

The Significance of Iron-Free Foci on Liver Biopsy

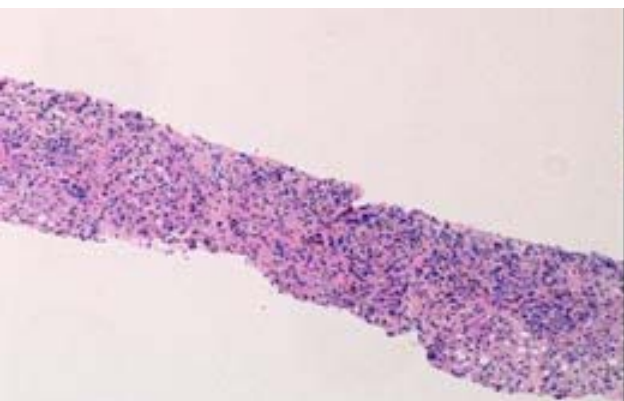
M. Isabel Fiel, M.D.

The Mount Sinai School of Medicine

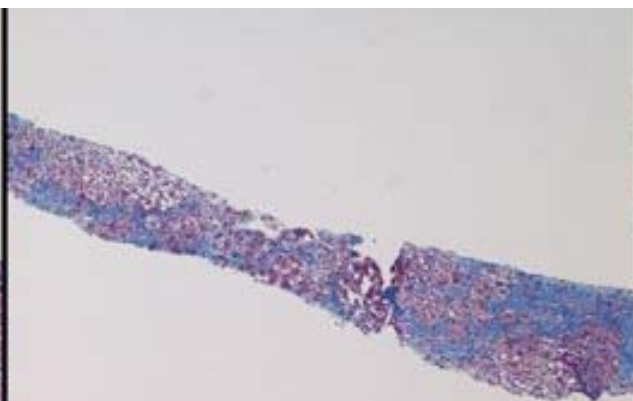
New York, NY

Iron Overload Evaluation

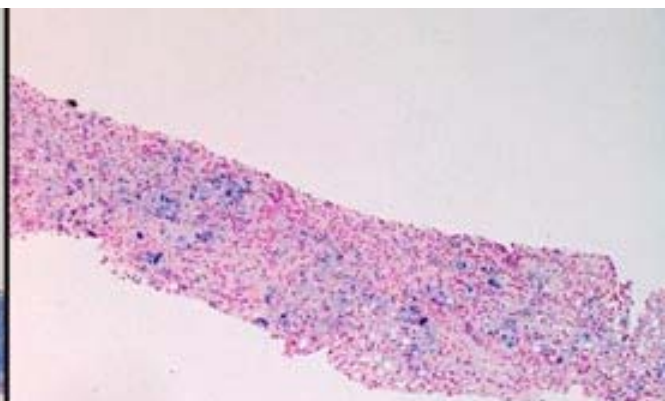
- Clinical
- Biochemical
 - Transferrin saturation
 - Ferritin
- Liver biopsy
 - Performed if liver chemistry tests are abnormal or
 - A lesion is detected on imaging studies



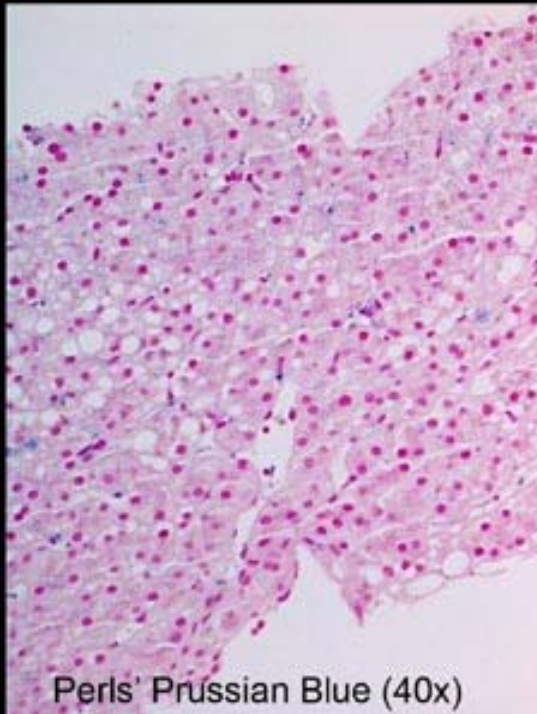
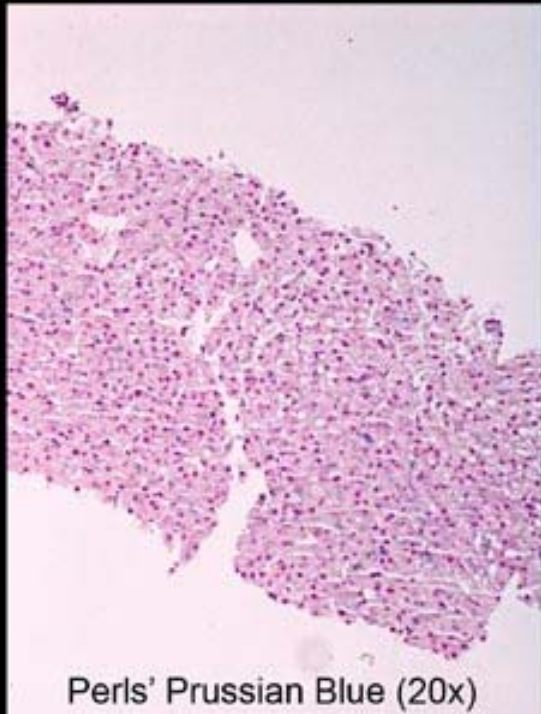
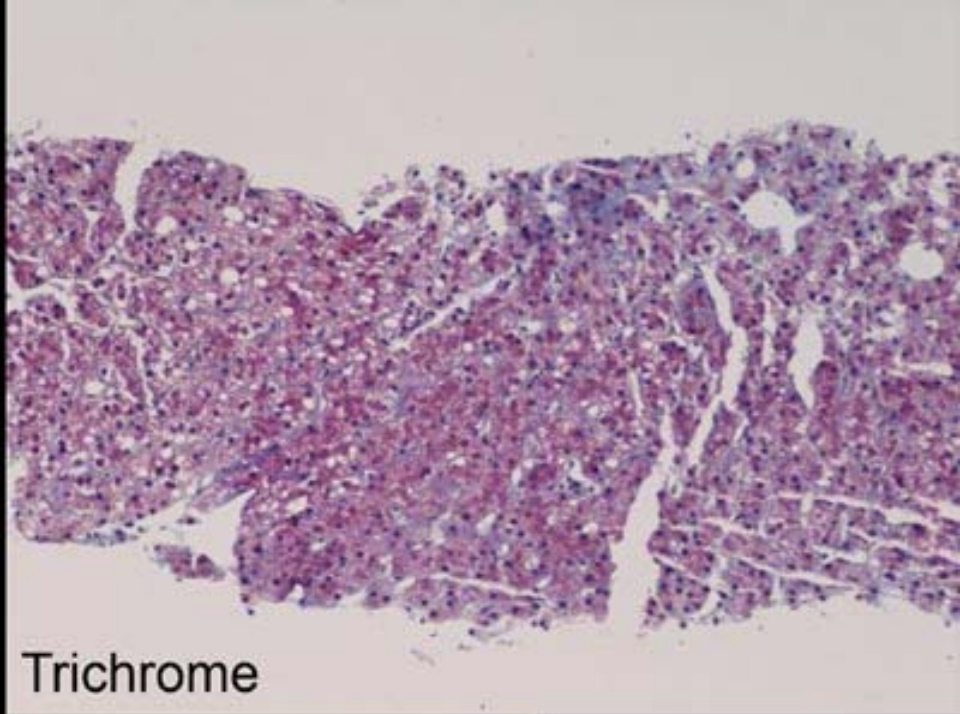
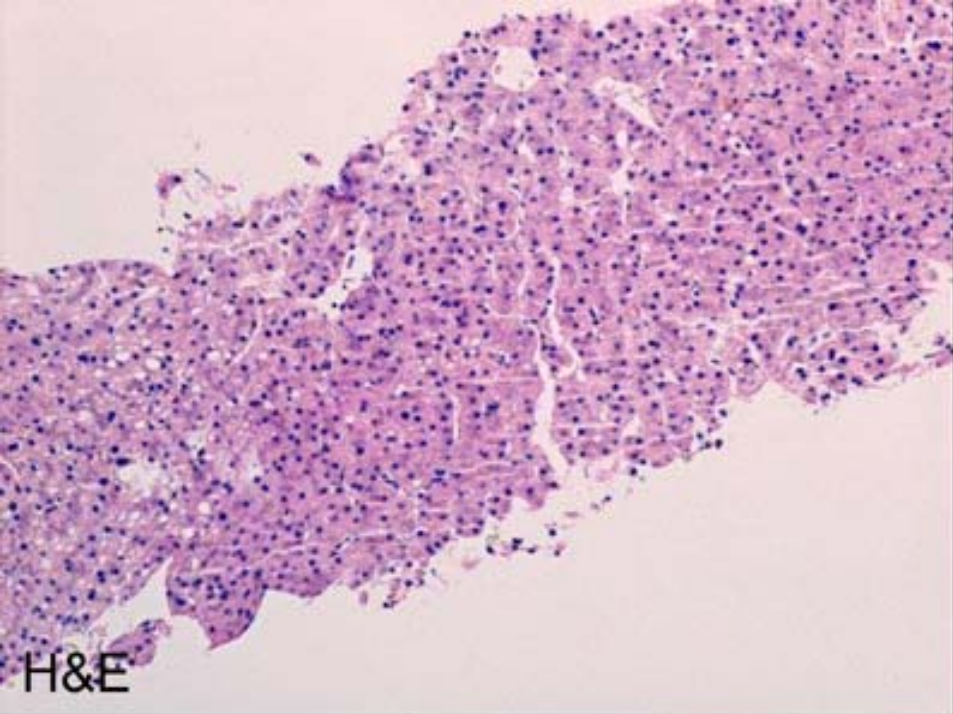
H&E



Trichrome



Perls' Prussian Blue



Diagnosis

- Cirrhosis
- Steatohepatitis
- 3-4+ iron deposition
- Iron-free focus

Evaluation of iron in the liver

1. Determine the location: parenchymal, mesenchymal or mixed type
2. Quantify liver iron:
 - Histological
 - Biochemical
3. Look for associated iron-related lesions
 - Sideronecrosis
 - Fibrosis
 - Iron-free foci
4. Assess any other liver damage

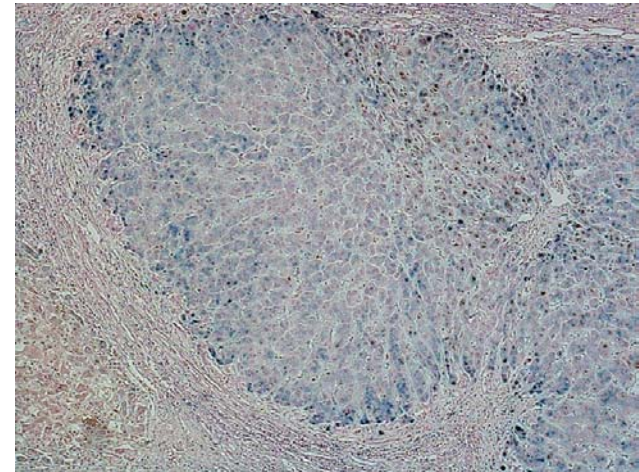
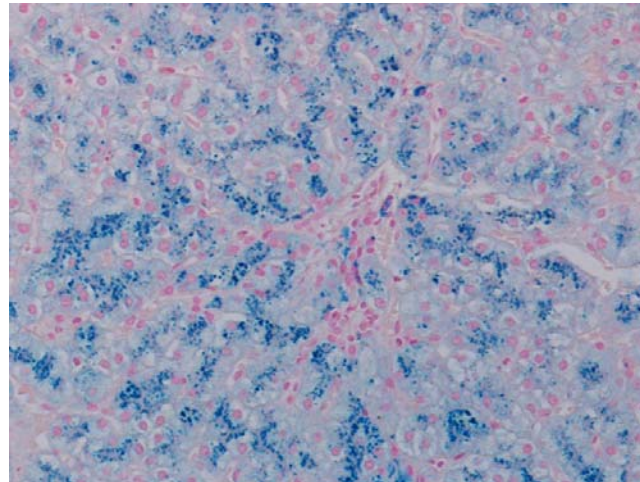
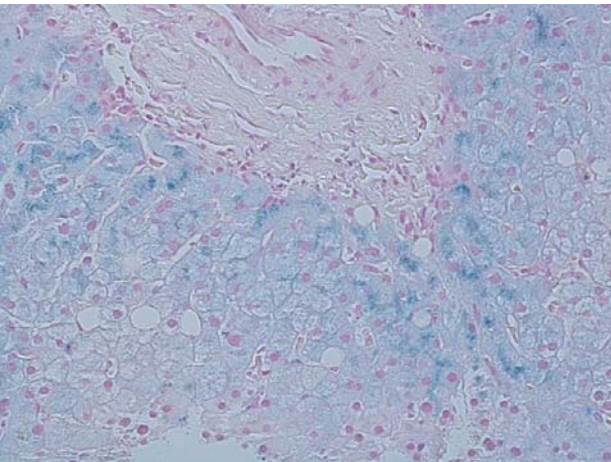
Histological Assessment

Qualitative

Distribution within the lobule – patterns

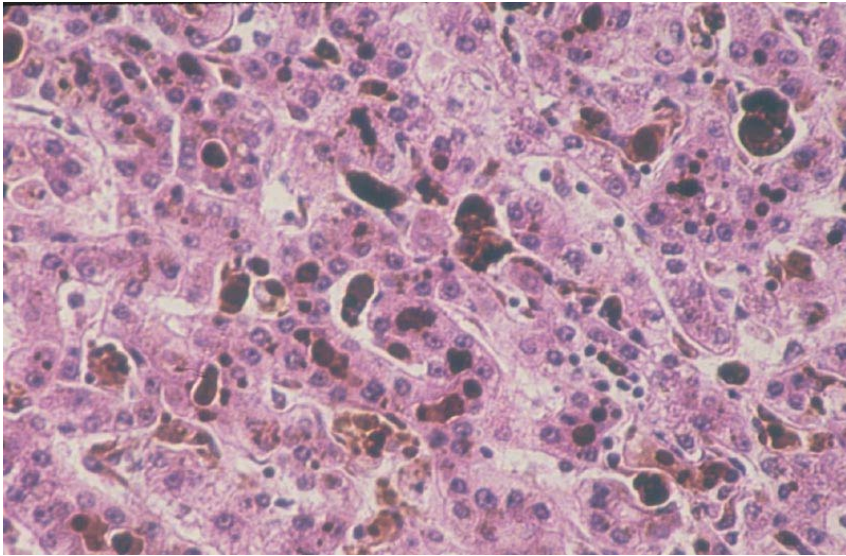
Parenchymal or hepatocellular pattern

- Iron predominantly within hepatocytes
- Gradient from periportal to centrilobular



Histological Assessment

Qualitative



- Mesenchymal pattern:
 - Parenteral iron overload
 - Iron within sinusoidal cells: Kupffer cells and connective tissue of portal tracts and fibrous septa
- Mixed pattern
 - Several causes: e.g. alcohol, hemochromatosis

Table 1. Patterns and Pattern Scores for Histological Evaluation of Hepatic Iron Deposition

HH Pattern and Score

1. Any quantitative grade of iron granule deposition in scattered hepatocytes in acinar zone 1.
2. Hepatocytes in >50% of acinar zones 1 are reactive; Kupffer cells and/or portal macrophages \pm reactive.
3. Hepatocellular iron, zone 1 or panacinar, with zonal gradient in acini or within regenerative nodules. Kupffer cell aggregates, portal/septal macrophage iron common; may include reactivity in biliary epithelium or vascular endothelium.
4. Prussian Blue reactivity seen on glass slides by the naked eye. Microscopically, coalesced hepatocellular and Kupffer cell iron granules with little or no gradient are present. This grade includes iron-free foci. Biliary epithelium and vascular endothelium are commonly involved.

Non-HH Pattern and Score

1. Scattered sinusoidal lining cells or portal macrophages are reactive. May see occasional zone 1 hepatocytes with faint granular reactivity.
 2. Panacinar Kupffer cell/sinusoidal lining cell reactivity, \pm portal macrophages are seen. May see occasional zone 1 hepatocyte reactivity.
 3. Panacinar Kupffer cell reactivity and portal macrophage reactivity are present; diffuse zone 1 or periseptal hepatocellular reactivity is noted.
 4. As in 3, with iron deposition in fibrous tissue of portal tracts or septa.
-

Iron Overload Syndromes

- Hereditary hemochromatosis (HH)
- Nonhemochromatosis iron overload syndromes
 - Juvenile hemochromatosis - rare
 - Secondary iron overload
 - Excessive iron supply
 - Transfusion
 - Inflammatory syndrome
 - Chronic liver diseases: alcohol, HCV, HBV
 - Cirrhosis
 - Hematological disorders

Hereditary hemochromatosis (HH)

- Autosomal recessive disorder
- Intestinal hyperabsorption of iron
- Progressive iron deposition within parenchymal organs: liver, pancreas, heart
- 85% of patients are homozygous for C282Y mutation

Pattern of iron deposition in HH

Parenchymal (HH) type with decreasing gradient from zone 1 to zone 3

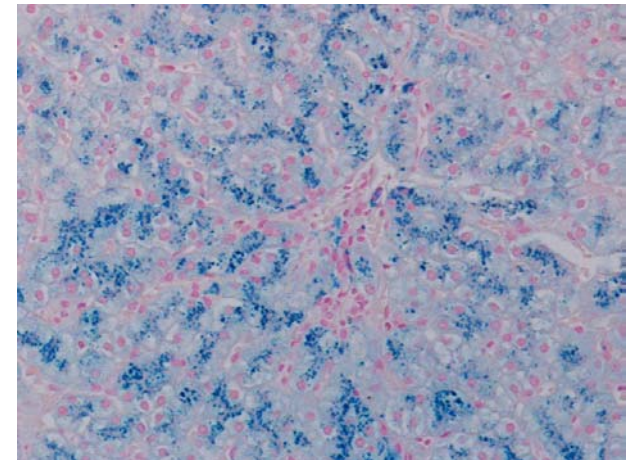
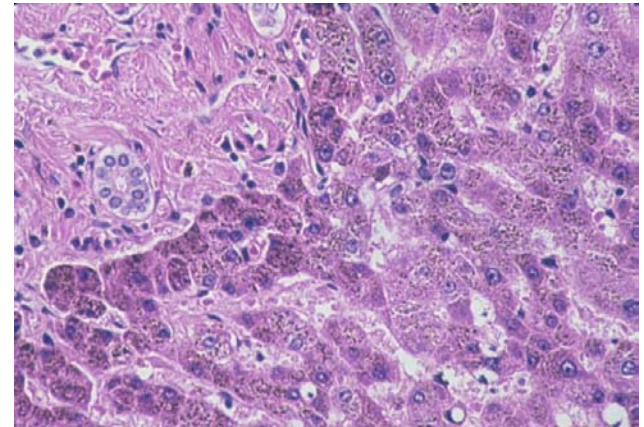
- Iron predominantly within hepatocytes
- Mesenchymal deposits may be present but less abundant

HH pattern:

- 58% PPV for C282Y homozygosity
- Non-HH pattern = 100% negative predictive value for C282Y homozygosity

Pattern scores + quantitation scores

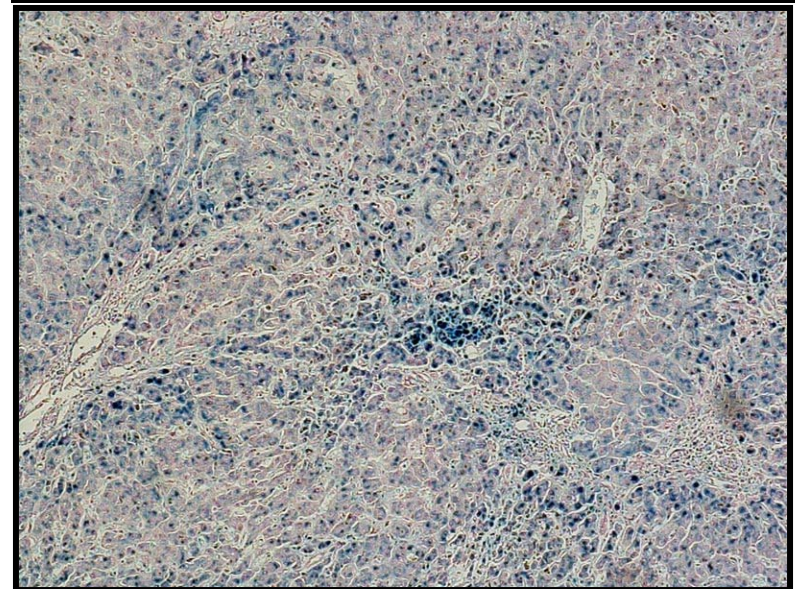
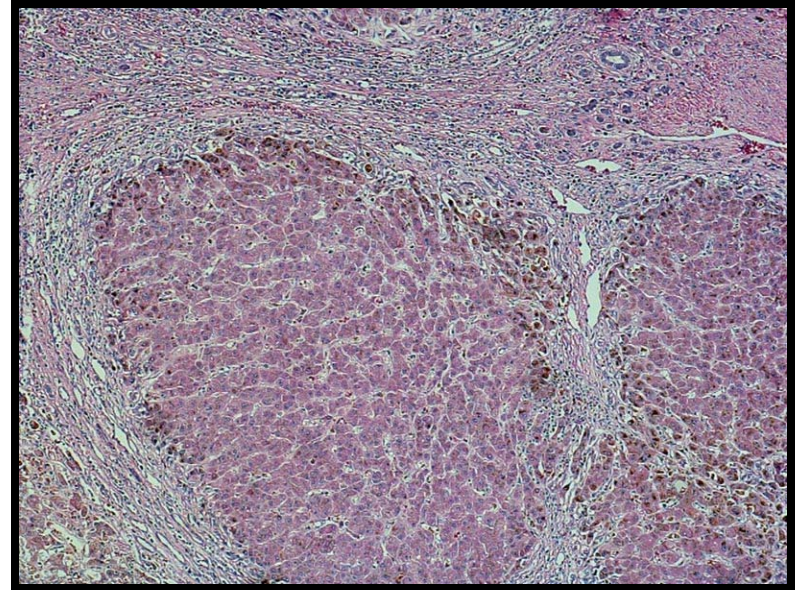
- 3+ or 4+, the PPV = 73.2% for C282Y homozygosity



Liver pathology in HH

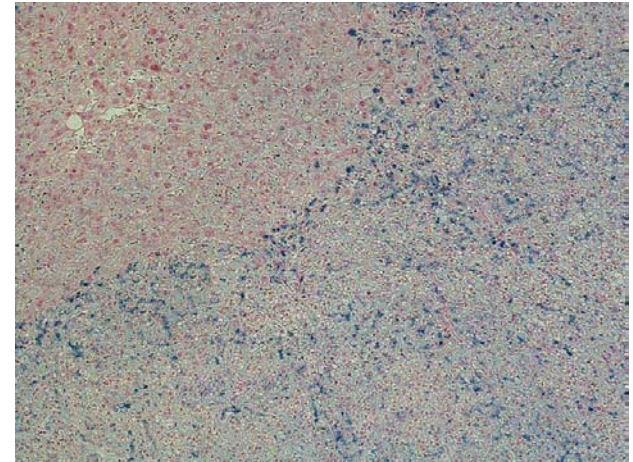
- Sideronecrosis
- Mild inflammation
- Progressive fibrosis

*Iron-free foci



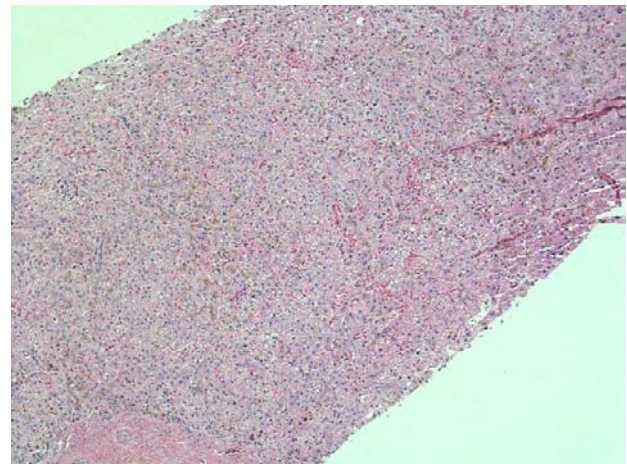
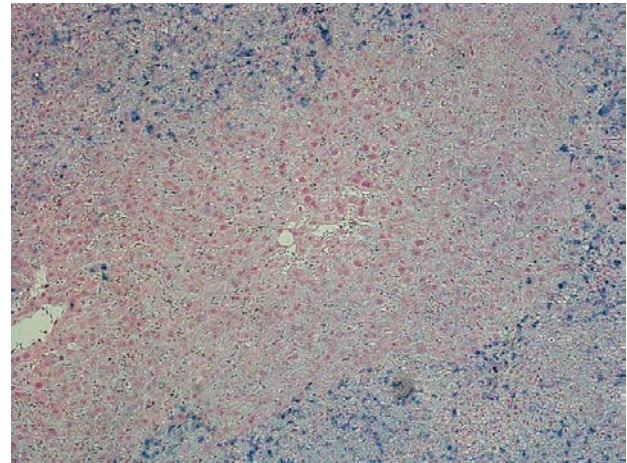
Iron-Free Foci (IFF)

- Resistance to iron accumulation
- Sublobular nodules of hepatocytes free of iron or
- Hepatocytes exhibiting much less iron than the surrounding parenchyma (Deugnier 1993)
- Phenotypic marker of neoplasia and preneoplasia (Terada & Nakanuma 1989)
 - Iron stain valuable for identification of neoplastic or borderline lesions



Iron-free foci

- Nodules comprising more than 20 hepatocytes free of iron or significantly less iron than the surrounding parenchyma



Significance of IFF

- Proliferative lesions
- Preneoplastic foci
- The finding of IFF in the initial liver biopsy specimen from a patient with HH should lead to regular HCC screening

Iron-free foci

- Hirota et al (1982) first suggested iron-free foci to be precursors to primary liver carcinoma
- Resistance to iron accumulation
- HCC usually free of stainable iron

Iron-free foci (IFF)

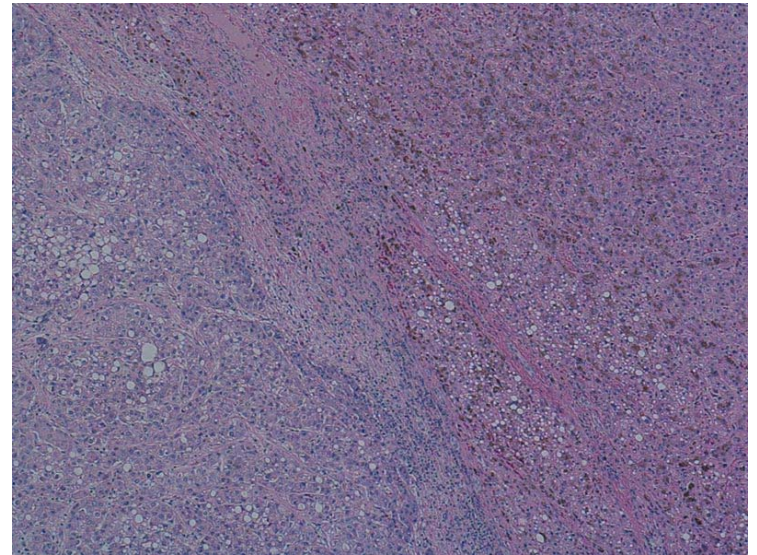
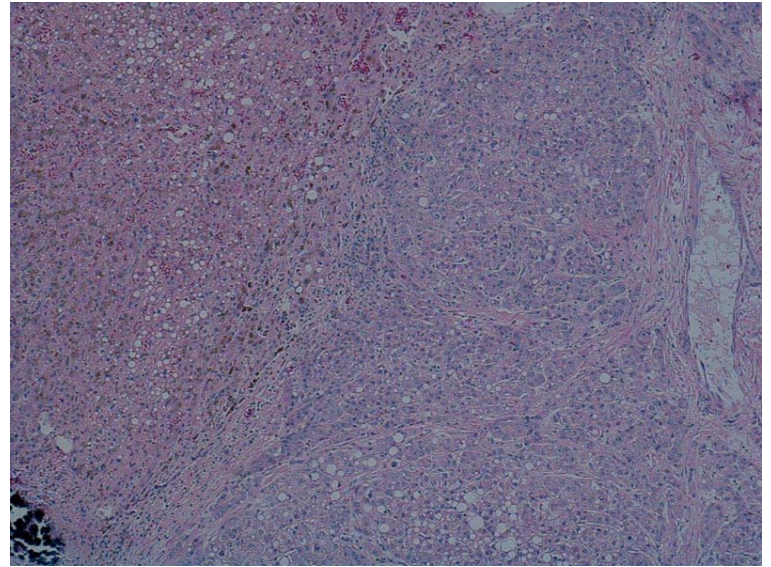
- Found in 14/185 patients (7.6%) with hereditary hemochromatosis
 - 6/12 (50%) developed HCC vs 2/24 (8%) in control group without IFF
 - Mean number of IFF = 3.2 +/- 2.1
 - 10/14 with dysplastic features
 - PCNA+ in 75% → proliferative lesion or preneoplastic foci

Primary Liver Cancer in HH

- Accounts for 6.7 up to 45% of deaths
- Relative risk for development >200
- Deugnier et al (Gastroenterology 1993)
 - 54 patients with liver cancer
 - 53 HCC, 1 CholangioCa
 - Male > female
 - > 55 y.o
 - Majority symptomatic
 - 8 macronodular, 8 micronodular cirrhosis
 - 3 were fibrotic and non-cirrhotic
 - 10/12 (83%) presented with IFF



HCC in a patient with HH





Dysplastic nodule with iron overload adjacent to an HCC