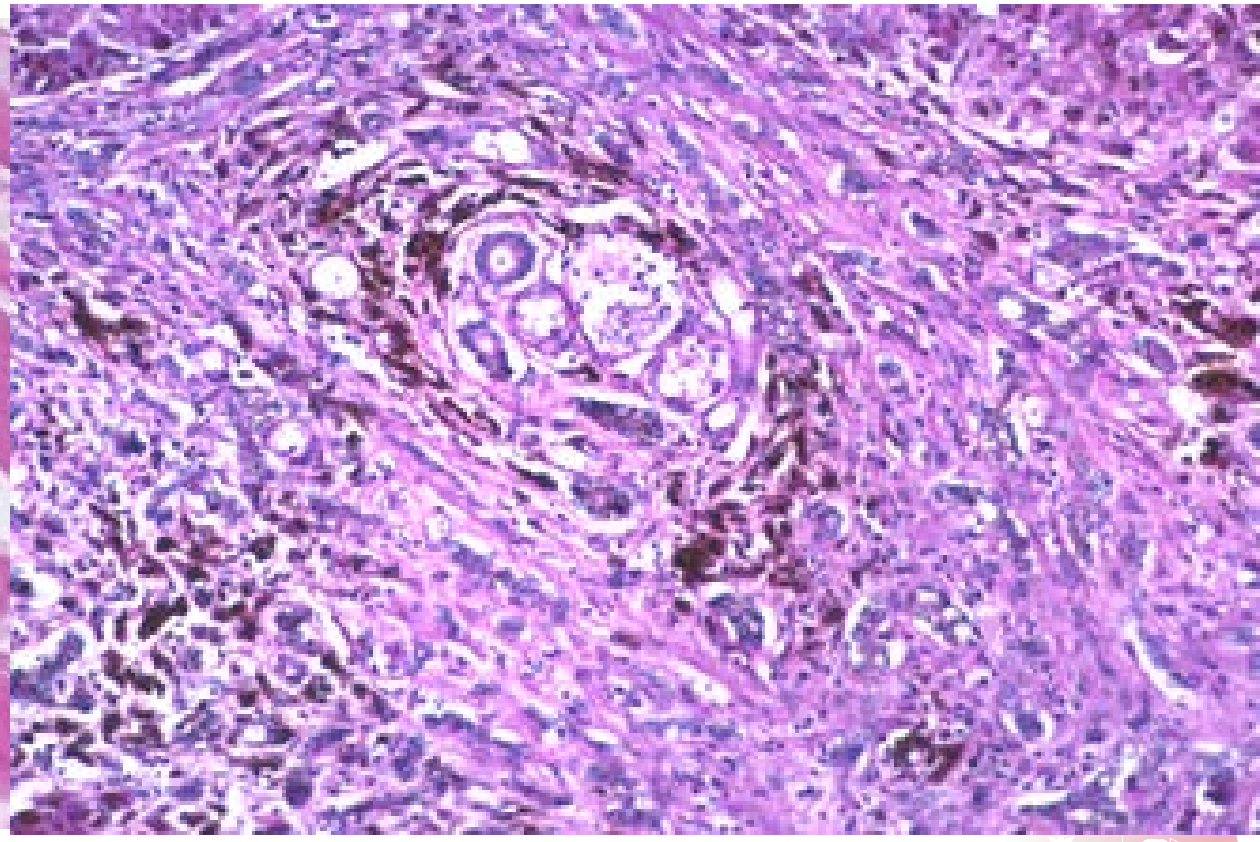


23 yo brother of previous patient:
3 + liver iron

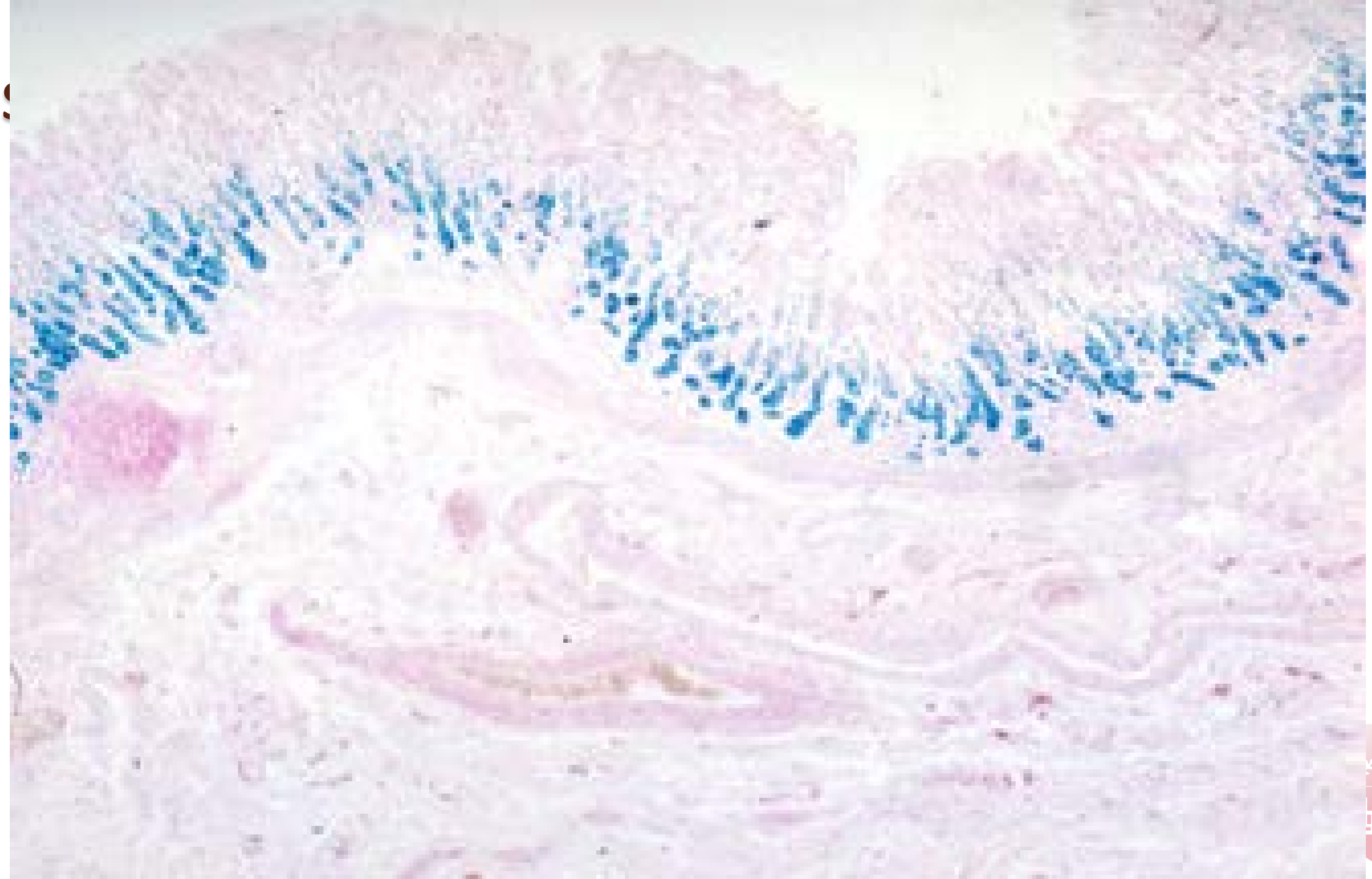
# Extrahepatic deposition of iron in hemochromatosis

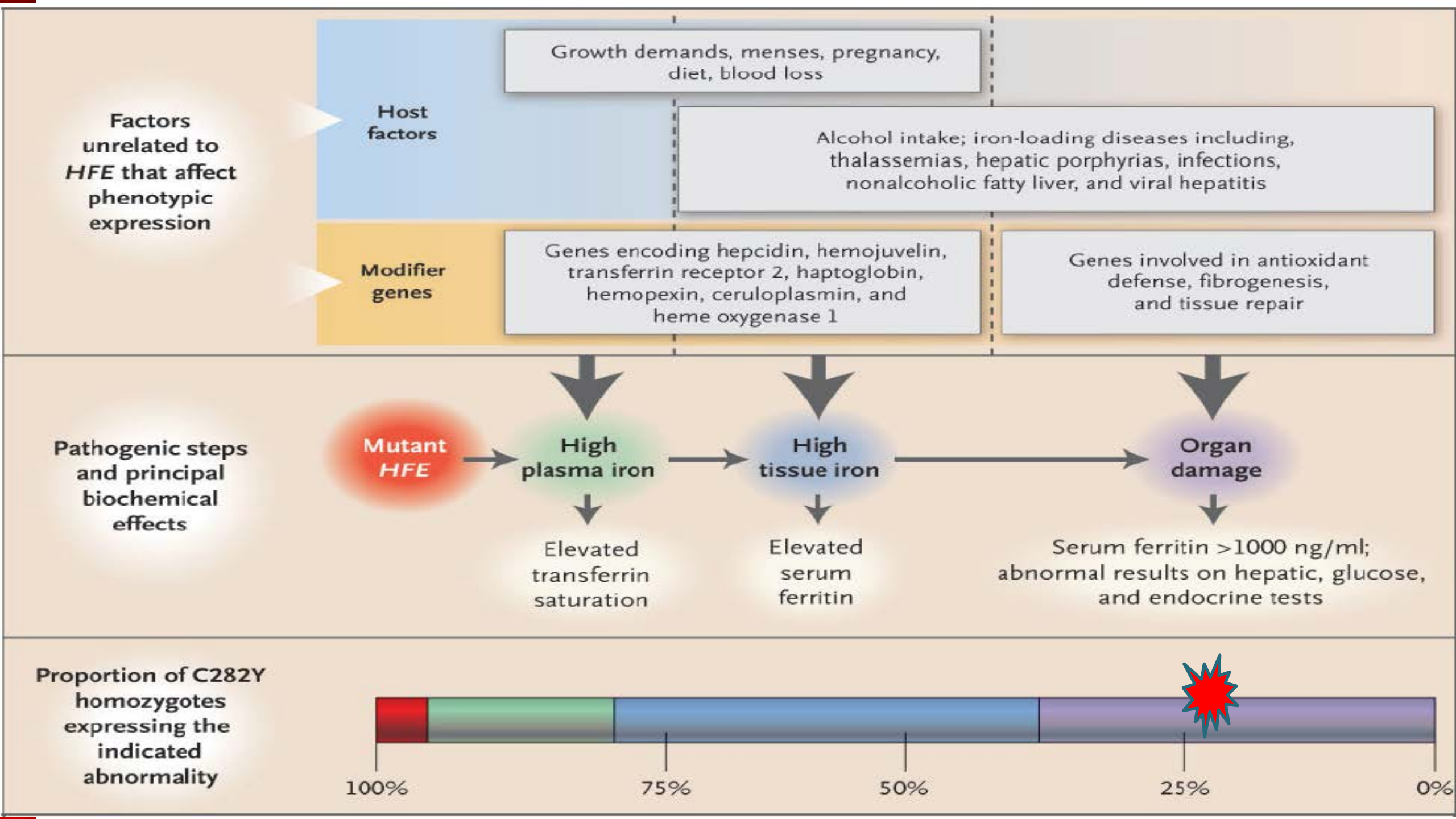


HEART



PANCREAS

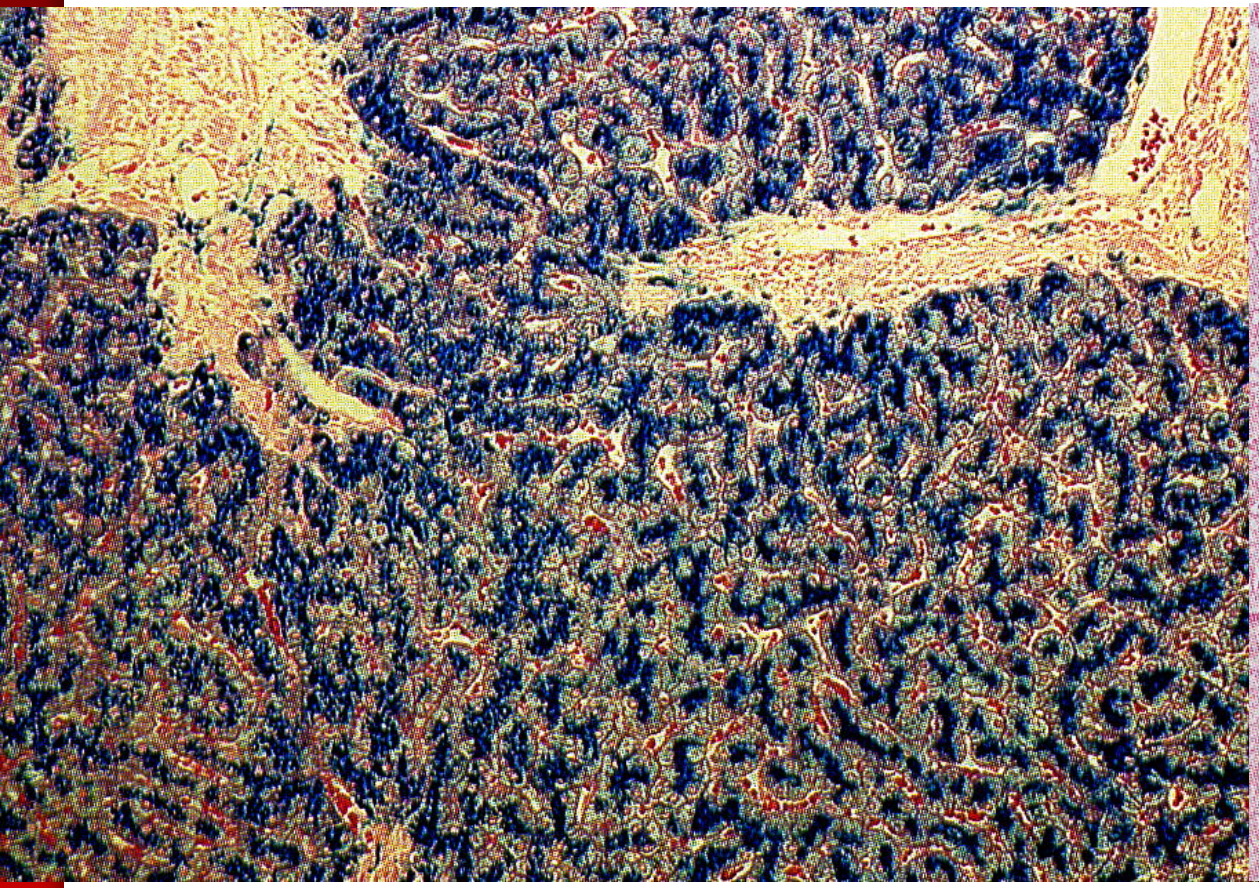


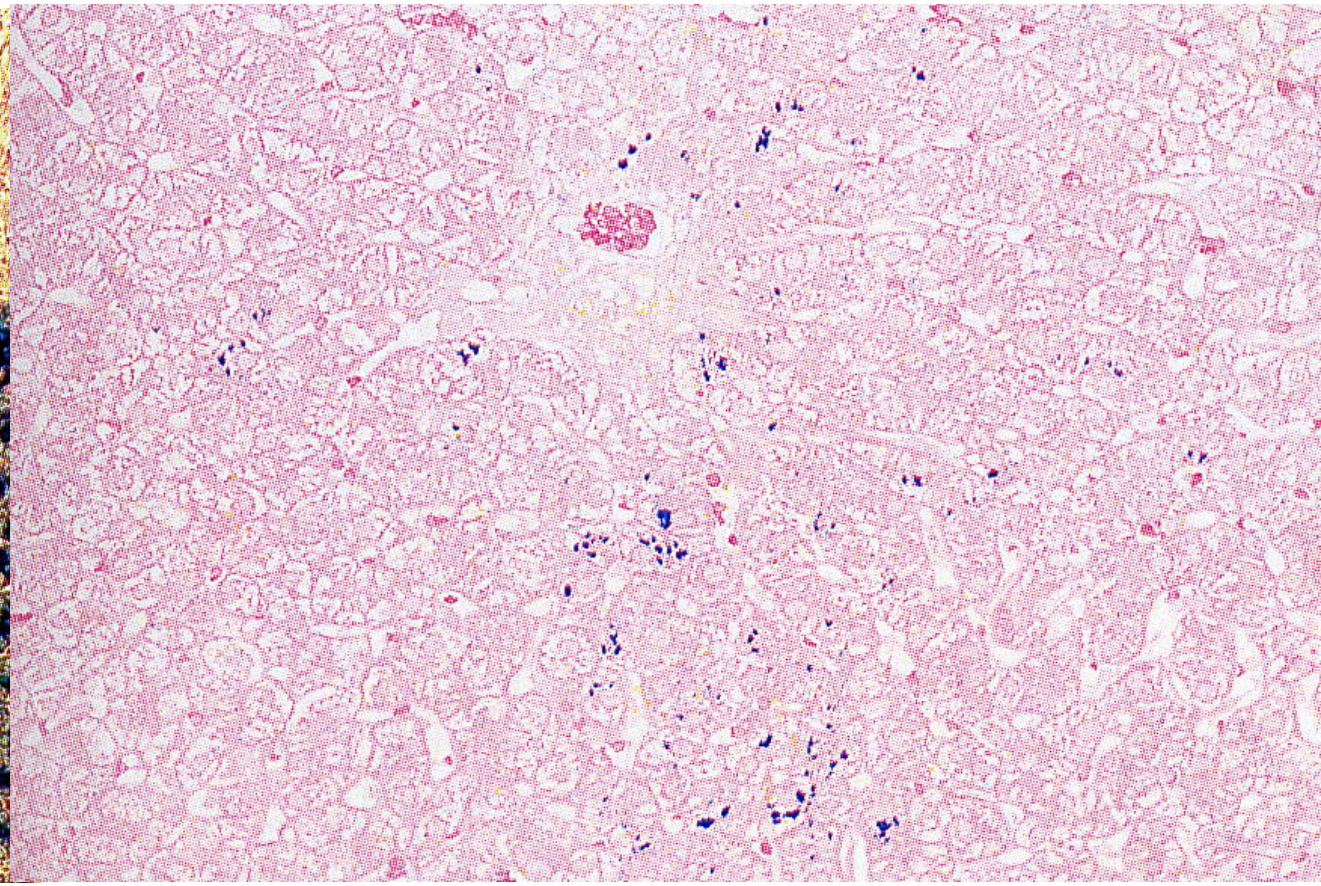

Factors unrelated to *HFE* that affect phenotypic expression
Host factors
Growth demands, menses, pregnancy, diet, blood loss
Alcohol intake; iron-loading diseases including, thalassemias, hepatic porphyrias, infections, nonalcoholic fatty liver, and viral hepatitis
Modifier genes
Genes encoding hepcidin, hemojuvelin, transferrin receptor 2, haptoglobin, hemopexin, ceruloplasmin, and heme oxygenase 1
Genes involved in antioxidant defense, fibrogenesis, and tissue repair
Pathogenic steps and principal biochemical effects
Mutant *HFE*
High plasma iron
High tissue iron
Organ damage
Elevated transferrin saturation
Elevated serum ferritin
Serum ferritin >1000 ng/ml; abnormal results on hepatic, glucose, and endocrine tests
Proportion of C282Y homozygotes expressing the indicated abnormality
100%
75%
50%
25%
0%

# Primary Hemochromatosis: Treatment

- Weekly phlebotomy for 2-3 years (fully developed disease)
- Then every 2-3 months
- 5 year survival:
  - Untreated: 18%
  - Treated: 92% (76 % at 10 years)
- Survival close to normal if treatment started before cirrhosis, DM, CHF ensues

# Phlebotomies for treatment of hemochromatosis





**60 yo homozygote for C282Y mutation:**
**4 + iron stores**

**Liver after one year of regular phlebotomies**

# Wilson's Disease

- Inborn error in copper metabolism
- Autosomal recessive (Chromosome 13)
- Copper-transporting P-type ATPase ATP7B
  - 518 variants
  - Most cases are "compound heterzygotes"
- Prevalence:  1:30,000

# Wilson's Disease

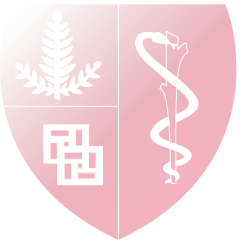
- Normal copper excretion in bile is decreased
- Elevated serum and urinary copper
- Decreased ceruloplasmin (<0.2 g/dl)
- Increased copper deposition in parenchymal tissues with resulting pathology
  - Stimulates Oxygen radical production
  - Triggers apoptosis via activation of acid sphingomyelinase
    - Animal models with defective or blocked ASM are protected

# Pathogenesis of Wilson's disease

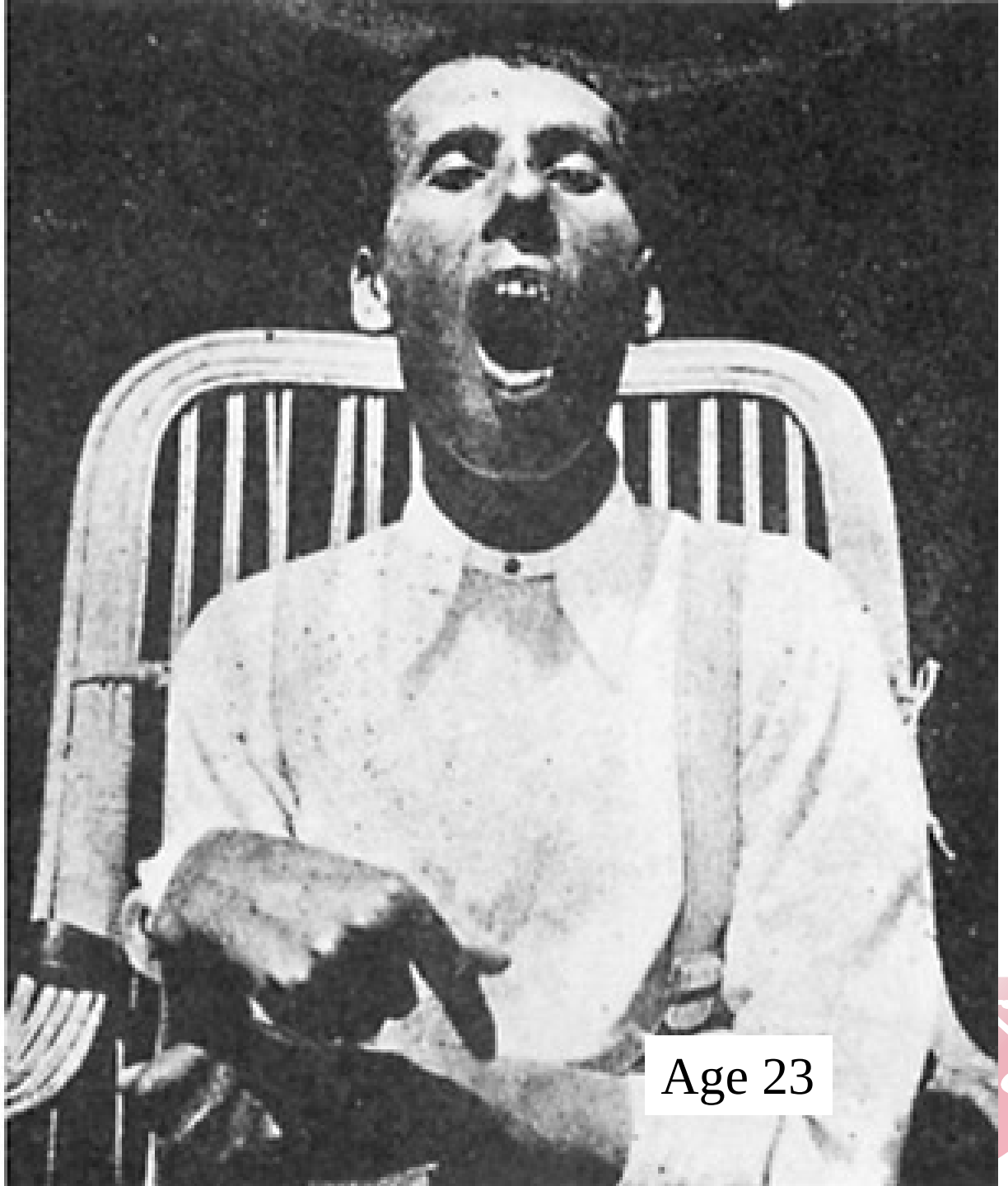
- Copper accumulates 1st in mitochondria of liver
  - Attempts to act as "buffer" by distributing the excess copper to its copper dependent enzymes
  - Early damage to mitochondria with fragmentation of mitochondrial lipids and eventual membrane disintegration which triggers cell death
- Altered cholesterol synthesis
  - Decreased liver and serum cholesterol

# Wilson's Disease: Organ involvement and Clinical presentation

- Organ Involvement
  - Liver
  - Brain
  - Eyes
  - Kidneys
  - Red Cells
- Neurologic
  - Basal Ganglia-related symptoms
  - Psychiatric abnormalities
- Hepatic
  - Fulminant Hepatic Failure
  - Chronic Hepatitis
  - Cirrhosis

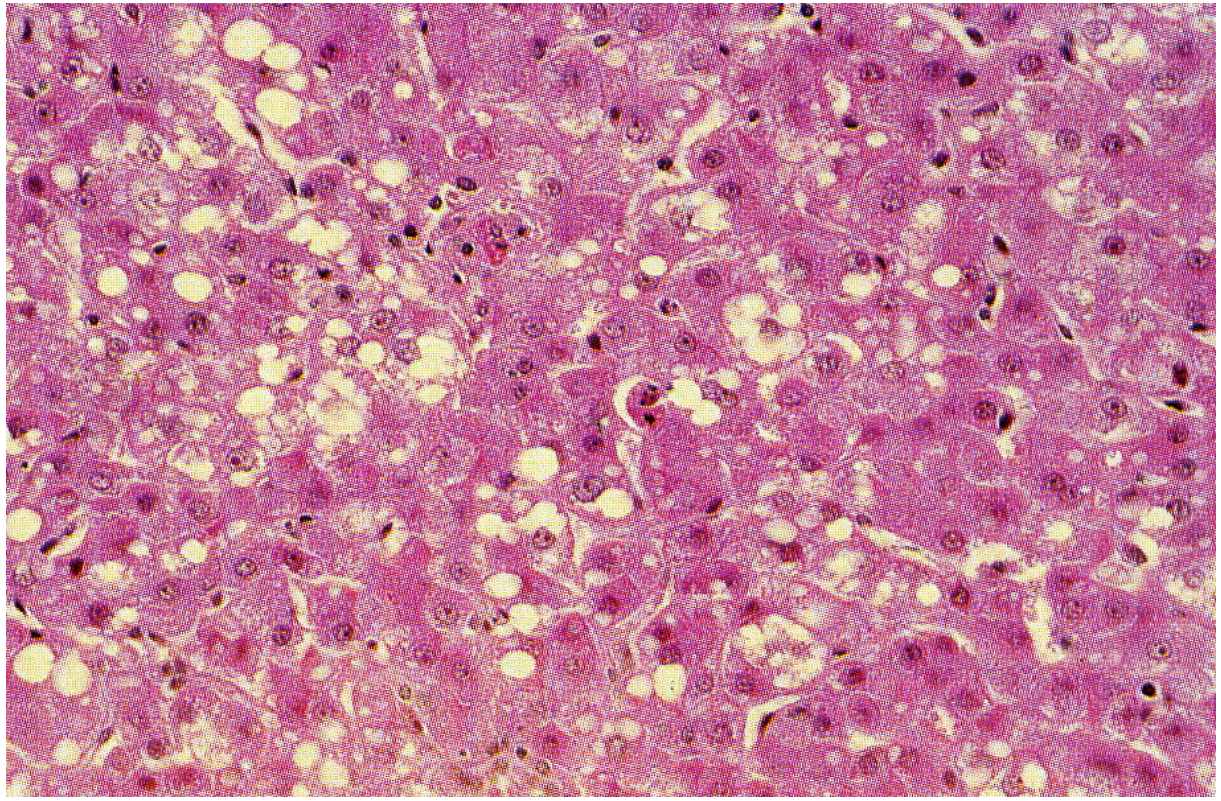


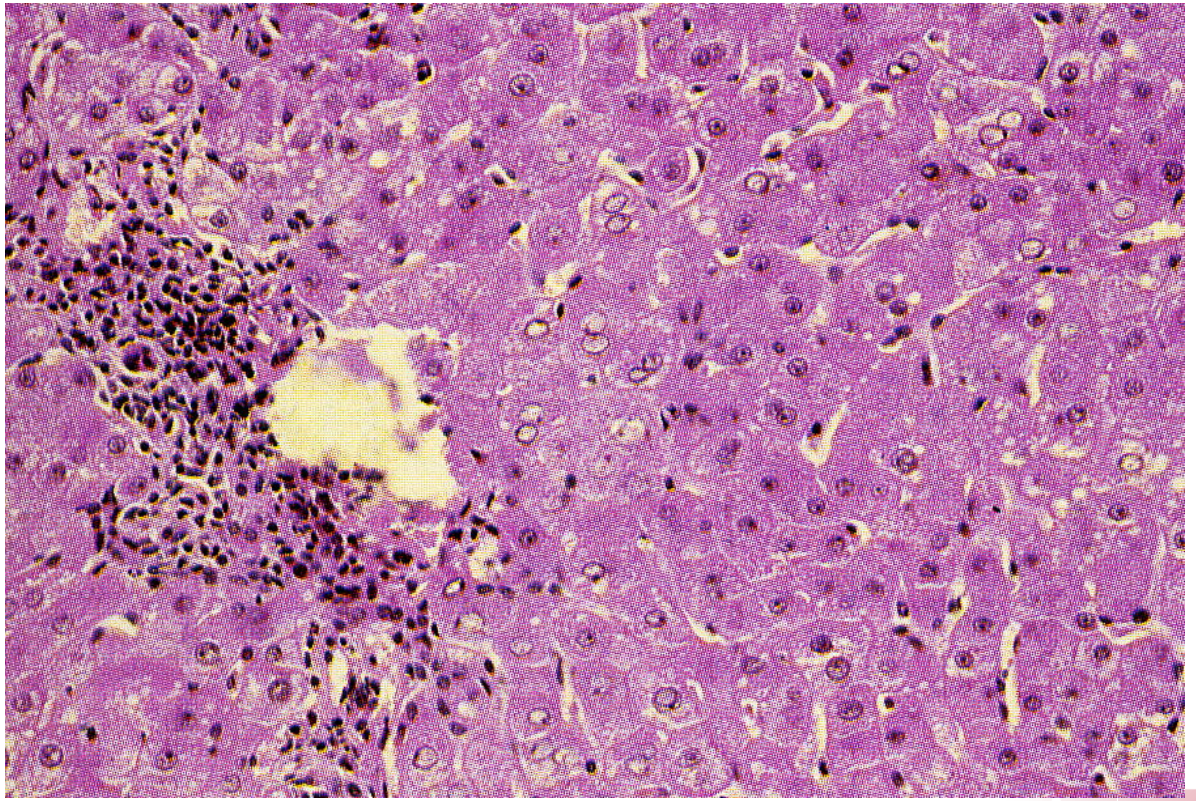
Age 19

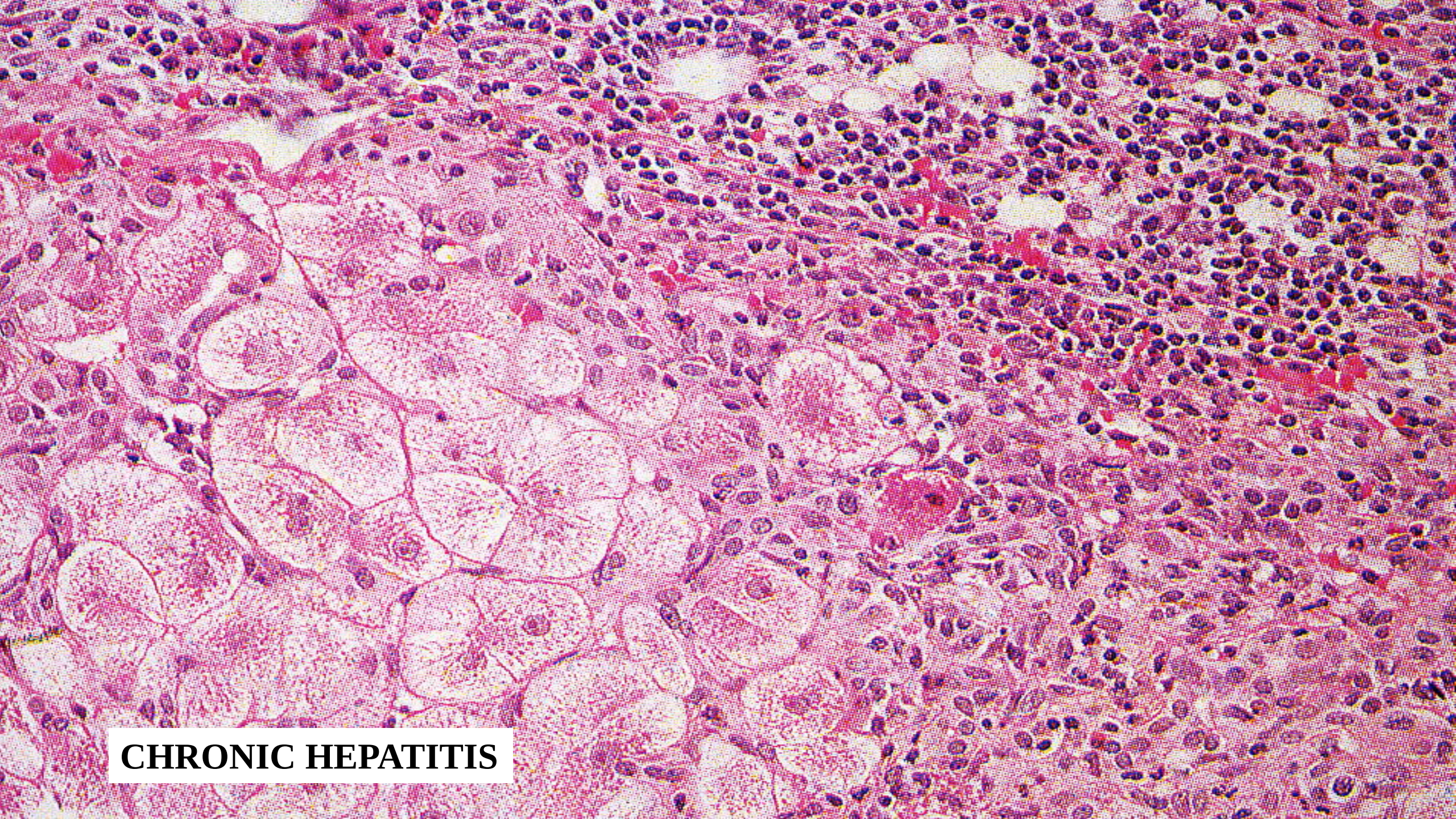


Age 23

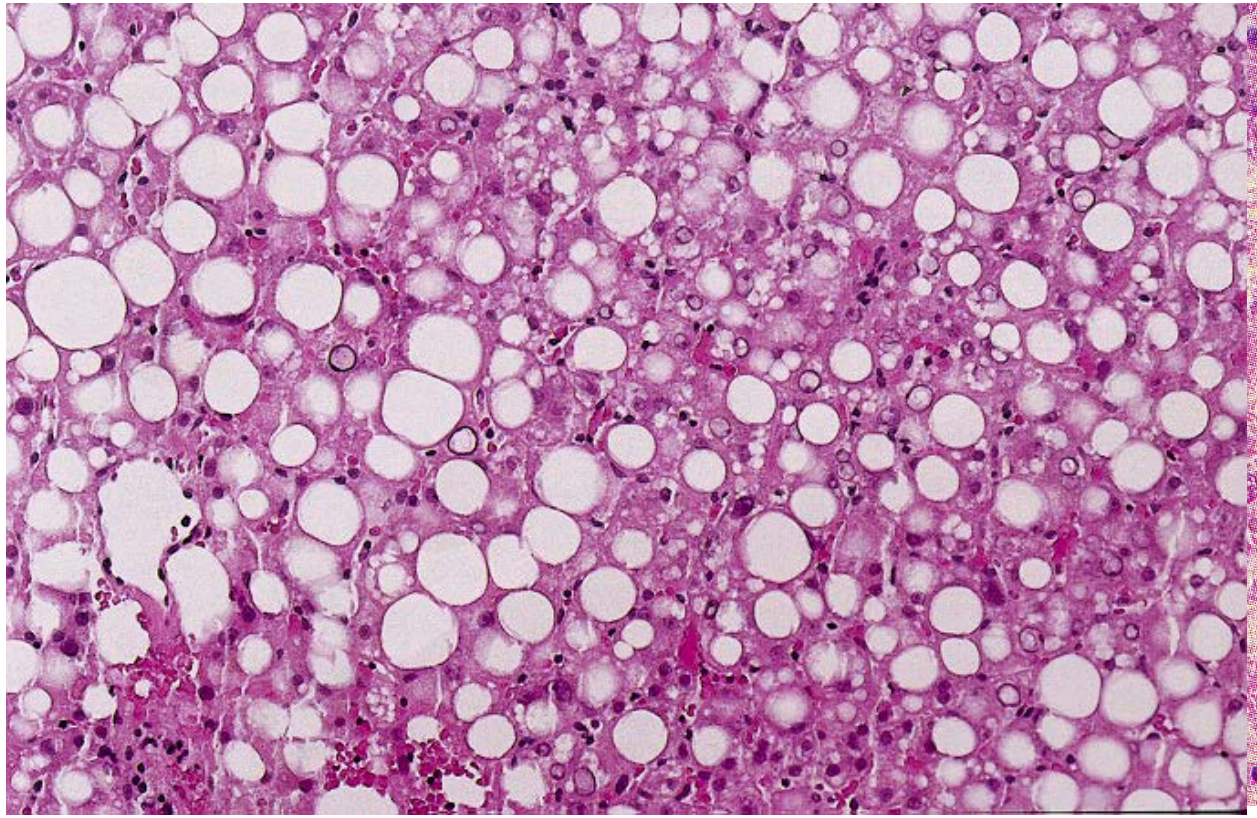
# Wilson's disease: Early pathologic findings in the liver



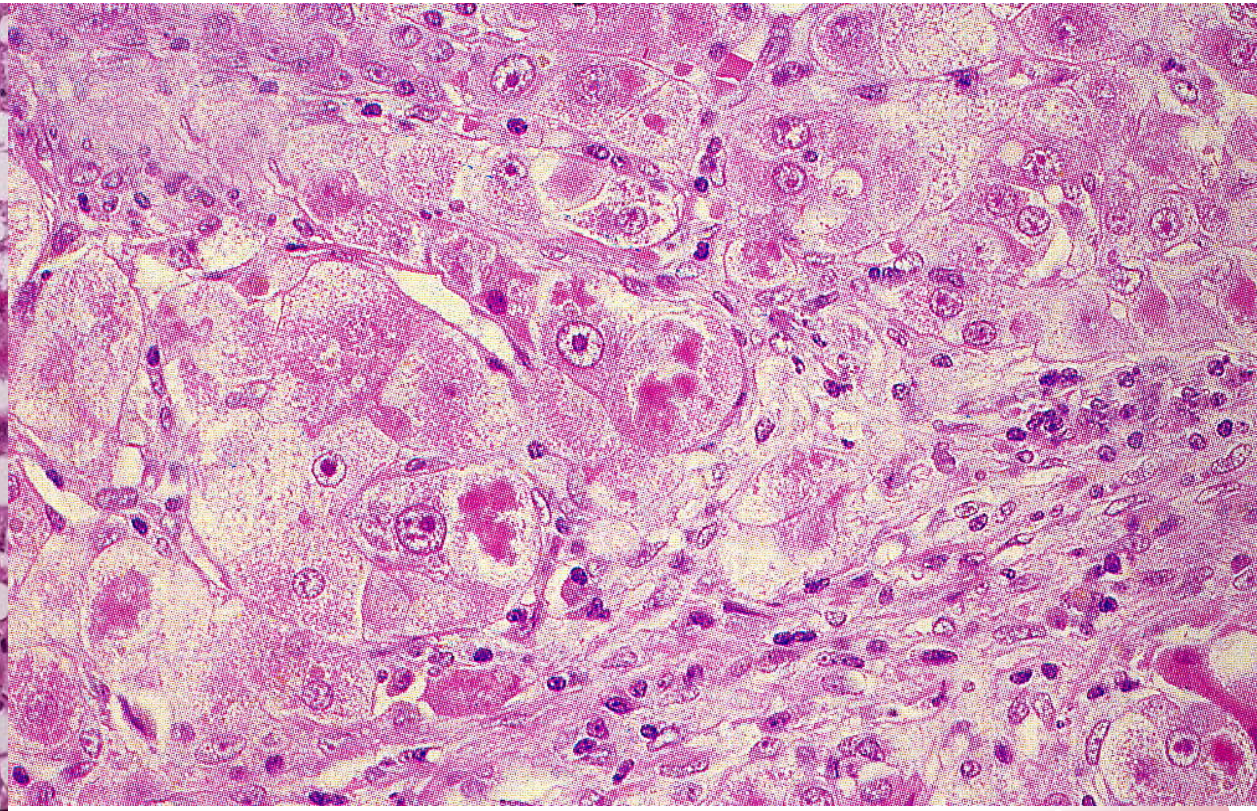



CHRONIC HEPATITIS

# Wilson's disease: Late pathologic findings in the liver

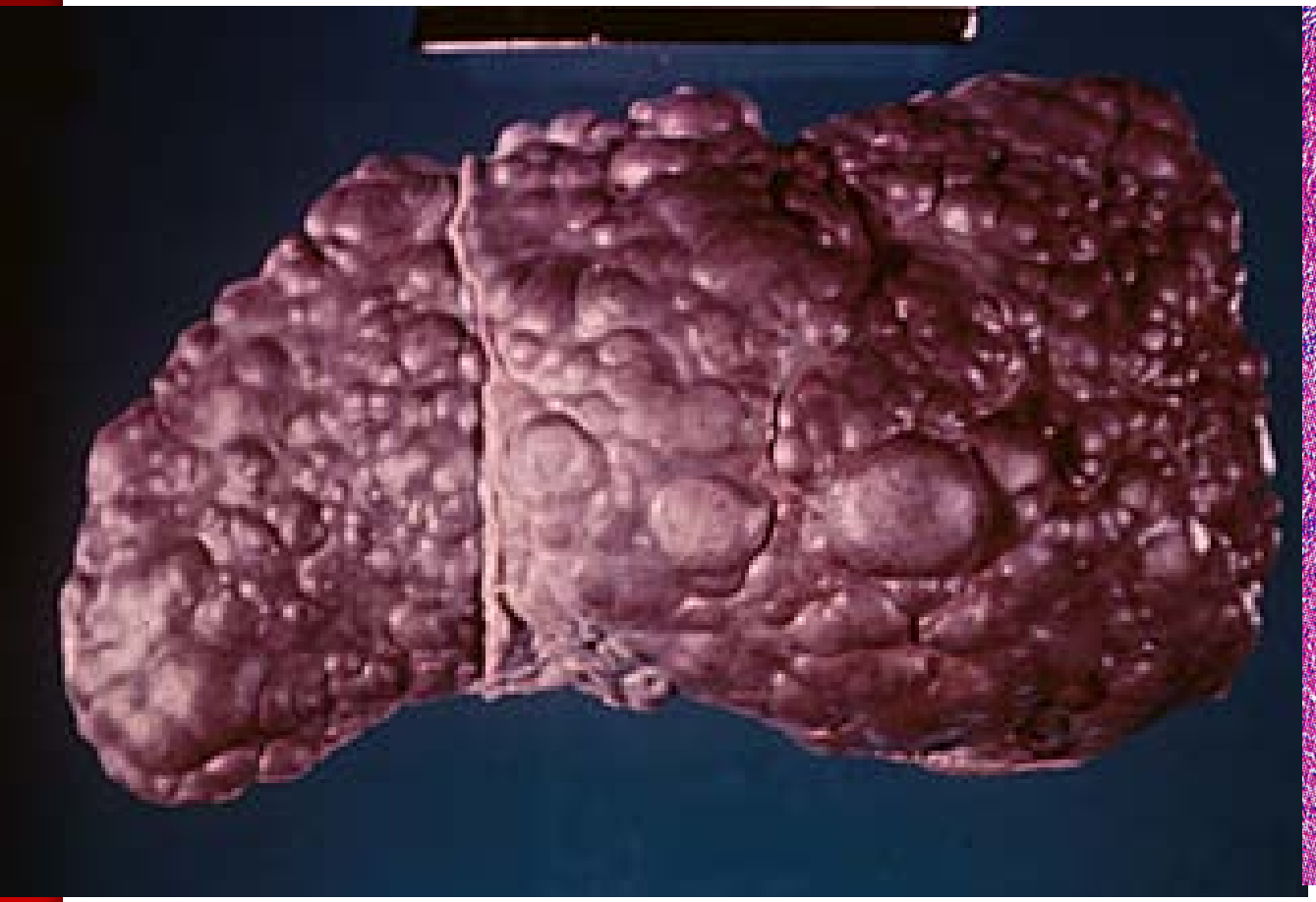


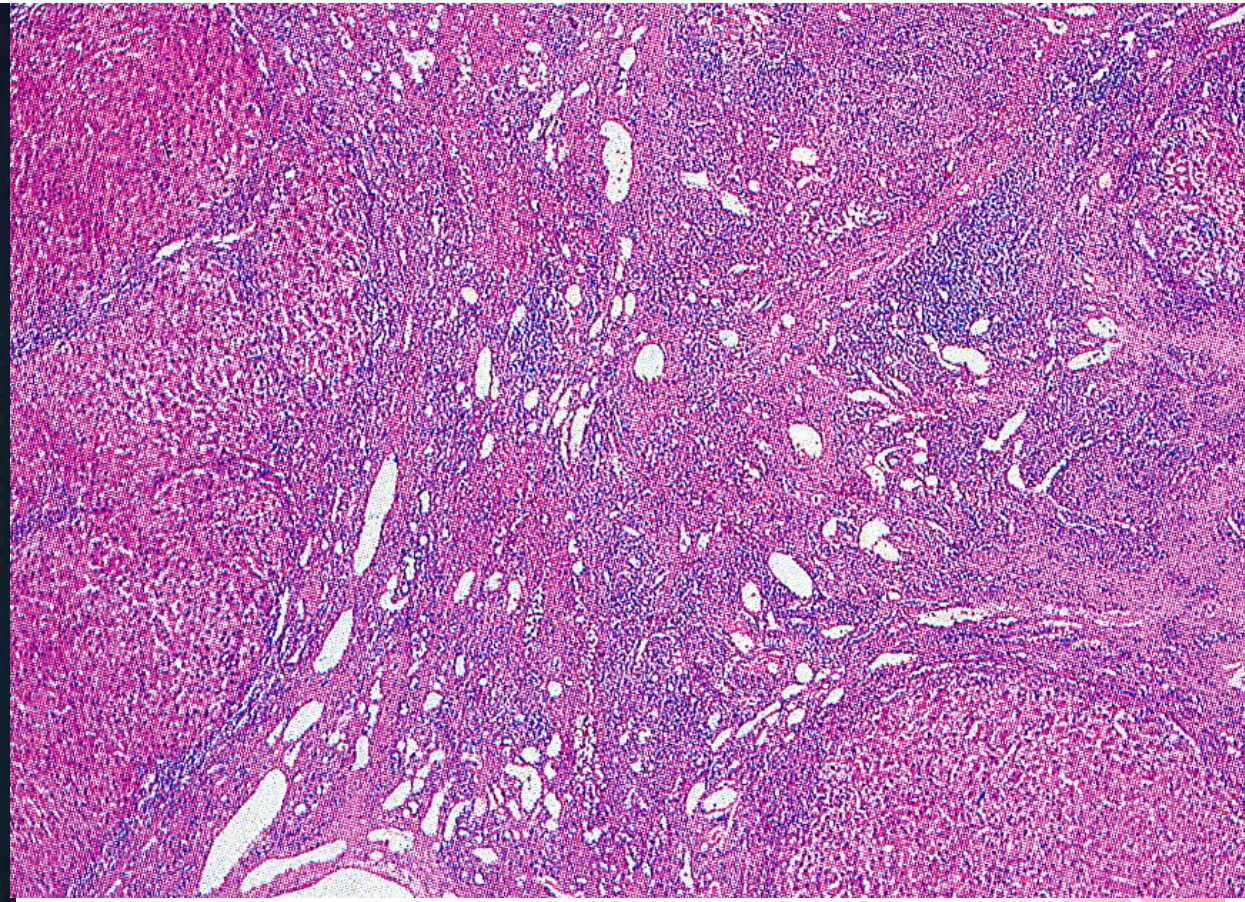
Macrovesicular fatty change



Mallory Bodies

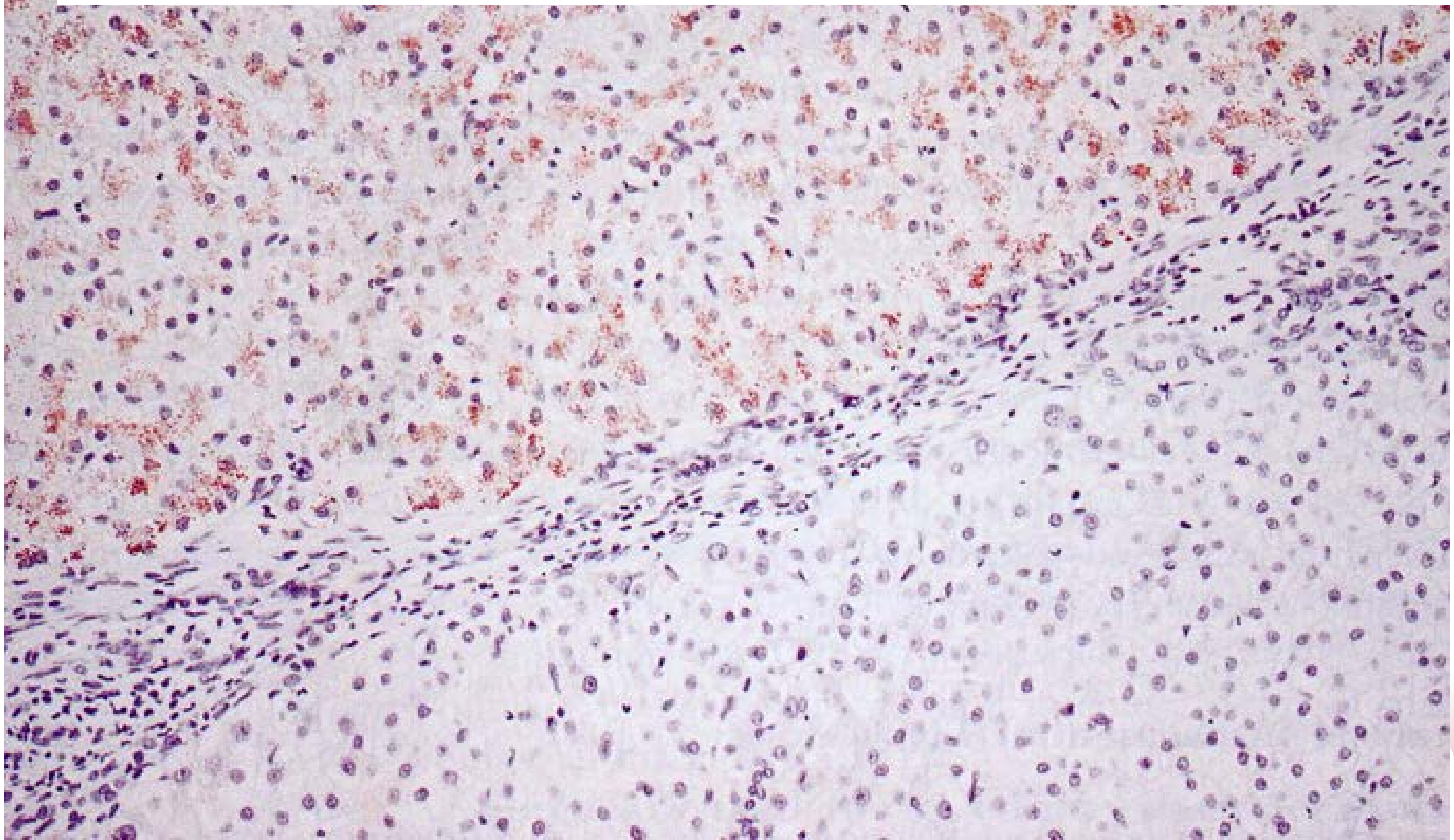
# Wilson's disease: Late pathologic findings in the liver



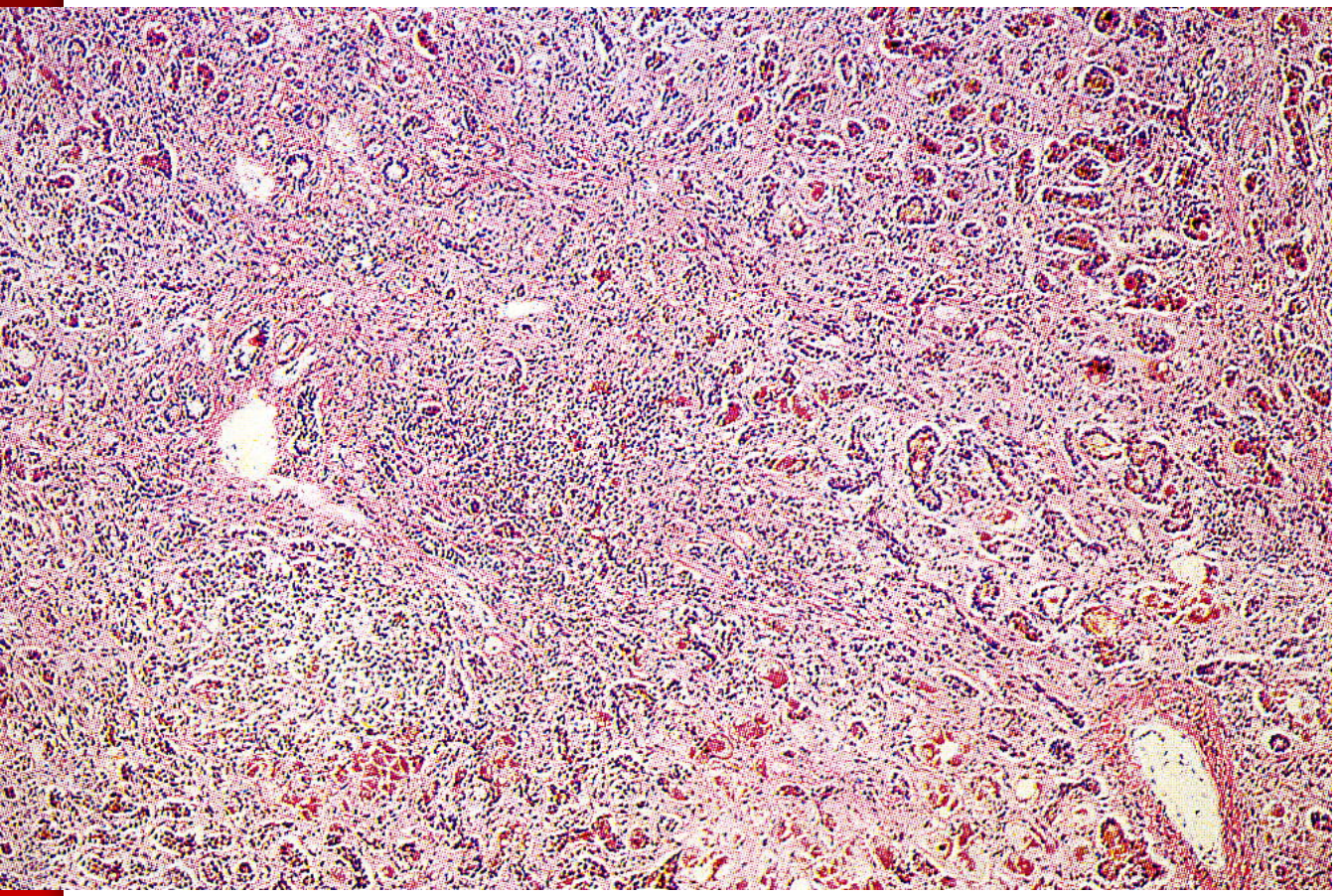


**Cirrhosis**

**Copper stain demonstrating heterogeneous deposition of copper in liver of patient with Wilson's disease**

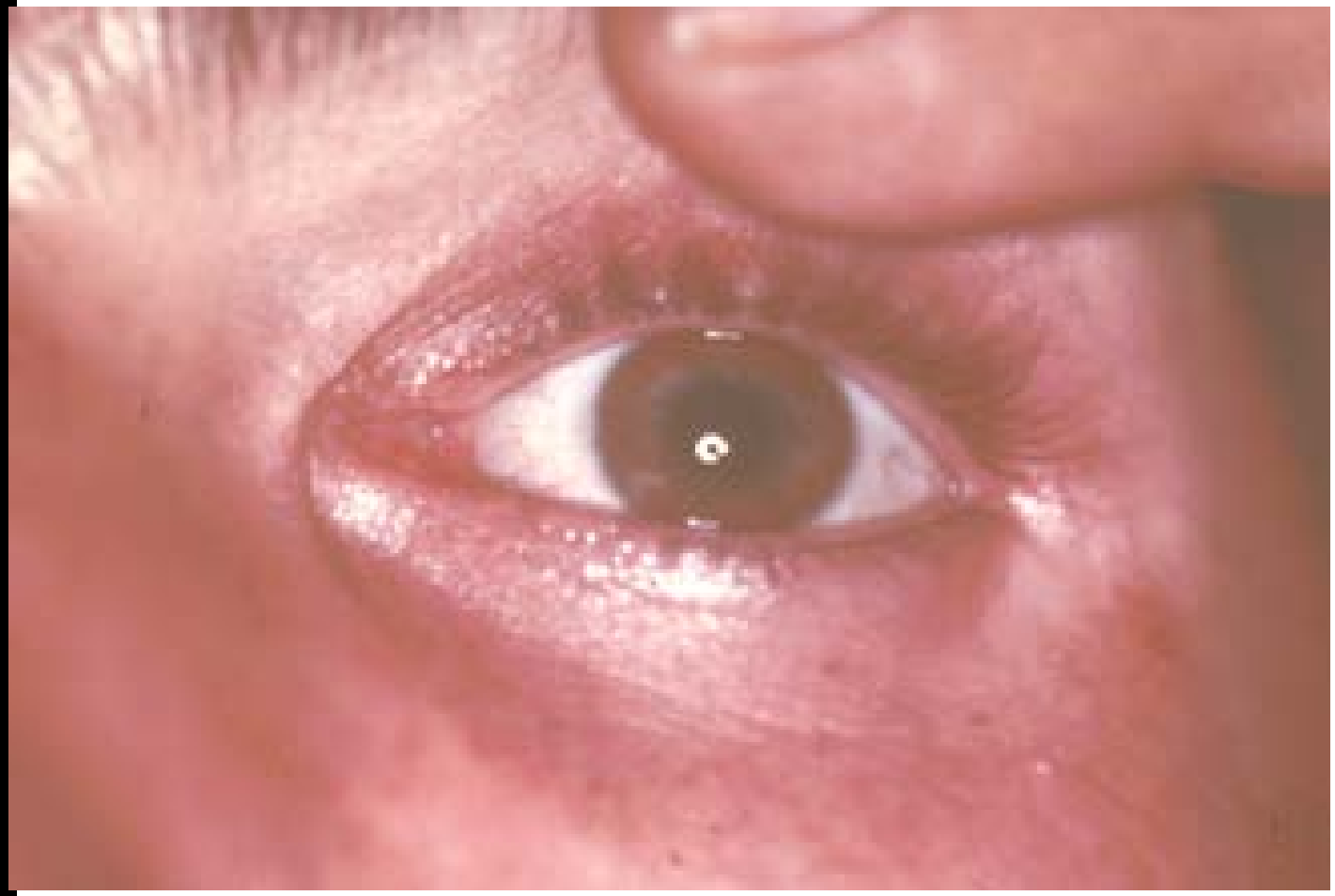


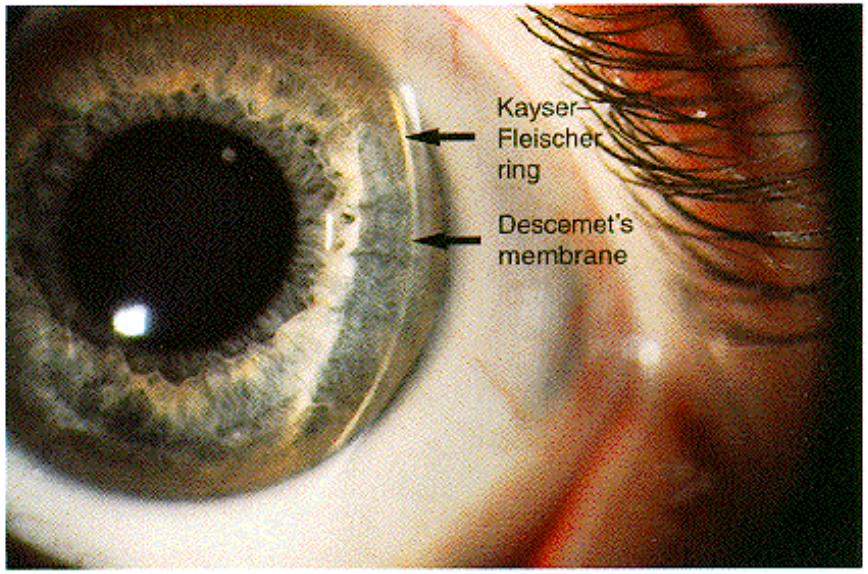
# Fulminant hepatic failure:  Wilson's disease



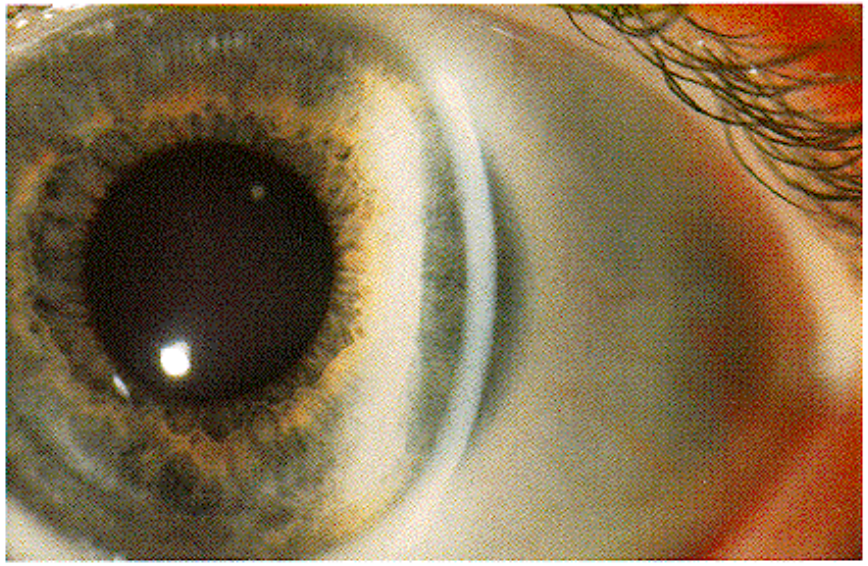
- Invariably fatal without transplantation
- Early Clues to DX:
  - s Cu >200 ug/dl
  - Alk Ø : t Bili < 4
  - AST:ALT > 2.2

# Kaiser-Fleischer Rings



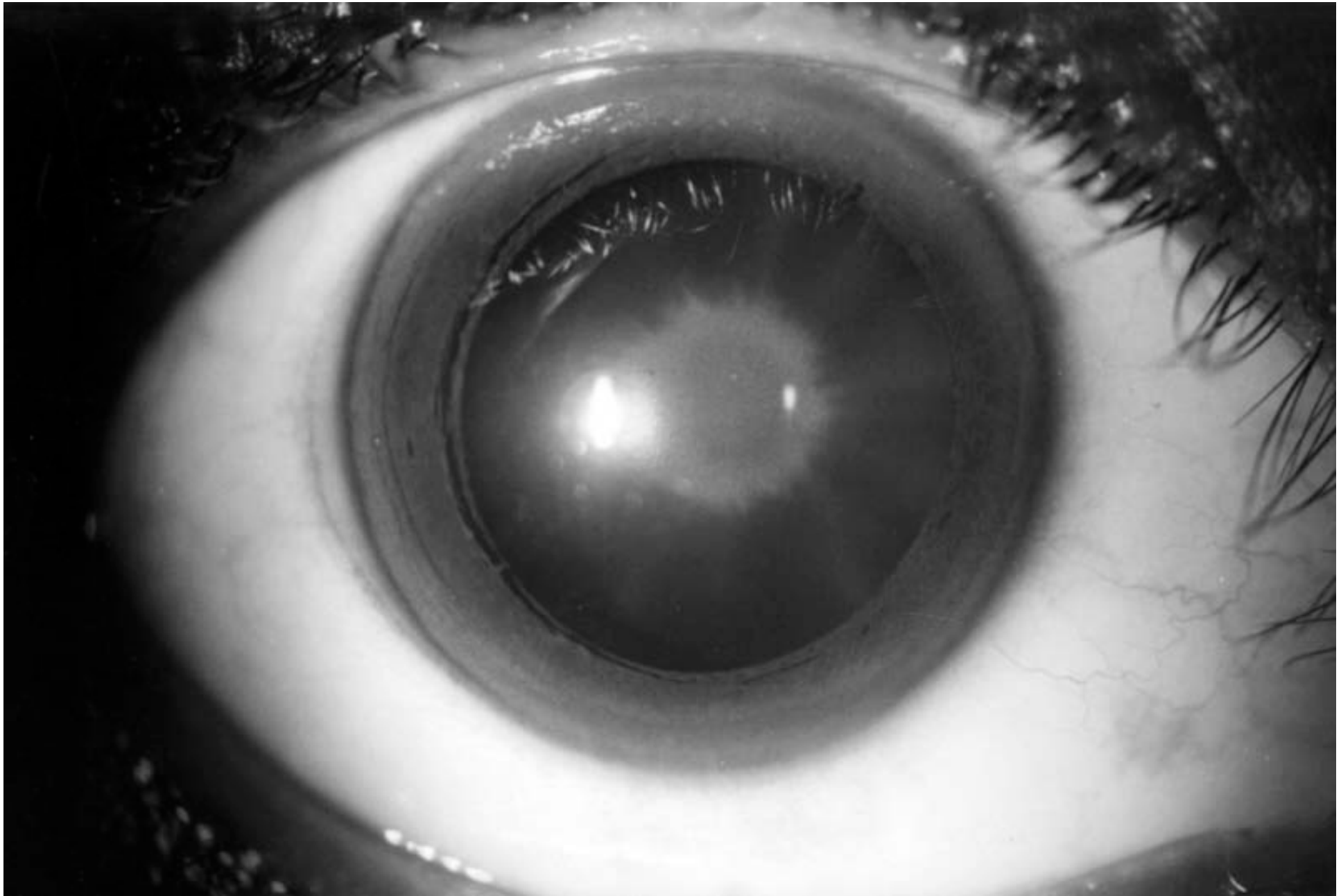



A



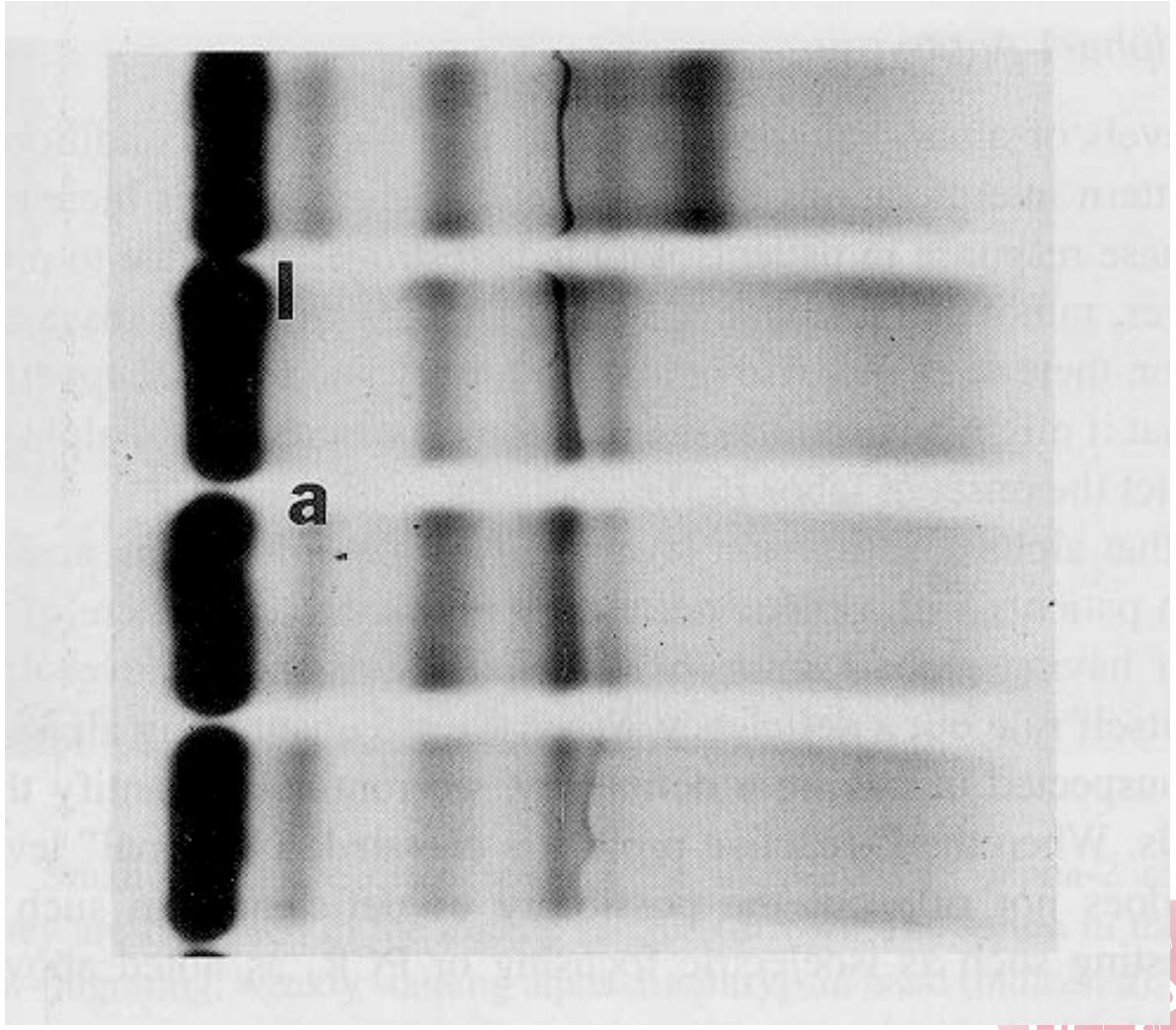
B

# Sunflower Cataract in Wilson's Disease



# Alpha-1-antitrypsin Deficiency

- Inherited metabolic abnormality
- Deficiency in circulating protease inhibitor
- 4 major electrophoretic variants



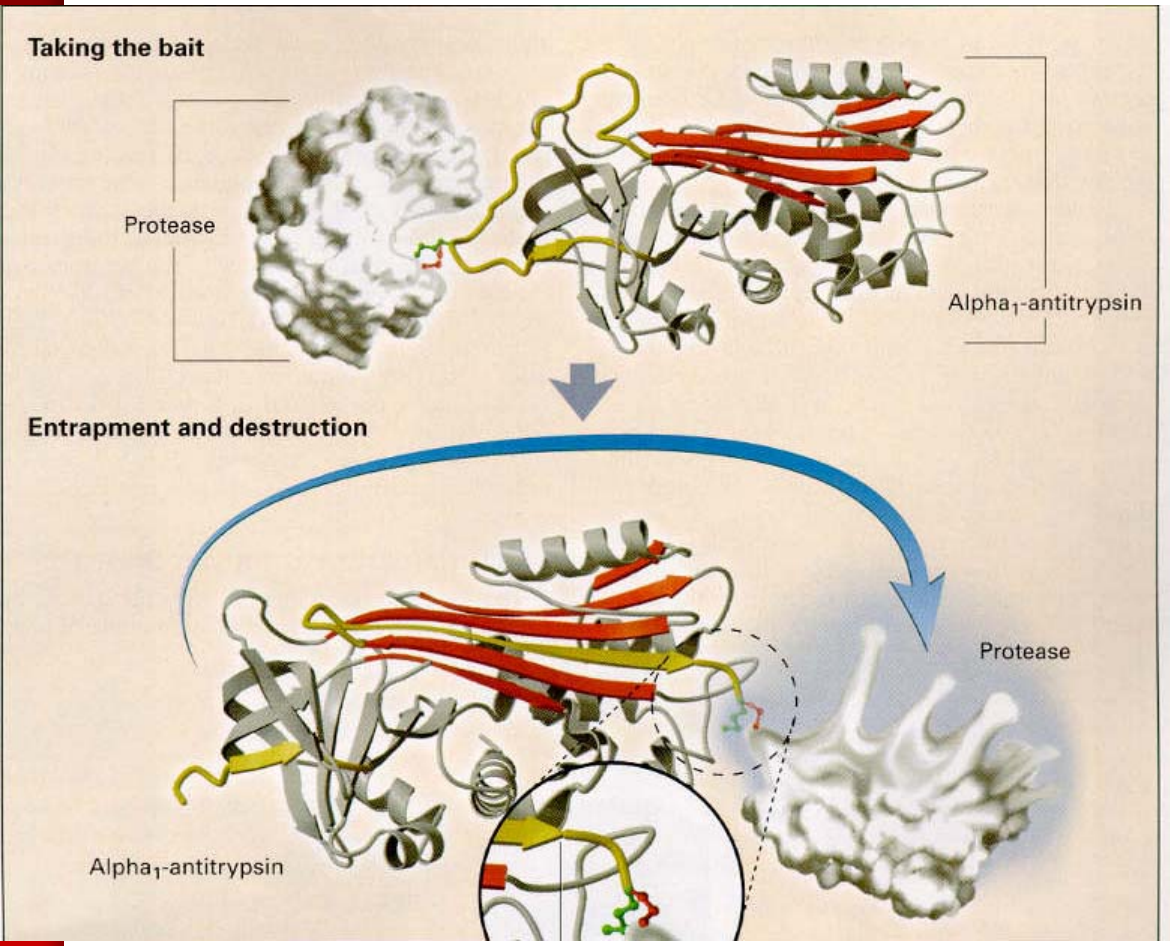
# Alpha-1-Antitrypsin Deficiency

- Mutation at hinge in reactive loop
- Allows for inappropriate entry of loop into the reactive center
- Tendency for protein to spontaneously lock at time of synthesis
  - Increased intracellular catabolism
  - Formation of linked loop sheet polymers
- Normal synthesis but only 15 % excreted
  - Accumulations in liver interferes with glycogen storage/metabolism
  - Promotes hepatocellular apoptosis

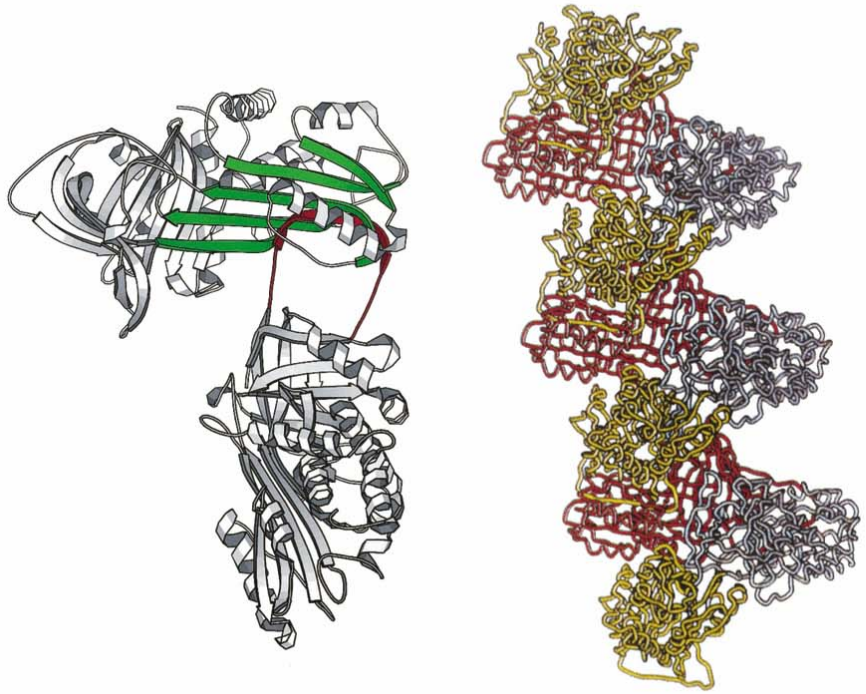
# Alpha-1-Antitrypsin Deficiency: Pathogenesis

- Abnormal proteins are “screened” by ER
  - Directs mutant Z to proteolytic pathway
  - Those that ?escape form abnormal polymers
  - Second proteolytic pathway autophagy to clear these polymers
  - Large accumulations lead to cell injury/death

# Alpha-1-Antitrypsin

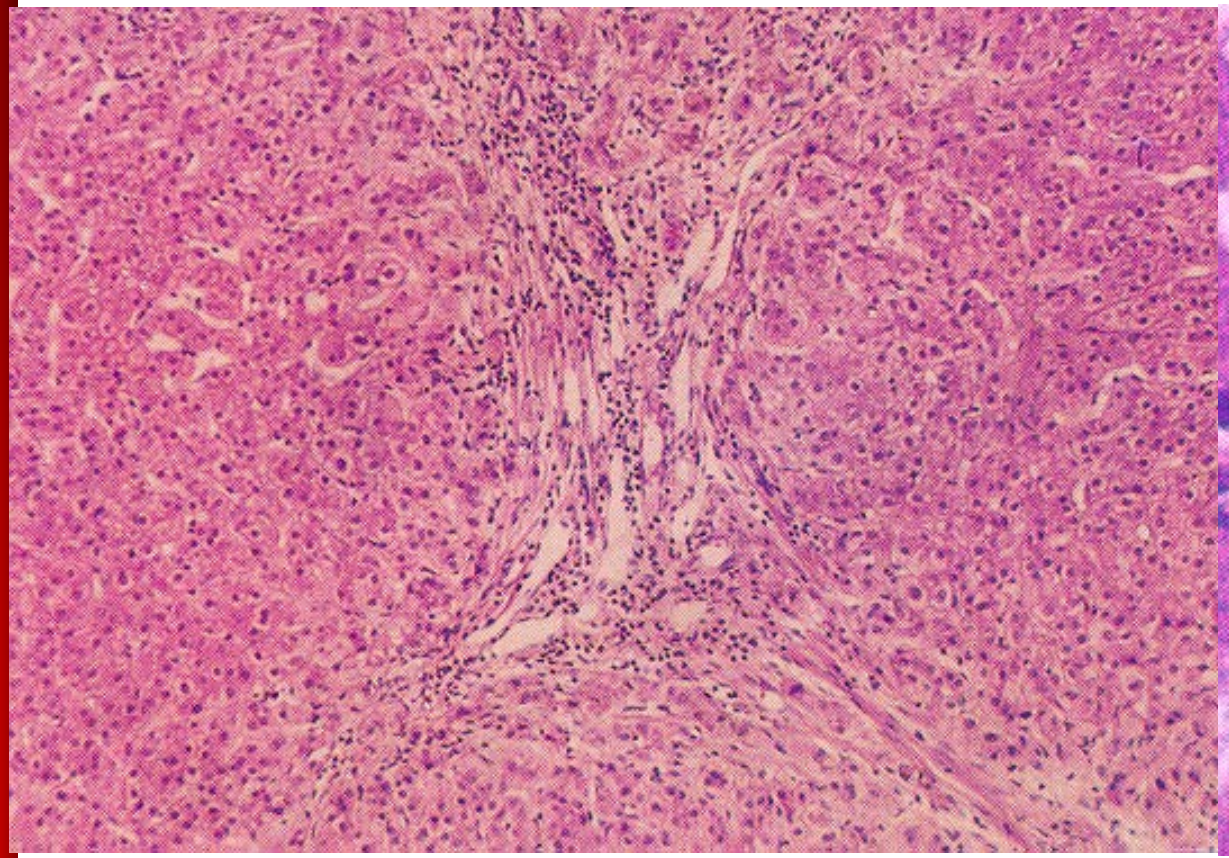


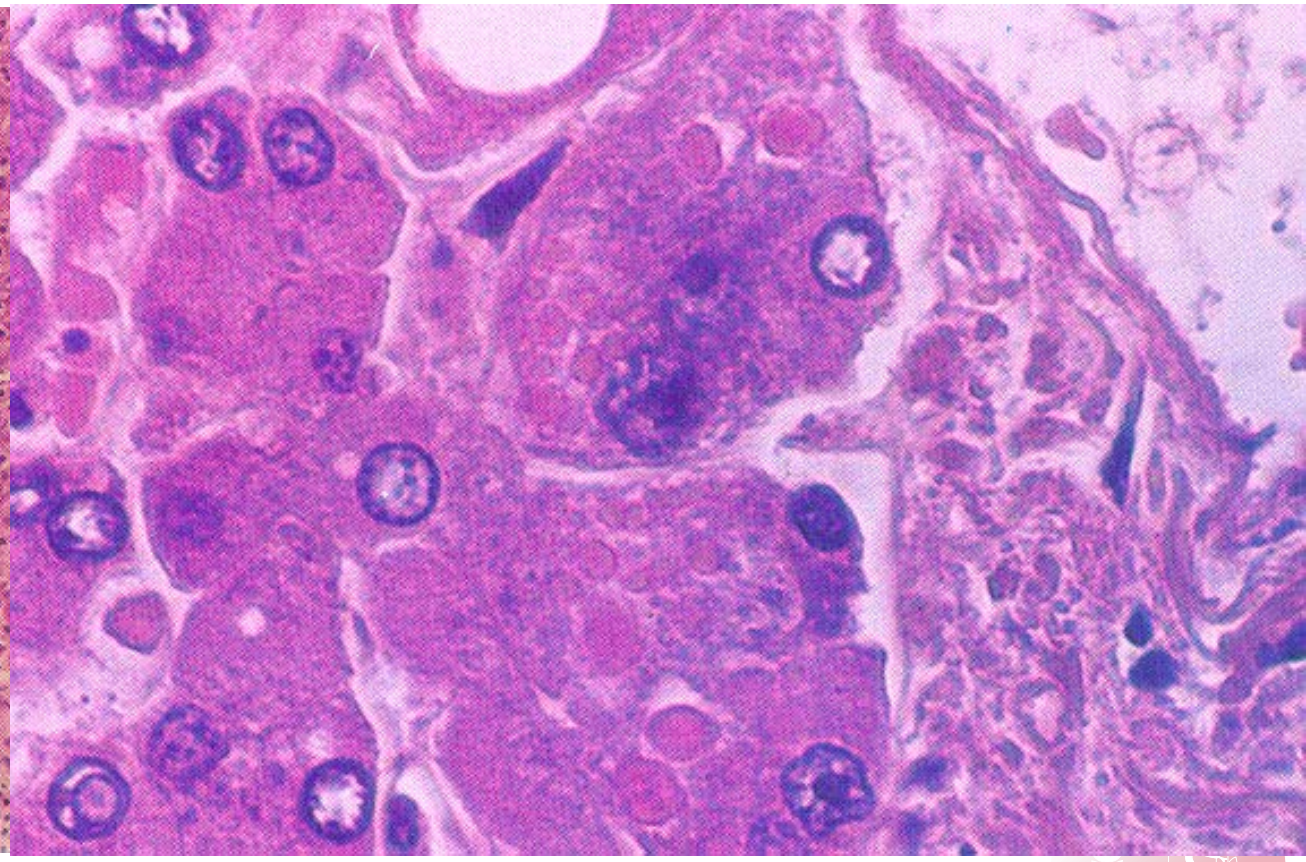

**Normal Function**

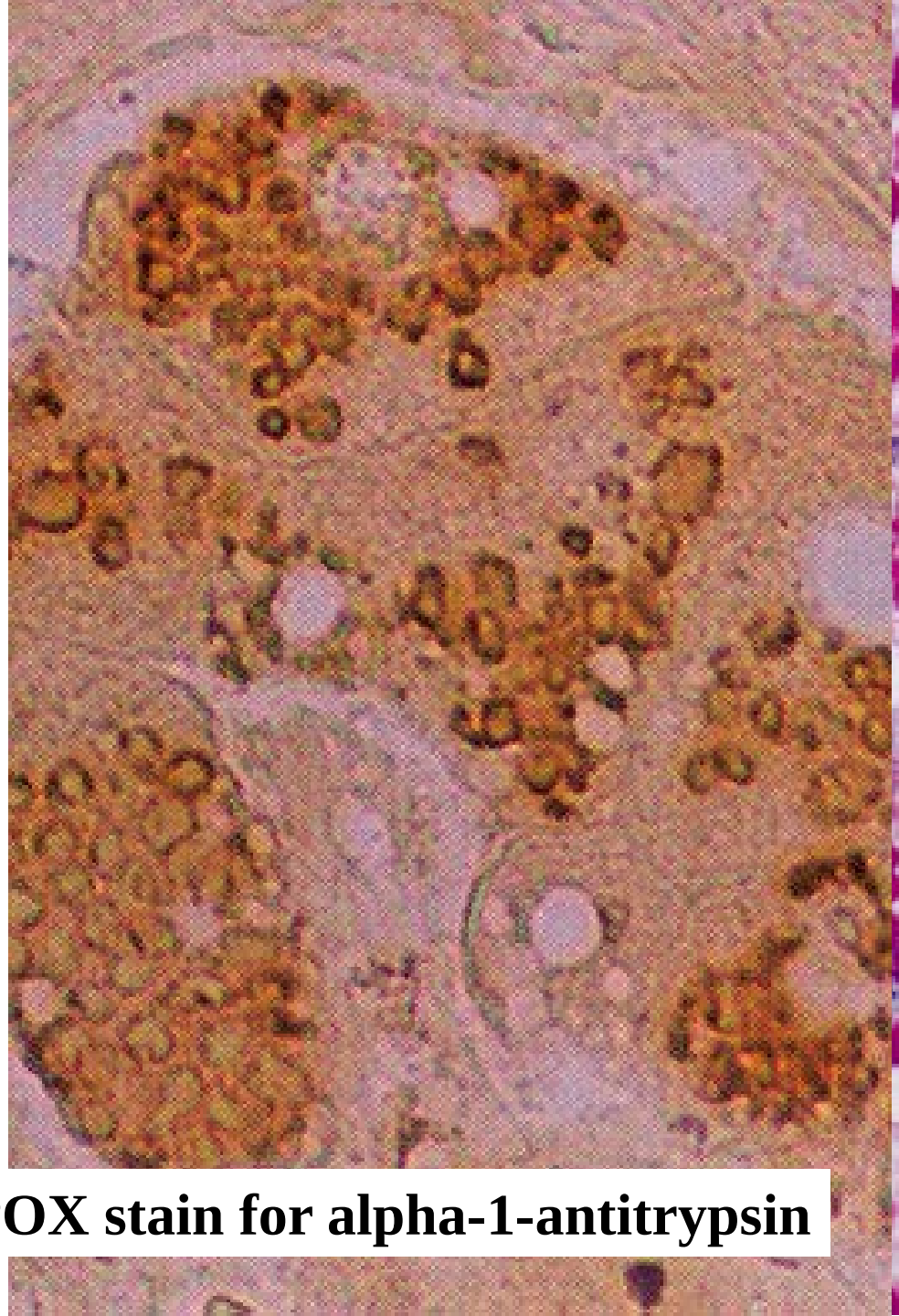


**Abnormal Polymerization**

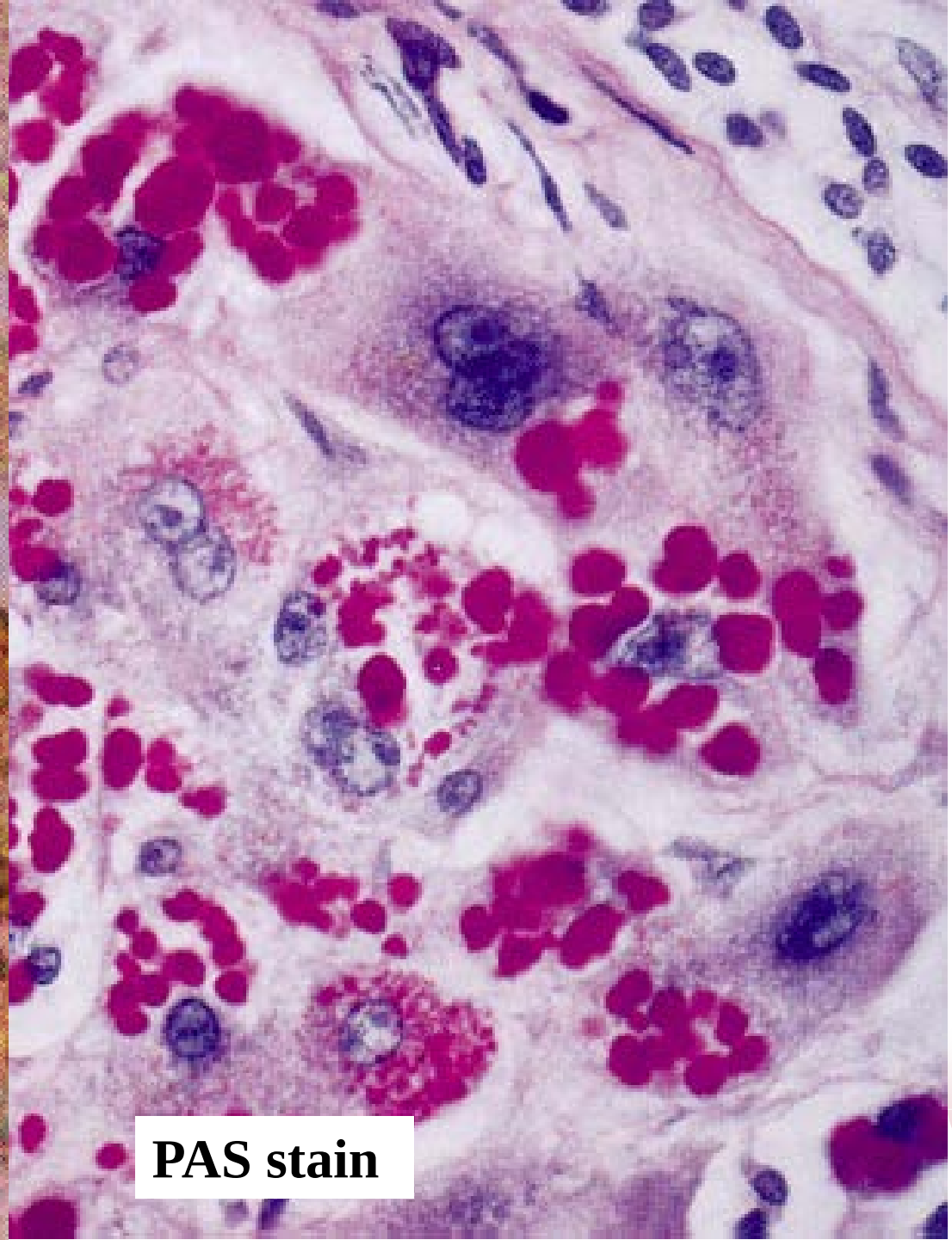
# Alpha-1-Antitrypsin Deficiency associated cirrhosis







IPOX stain for alpha-1-antitrypsin



PAS stain

# Liver in Childhood

## Alpha-1-antitrypsin deficiency

- AAT accumulates early
- Hepatic enzymes abnormalities (10-20%)
- Cholestatic Hepatitis
- Hyperbilirubinemia resolves 6-8 months
- Elevated transaminases persist
- Macronodular cirrhosis develops
- ? Concomitant abnormality

# Liver in Adults
# Alpha-1-Antitrypsin Deficiency

- Significant heterogeneity in extent of mutant Z protein that accumulates in liver of ZZ patients
  - Unclear why???
- 10 % of Pi ZZ allele adults have cirrhosis of the liver that is unaccounted for by any other etiology.
- 10-20 % develop Hepatocellular cirrhosis

# The End

**Table 1**

Representative examples of innate immune cell manipulation in animal models of liver fibrosis

| Cell type | Method of inducing fibrosis | Method of cell manipulation | Effect on fibrosis | Refs. |
|---|---|---|---|---|
| Macrophages | $CCl_4$ intoxication | Selective depletion of macrophages during liver injury and repair | Functionally distinct subpopulations of macrophages in the same tissue have critical roles in both the injury and recovery phases of inflammatory scarring | 62 |
| Mast cells | In rats: bile duct resection, $CCl_4$ intoxication, or porcine serum; in mice: bile duct resection or $CCl_4$ intoxication | Mast cell–deficient mutant *Ws/Ws* rats and *W/Wv* mice | No effect on development of liver fibrosis | 66 |
| Neutrophils | BDL | In rats: administration of neutrophil-specific antiserum; in mice: transgenic expression of IL-8 causes an underlying defect in neutrophil function | No effect on hepatic fibrogenesis | 68 |
| | Administration of α-naphthylisothiocyanate | *Cxcr2*$^{-/-}$ mice with resultant 50% reduction in neutrophil recruitment | No effect on hepatic fibrosis | 69 |
| NK cells | 3,5-diethoxycarbonyl-1,4-dihydrocollidine diet or $CCl_4$ intoxication | Activation and depletion of NK cells | NK cells ameliorate liver fibrosis by killing activated HSCs | 63 |

*Cxcr2*$^{-/-}$, CXC chemokine receptor 2–deficient.

**Iredale, J. P. J. Clin. Invest. 2007;117:539-548**

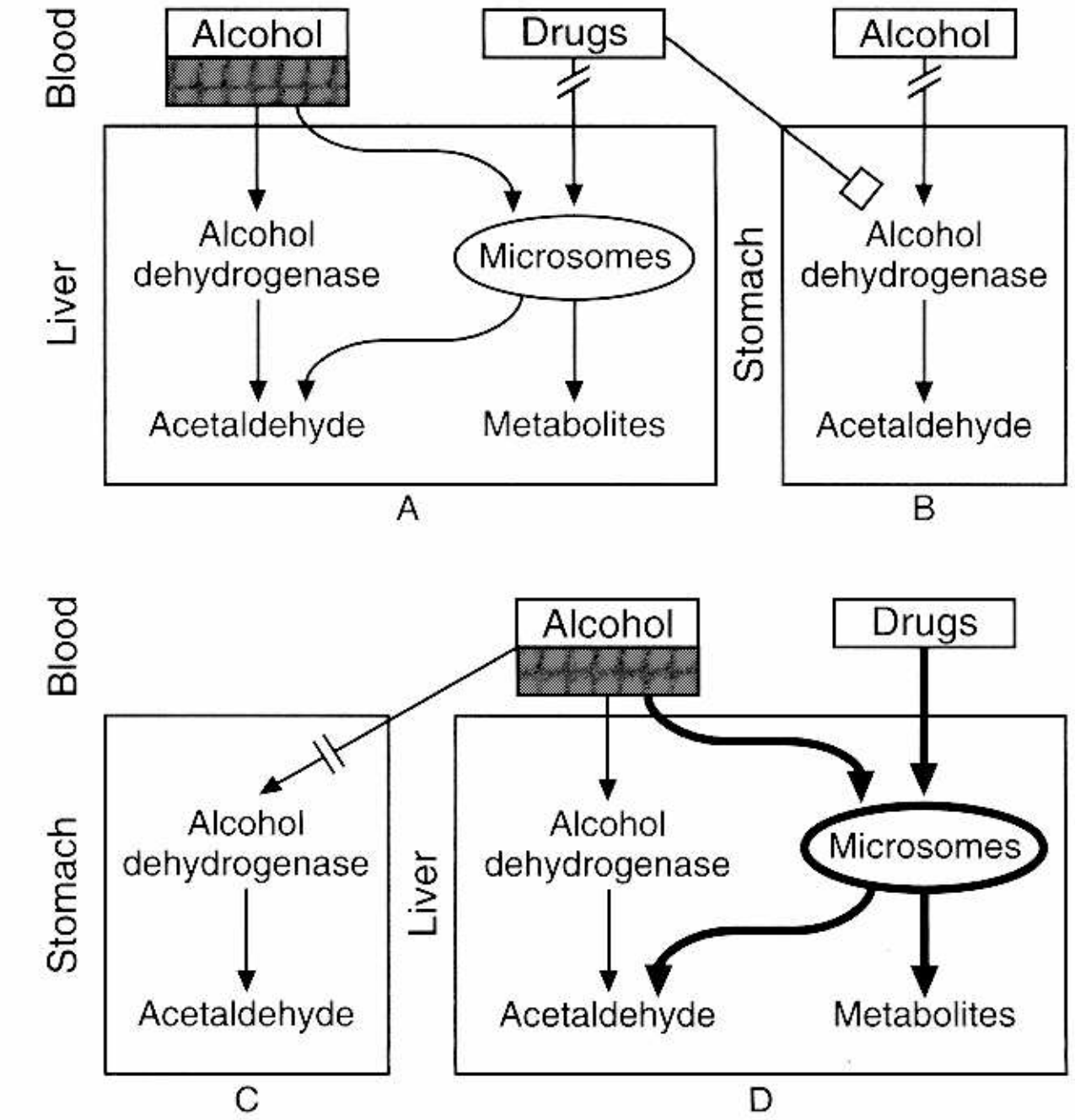
**Table 2**

Representative examples of adaptive immune cell manipulation in animal models of liver fibrosis

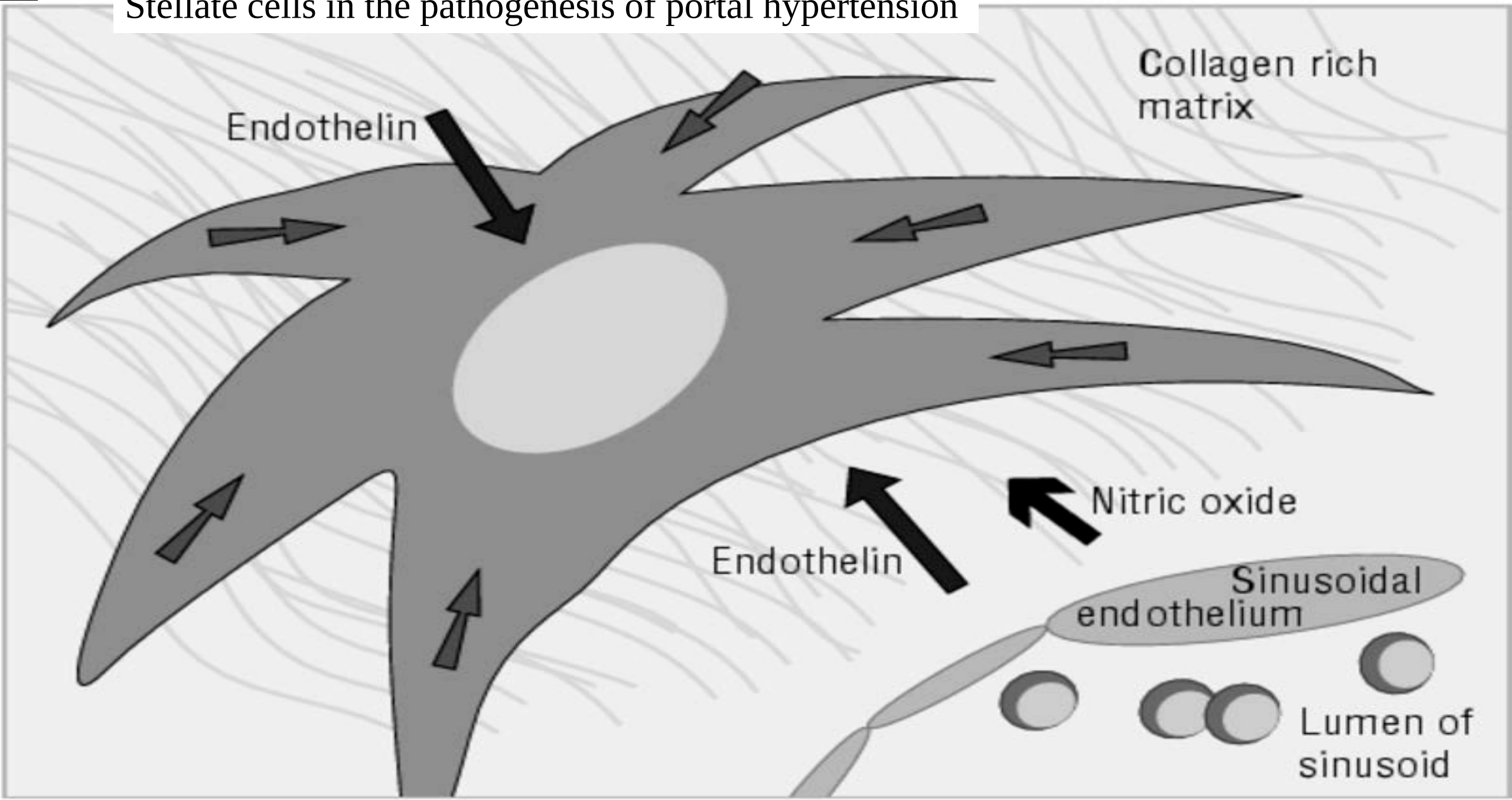
| Cell type | Method of inducing fibrosis | Cell type affected or manipulated | Effect on fibrosis | Refs. |
|---|---|---|---|---|
| T cells | $CCl_4$ intoxication or thioacetamide | Transgenic mice with hepatocyte expression of rat IL-10; adoptive transfer of various lymphocyte subsets to SCID mice | Fibrosis promoted by $CD8^+$ T cells in adoptive transfer experiment; $CD8^+$ T cell–mediated disease is attenuated by recombinant IL-10 | 74 |
| | $CCl_4$ intoxication | Series of $CCl_4$-induced liver injury experiments with mice that lack $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells, or both B and T cells | $CD4^+$, $CD8^+$, and γδ T cells do not substantially affect hepatic fibrosis | 75 |
| | Infection with *Schistosoma mansoni* | Treatment of *S. mansoni*–infected mice with an inhibitor of IL-13 | Development of hepatic fibrosis blocked by IL-13 inhibitor during a Th2-dominated inflammatory response | 76 |
| B cells | $CCl_4$ intoxication | B cell–deficient mice | Absence of B cells attenuates liver fibrosis in an antibody- and T cell–independent manner | 77 |
| | Infection with *S. mansoni* | B cell–deficient mice | Increased hepatic fibrosis | 120 |

Iredale, J. P. J. Clin. Invest. 2007;117:539-548

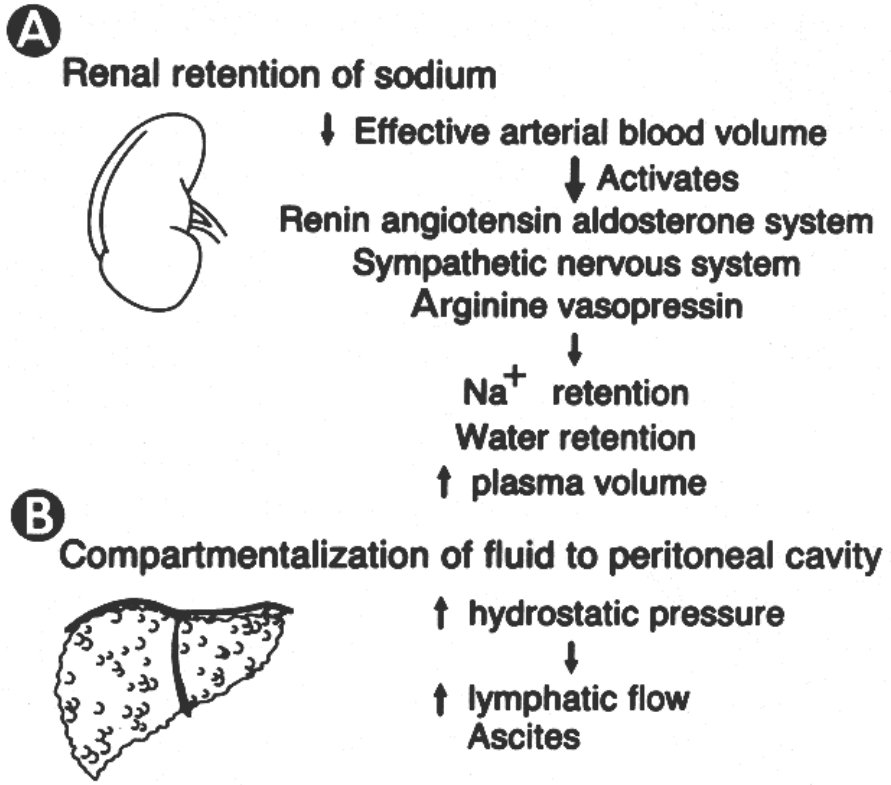
# Alcohol i


Blood
Alcohol
Drugs
Alcohol
Liver
Alcohol dehydrogenase
Microsomes
Acetaldehyde
Metabolites
A
Stomach
Alcohol dehydrogenase
Acetaldehyde
B
Blood
Alcohol
Drugs
Stomach
Alcohol dehydrogenase
Acetaldehyde
C
Liver
Alcohol dehydrogenase
Microsomes
Acetaldehyde
Metabolites
D

# Stellate cells in the pathogenesis of portal hypertension



# Mechanism of Ascites in Cirrhosis

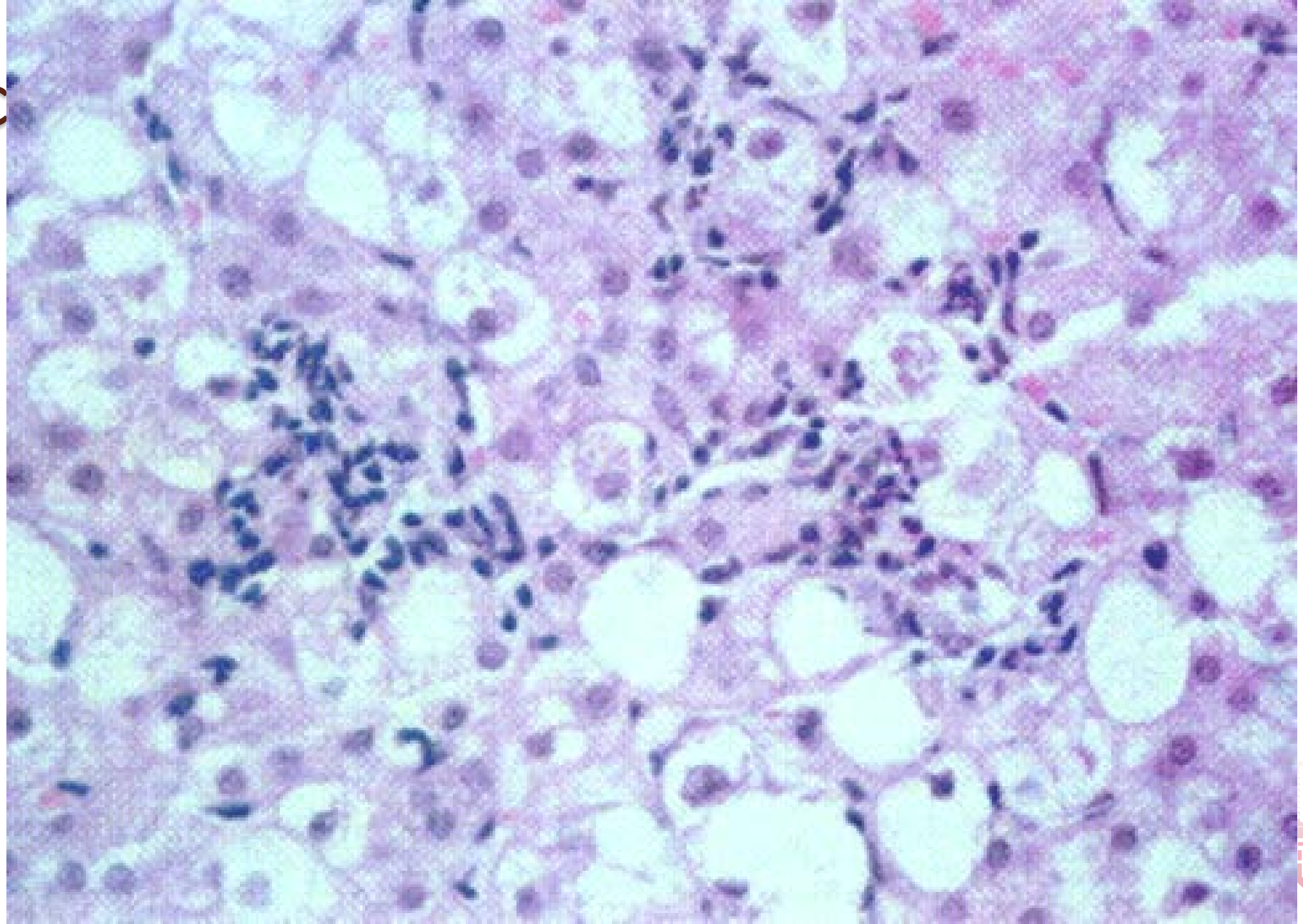


# Non-alcoholic steatohepatitis

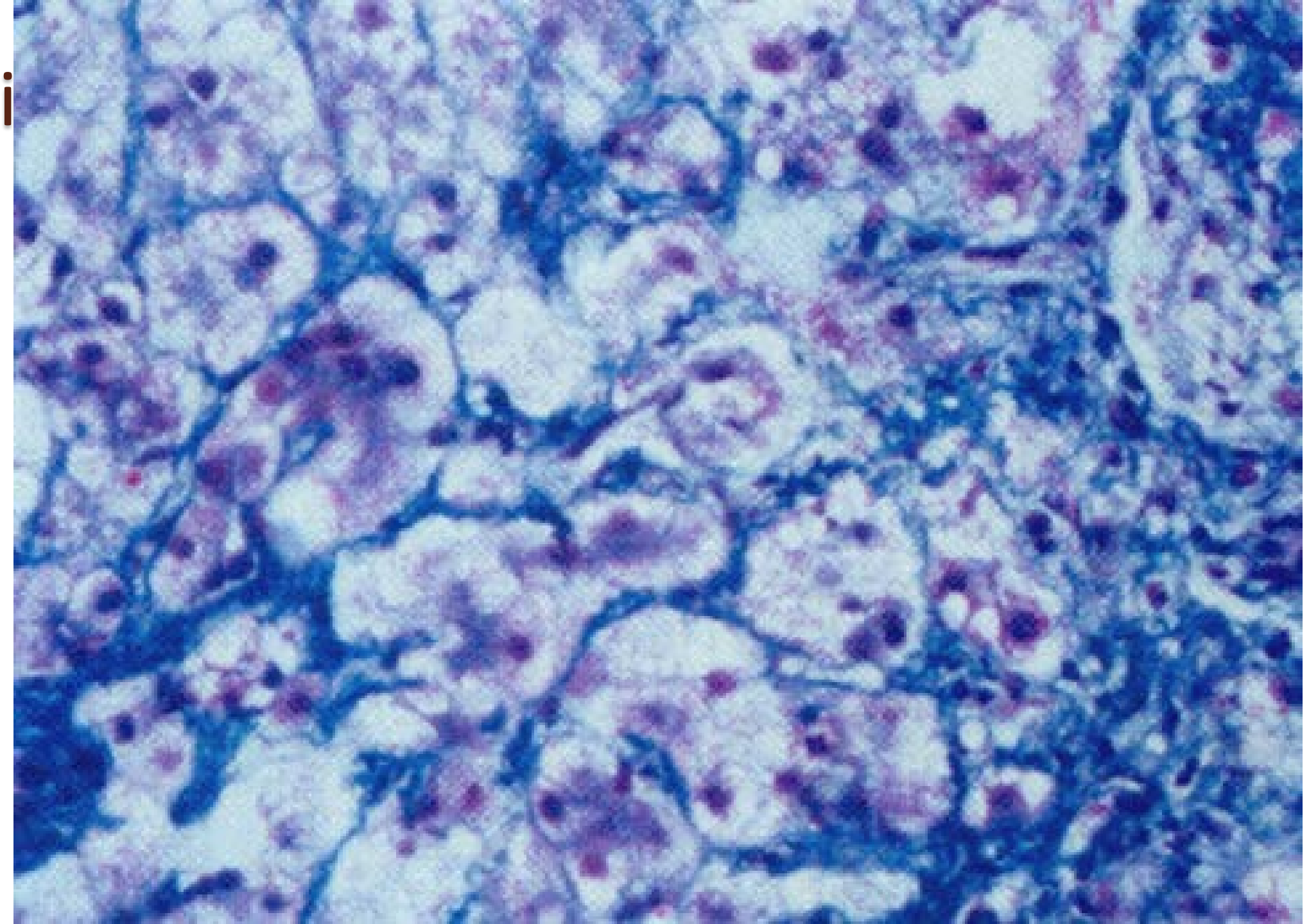
| Reference | No. of patients | Females (%) | Obesity (%) | Diabetes mellitus (%) | Hyper-lipidemia (%) |
|---|---|---|---|---|---|
| Ludwig et al[1] | 20 | 65 | 90 | 50 | 67 |
| Itoh et al[6] | 16 | 75 | 100 | 5 | 63 |
| Diehl et al[7] | 39 | 81 | 71 | 55 | 20 |
| Lee[8] | 49 | 78 | 95 | 51 | NR |
| Powell et al[9] | 42 | 83 | 95 | 36 | 81 |
| Bacon et al[10] | 33 | 42 | 39 | 21 | 21 |
| Laurin et al[11] | 40 | 73 | 70 | 28 | NR |
| Pinto et al[12] | 32 | 75 | 47 | 34 | 28 |

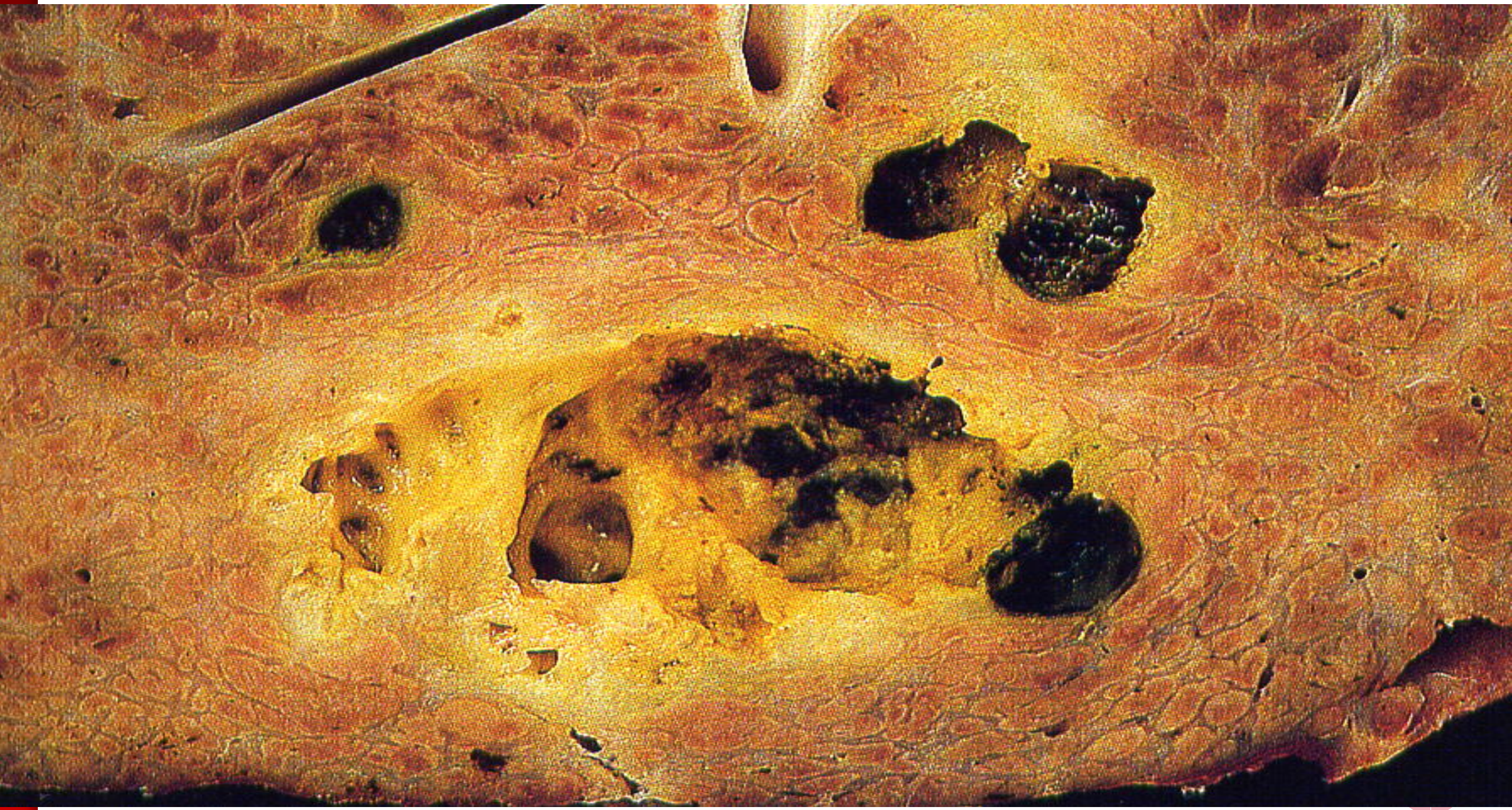
*There is wide variability among these studies regarding definitions used (especially for obesity and diabetes), population sampled, etc, and this greatly limits comparability among studies. NR = not reported.

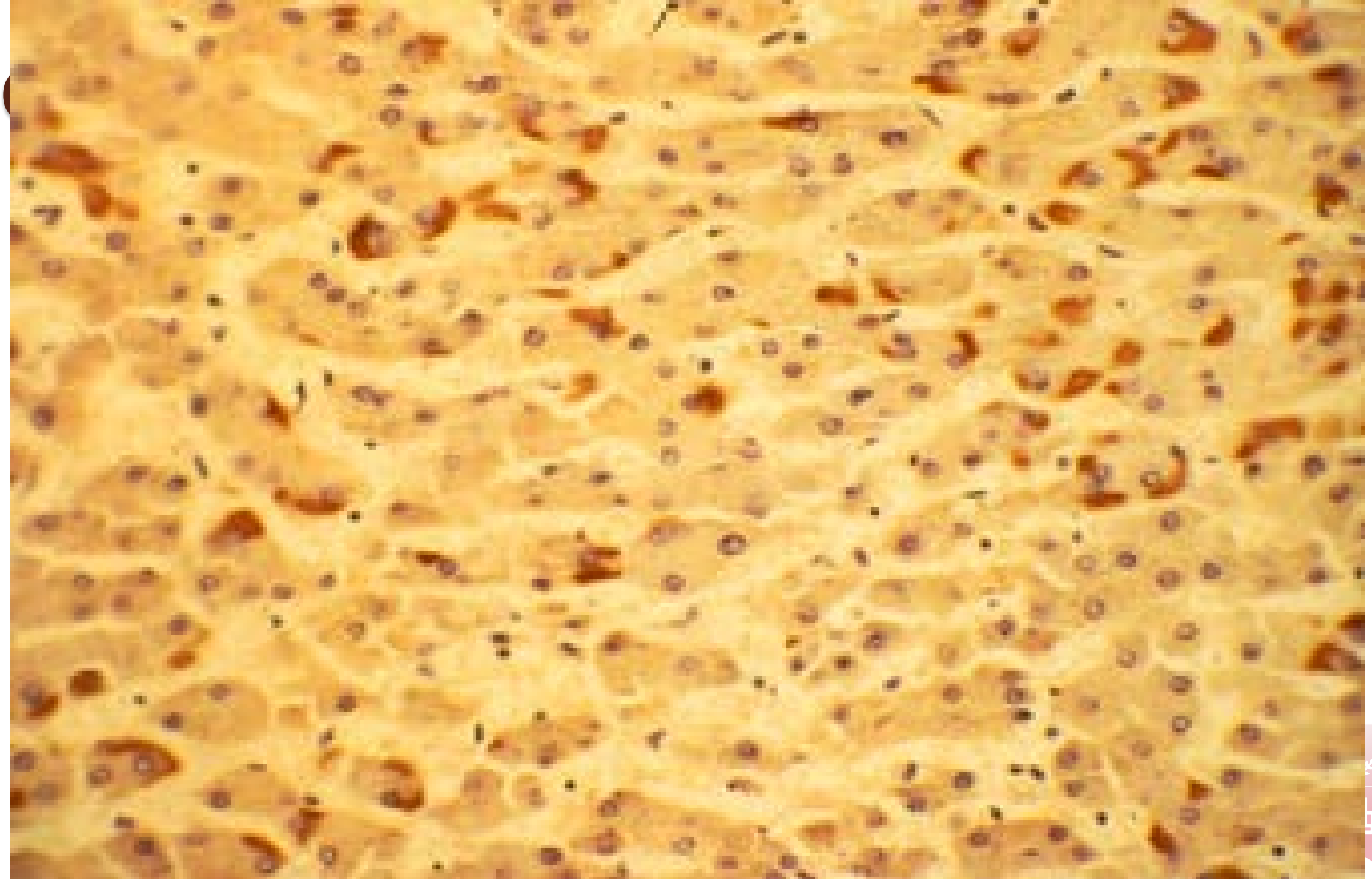
# Mic



# Tri

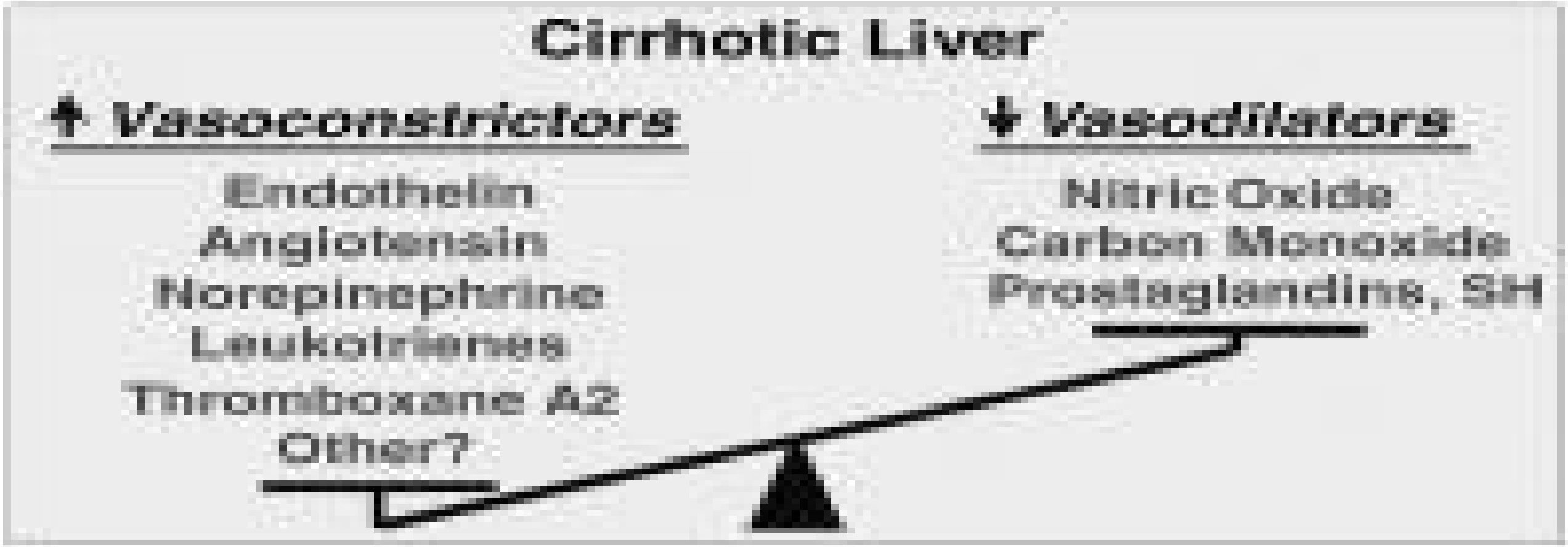


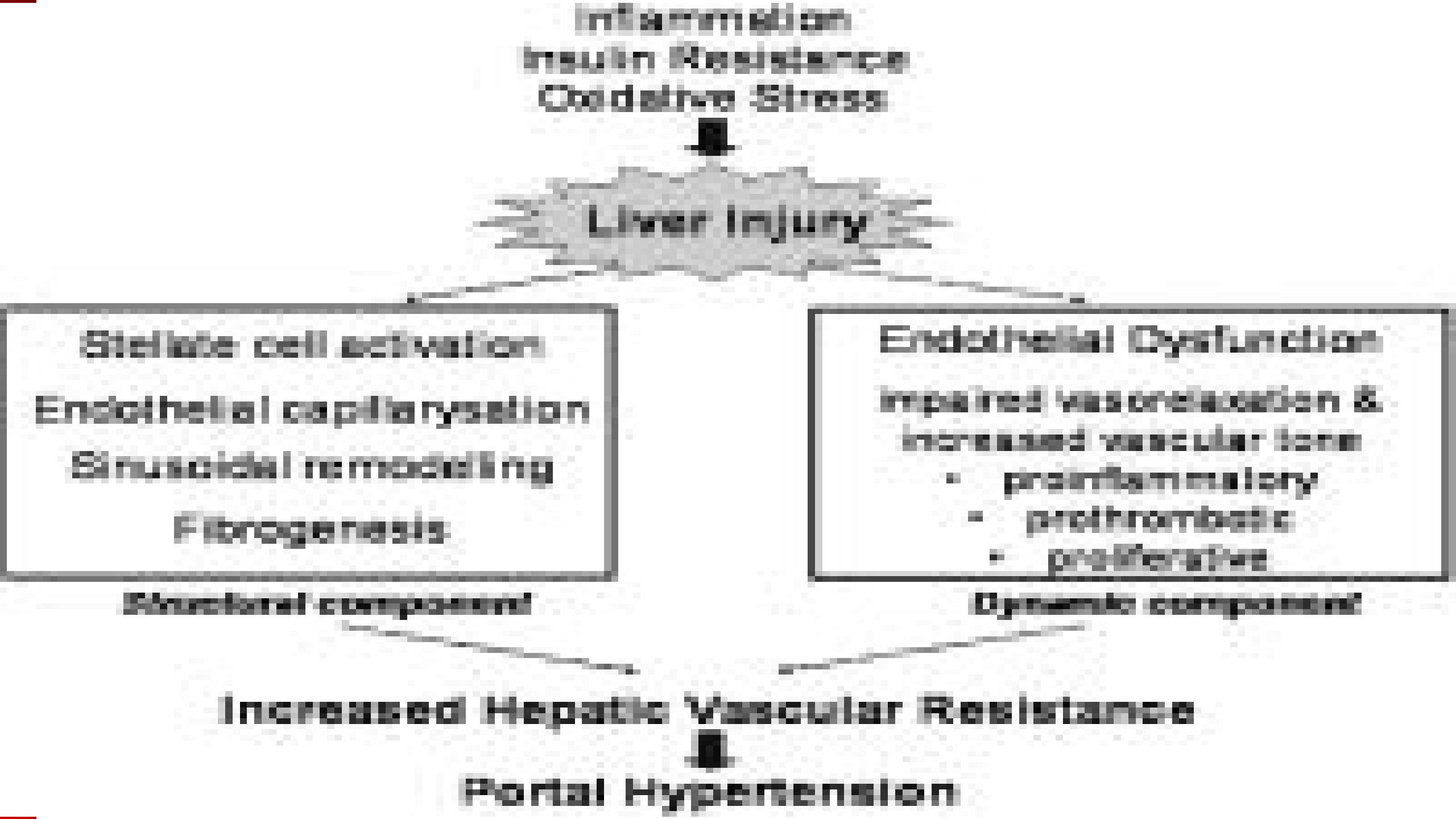




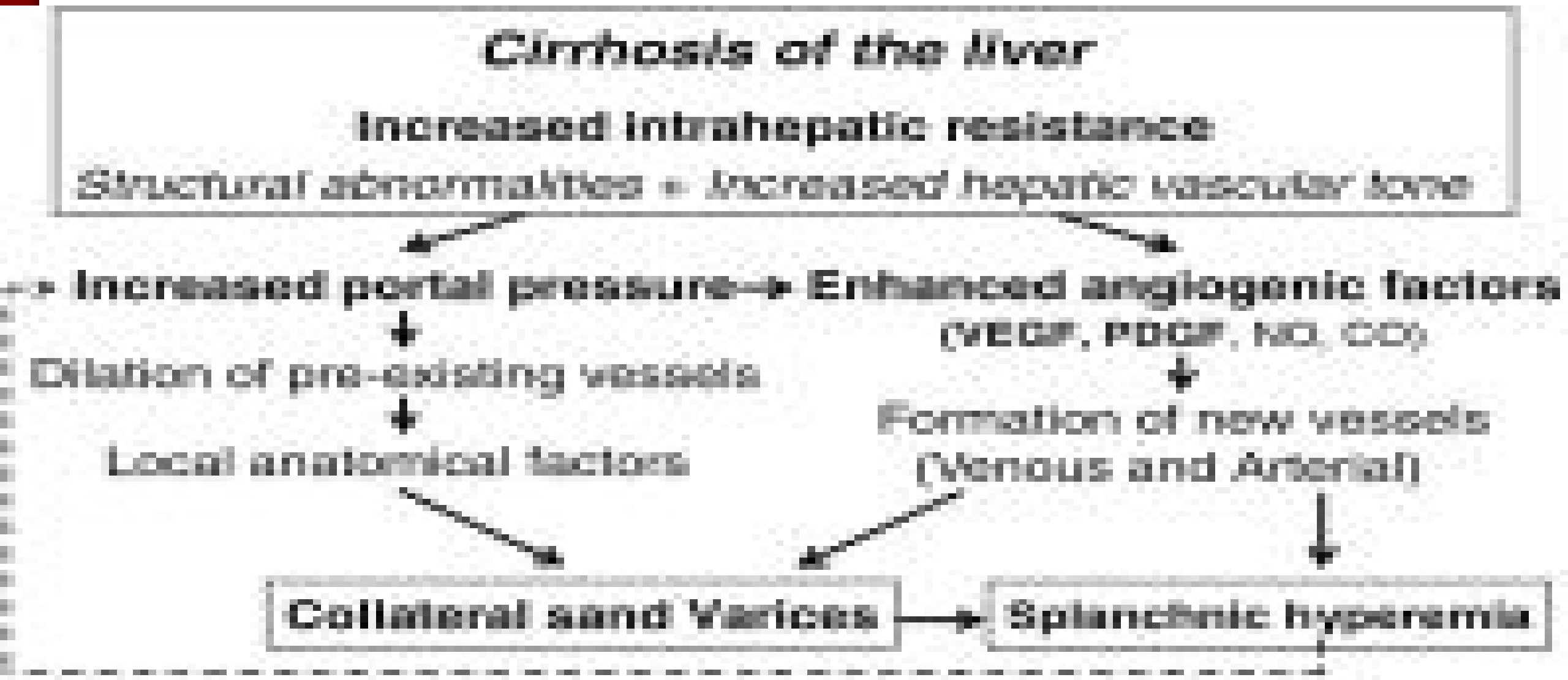

C

# Vasodilator / Vasoconstrictor Imbalance in the Pathogenesis of the Increased Intrahepatic Vascular Resistance in Cirrhosis



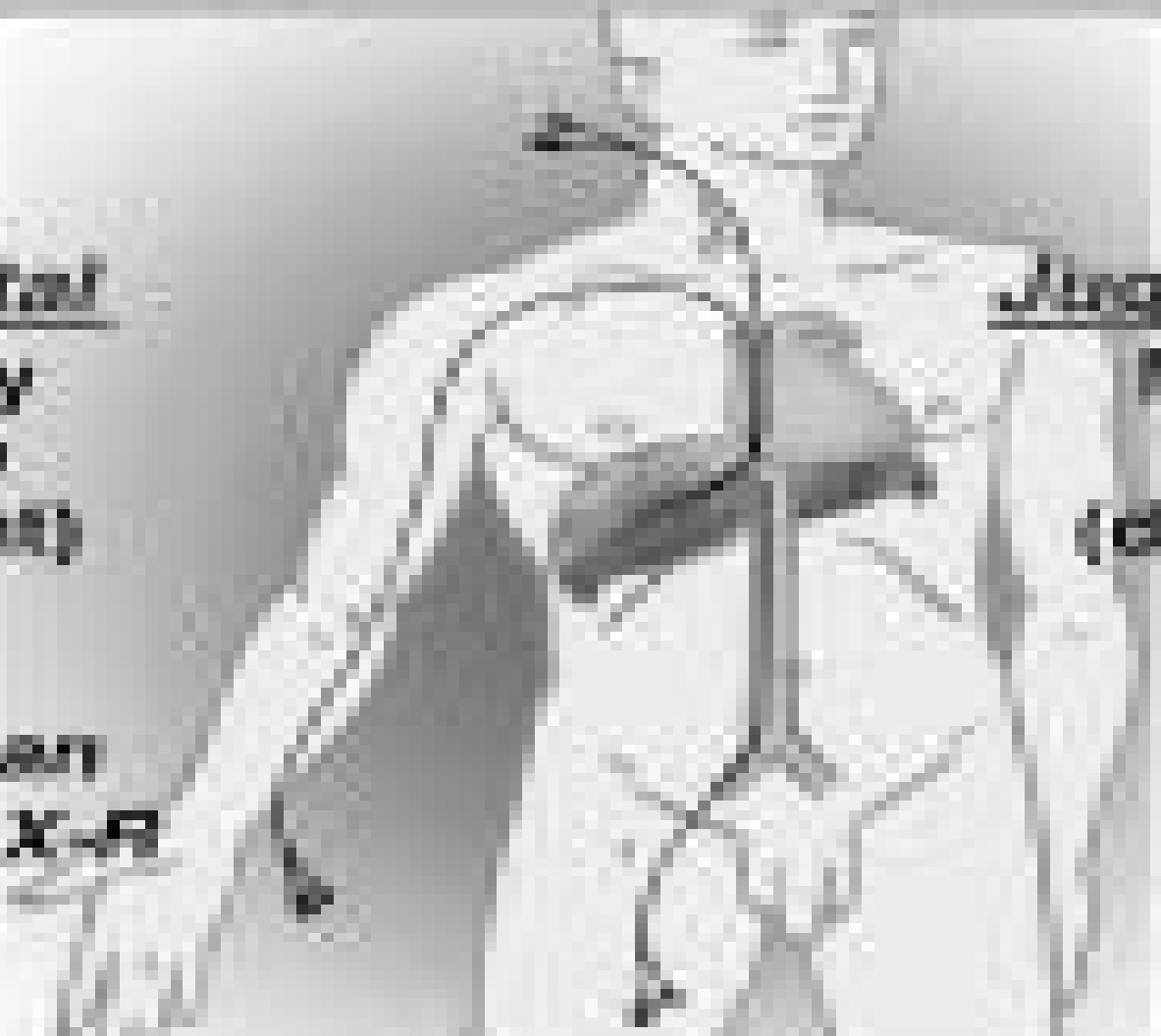

Inflammation
Insulin Resistance
Oxidative Stress
Liver Injury
Stellate cell activation
Endothelial capillarysation
Sinusoidal remodelling
Fibrogenesis
Endothelial Dysfunction
Impaired vasorelaxation &
increased vascular tone
• proinflammatory
• prothrombotic
• proliferative
Structural component
Dynamic component
Increased Hepatic Vascular Resistance
Portal Hypertension

| Target | Mechanism | Drugs |
|---|---|---|
| Cirrhosis | HCV, HBV | Interferons, antivirals |
| | Alcohol, NASH | Abstinence, weight loss, antioxidants |
| | Hemochromatosis | Phlebotomy |
| | Autoimmune | Corticosteroids |
| Vascular thrombosis | Thrombophilic disorders | Anticoagulation |
| Increased hepatic vascular tone | Decreased NO release | NO donors (liver specific) |
| | | NOS3/aAKT gene transfer |
| | | Statins |
| | | BH4 |
| | | Antioxidants |
| | Increased TX-A2 | Thromboxane inhibitors |
| | | COX-1 inhibitors |
| | Increased endothelin | ET antagonists |
| Angiogenesis | Increased VEGF, PDGF | Monoclonal antibodies |
| | | VEGF-R2 antagonists |
| | | Mixed VEGF/PDGF blockers |


Cirrhosis of the liver
Increased intrahepatic resistance
Structural abnormalities + Increased hepatic vascular tone
Increased portal pressure
Enhanced angiogenic factors
(VEGF, PDGF, NO, CO)
Dilation of pre-existing vessels
Formation of new vessels
(Venous and Arterial)
Local anatomical factors
Collateral and Varices
Splanchnic hyperemia

# HVPG

*Invasive, but depends on venous access site*



**Antecubital**

**Minimally invasive (outpatient)**

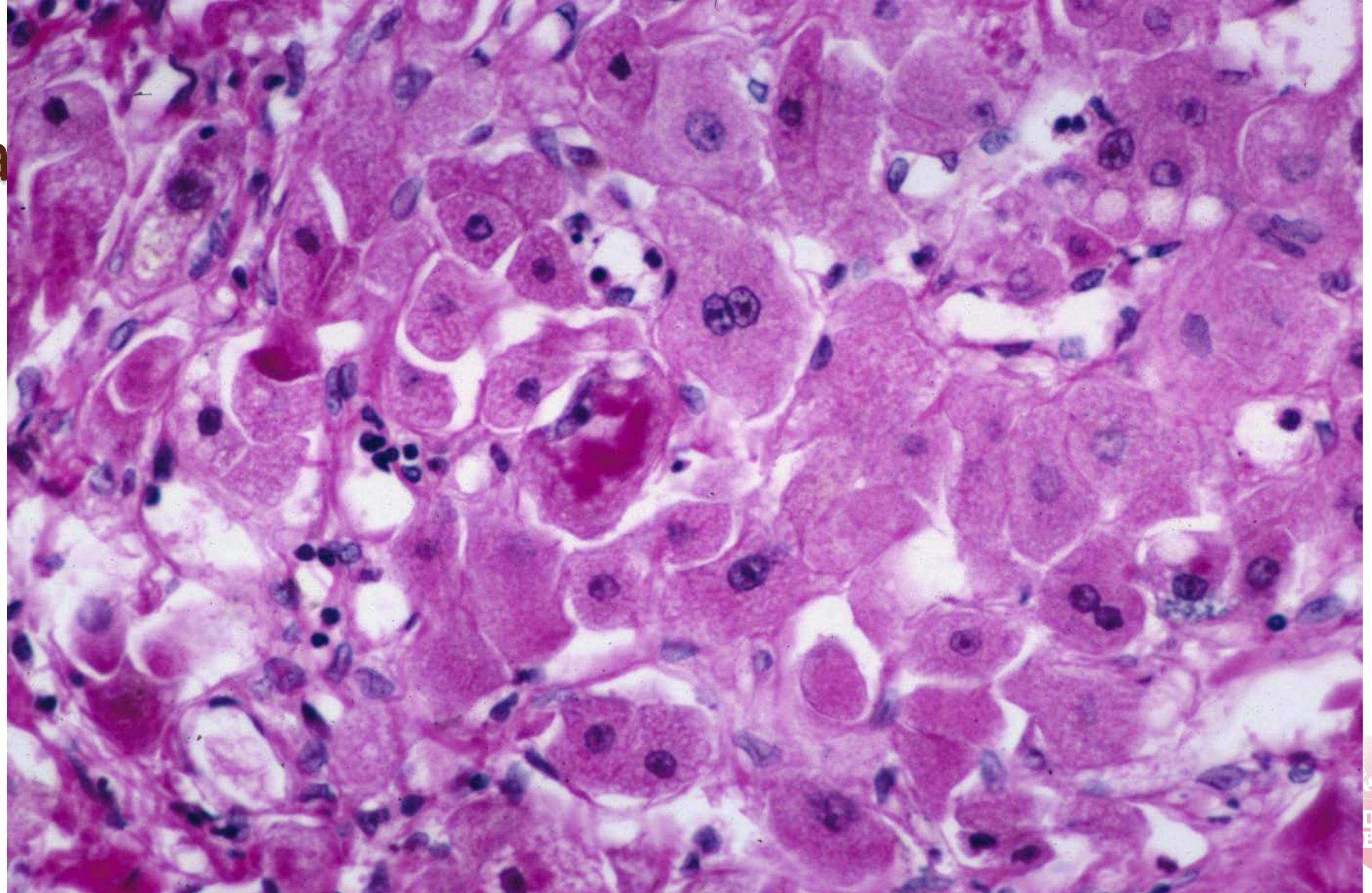
**~ CT scan contrast X-R**

**Jugular/Femoral**

**Moderately invasive (day hospital)**

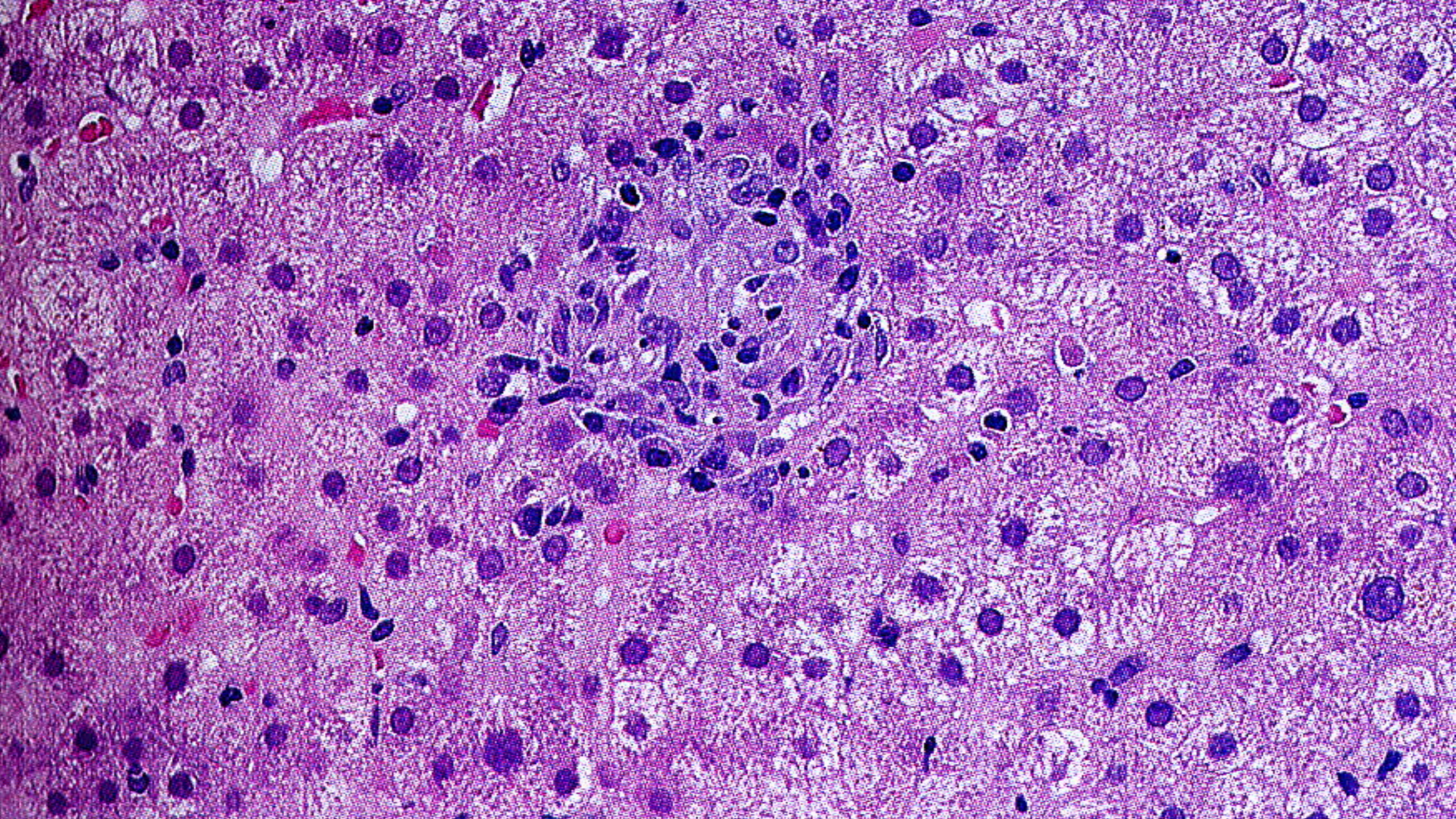
**~ endoscopy sedatedproc**

Ma



# Differential Diagnosis of Fatty Liver

- Metabolic factors
  - Obesity
  - Diabetes and hyperglycemia
  - Hyperlipidemia
  - Rapid weight loss
  - Acute starvation
  - Intravenous glucose therapy in the week before death
  - Total parenteral nutrition
- Surgical procedures
  - Jejunal bypass
  - Gastroplasty for morbid obesity
  - Biliopancreatic diversion
  - Extensive small-bowel resection
- Drug treatments
  - Amiodarone
  - Perhexiline maleate
  - Glucocorticoids
  - Synthetic estrogens
  - Tamoxifen
- Miscellaneous factors
  - Jejunal diverticulosis with bacterial overgrowth
  - Partial lipodystrophy
  - Abetalipoproteinemia
  - Weber–Christian disease



# If AMA is pathogenetic why is disease limited to the liver?

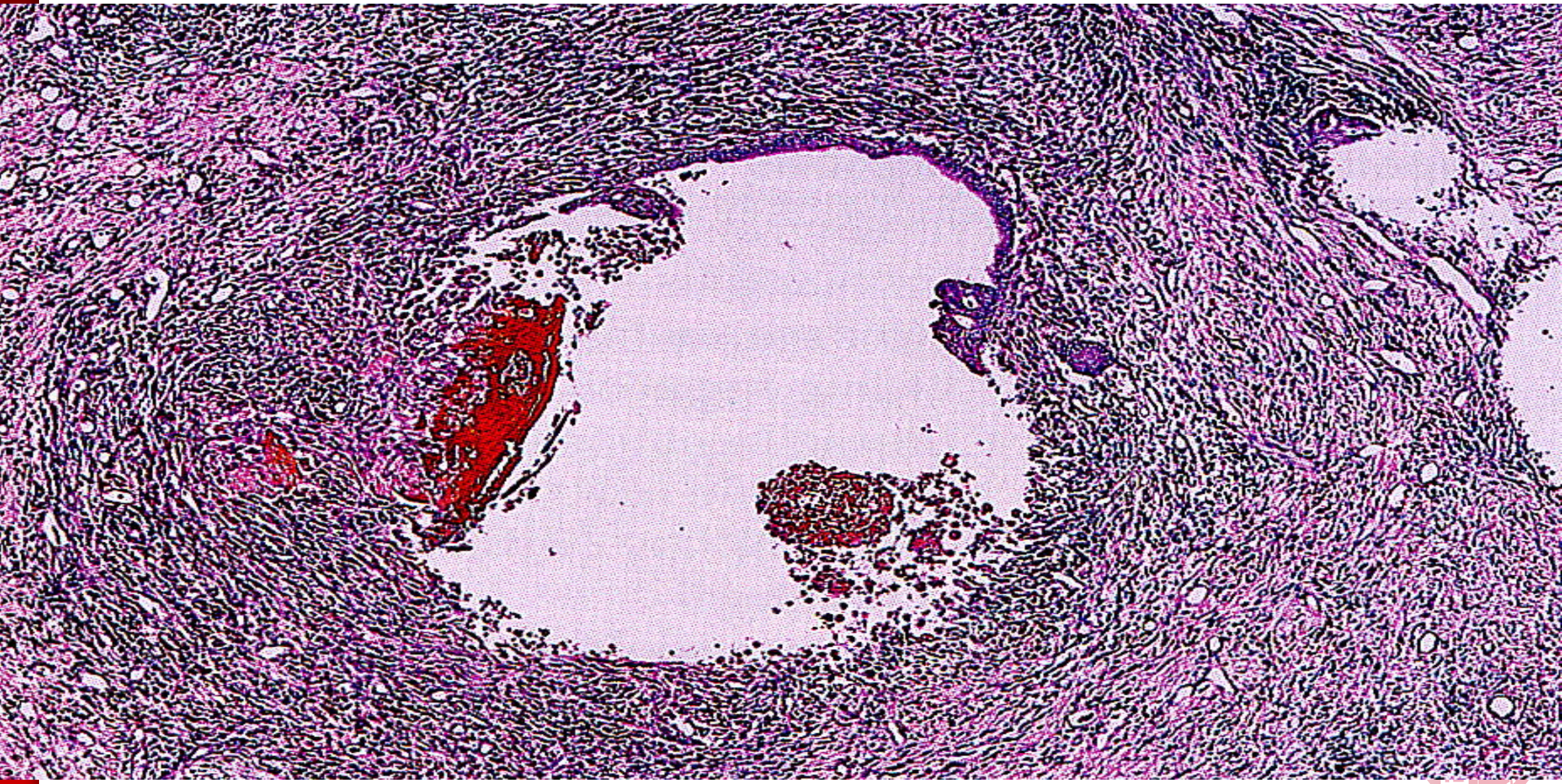
Biliary epithelial cells show aberrant cellular expression of
an antigen that reacts with AMA

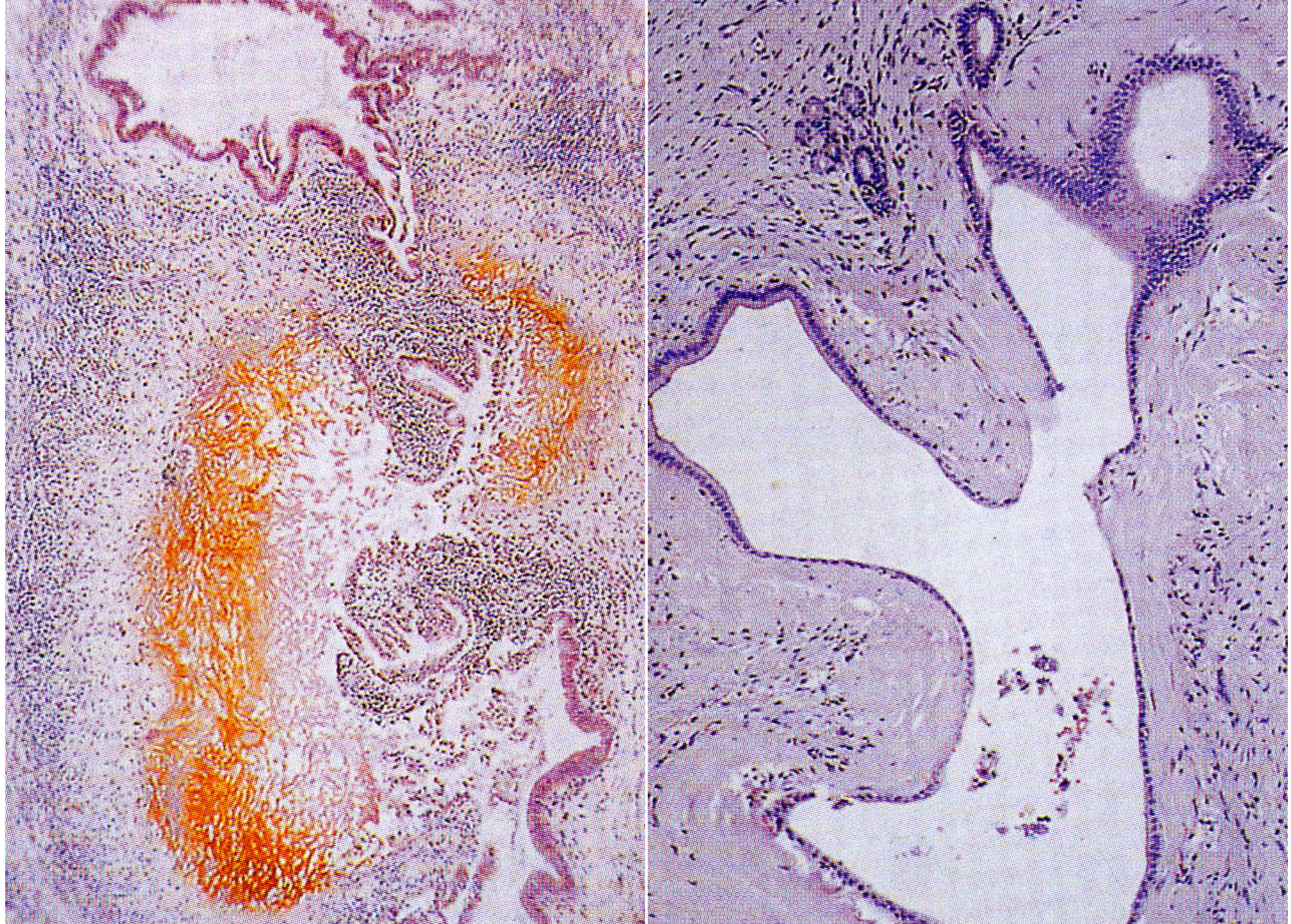
- ? Molecular Mimicry (Xenobiotic vs. Infection-related)
- ? Altered form of Mitochondrial PDC-E2

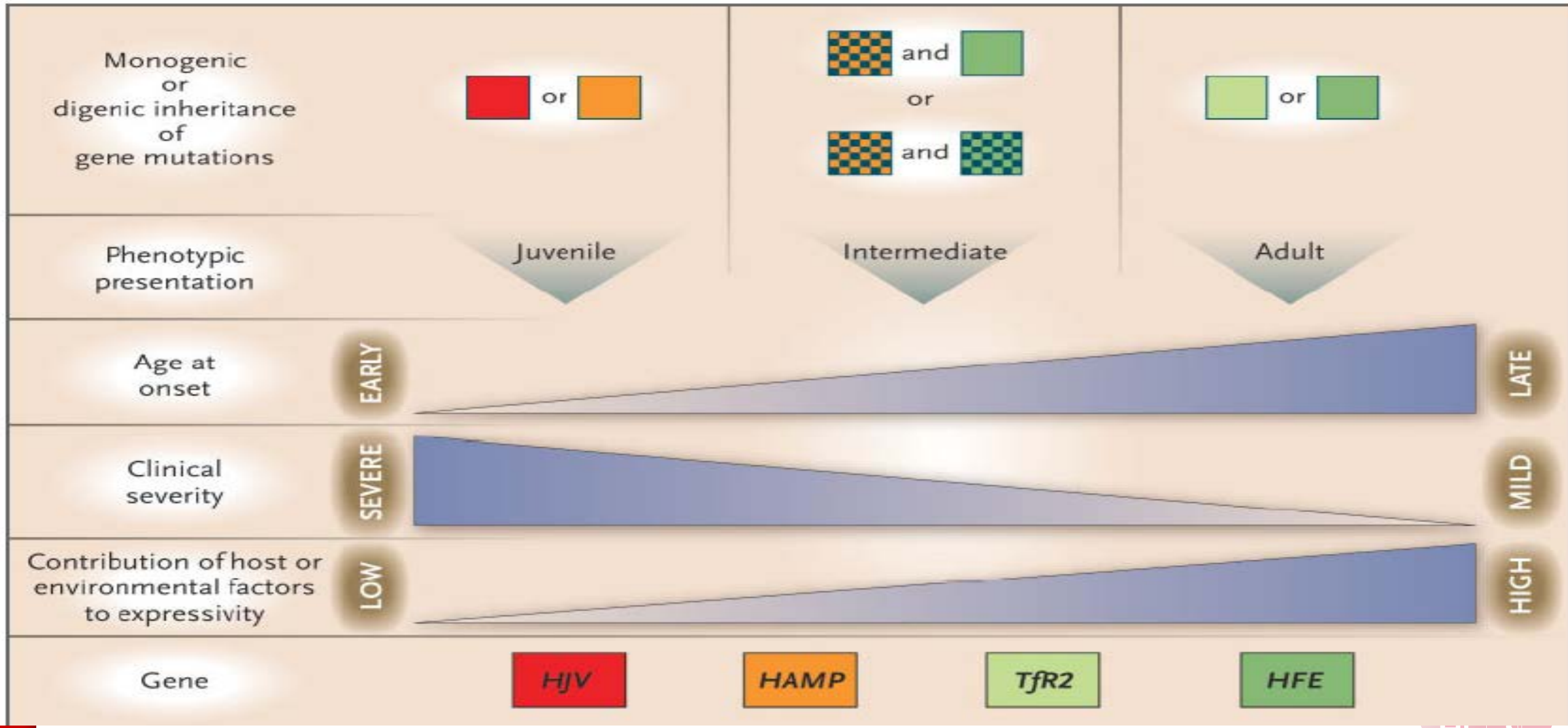
Aberrent expression of Antigen may be seen without inflammation

Is chronic viral/bacterial infection involved?

- Clustering of cases
- Increase in 1st degree relatives without HLA/genetic association
- PBC is not found in children
- Lack of response to immunosuppression
- Recurrs in liver transplants



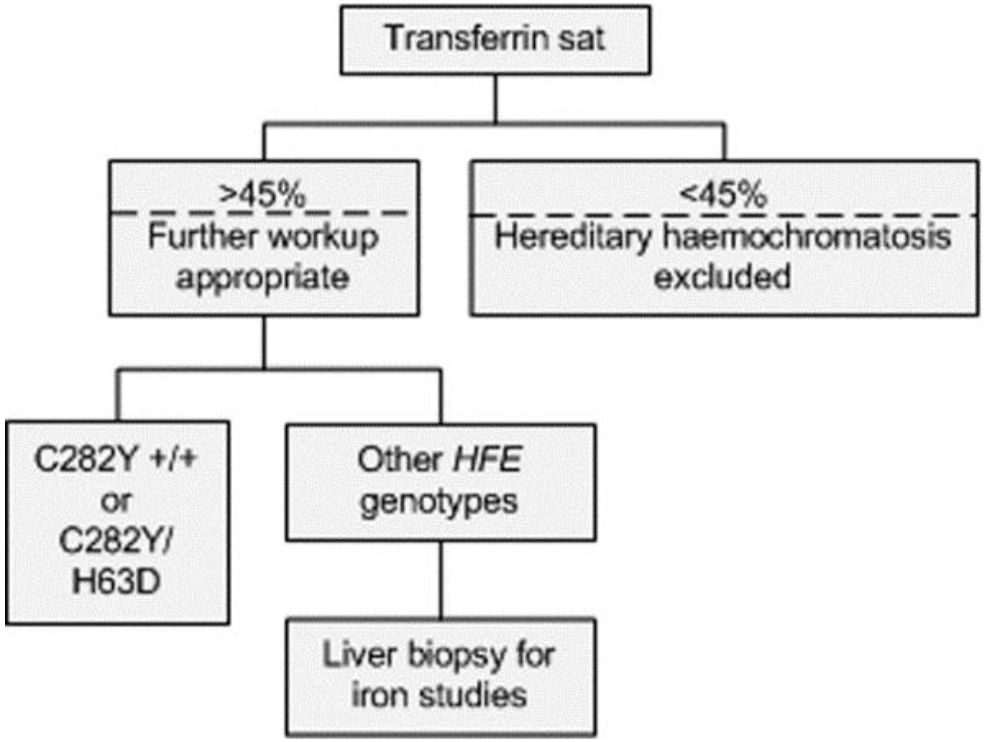



Monogenic or digenic inheritance of gene mutations
or
and
or
and
or
Phenotypic presentation
Juvenile
Intermediate
Adult
Age at onset
EARLY
LATE
Clinical severity
SEVERE
MILD
Contribution of host or environmental factors to expressivity
LOW
HIGH
Gene
HJV
HAMP
TfR2
HFE

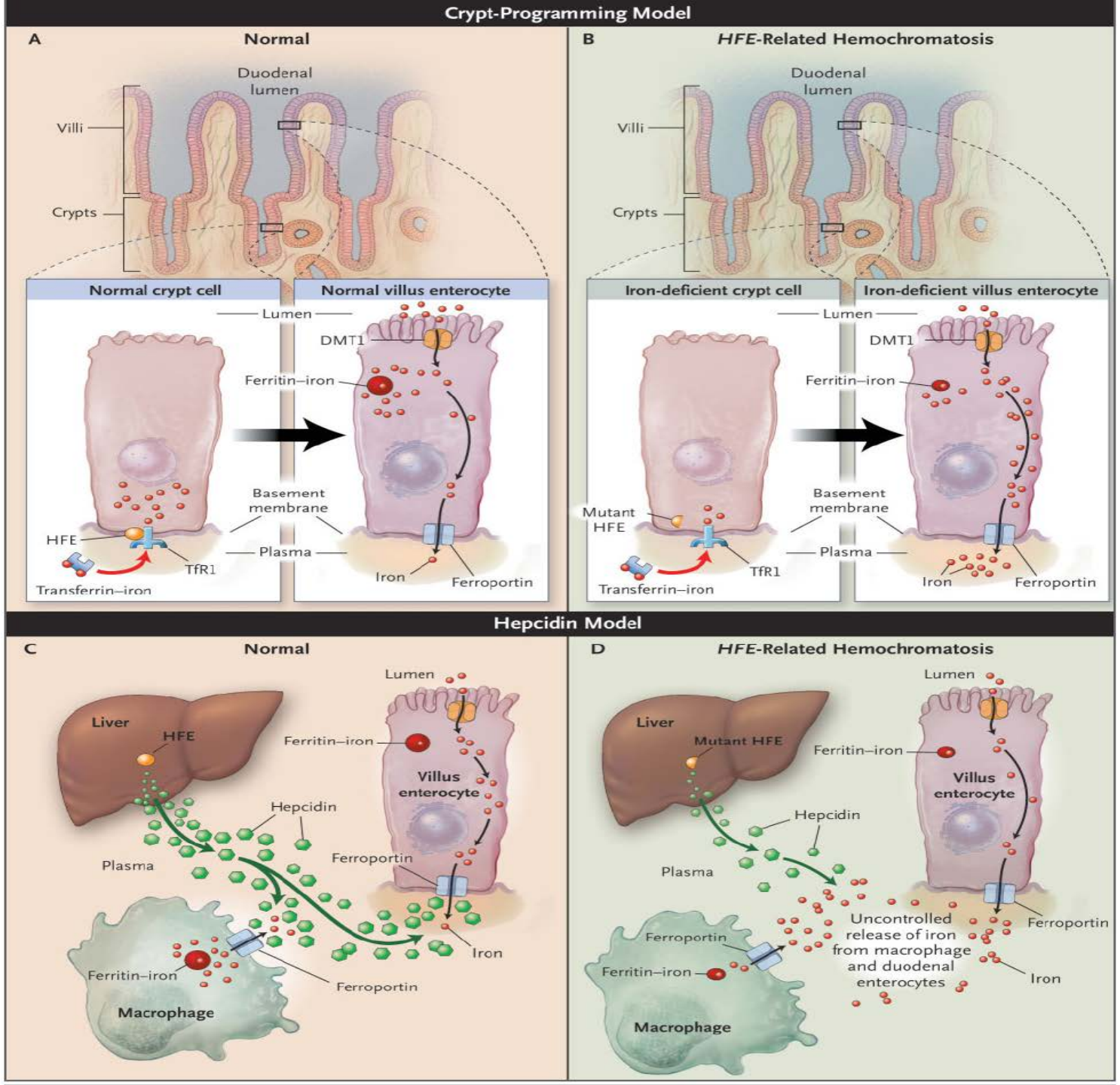
# DDX: iron o

| Types of Iron Overload | Cause |
|---|---|
| Primary Iron Overload | |
| HFE gene mutation-associated hemochromatosis (hereditary hemochromatosis) | C282Y homozygotes |
| | C282Y simple heterozygotes |
| | H63D homozygotes |
| | Compound heterozygotes |
| Non-HFE-associated hemochromatosis | Autosomal dominant (South Pacific region) |
| | Sporadic familial clusters |
| | Nonhereditary |
| | African iron overload |
| | Juvenile hemochromatosis |
| | Atransferrinemia |
| | Aceruloplasminemia |
| | Friedreich ataxia |
| Secondary iron overload and miscellaneous causes | Ineffective erythropoiesis |
| | Chronic anemias (thalassemia major, sideroblastic anemia) |
| | Multiple transfusions |
| | Primary liver diseases |
| | Porphyria cutanea tarda |
| | Iatrogenic (parenteral or oral) |
| | Chronic hemodialysis |

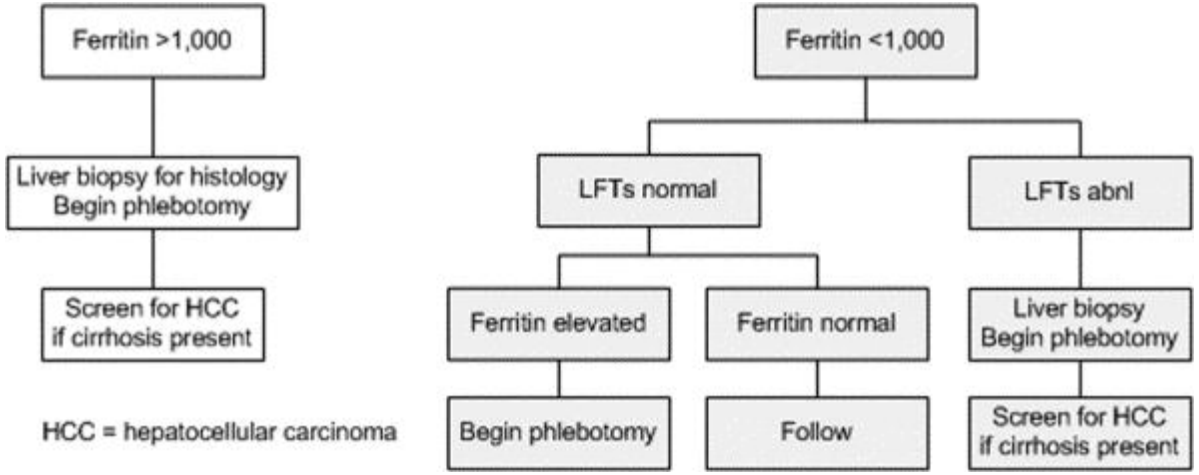
# Fig. 2.




Algorithm for the diagnosis of HH-HFE.

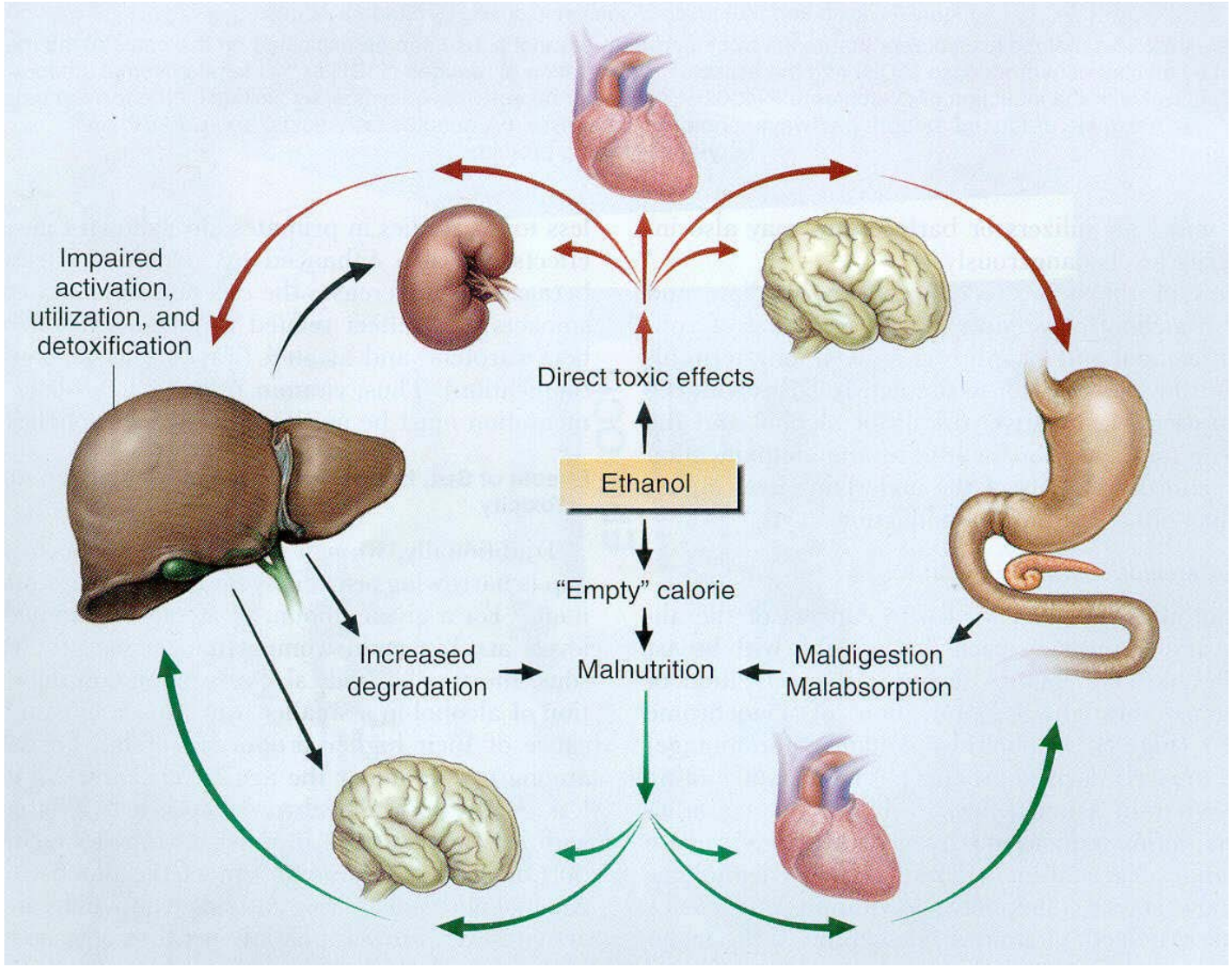

Crypt-Programming Model
A
Normal
Duodenal lumen
Villi
Crypts
Normal crypt cell
Normal villus enterocyte
Lumen
DMT1
Ferritin–iron
Basement membrane
HFE
TfR1
Plasma
Transferrin–iron
Iron
Ferroportin
B
HFE-Related Hemochromatosis
Duodenal lumen
Villi
Crypts
Iron-deficient crypt cell
Iron-deficient villus enterocyte
Lumen
DMT1
Ferritin–iron
Mutant HFE
Basement membrane
TfR1
Plasma
Transferrin–iron
Iron
Ferroportin
Hepcidin Model
C
Normal
Lumen
Liver
HFE
Ferritin–iron
Villus enterocyte
Hepcidin
Plasma
Ferroportin
Iron
Ferritin–iron
Ferroportin
Macrophage
D
HFE-Related Hemochromatosis
Lumen
Liver
Mutant HFE
Ferritin–iron
Villus enterocyte
Hepcidin
Plasma
Uncontrolled release of iron from macrophage and duodenal enterocytes
Ferroportin
Iron
Ferroportin
Ferritin–iron
Macrophage

# Fig. 3.

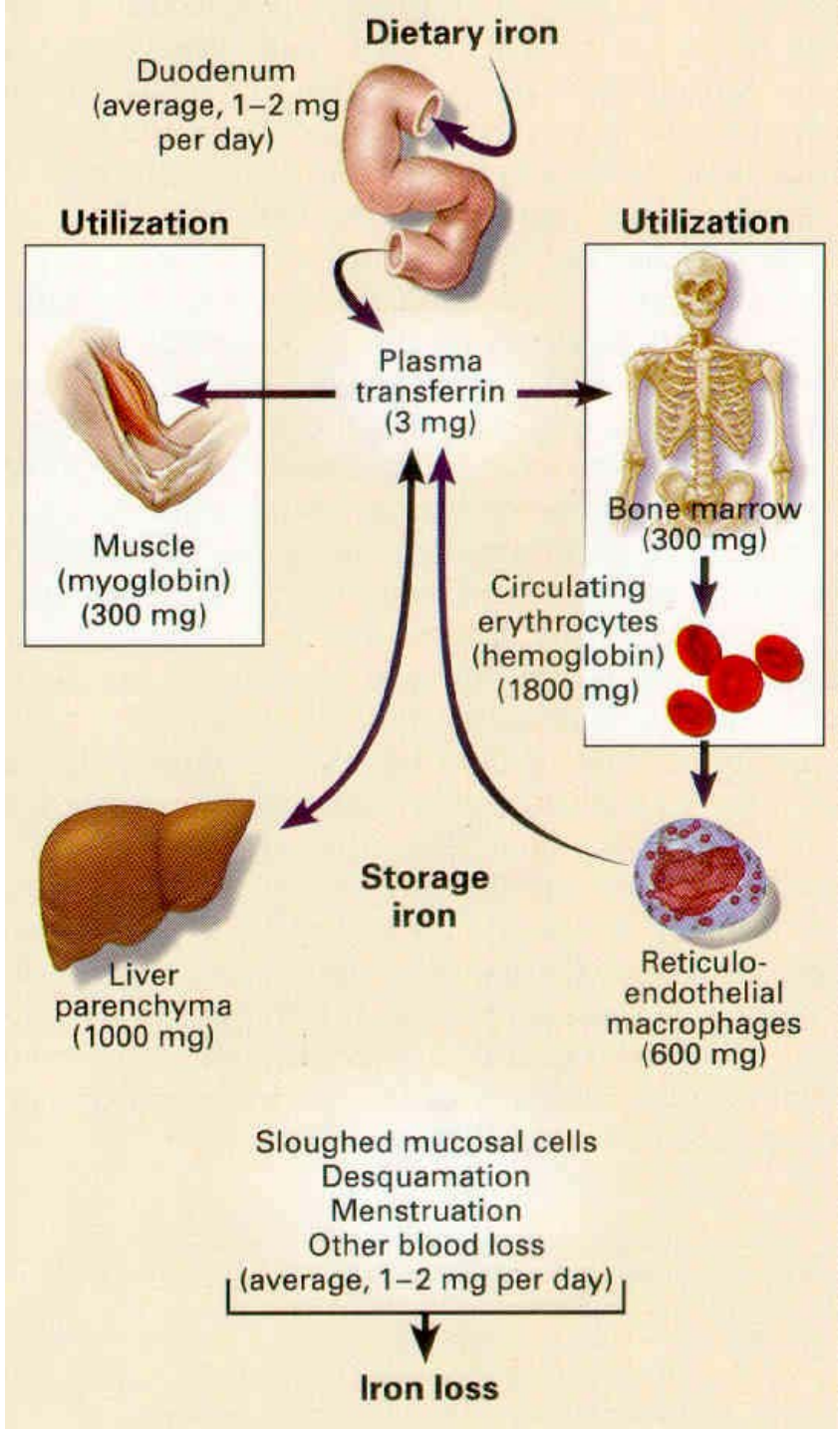



Algorithm for the management of HH-HFE.

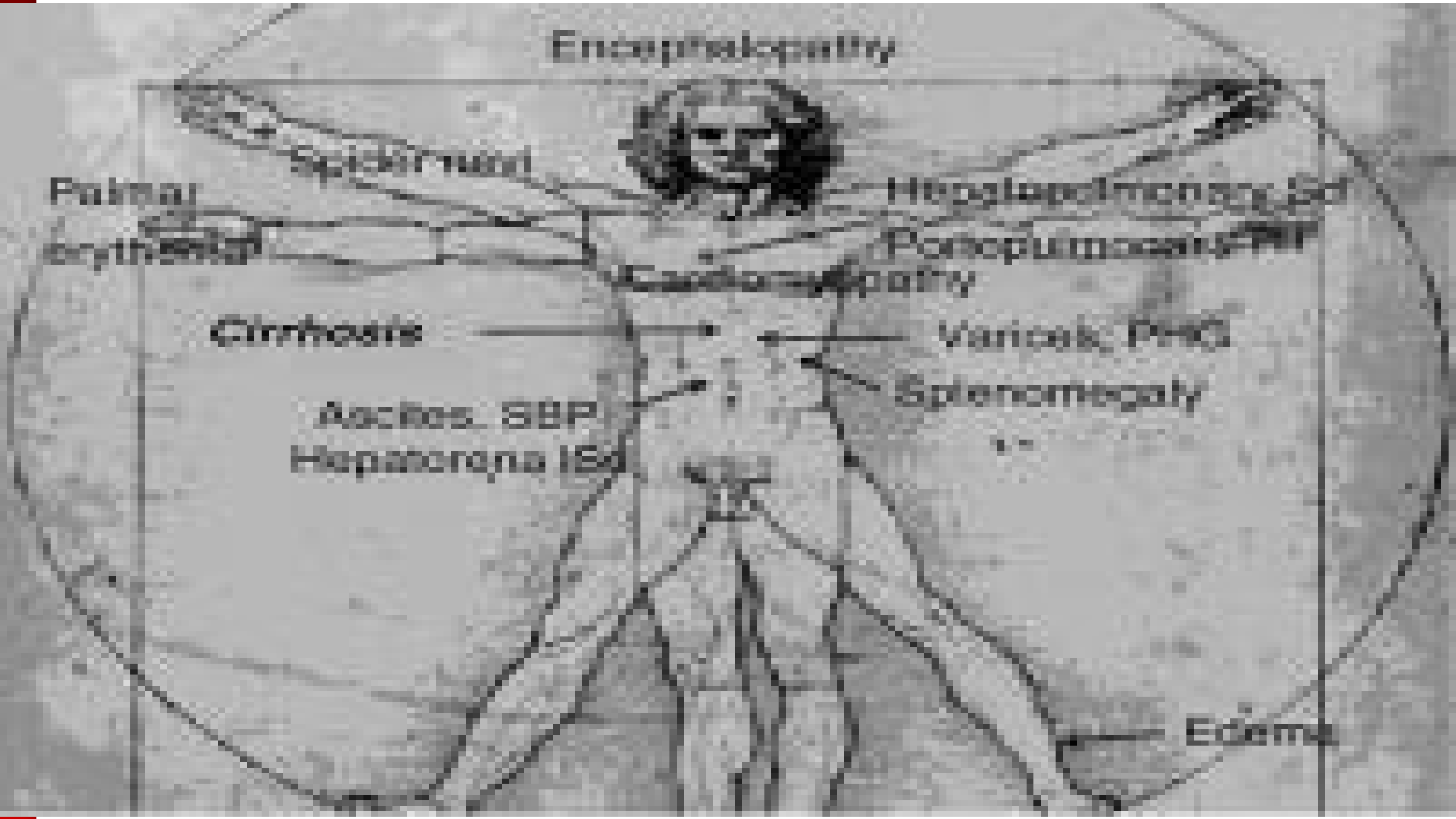
# Adverse effects of alcohol



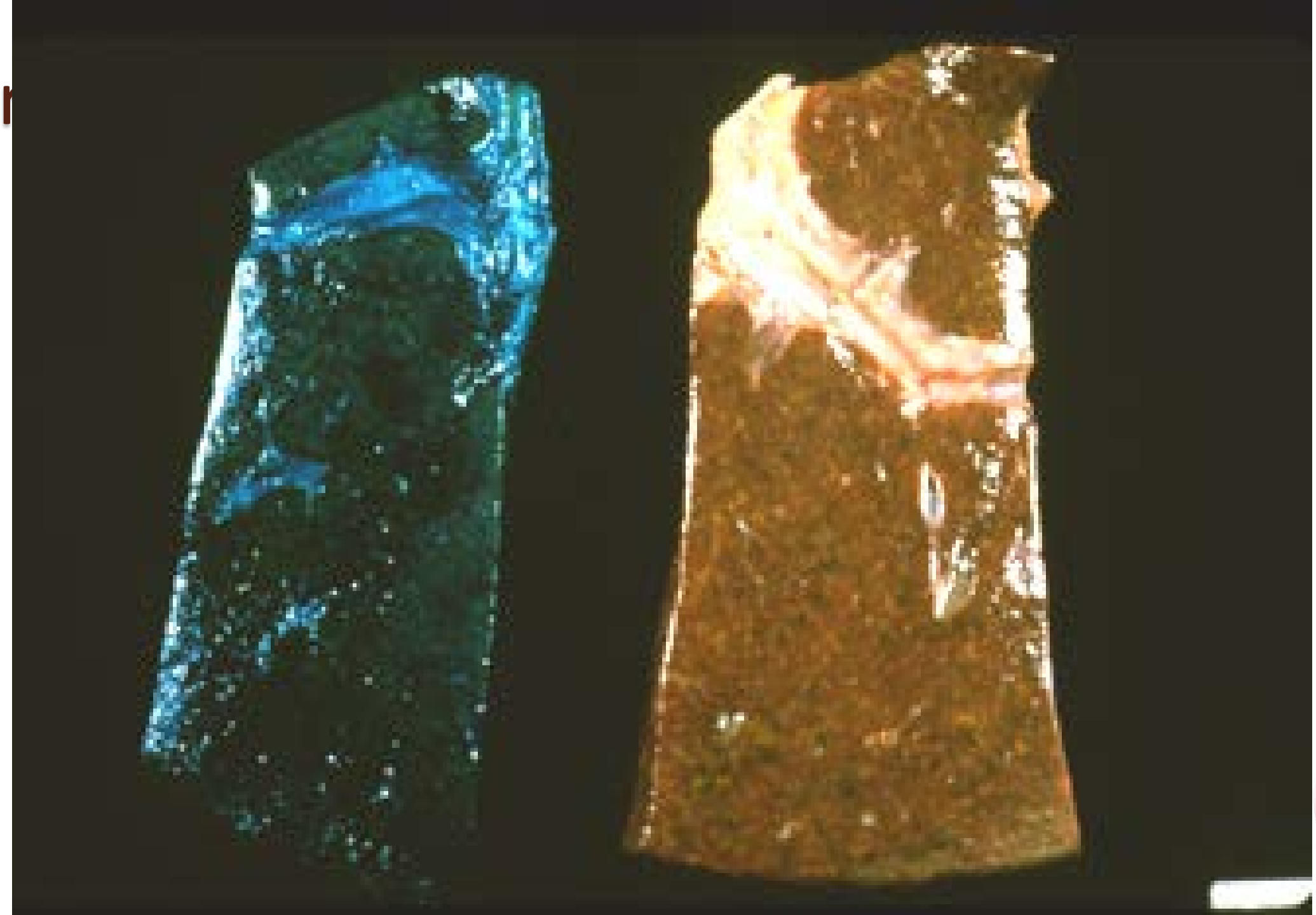
# Iron metabo



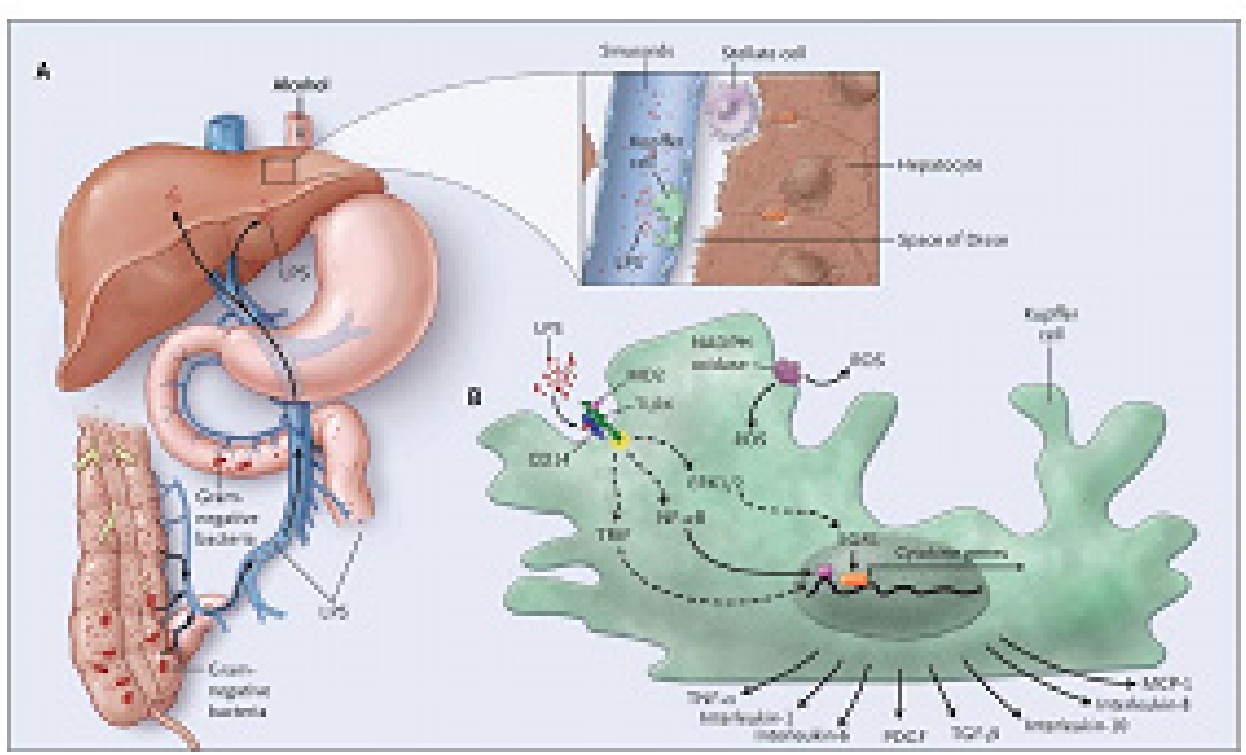

**Iron Metabolism**

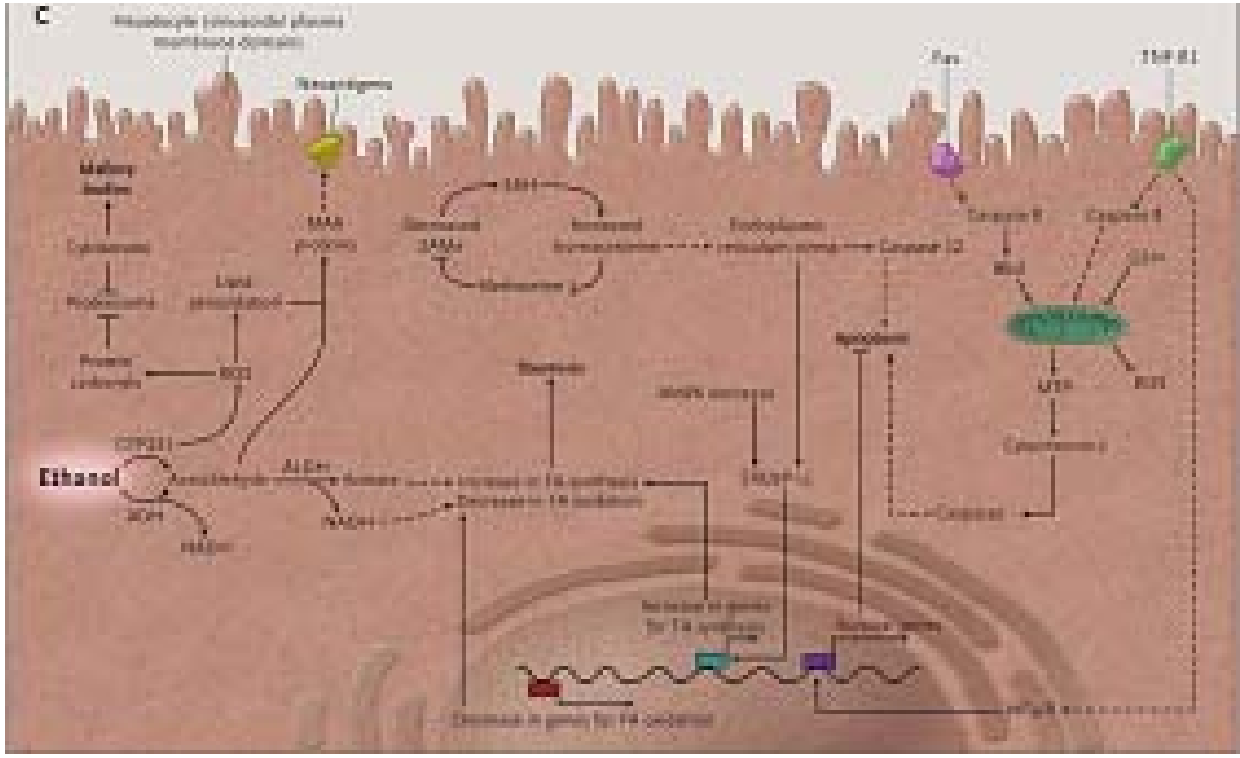

Encephalopathy
Spider naevi
Palmar erythema
Hypogonadism
Cirrhosis
Varicose veins
Splenomegaly
Ascites, SBP
Hepatorenal syndrome
Oedema

# Gr



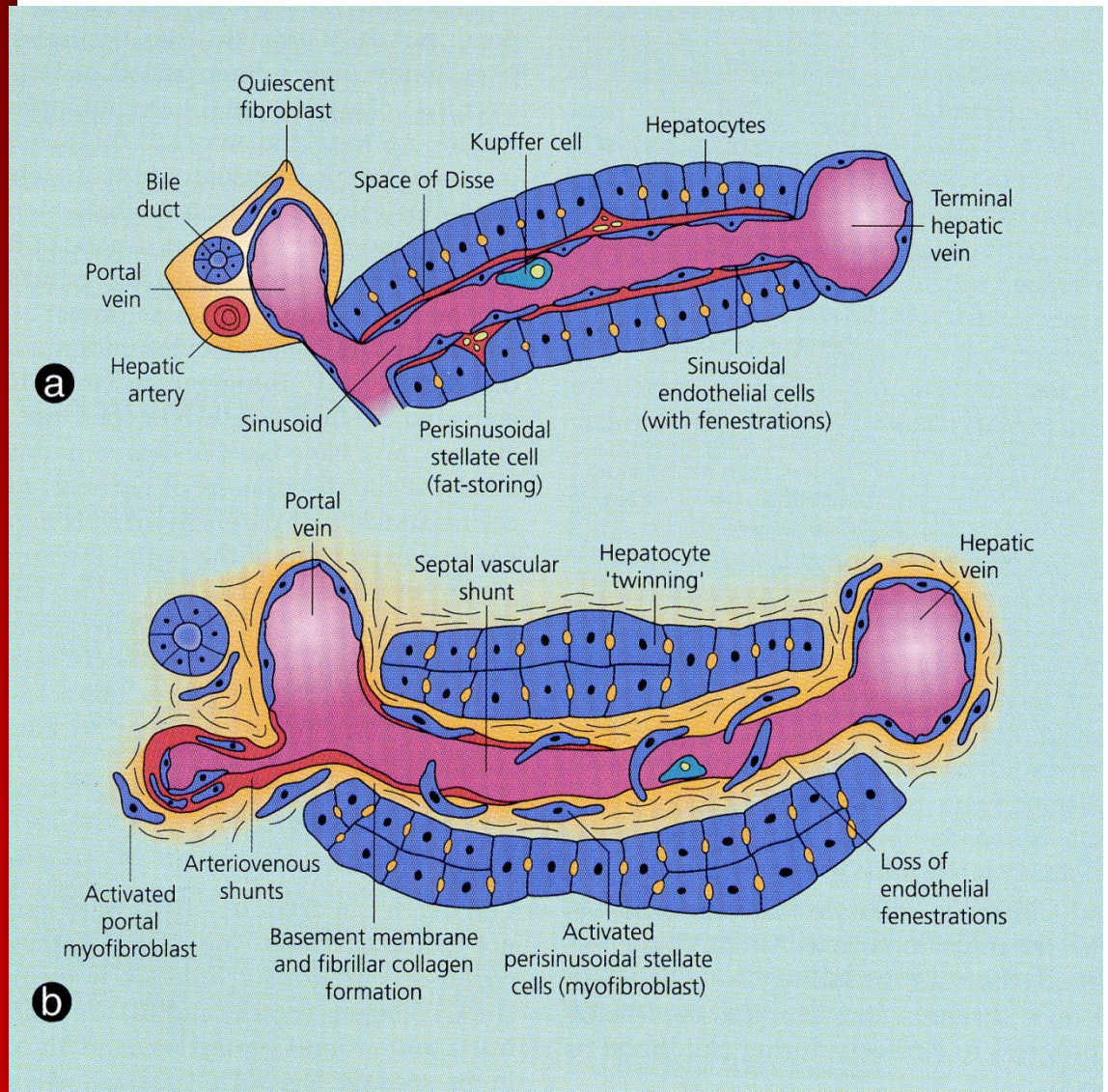
# Mechanisms of injury in alcoholic liver disease

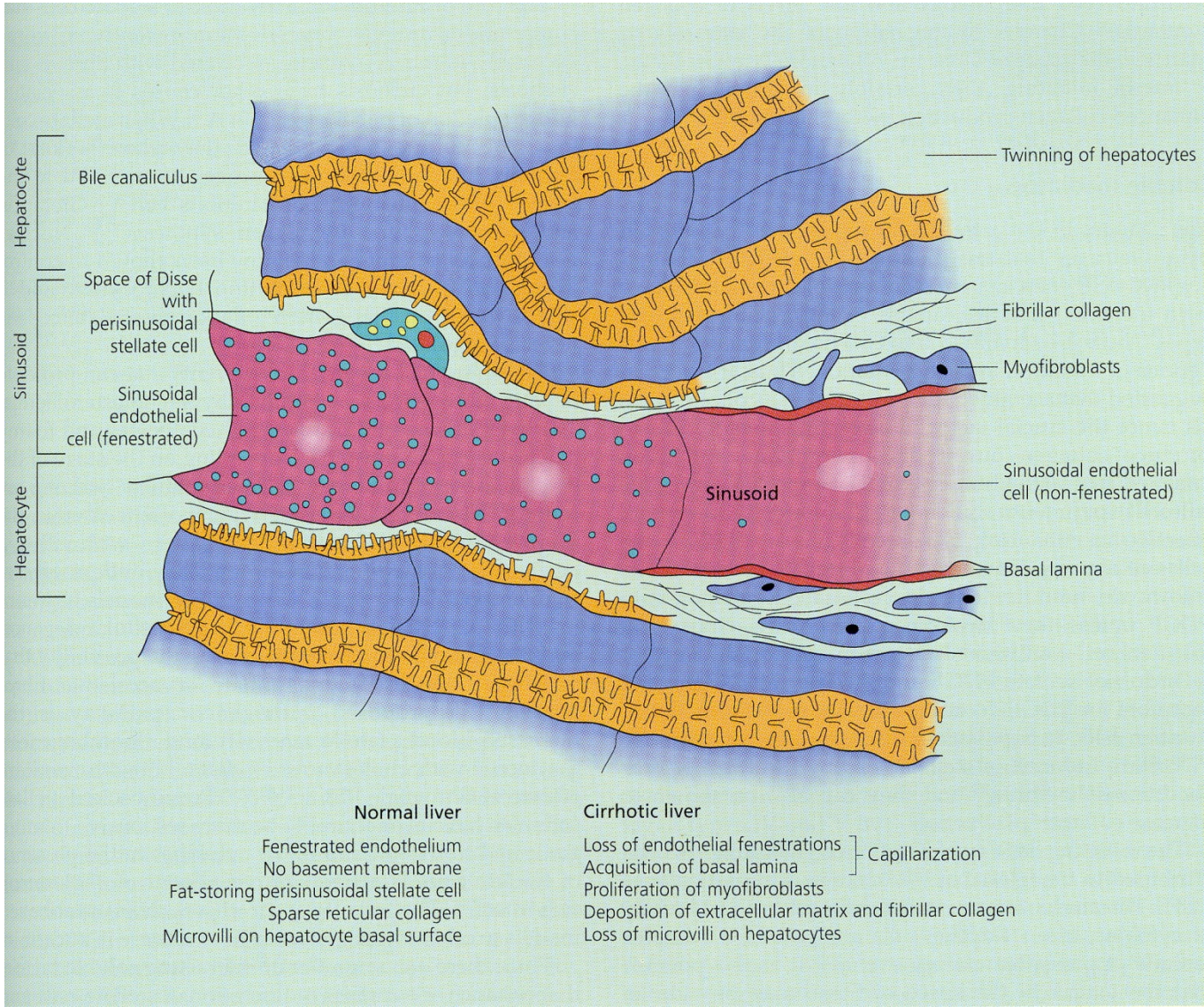



**Endotoxin activation of stellate cells**

# Restructuring of the liver in cirrhosis



# UDCA (Ursodiol)

- Naturally occuring bile acid
  - Expands hydrophilic bile pool
  - Choleretic effect
  - Anti-inflammatory and anti-apoptotic effects
- Improves serum liver biochemistries
- May slow disease progression in early stage PBC
  - 2/3rds of patients respond
  - Some may reach normal life expectancy