Current Issues in Surgical Pathology 2014

Special stains in liver pathology

Which, why, how……Really?

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Outline

- Which stains
- Why the stain is done
- How the stain is interpreted
  - Pitfalls, technical aspects
- Really
  - Reflex use of special stains

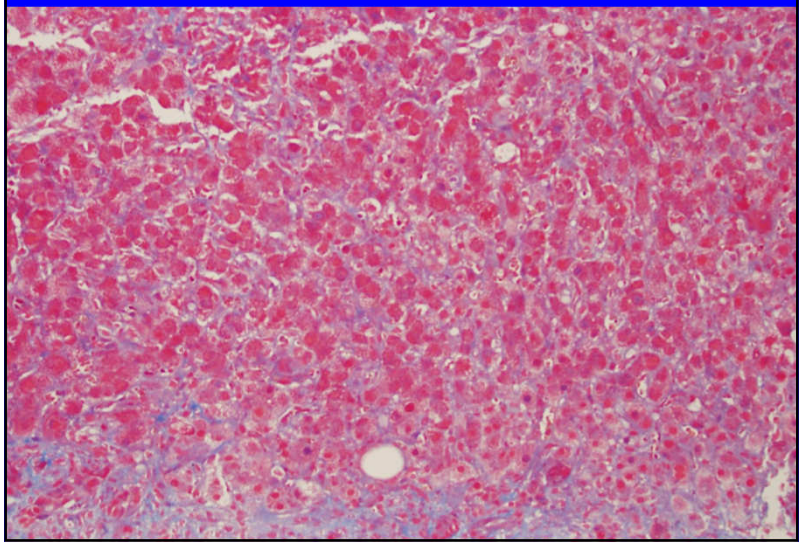
Special stains: liver pathology

- Trichrome
- Iron
- PAS-diastase
- Reticulin
- Copper
- Other: elastic, PAS, bile

Process	Role	Principle
Iron hematoxylin	Nuclear stain	Works well in acidic solutions
Red dye: Acid fuchsin (Biebrich scarlet) chromotrope 2R	Stains cytoplasm, muscle	Intermediate molecular weight, stain both collagen and muscle
Polyacid (phospho-tungstic acid)	Removes red dye from collagen	Large molecules
Blue/green dye: Methyl green Fast Green Aniline Blue	Stains collagen	Large molecule dye: stains only collagen

Masson: sequential staining, Gomori: single step

Pale staining, no nuclear staining



Trichrome stain

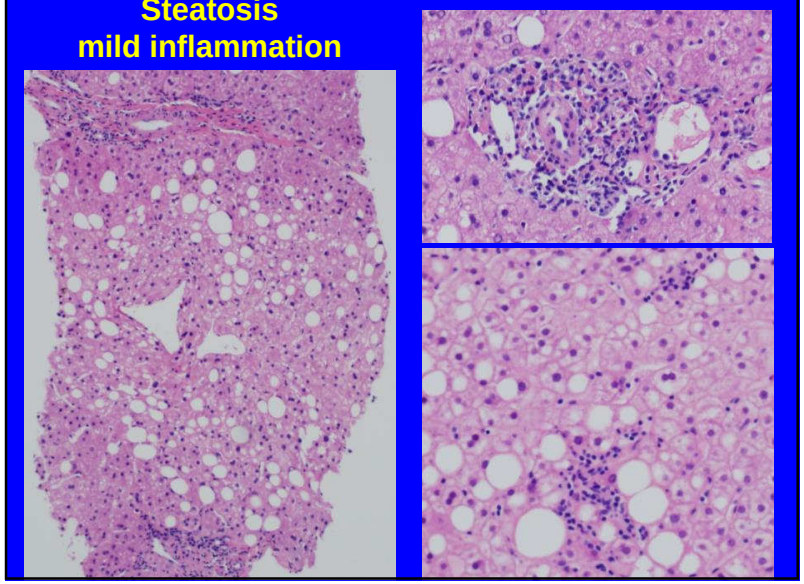
- Why
  - Staging: viral hepatitis, steatohepatitis
  - Diagnosis of steatohepatitis
  - Regression of cirrhosis
  - Fibrosis vs. necrosis
  - Recognizing unsuspected amyloidosis
- How
  - Interpretation and pitfalls

Steatohepatitis: essential features

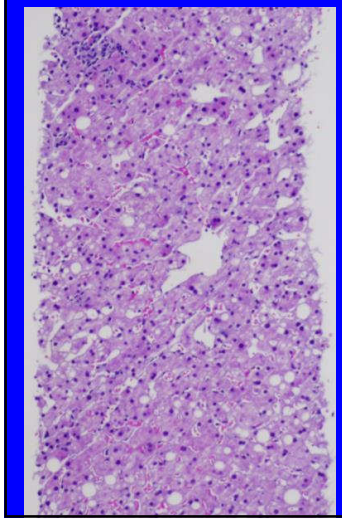
AASLD/NASH Clinical Research Network

- Steatosis
- Inflammation
- Hepatocellular injury
  - Ballooned hepatocytes
  - Pericellular fibrosis

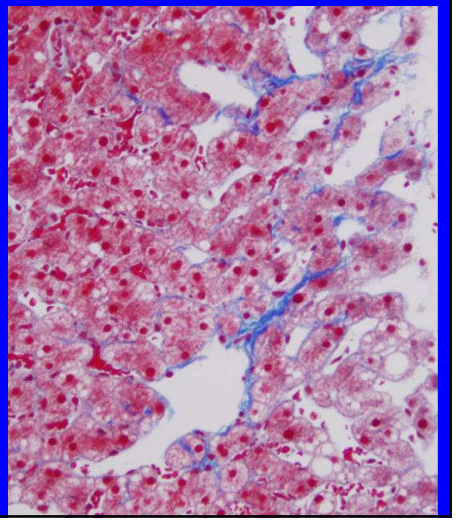
Steatosis
mild inflammation



Steatosis



Pericellular fibrosis



Steatosis vs. steatohepatitis

- Disease progression
- Treatment

Steatohepatitis guidelines

The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Naga Chalasani, MD, FACG[1], Zobair Younossi, MD, FACG[2], Joel E. Lavine, MD, PhD[3], Anna Mae Diehl, MD[4], Elizabeth M. Brunt, MD[5], Kenneth Cusi, MD[6], Michael Charlton, MD[7] and Arun J. Sanyal, MD[8]

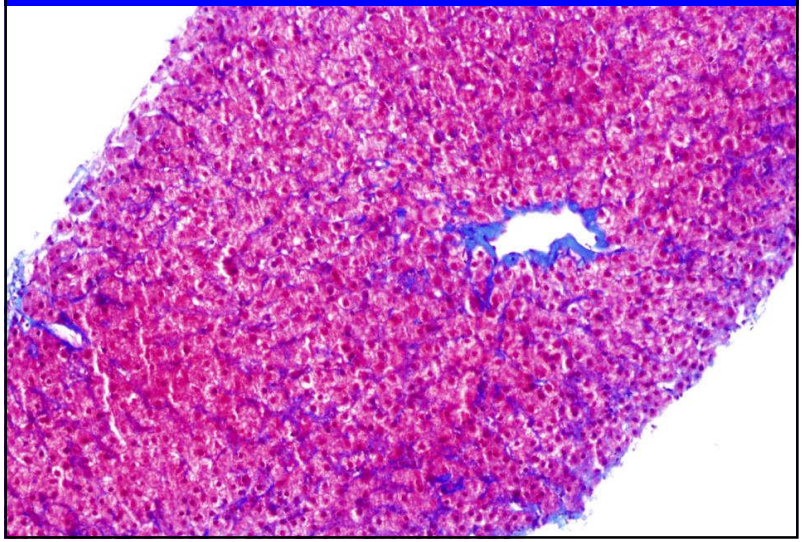
Recommendation

20. Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established. (Strength – 1, Evidence - B)

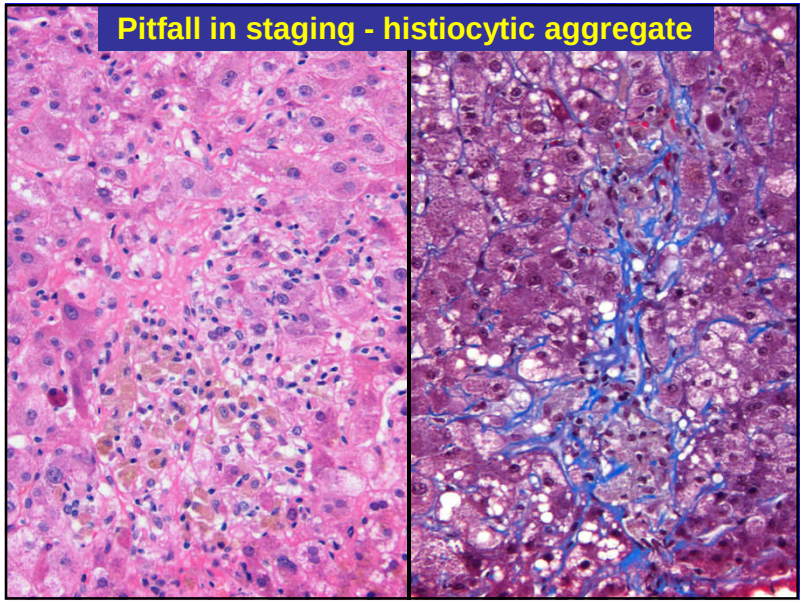
Recommendation

21. Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. (Strength - 1, Quality - B)

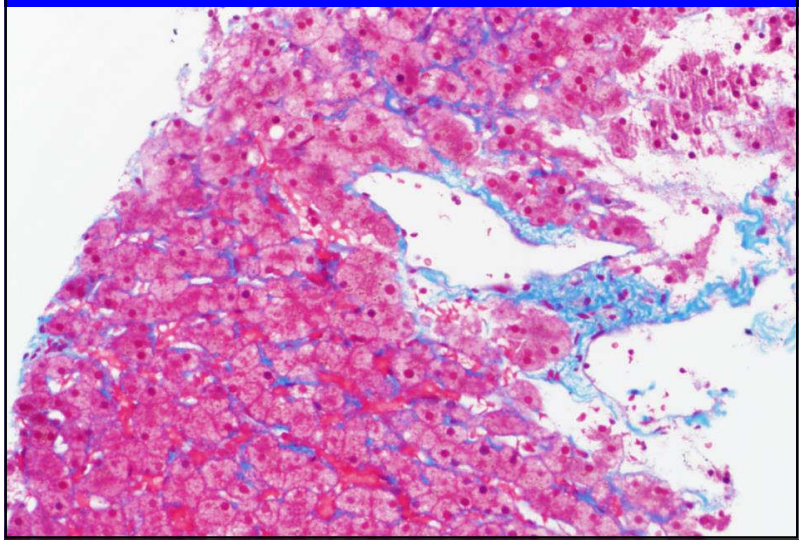
Overstained trichrome



Pitfall in staging - histiocytic aggregate



Chronic venous outflow obstruction



Trichrome stain

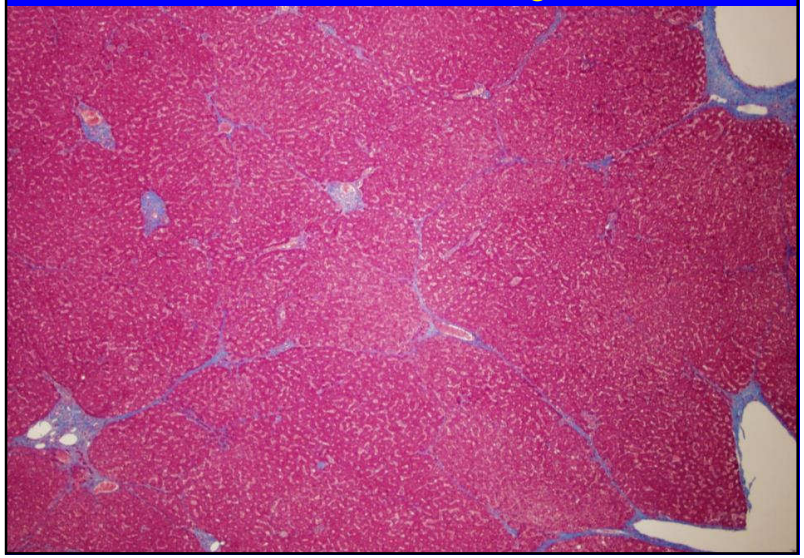
- Staging: viral hepatitis
- Steatohepatitis
- Regression of cirrhosis
- Fibrosis vs. necrosis

Cirrhosis regression

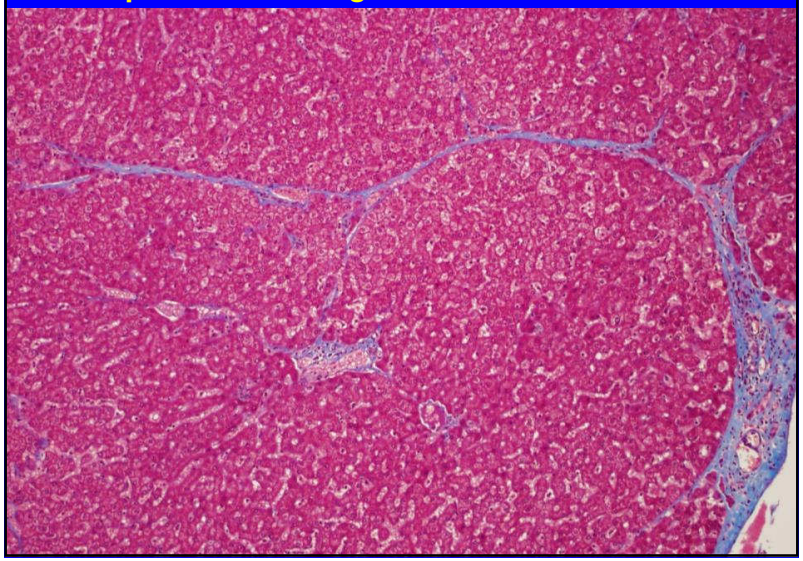
- Thin fibrous septa with perforations
- Prominent vessels and ductular reaction disappear
- Nodularity may persist

Wanless, Arch Pathol Lab Med, 2000
Friedman, Hepatology 2006
Chang, Hepatology, 2010

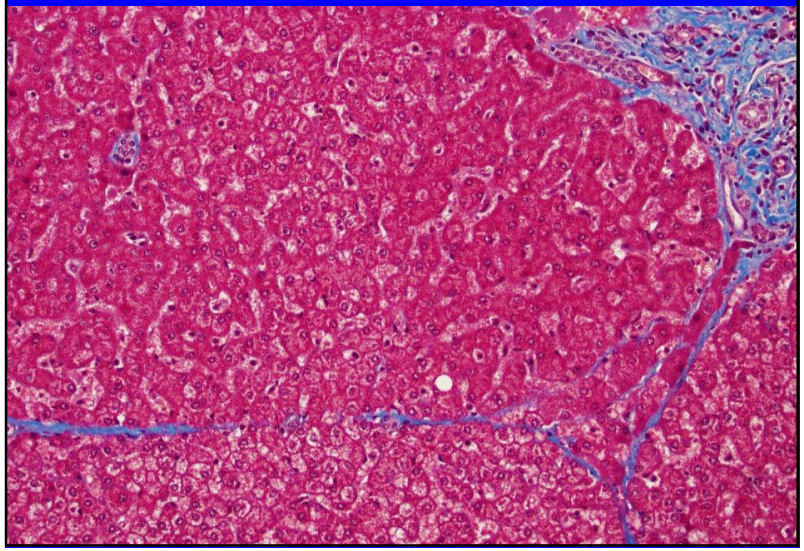
Alcoholic cirrhosis with regression

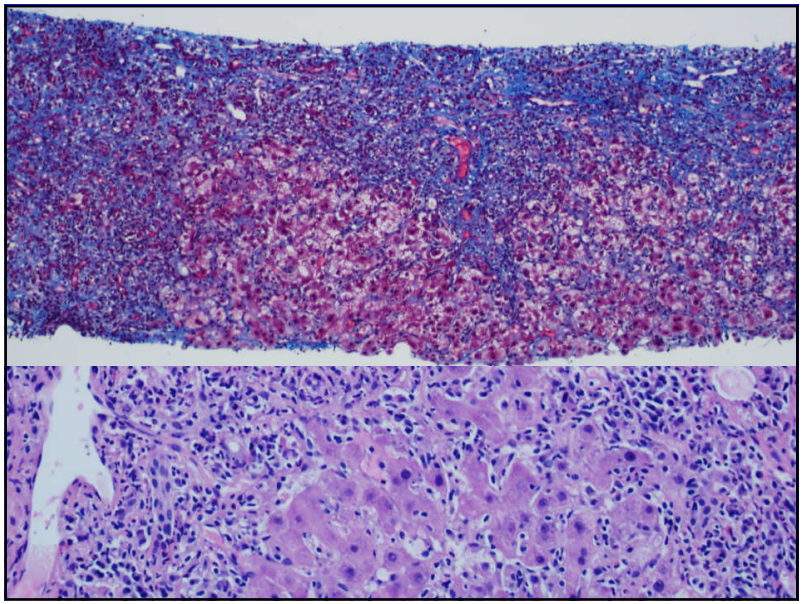


Thin septa: no shunting vessels or ductular reaction

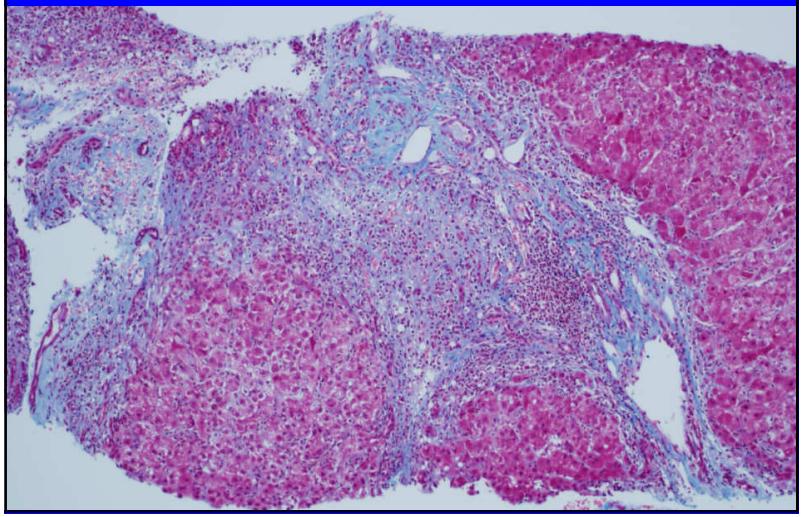


Regression: perforated fibrous septa

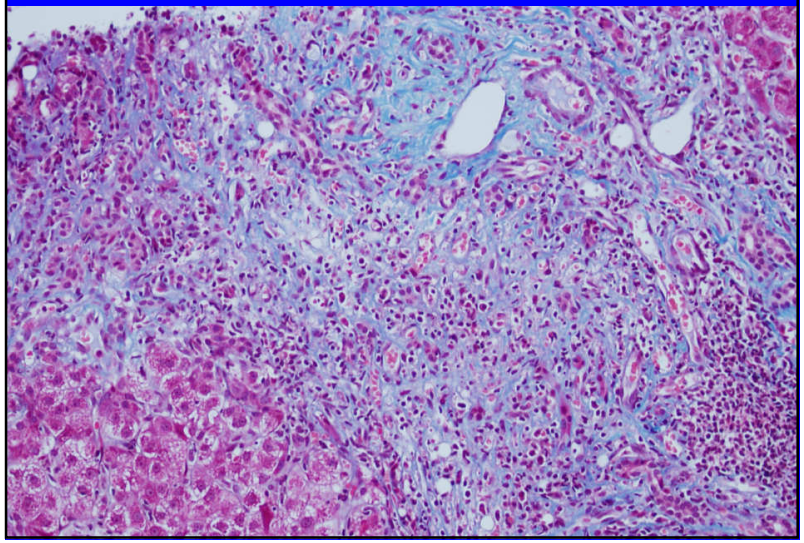




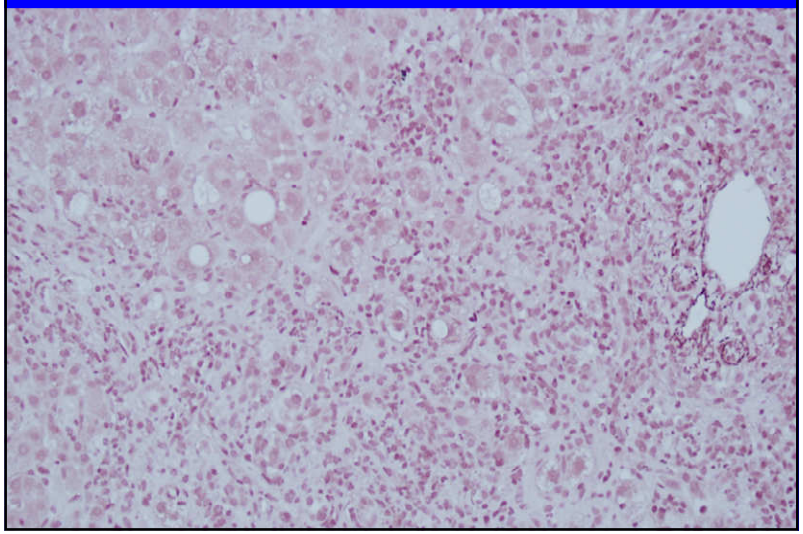
Repeat trichrome



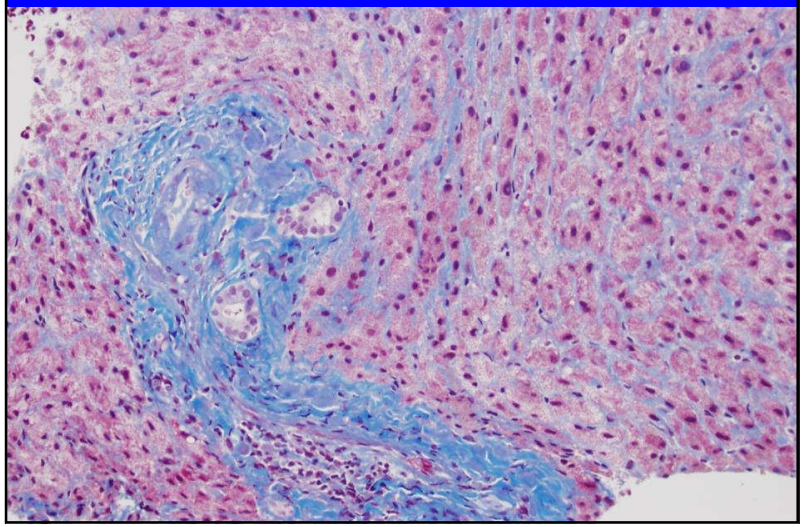
Dark: portal collagen, Light: necrosis



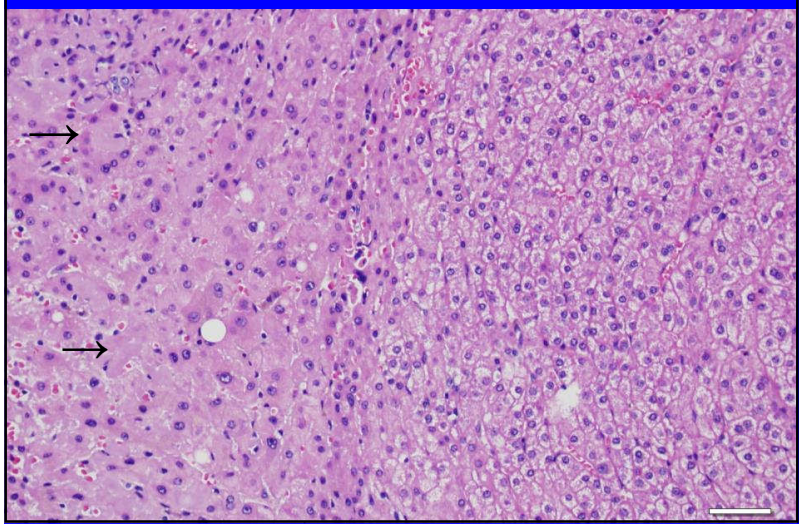
Orcein stain: no elastic fibers in necrotic area



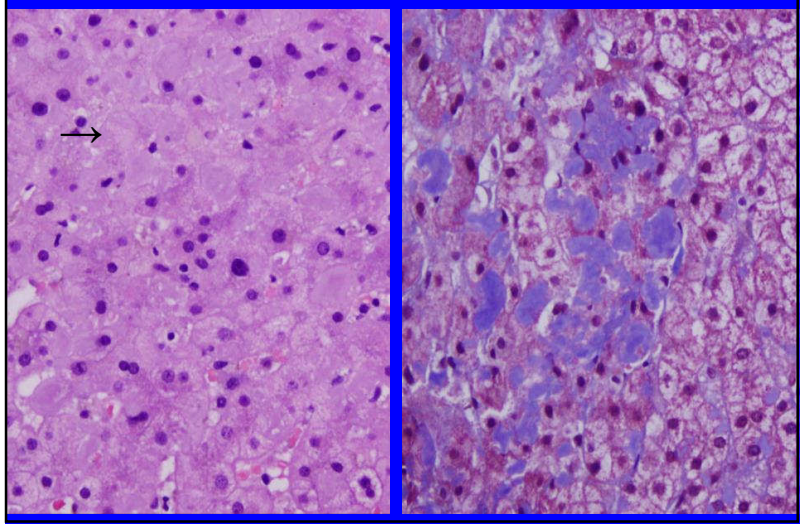
Amyloid: pale deposits



Globular amyloid deposits: subtle on HE stain



Globular amyloid: highlighted by trichrome



Special stains: liver pathology

- Trichrome
- Iron
- PAS-diastase
- Reticulin
- Copper
- Other: elastic, PAS, bile

Perls iron stain (not Perl's)

- K ferrocyanide + HCl
- Ferric ferrocyanide (Prussian blue)
- Max Perls: German pathologist

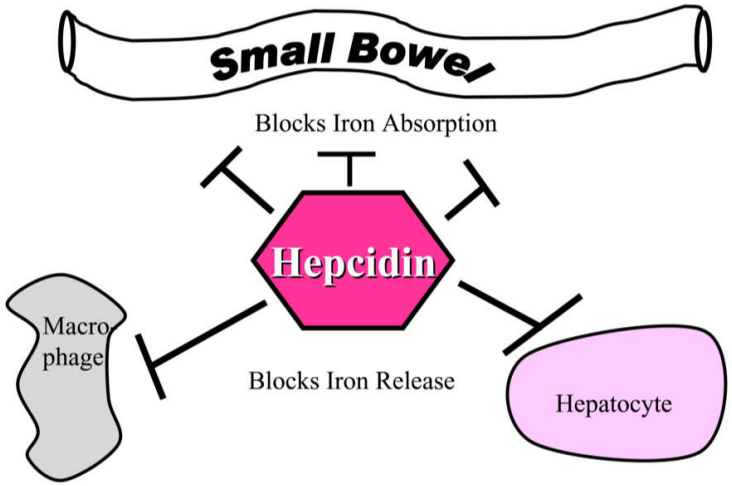
Entombment of Christ: Peter van der Werff, 1709

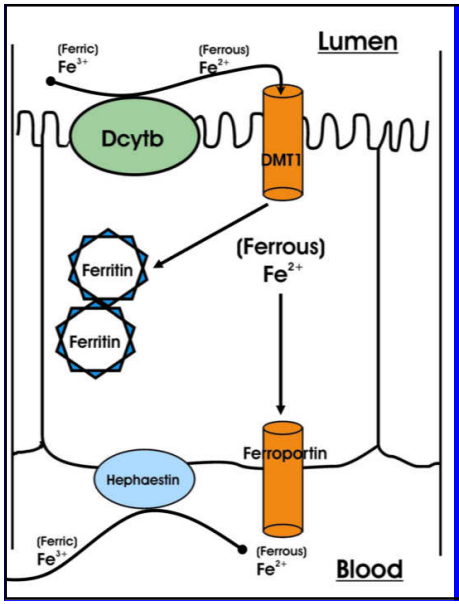
Starry Night: van Gogh

Iron stain

- Why
  - Distinguish from other pigments
  - Semiquantitative analysis
- How
  - Patterns of hepatic iron overload
  - Grading of iron overload

Normal iron regulation

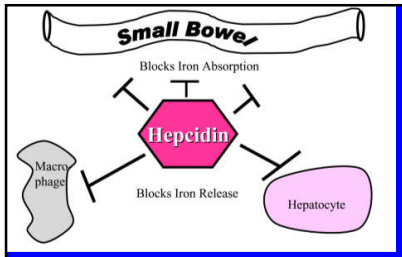




Hepcidin

- Activity depends on iron stores
- Binds ferroportin

Fig: Textbook of Liver Pathology: Kakar, Ferrell, Eds. Chapter by M Torbenson



- Genetic/acquired
  - Hepcidin
  - Ferroportin
  - Transferrin
- Increased iron
  - Dietary
  - Hemolysis

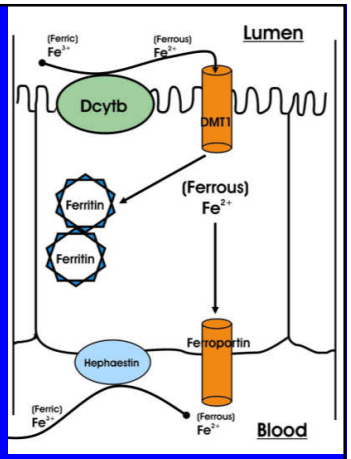


Fig: Textbook of Liver Pathology: Kakar, Ferrell, Eds. Chapter by M Torbenson

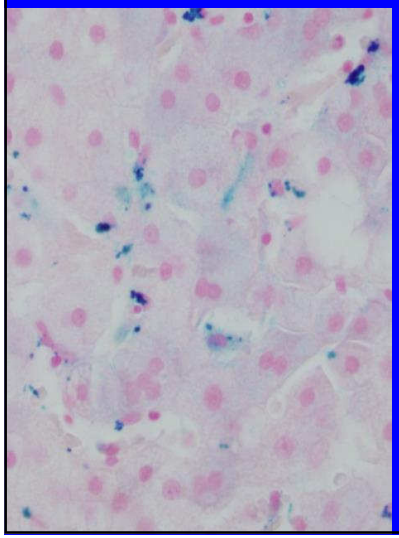
Primary	Pattern of siderosis	Mechanism
HFE hemochromatosis	Hepatocellular Starts periportal	*HFE* gene mutation
Non-*HFE* hemochromatosis	Mostly hepatocellular Some: macrophages	Non-*HFE* mutations

Secondary	Pattern of siderosis	Mechanism
Hemolysis, multiple transfusions	Macrophages	Excess iron from RBC
Chronic diseases	Macrophages	Excess iron in macrophages

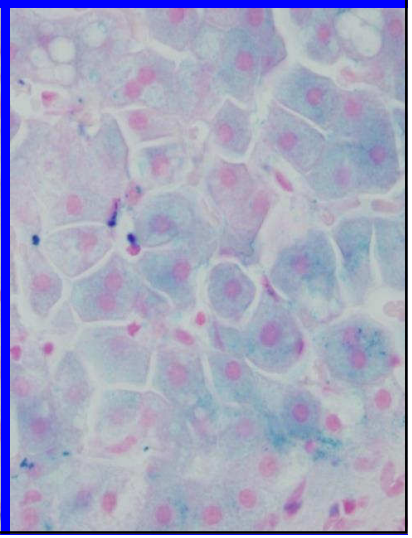
Iron storage

Storage form	Distribution
Ferritin Iron oxyhydroxide and apoferritin	Virtually all cells Trace amounts in the plasma
Hemosiderin Aggregates of iron oxyhydroxide crystals without apoferritin	Reticuloendothelial system including Kupffer cells

Hemosiderin



Ferritin blush



Iron stain: interpretation

- **Grading of iron overload**
- **Patterns of hepatic iron overload**

Modified Scheuer grading scheme

Grade	Definition
Grade 0	Granules absent or barely discernible at 400x
Grade 1	Granules discernible at 250x
Grade 2	Granules discernible at 100x
Grade 3	Granules discernible at 25x
Grade 4	Masses visible at 10x or naked eye

Deugner-Turlin grading scheme

Hepatocytic iron	0, 3, 6, 9 or 12 According granules size In each Rappaport area	HIS 0-36
Sinusoidal iron	0, 1, 2, 3 or 4 According granules size In each Rappaport area	SIS 0-12
Portal iron	0, 1, 2, 3 or 4 According to % of iron overloaded macrophages, biliary cells, and vascular walls	PIS 0-12
Total iron score		0-60

HIS: hepatocytic iron score; SIS: sinusoidal iron score; PIS: portal iron score.

Iron grading: simple method

Grade	Extent of iron
Minimal	<5%
Mild	5-33%
Moderate	34-67%
Marked	68-100%

- **Separate grade: hepatocellular, Kupffer cell**
- **Hepatocellular: periportal vs. random**

Iron: quantitative analysis

Can be performed from paraffin embedded tissue Allows correlation with H&E morphology	
Normal iron	**10-36 µmol/g of liver tissue**
Mild increase	**Up to 150 µmol/g of liver tissue**
Moderate	**151-300 µmol/g of liver tissue**
Marked	**>300 µmol/g of liver tissue**

Hepatic iron index

$$\frac{\text{µg iron per gram dry weight of liver}/55.846}{\text{patient's age}}$$

>1.9: suggests hemochromatosis (non-cirrhotic)

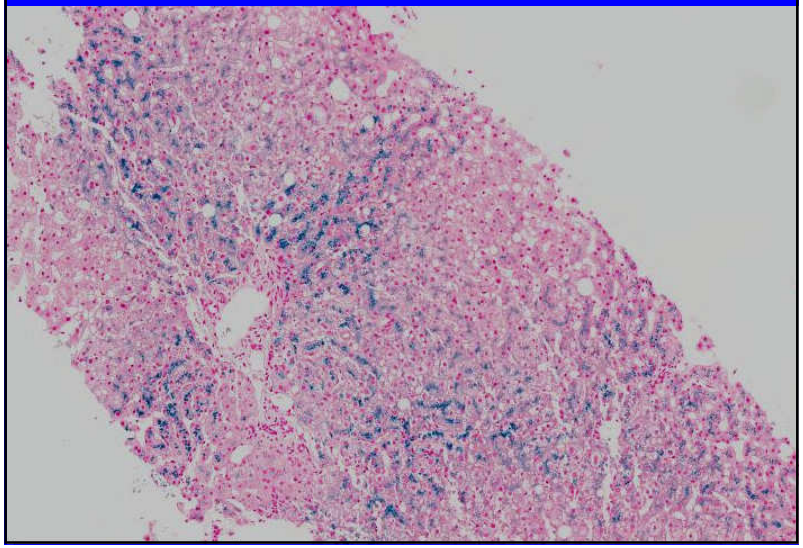
Iron stain: interpretation

- Grading of iron overload
- Patterns of hepatic iron overload

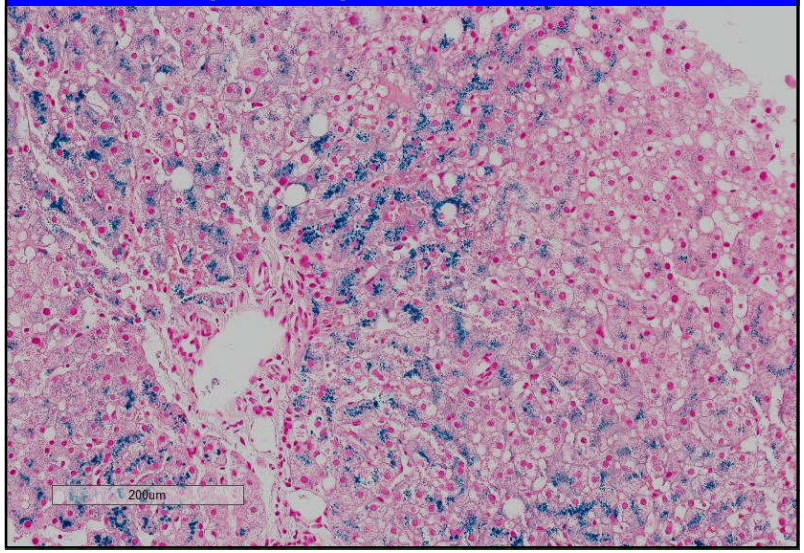
History

- 35/M with obesity
- Elevated serum ferritin
- Liver biopsy: steatohepatitis

Periportal hepatocellular siderosis



Periportal hepatocellular siderosis



Iron overload in NASH

- 20-50% serum ferritin elevated
- 15-60% increased hepatic iron

Distribution	Interpretation
Kupffer or hepatocellular mild/moderate, random	Secondary
Hepatocellular, periportal	HH or secondary

Periportal siderosis

- *HFE* hemochromatosis
- Non-*HFE* hemochromatosis
- Secondary iron overload
  - Steatohepatitis
- Rare conditions
  - Porphyria cutanea tarda
  - Hereditary aceruloplasminemia

Diagnosis

HFE 282Y homozygous

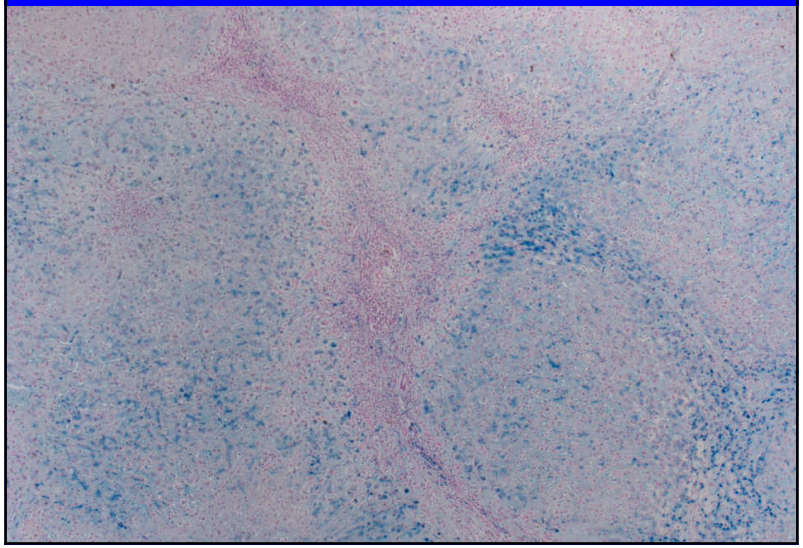
- Steatohepatitis
- *HFE* hemochromatosis with mild periportal hepatocellular siderosis, no portal based fibrosis

Significance of iron overload or *HFE* mutations in progression of steatohepatitis is not clear

History

- 55/M with cirrhosis
- No *HFE* mutation
- No known etiology

HII>2, heterogeneous iron overload



Cirrhosis with siderosis

- Non *HFE* hemochromatosis
- Secondary siderosis in cirrhosis of another etiology

Hemochromatosis

	Genetics	Liver biopsy	Clinical presentation
Type 1 (HFE HH)	Autosomal recessive C282Y homozygous, C282Y /H63D	Hepatocytes	3rd or 4th decade Liver, pancreas, heart, skin, joints
Type 2 (Juvenile HH)	Autosomal recessive Hemojuvelin (2A) or hepcidin (2B)	Hepatocytes	1st three decades More severe disease than HFE HH
Type 3	Autosomal recessive Transferrin receptor type 2 mutation	Hepatocytes	Similar to HFE HH Intermediate between HFE HH and juvenile HH
Type 4	Autosomal dominant Ferroportin mutation	1st subtype: hepatocytes 2nd subtype: Kupffer cells	4th or 5th decade Severity varies with type of mutation

Siderosis in cirrhosis

Ludwig, Gastroenterology, 1997 (n=447, HII>1.9)	
Hereditary hemochromatosis	100%
Alpha-1-antitrypsin deficiency	28%
Cryptogenic cirrhosis	19%
Alcoholic cirrhosis	14%
Chronic hepatitis B, hepatitis C	18%, 7%
PBC, PSC	1% each

- **Marked siderosis can occur in the absence of HH**
- **Siderosis rare in biliary diseases**
- **Siderosis is an adverse risk factor***

***Brandhagen, Hepatology, 2000**

HFE HH: Homogeneous distribution

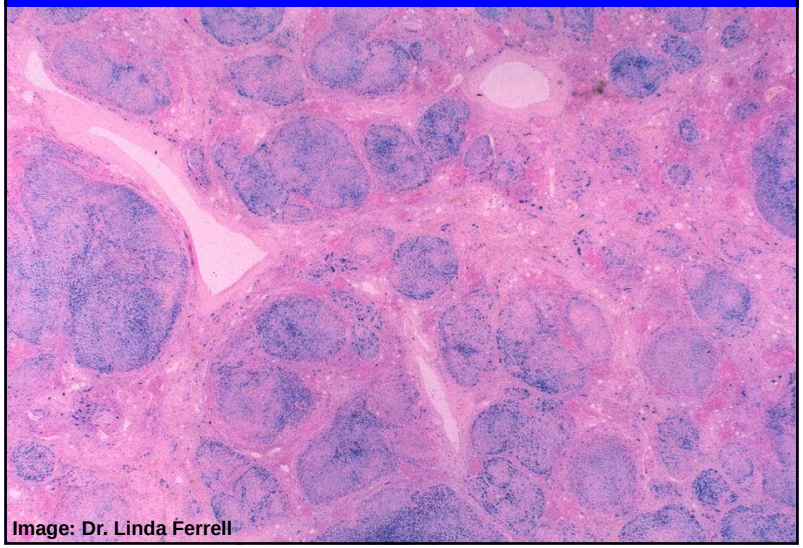
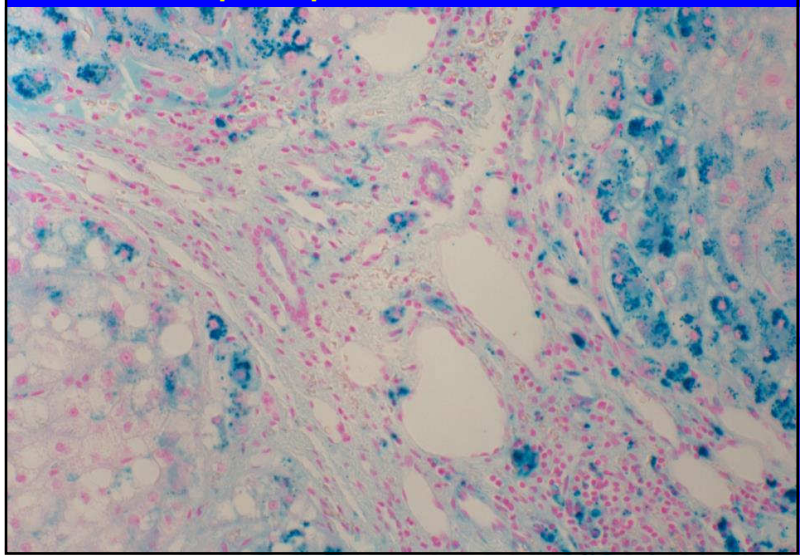
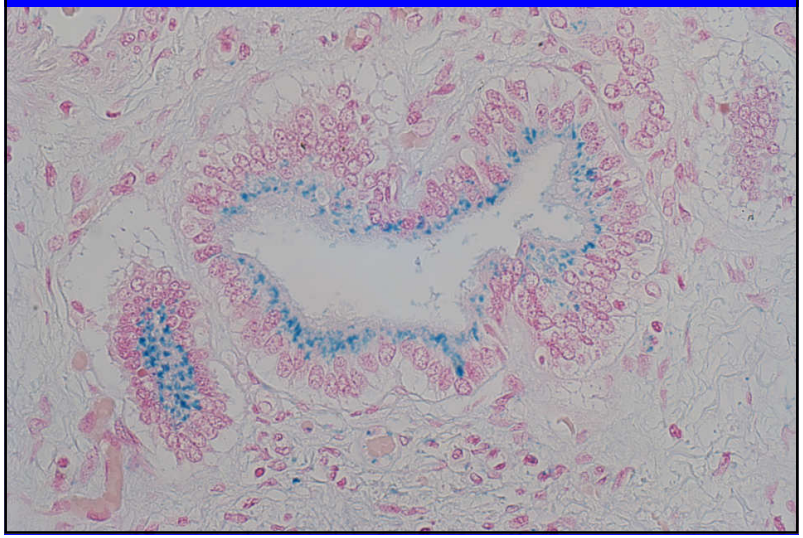


Image: Dr. Linda Ferrell

Siderosis: periseptal, stroma, endothelial cells



Bile duct siderosis

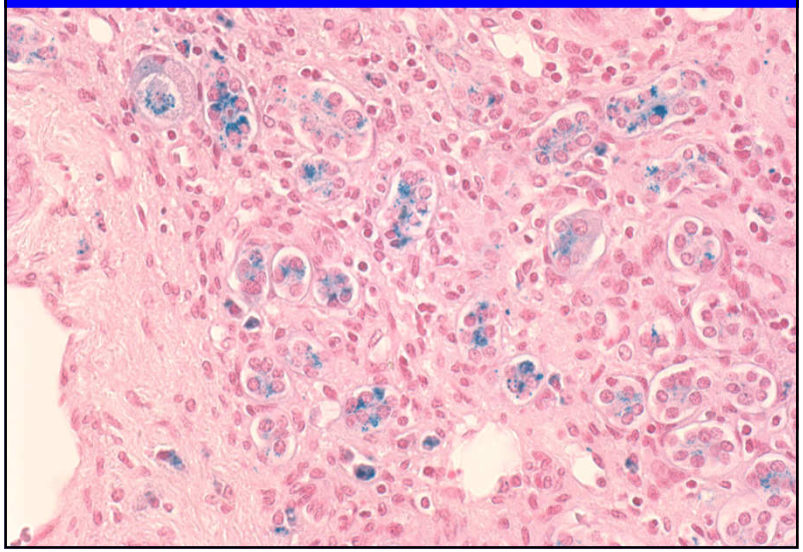


Cirrhosis: HH or secondary siderosis

Hereditary hemochromatosis	Cirrhosis with marked secondary siderosis
Homogeneous distribution	Heterogeneous
Siderosis in bile ducts, stroma, endothelial cells	Generally absent
HFE mutation (in *HFE* HH)	Not present

Diagnosis:
Cryptogenic cirrhosis with secondary iron overload

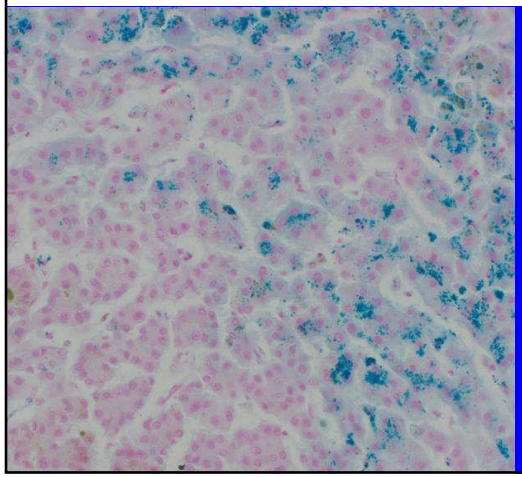
Collapse with ductular reaction with siderosis: often nonspecific



Hepatology. 1993 Dec;18(6):1363-9.

Preneoplastic significance of hepatic iron-free foci in genetic hemochromatosis: a study of 185 patients.

Deugnier YM[1], Charalambous P, Le Quilleuc D, Turlin B, Searle J, Brissot P, Powell LW, Halliday JW.



-High grade dysplastic lesions

-50% develop HCC on follow-up

Image: Dr. L Ferrell

Iron stain: role of the pathologist

Clinical setting	Interpretation
HFE C282Y homo C282Y/H63D	Extent of iron Extent of fibrosis
HFE other mutations	Extent of iron No risk for *HFE* HH

Iron stain: role of the pathologist

Clinical setting	Interpretation
HFE not known	Raise possibility of HH Periportal siderosis, or moderate to marked hepatocellular iron
Chronic viral hepatitis Steatohepatitis Cirrhosis	Recommend *HFE* testing Possible disease progression Possible poor prognosis

Special stains: liver pathology

- Trichrome
- Iron
- PAS-diastase
- Reticulin
- Copper
- Other: elastic, PAS, bile

PAS-diastase stain

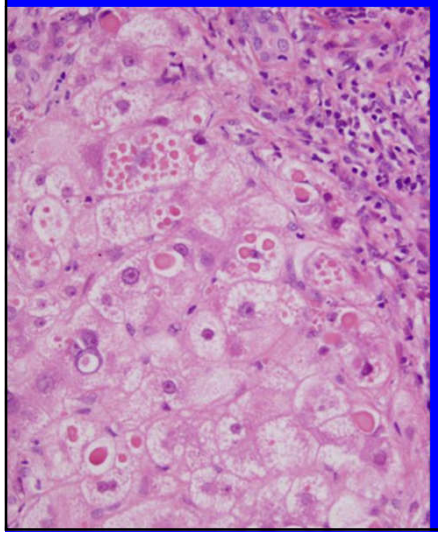
Glycogen, other carbohydrates

- Periodic acid converts –OH component to aldehyde
- Combines with Schiff reagent: magenta complex
- Diastase digests glycogen

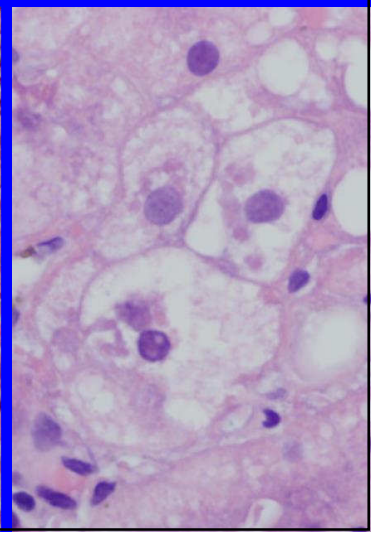
PAS-D stain

- Why
  - Alpha-1-antitrypsin deficiency
  - Highlight macrophages
  - Glycogen (with PAS stain)
  - Highlights basement membrane
- How
  - Pitfalls
  - Interpretation

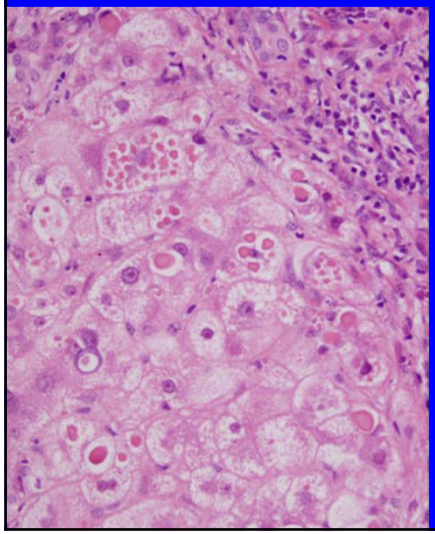
A1AT deficiency



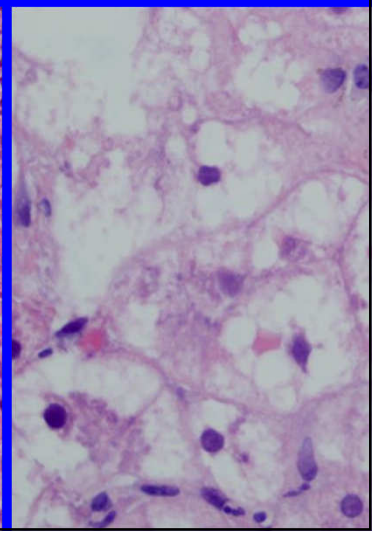
Mallory hyaline



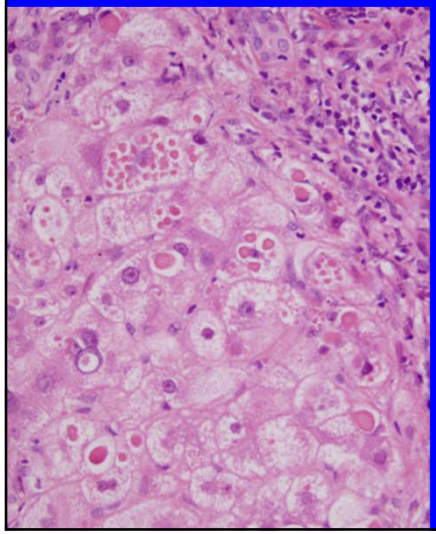
A1AT deficiency



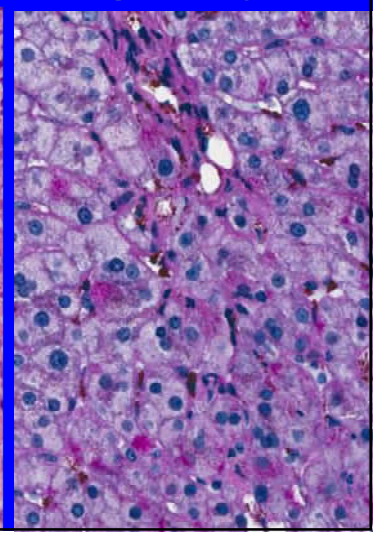
Giant mitochondria



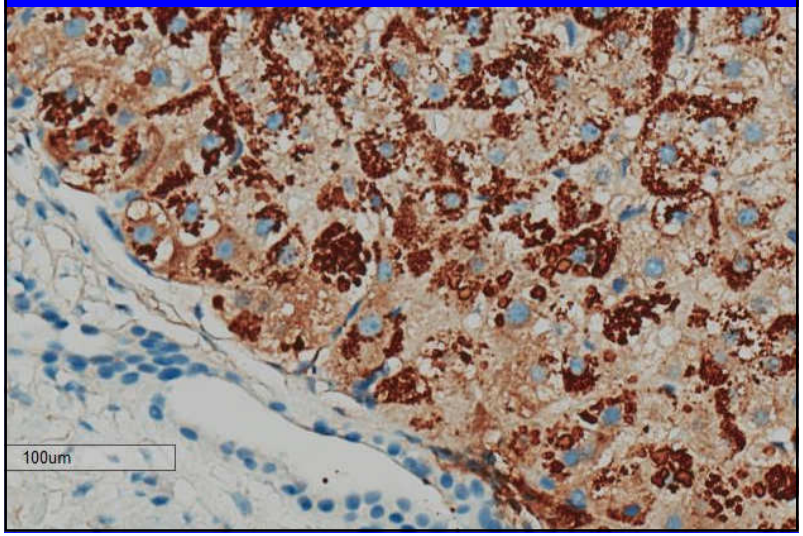
A1AT deficiency



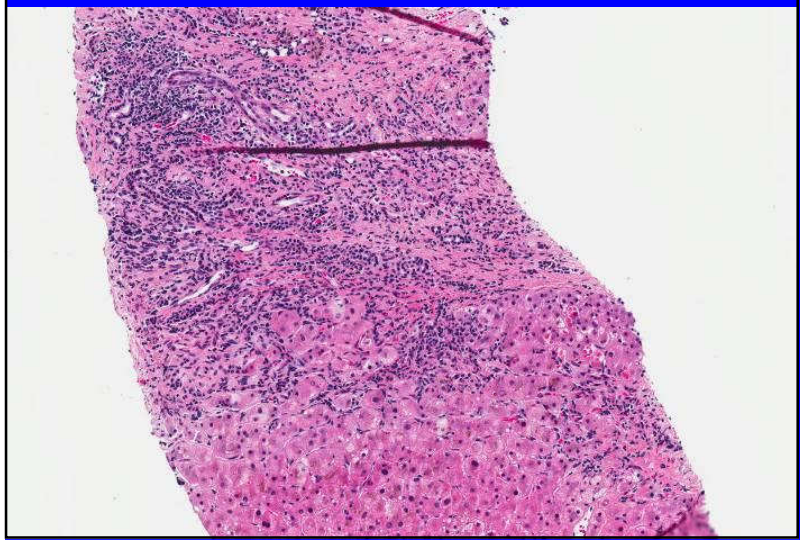
Incomplete digestion



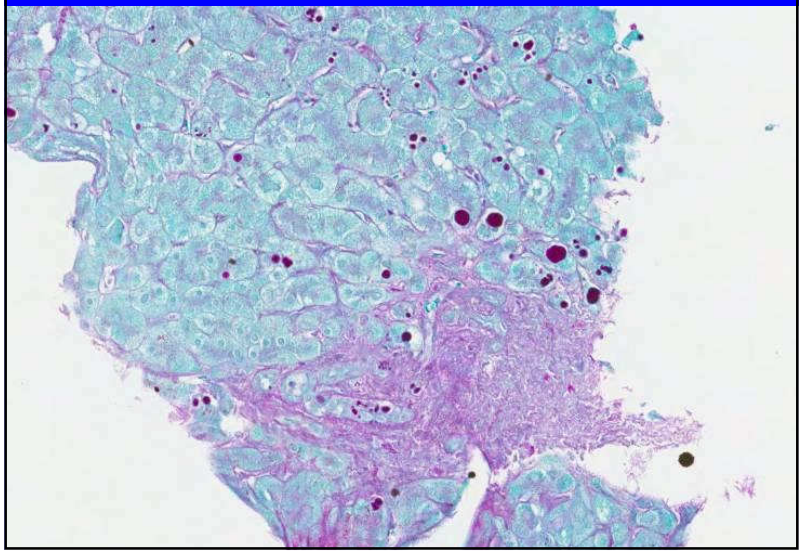
Immunohistochemistry: alpha-1-antitrypsin



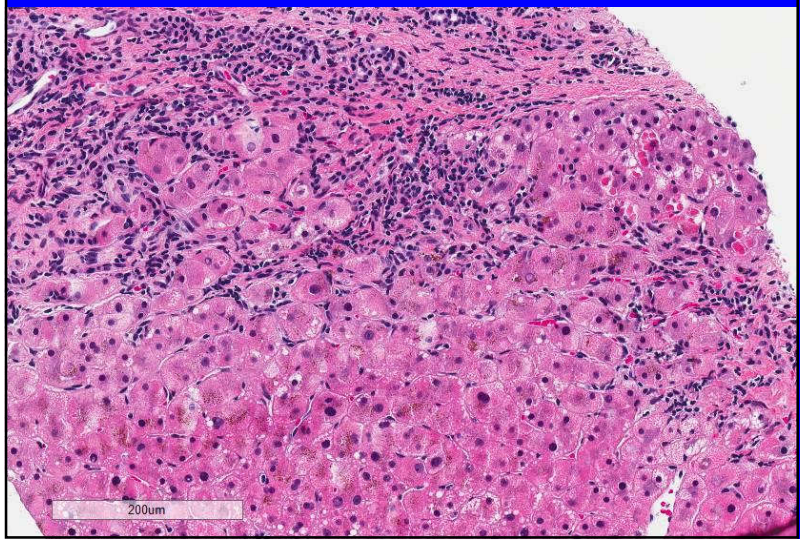
50/F with cirrhosis, obese, serum A1AT normal



PAS-D stain



Cytoplasmic globules



Alpha-1-antitrypsin deficiency

- Normal allele PiMM
- Homozygous state (PiZZ)
  - Chronic hepatitis and cirrhosis
- Heterozygous state (PiMZ)
  - Significance unclear
  - Progression of fibrosis in other liver diseases

Alpha-1-antitrypsin deficiency

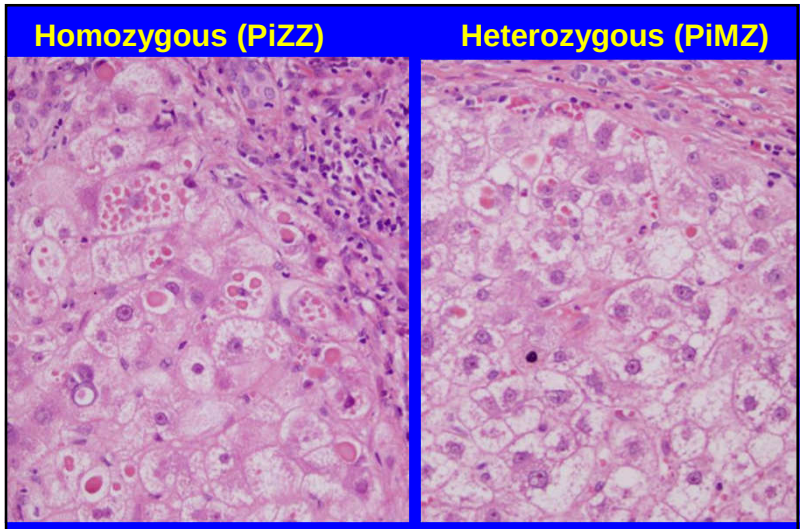
Challenges in diagnosis (clinical)

- Uncommon disease
- Can occur in the absence of child hood symptoms and lung disease
- Serum levels unreliable

Alpha-1-antitrypsin deficiency

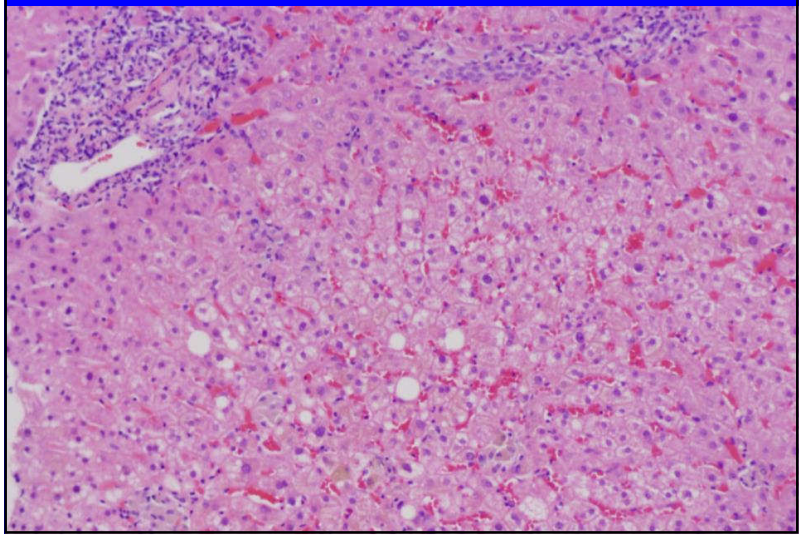
Challenges in diagnosis (pathologic)

- Cytoplasmic globules can be subtle
- PAS-D: periportal location
- Globules not specific for diagnosis
  - Vascular etiologies
  - Acute hepatitis
- PiZZ vs. PiMZ cannot be distinguished on biopsy

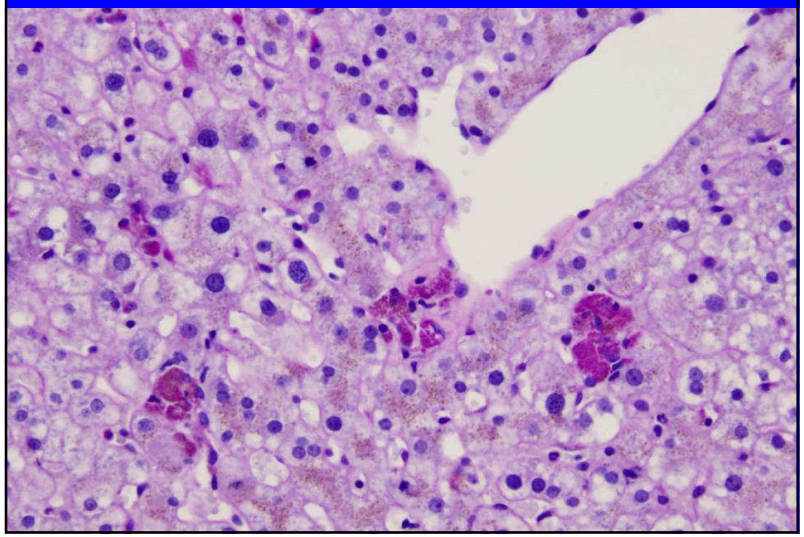


Gold standard for diagnosis: Protease inhibitor phenotyping

Mild portal inflammation



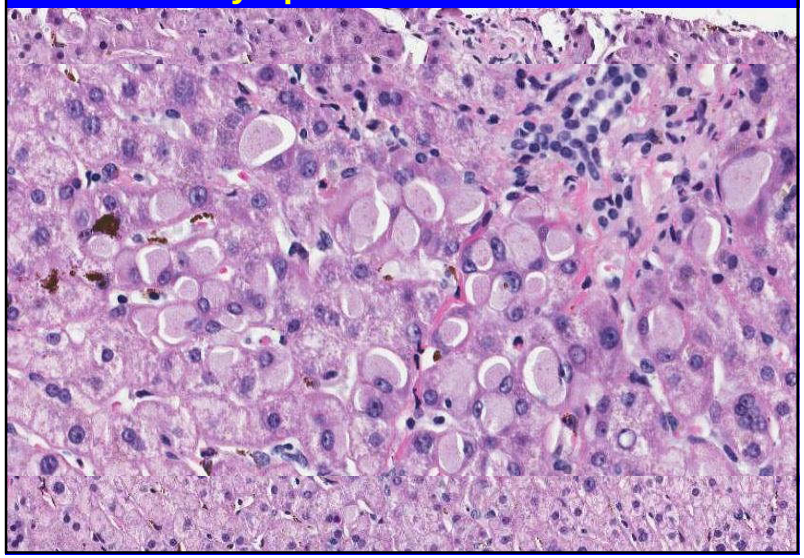
Resolving hepatitis: PAS-D stain highlights macrophages



History

- 40/M with renal transplant
- Persistent elevation of ALT, AST 5-6x
- No history of viral hepatitis

Cytoplasmic inclusions



‘Ground glass’ appearance

- Hepatitis B
- Drugs: Barbiturates, cyanamide
- Metabolic diseases
  - Glycogen storage IV
  - Lafora disease
  - Hypo(a)fibrinogenemia

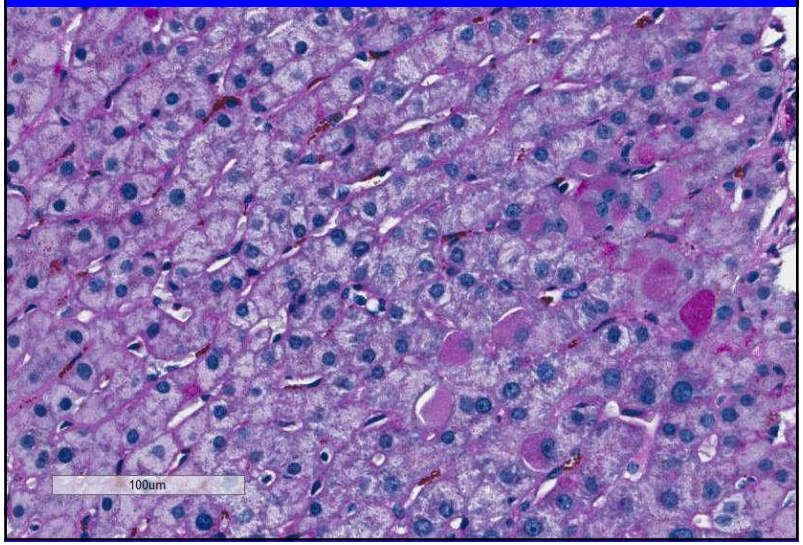
Wisell, AJSP, 2006; Bejarano, Virchow Arch, 2006

Glycogen inclusions (‘pseudo ground glass’)

- Often on multiple immunosuppressive medications
- No correlation with any specific drug

Wisell, AJSP, 2006; Bejarano, Virchow Arch, 2006

PAS-D stain: partial digestion



Special stains: liver pathology

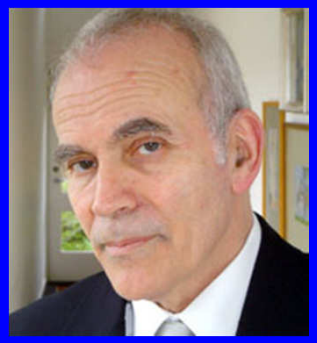
- Trichrome
- Iron
- PAS-diastase
- Reticulin
- Copper
- Other: elastic, PAS, bile

Reticulin stain

Argylophilic reaction

- Sensitization: heavy metals
- Ammoniacal silver
- Reducing agent (formaldehyde)
- Toning: gold
- Removal of unreacted silver

Gomori reticulin



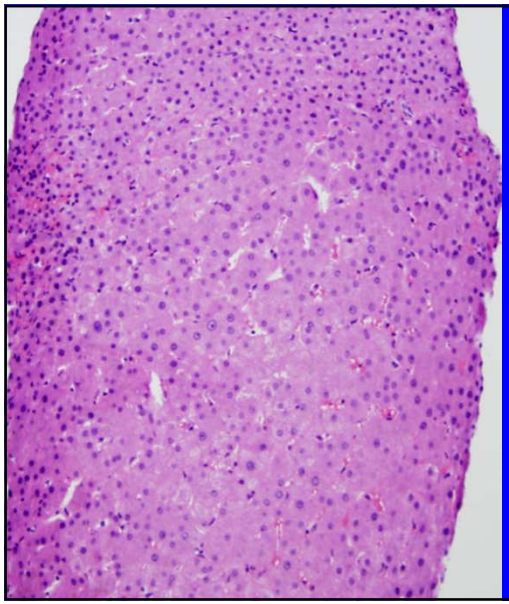
- 1928: Pathologist, Budapest
- 1932: Surgeon, Budapest
- 1943: Internal Medicine, Chicago
- 1956: Research in histochemistry, Palo Alto

Reticulin stain

- Why
  - Collapse of reticulin fibers: necrosis
  - Nodular liver architecture (NRH)
  - Abnormal reticulin network (HCC)
- How
  - Interpretation
  - Pitfalls

History

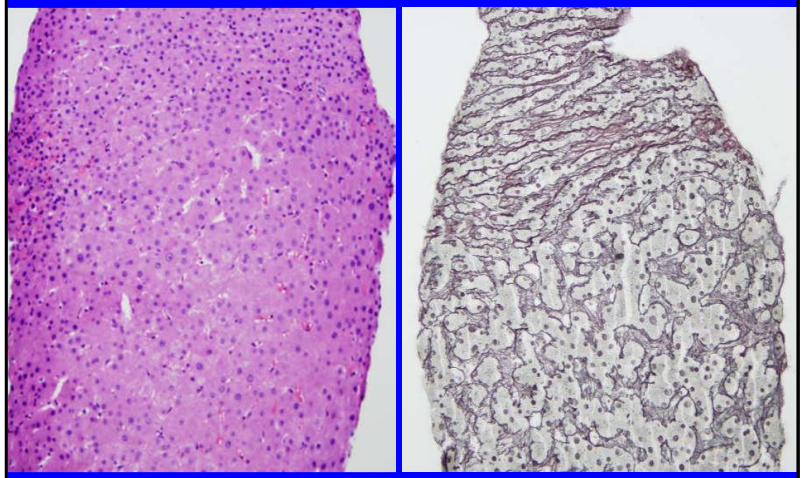
- 60/F with long history of rheumatoid arthritis
- Portal hypertension
- Ultrasound: cirrhosis



Biopsy

- Normal portal tracts
- Hepatocellular damage: none
- No inflammation
- No fibrosis

Nodular architecture: reticulin

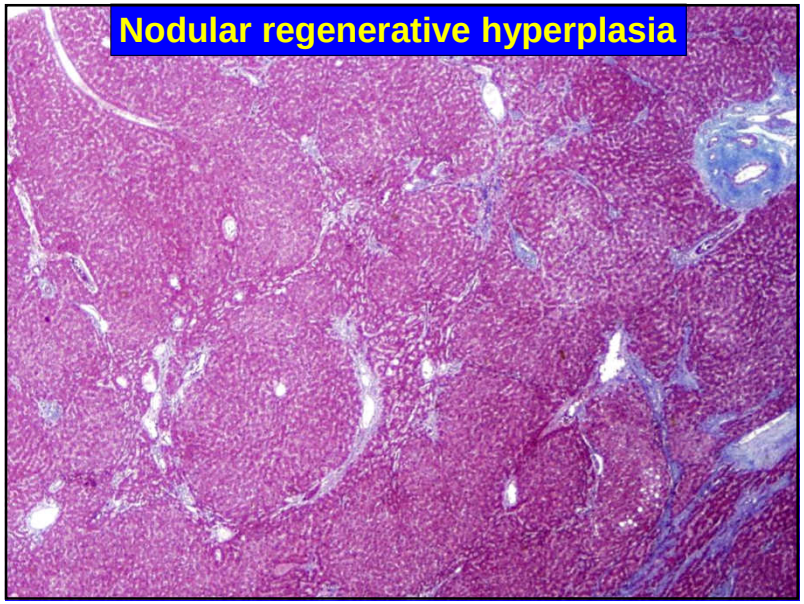


Nodular regenerative hyperplasia

Wanless criteria

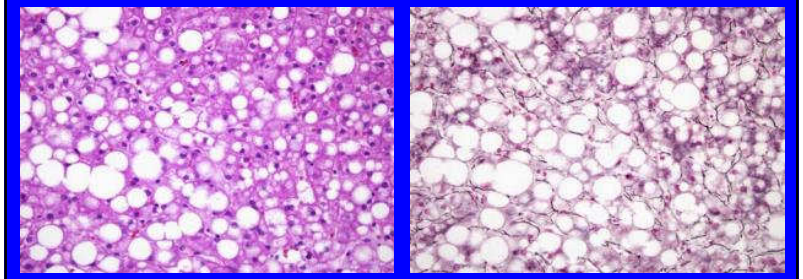
- Hepatocellular nodules, often <0.3 cm
- Often diffuse involvement of the liver
- Fibrosis absent or minimal

Wanless IR, Hepatology, 1990



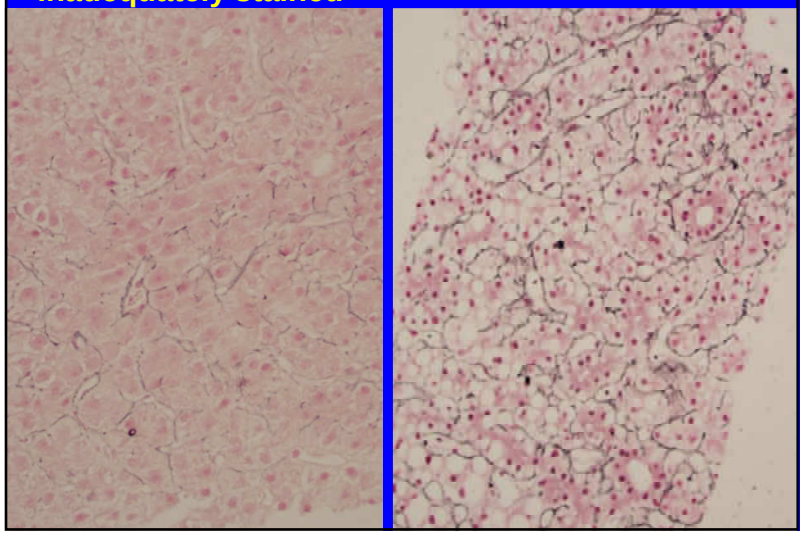
Reticulin Loss in Benign Fatty Liver: An Important Diagnostic Pitfall When Considering a Diagnosis of Hepatocellular Carcinoma

Aatur D. Singhi, MD, PhD, Dhanpat Jain, MD, PhD,† Sanjay Kakar, MD,‡ Tsung-Teh Wu, MD, PhD,§ Matthew M. Yeh, MD, PhD,‖ and Michael Torbenson, MD**

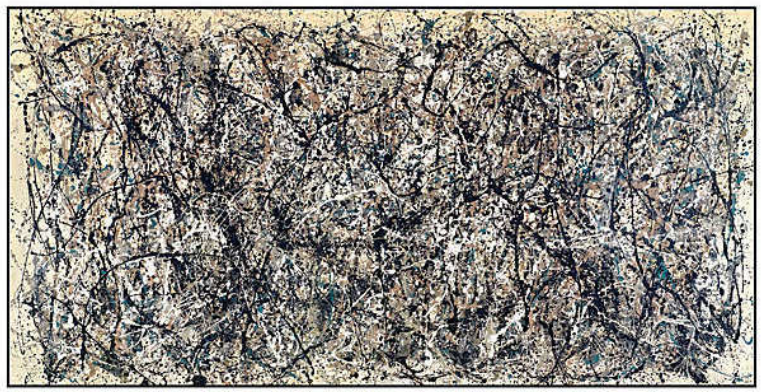


Reticulin: inadequately stained

Regenerative area



Jackson Pollock: One, number 31



Special stains: liver pathology

- Trichrome
- Iron
- PAS-diastase
- Reticulin
- **Copper**
- Other: elastic, PAS, bile

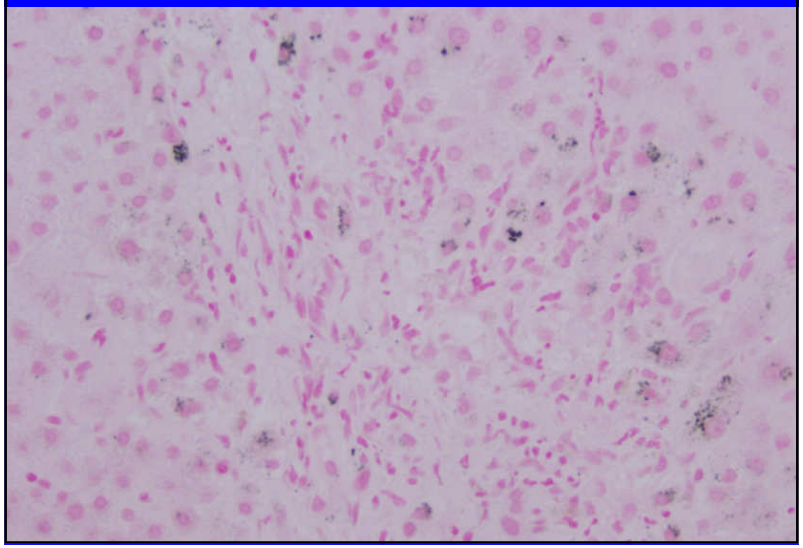
Copper stain

- Why
  - Chronic biliary disease
  - Wilson disease: not reliable
- How
  - Interpretation
  - Pitfalls

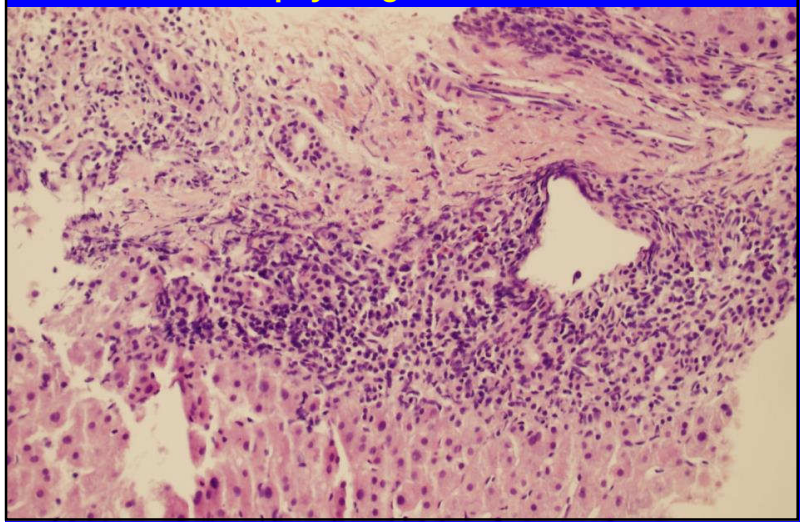
Copper stain

- Orcein: black granules
- Rubeanic acid: black granules
- Rhodanine: red granules

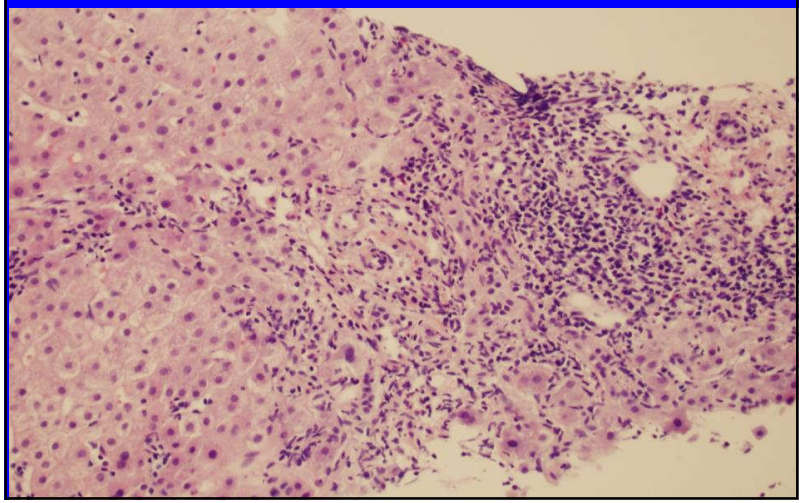
Rubeanic acid: copper in periportal hepatocytes



40/F with positive ANA, SMA
Biopsy diagnosis of AIH

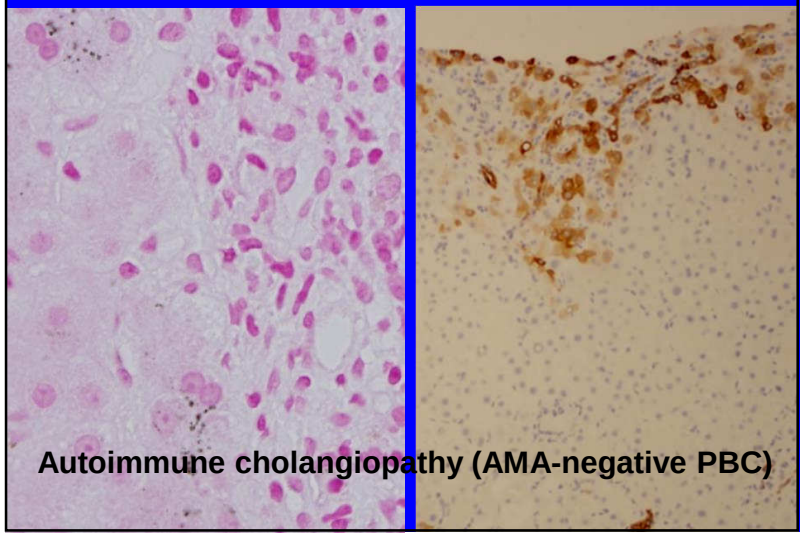


Clinical picture and liver enzymes favored biliary disease
Hepatocellular injury mild, bile duct damage can be patchy



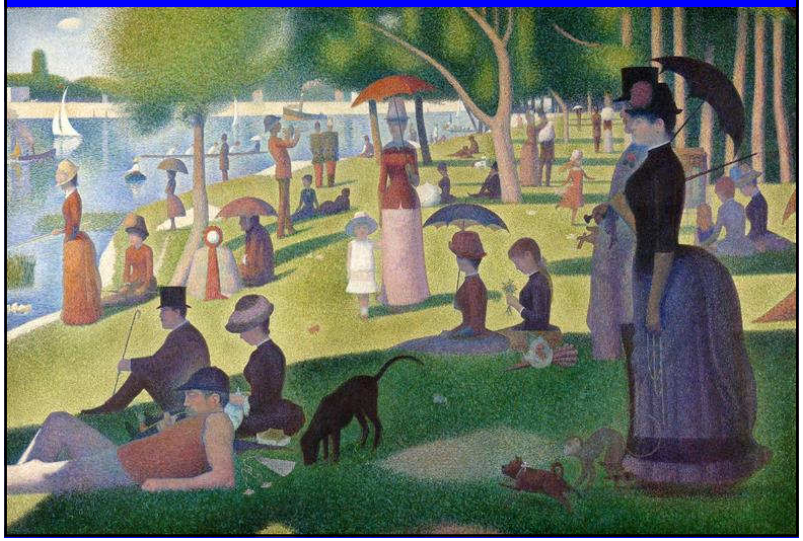
Periportal copper

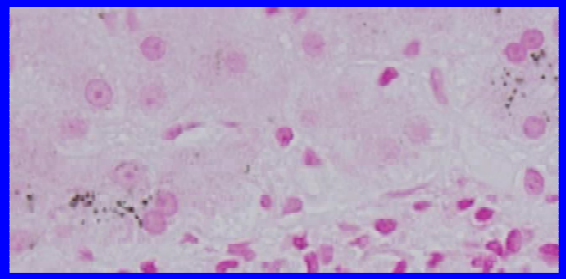
Periportal CK7+



Autoimmune cholangiopathy (AMA-negative PBC)

A Sunday on La Grand Jatte: George Seurat (pointillism)





Copper stain

Hepatitic vs. biliary etiology not clear

- Careful review in periportal region
- Conjunction with CK7
- Not useful in advanced disease
- Negative results do not exclude biliary disease

Wilson disease: quantitative copper reliable

…Really

Survey

Which stain(s) should be performed up front for every liver biopsy?

	Trichrome	PAS-D	Iron	Retic	Copper
N=15	100%	40%	40%	20%	0
Univ (n=10)	100%	60%	60%	30%	0
UCSF (n=5)	100%	40%	20%	0	0

- PAS-D: Globules of A1AT
- Iron: Mild periportal siderosis in early HH

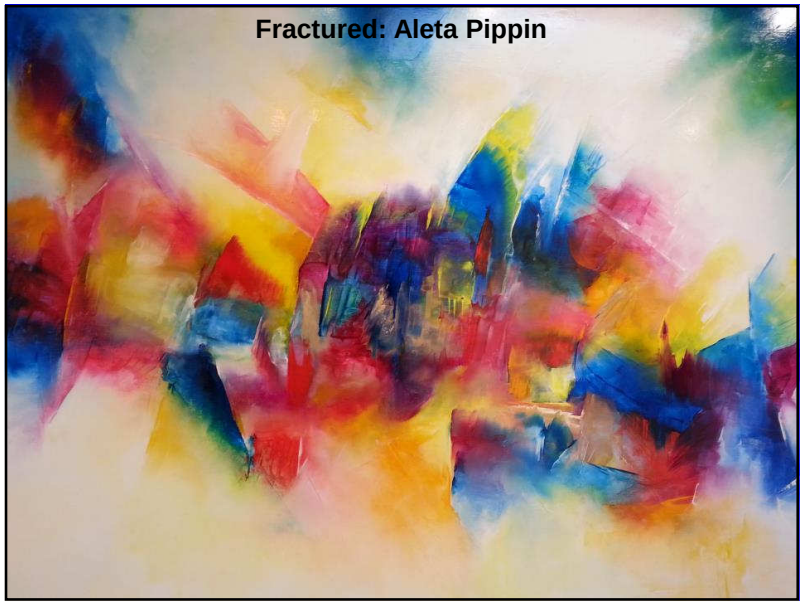
LIVER TRANSPLANTATION 14:695-700, 2008

ORIGINAL ARTICLE

Should Trichrome Stain Be Used on All Post–Liver Transplant Biopsies with Hepatitis C Virus Infection To Estimate the Fibrosis Score?

David Tretheway,[1] Ashok Jain,[2] Randi LaPoint,[1] Rajeev Sharma,[2] Mark Orloff,[2] Patricia Milot,[2] Adel Bozorgzadeh,[2] and Charlotte Ryan[1]

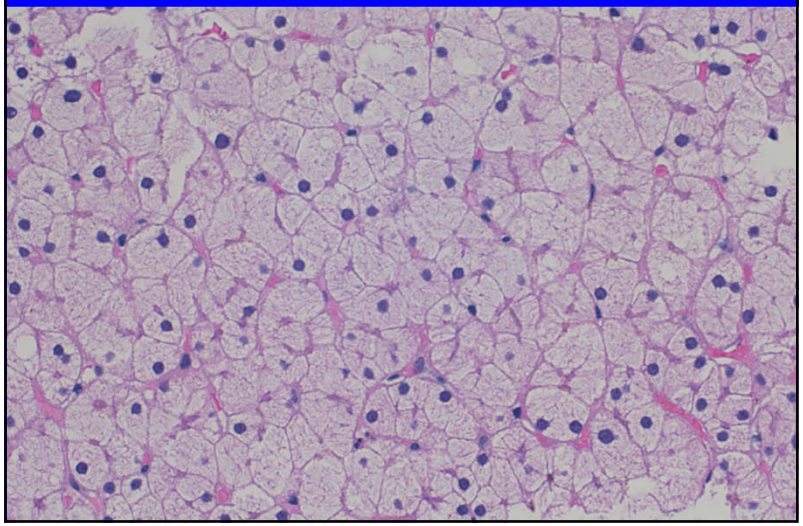
- Mean stage 1.0 with H&E, 1.69 with trichrome
- Trichrome stage was higher in 53.3%
- Fibrosis stage was raised by 2 or more points in 17.8% with trichrome stain
- The hepatic fibrosis score is significantly underestimated by H&E stain in the posttransplant setting in hepatitis C



Special stains: liver pathology

- Trichrome
- Iron
- PAS-diastase
- Reticulin
- Copper
- Other: elastic, PAS, bile

Glycogenic hepatopathy



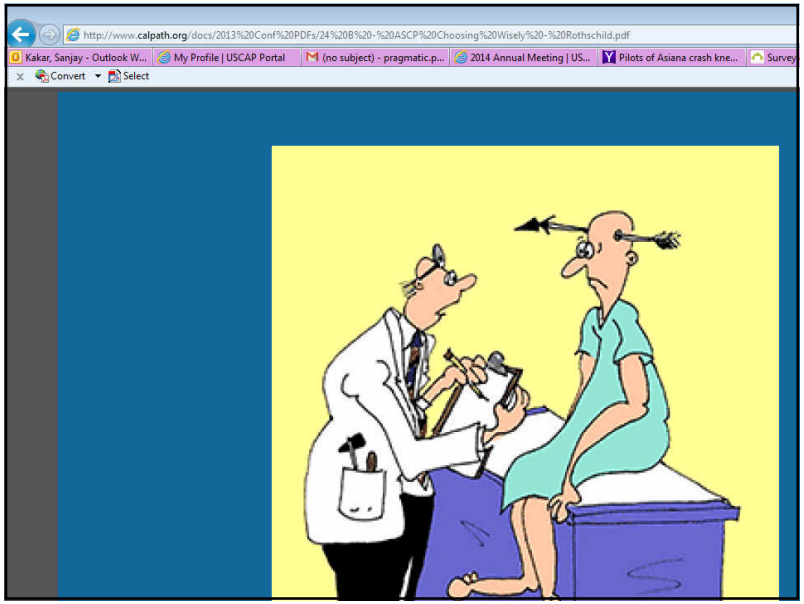
Glycogenic hepatopathy

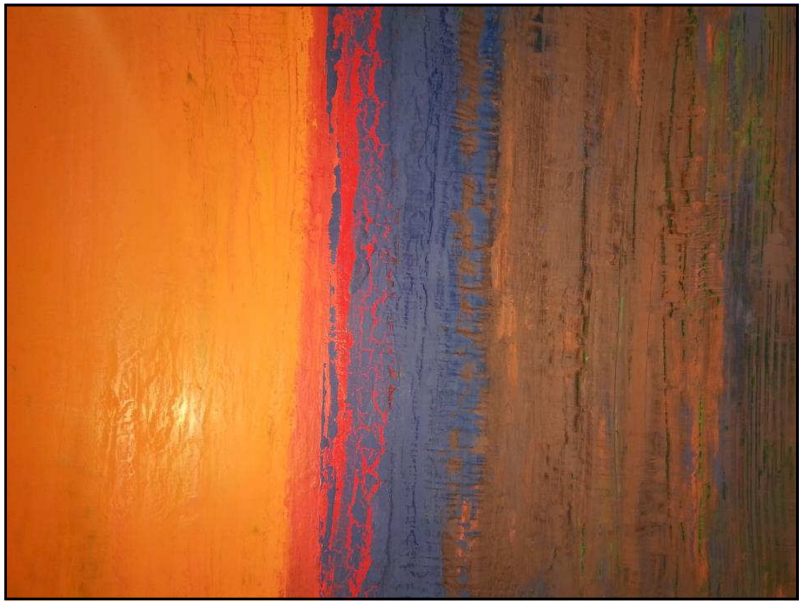
- Type 1 diabetes
- Elevated transaminases
- Hepatomegaly
- Glycogen storage disease
  - More swelling, fibrosis
  - Clinical setting

Torbenson, AJSP,2003

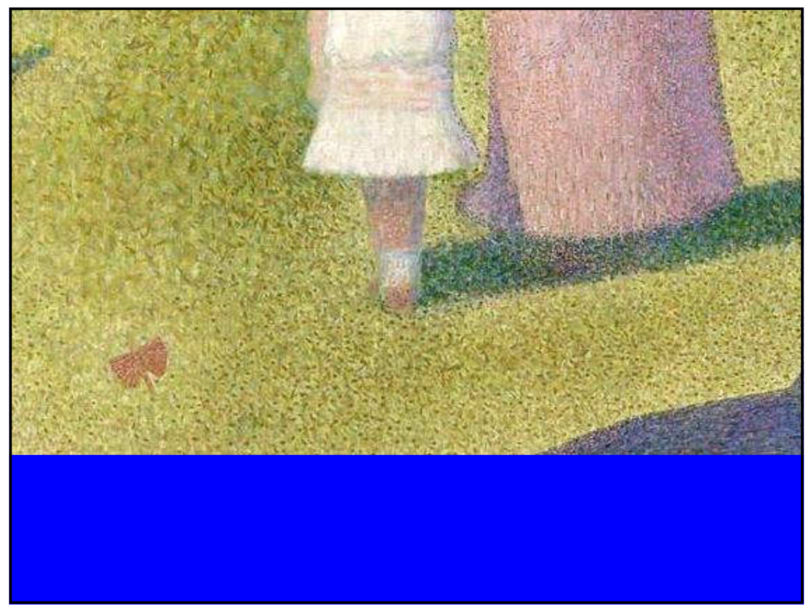
Two common errors

- Portal inflammation is not equivalent to chronic hepatitis
- Lobular inflammation does not necessarily indicate hepatitic disease






Live in this Moment
Mixed media
36 x 48 X 2
$4400
STEPHANIE
This piece to me represents what my art is all about, In this Moment I am Alive! Mother Earth gives us so many beautiful gifts all around us in every moment and all we have to do is stop, breathe and be grateful! Live in this moment is where I believe true happiness is!



9th International Conference on NDT of Art, Jerusalem Israel, 25-30 May 2008
For more papers of this publication click: www.ndt.net/search/docs.php3?MainSource=65

THE EARLY USE OF PRUSSIAN BLUE IN PAINTINGS

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Prussian Palaces and Gardens Foundation, Berlin-Brandenburg,
Department of Conservation, Scientific Laboratory, POB 601462
D-14414 Potsdam, Germany, j.bartoll@spsg.de

ABSTRACT

As far as is known, the pigment Prussian blue was syntheised for the first time in Berlin in the early 1700s. It is commonly assumed that the pigment was not used in paintings before the 1720s. The presence or absence of this pigment is often used to answer questions concerning the dating and authenticity of art objects from the 18th Century.

For the very first time, a large collection of French 18th Century paintings by Antoine Watteau (1684-1721) and his circle has been studied in detail. The pigments of more than fifty paintings from the collection of Frederick II of Prussia have been analysed with non-destructive methods using a complementary combination of micro X-ray florescence analysis, optical microscopy and spectroscopy in reflection mode.

Most interesting in this context is evidence of Prussian blue in two earlier works by Watteau from about 1710. It shows that Prussian blue must have found its way from Berlin to Paris by around 1710 at the latest.

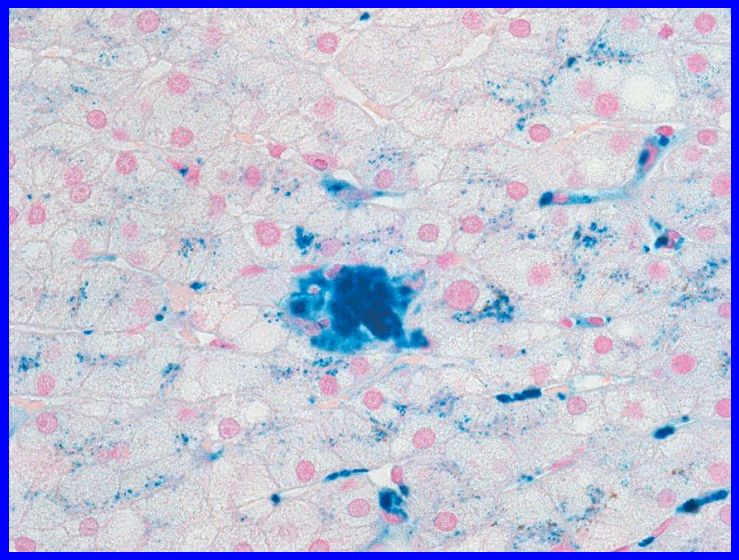
In the search for further proof that Prussian blue was used in paintings dating back to the same years, we also analysed blue pigments in works by painters of the Prussian court, and of other European courts. The court painters were closely connected to the Royal Academy of Arts in Berlin, where the pigment was available no later than 1709.

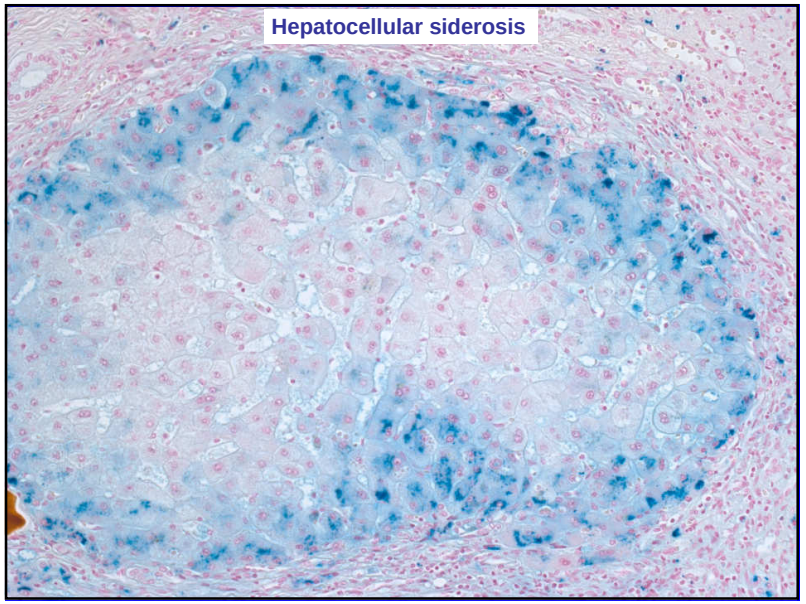
This investigation shows that Prussian blue was used by painters at the Prussian court, in Rotterdam, and Paris much earlier than previously assumed. It was already used in 1710, and this to a surprisingly large extent. To date, the painting "Entombment of Christ", dated 1709 by Pieter van der Werff (Picture Gallery, Sanssouci, Potsdam) is the oldest known painting where Prussian blue has been used.

Historical sources and the material findings mentioned above date the first synthesis of the pigment by Johann Jacob Diesbach in Berlin to about 1706.

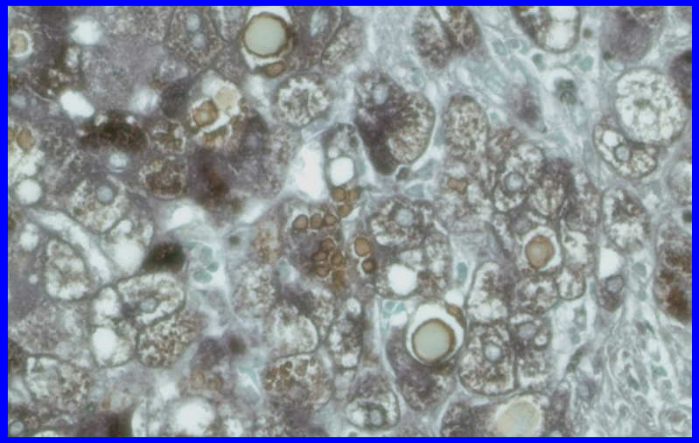
HFE hemochromatosis

HFE gene involved	Manifestation
C282Y homozygous	Iron overload: 30-50% Hemochromatosis:10-30%
C282Y/H63D	Iron overload Hemochromatosis
C282Y heterozygous H63D homo/heterozygous H63D homozygous C282Y/H65C	No or minimal iron overload No risk of hemochromatosis

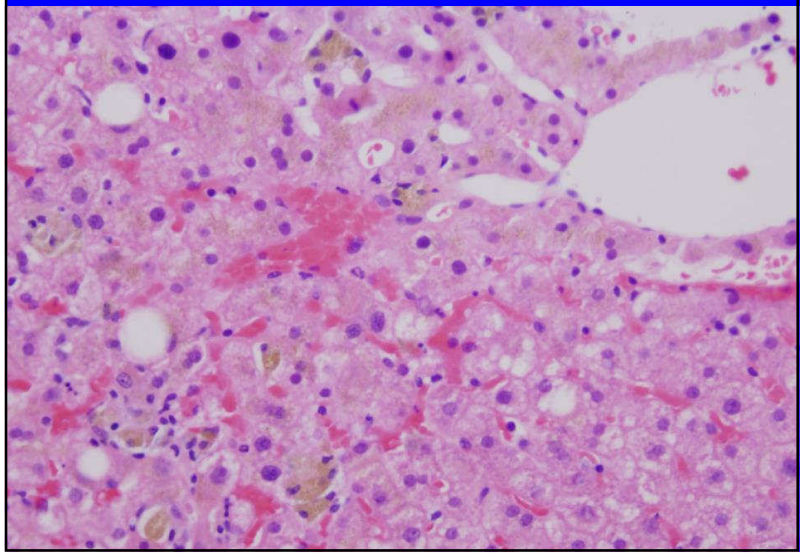




A1AT immunohistochemistry



Mild lobular inflammation

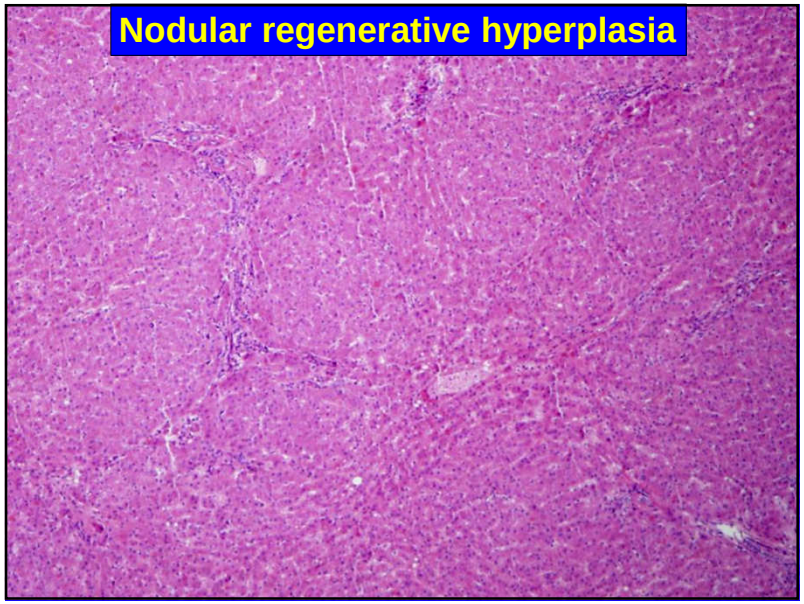


PAS-D stain

…Really

- All biopsies with unexplained liver dysfunction
- All nonneoplastic liver biopsies

Nodular regenerative hyperplasia



Nodular regenerative hyperplasia

- Asymptomatic for prolonged period of time
- Liver function and liver enzymes normal
- Present with portal hypertension

Portal hypertension without cirrhosis

- Nodular regenerative hyperplasia
- Sarcoidosis
- Portal vein thrombosis
- Idiopathic portal hypertension (noncirrhotic portal fibrosis)

Idiopathic portal hypertension

- Portal vein thrombosis which has recanalized
- Portal vein changes
  - Obliteration (small veins)
  - Intimal thickening (large veins)
- Portal fibrosis, thin bridging septa
- Normal or nonspecific changes

Am J Gastroenterol. 2007 Nov;102(11):2536-40. Epub 2007 Jul 19.

Hepatoportal sclerosis as a cause of noncirrhotic portal hypertension in patients with HIV.

Schiano TD, Kotler DP, Ferran E, Fiel MI.

The Recanati/Miller Transplantation Institute, and the Division of Liver Diseases, Department of Medicine, The Mount Sinai Medical Center, New York, New York 10029, USA.

Am J Gastroenterol. 2009 Jul;104(7):1707-14. Epub 2009 May 26.

Idiopathic portal hypertension in patients with HIV infection treated with highly active antiretroviral therapy.

Chang PE, Miquel R, Blanco JL, Laguno M, Bruguera M, Abraldes JG, Bosch J, Garcia-Pagan JC.

Hepatic Hemodynamic Laboratory, Liver Unit, Institut de Malalties Digestives i Metabòliques, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain.

Clin Infect Dis. 2009 Aug 15;49(4):626-35.

Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study.

Kovari H, Ledergerber B, Peter U, Flepp M, Jost J, Schmid P, Calmy A, Mueller NJ, Muellhaupt B, Weber R; Swiss HIV Cohort Study.

No.5, 1948 - Jackson Pollock - world's most expensive painting

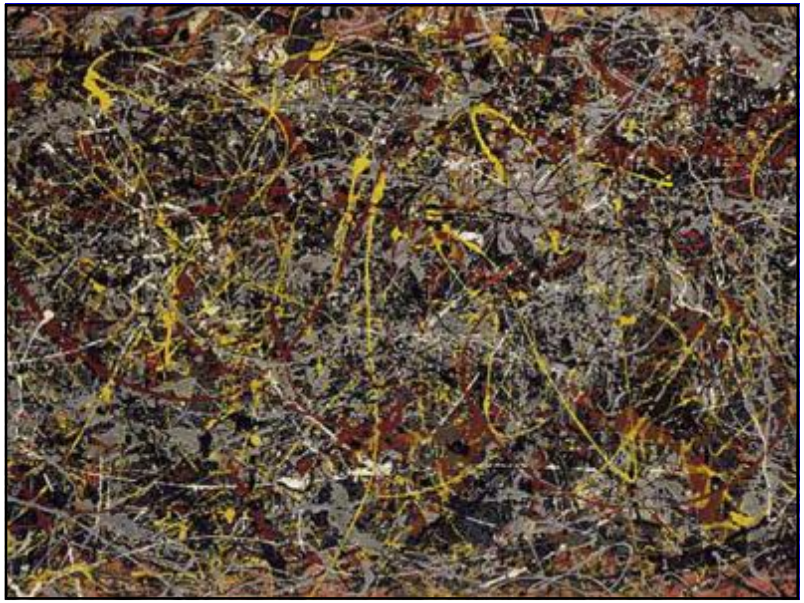
No.5, 1948, painted by Jackson Pollock, is currently the world's most expensive painting ever sold. It was priced at $140 million in 2006, when it changed hands from one collector to another. Here's my attempt at explaining what the buyer could have seen in Jackson Pollock's painting that could justify the price tag.

Art Collectors and investors are always on the look out for gaining exclusive collector's items, which could increase their prestige and also serve as an excellent investment medium. In the art field that means, an artwork that has made a significant impact on the history of art or an artwork created by a very influential artist. It is even better if the artist brought about a paradigm shift that changed the conventions of the time. Eg: da Vinci with Mona Lisa, Picasso with Cubism, Lichtenstein with Pop-Art.

Such works automatically assume an august stature which attracts art collectors and investors. There is also the economics of art that plays a role, the rarer the painting the better the investment. No.5, 1948 has all this going for it.

Pollock's radical techniques and methods made sure that his drip series were (still is) talk of the art community nationally and internationally, with several show conducted in leading the US and Europe. The drip series established Pollock as a leading figure of new American painting. Pollock was an iconoclast and a rebel, which got him a reputation that made him infamous. This in turn was great publicity for his drip series. Pollock with his unconventional methods influenced many artists to abandon conventions of fine art and encourages more creativity and boundary-less expression. Pollock created art history with his new kind of paintings.

There's also **a mathematical theory** that explains the popularity of Pollock's drip series. Mathematicians and Scientists believe that Pollok's drip series contains a mathematical, yet natural, concept called a fractal. It is a rough, geometric object that can be subdivided into parts, each of which looks like a reduced-size copy of the whole. In a fractal pattern, each smaller configuration is a miniature, though not necessarily identical, version of the larger pattern. Mathematicians

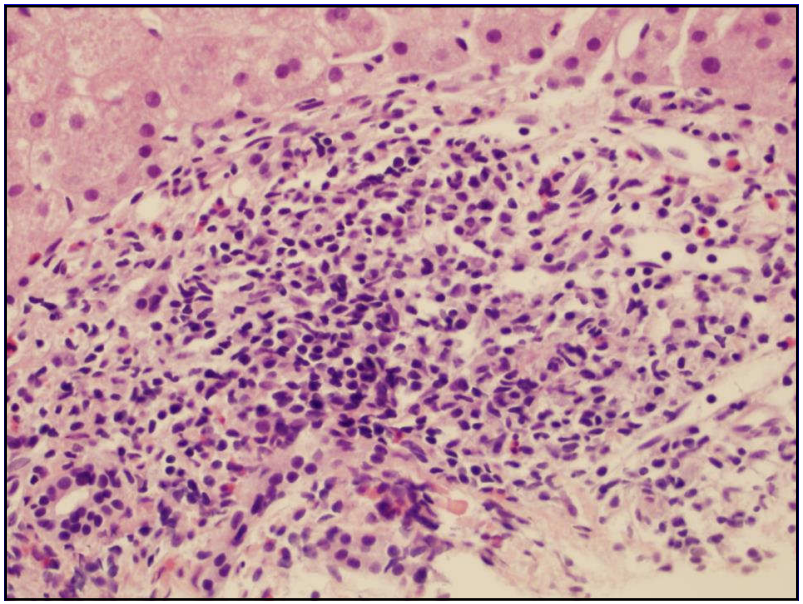


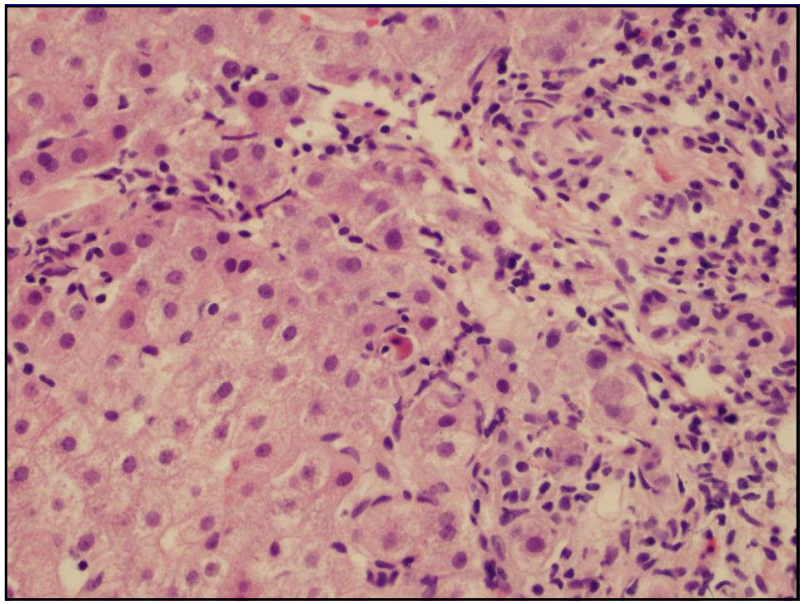
Nodular regenerative hyperplasia

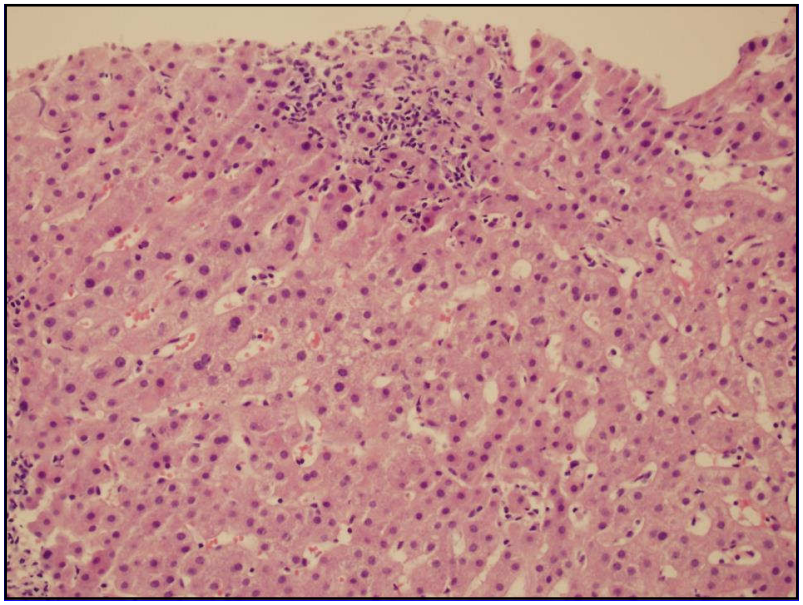
- Rheumatologic diseases: RA, SLE
- Vascular disorders:
  - BC syndrome, PV thrombosis
- Hematological diseases
  - Leukemia, lymphoma
  - Myeloproliferative diseases
- Drugs: azathioprine, oxaliplatin
- Other: PBC, celiac disease

NRH: portal vein obliteration

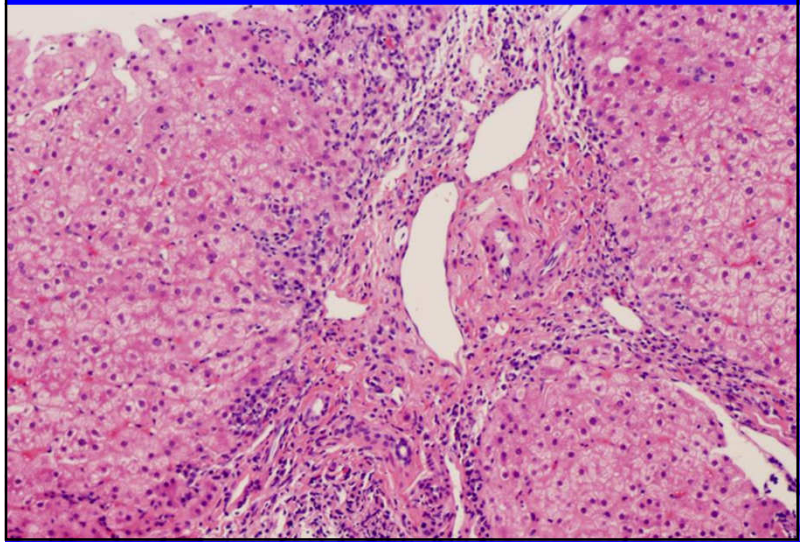
Kleiner, Hepatology, 2006



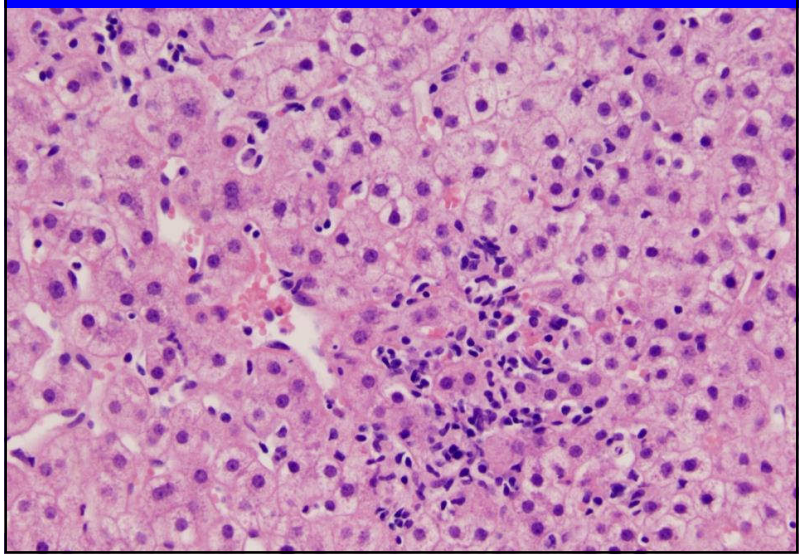




Portal inflammation, no bile duct injury



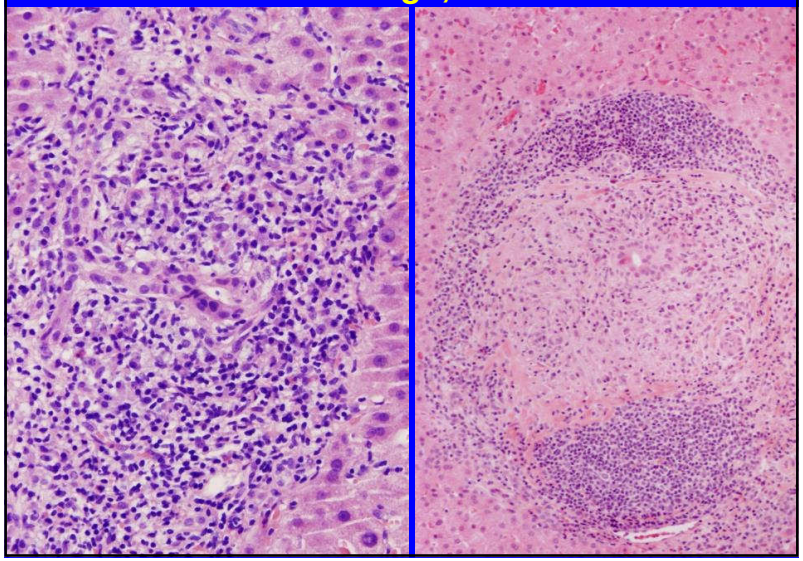
Mild lobular inflammation



Is this primary biliary cirrhosis?

- Significance of histologic findings
- Specificity of positive AMA

PBC: bile duct damage, florid duct lesion



Diagnostic dilemma

Is this primary biliary cirrhosis?

- **Significance of histological findings**
  The findings are nonspecific
- **Specificity of positive AMA**

Specificity of AMA

- High specificity for PBC
  - Autoimmune hepatitis
  - Infections like TB
- ELISA-based assay more specific

Long-Term Follow-Up of Antimitochondrial Antibody–Positive Autoimmune Hepatitis

Conor O'Brien,[1] Supriya Joshi,[1] Jordan J. Feld,[2] Maha Guindi,[3] Hans P. Dienes,[4] and E. Jenny Heathcote[1]

drogenase complex E2 subunit were reviewed in detail. Fifteen of 126 patients with typical features of AIH (pretreatment AIH score >10) had detectable AMAs in serum. None had any histologic features suggestive of PBC. None had detectable anti-liver–kidney–microsomal antibodies. Of these 15 patients, all have remained persistently AMA-positive via ELISA. All 15 patients have been followed long-term, and their clinical course remained typical for AIH. No bile duct damage typical of PBC was seen on initial or follow-up liver biopsies. *Conclusion:* Patients with overt AIH who test positive for AMAs at initial presentation and are treated with corticosteroid therapy have shown no clinical or histologic evidence of PBC despite the continued detection of AMAs over a follow-up of up to 27 years. (HEPATOLOGY 2008;48:550-556.)

Hepatology. 1986 Nov-Dec;6(6):1279-84.

Positive antimitochondrial antibody but normal alkaline phosphatase: is this primary biliary cirrhosis?

Mitchison HC, Bassendine MF, Hendrick A, Bennett MK, Bird G, Watson AJ, James OF.

- Positive AMA: asymptomatic, normal ALP
- Bx: Classic 12/29, consistent 12/29, N=2
- Most progressed to symptomatic PBC
  - 50% at 5 years, 95% at 20 years

Diagnosis

- Diagnosis:
  - Mild portal and lobular inflammation, suggestive of PBC; see note

Note:

- Patchy bile duct involvement in early PBC can be missed on biopsy
- Majority of AMA+ develop features typical of PBC on follow-up
- AMA+ and periportal copper suggest early PBC

Case 2

- 40/F with nonspecific abdominal symptoms
- “Elevated LFTs”
- ANA, SMA positive
  AMA negative
- Work up for other liver diseases negative (viral, drug, Wilson, A1AT deficiency)

Diagnosis

- ANA, SMA+
- Biopsy: interface activity
  foci of lobular inflammation
- Diagnosis:
  Autoimmune hepatitis

Do you agree with the diagnosis?

AIH: role of liver biopsy

- Acute hepatitis
- Chronic hepatitis with varying degree of activity
- Cirrhosis
- Typical histologic features:
  High necroinflammatory activity
  Numerous plasma cells

Serial liver enzymes

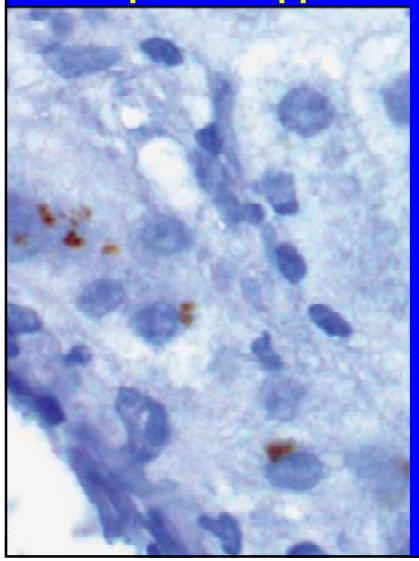
	1-2009	9-2009	1-2010	4-2010	6-2010
ALT (30)	58	62	83	159	133
AST (30)	40	38	65	100	110
ALP (130)	192	210	288	324	308

Diagnosis

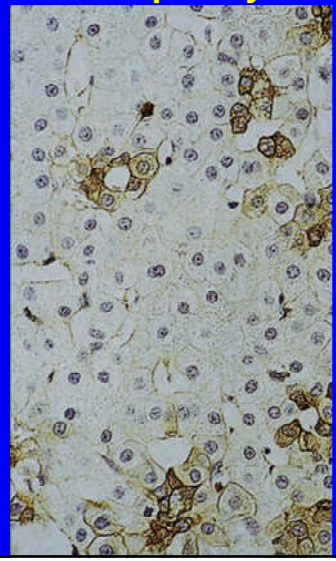
Portal and interface inflammation with focal bile duct damage, most c/w AMA negative PBC

- Moderate interface activity present
- Mild elevation of ALT/AST and absence of prominent hepatocellular injury does not provide definite evidence of AIH component
- If ALT/AST rise >400-500, overlap syndrome can be considered

Periportal copper



CK7+ hepatocytes



Great Wave of Kanagawa: Hokusai, 1830