Xenobiotic-Induced Toxicologic Pathology of the Liver

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Photomicrographs courtesy of the National Toxicology Program (http://ntp.niehs.nih.gov)
Specific hepatic changes often do not occur in isolation.
Outline

- Cytologic Alteration
- Degeneration
- Vascular Changes
- Cell Death/Necrosis
- Inflammation
- Proliferative Lesions
- Neoplastic Lesions
- Controversial Lesions
Cytologic Alteration

• Clear cell change
• Enzyme induction
• Peroxisome proliferation
• Fatty change
• Cholestasis
• Atrophy
Clear cell change - Glycogen accumulation
Normal glycogen accumulation

Glycogen depletion
Enzyme Induction
Constitutive Enzyme Activity
Enzyme Induction
Increased Smooth Endoplasmic Reticulum

Control

Treated
Persistent & Excessive Enzyme Induction
Persistent & Excessive Enzyme Induction
Peroxisome Proliferation
Peroxisome Proliferation Ultrastructure

Control

Treated
Peroxisome Proliferators

- Hypolipidemics
  - Clofibrate
  - Gemfibrozil
- Methaphenilenene
- Ibuprofen
- Diethylhexyl phthalate
Macrovesicular Fatty Change
Microvesicular Fatty Change
Cholestasis
Atrophy
Some Non-neoplastic Structural Alterations

**Degenerative Changes**
- Cystic degeneration (spongiosis hepatis)
- Biliary cysts
- Pigments
- Inclusions

**Vascular Changes**
- Peliosis (ectasia)
- Sinusoidal dilation
- Congestion
- Hemorrhage
- Endothelial change
- Thrombosis
Degeneration

- Cystic degeneration
- Biliary cysts
- Pigments
- Inclusions
Some Non-neoplastic Structural Alterations

Degenerative Changes
- Cystic degeneration (spongiosis hepatis)
- Biliary cysts
- Pigments
- Inclusions
- Fatty change (lipidosis)
- Atrophy

Vascular Changes
- Peliosis (ectasia)
- Sinusoidal dilation
Pigment Deposition
Hyaline Degeneration
(Inclusions)
Some Non-neoplastic Structural Alterations

Degenerative Changes
• Cystic degeneration (spongiosis hepatis)
• Biliary cysts
• Pigments
• Inclusions

Vascular Changes
• Vascular ectasia
• Sinusoidal dilation
• Hemorrhage
• Endothelial change
• Thrombosis
Cell Death

• Single cell
  - Apoptosis
• Focal necrosis
• Patchy necrosis
• Zonal necrosis
Single Cell Necrosis & Apoptosis
Focal Necrosis and Inflammation
Focal Necrosis and Inflammation
Inflammation

• Spontaneous
  – Acute, chronic, focal, diffuse
    • Hepatocellular
    • Biliary

• Xenobiotic-induced
  – Acute, chronic, focal, diffuse
    • Hepatocellular
    • Biliary

• Cirrhosis
• Cholangiofibrosis
Focal Inflammation
Chronic Active Inflammation
Bile Duct Hyperplasia and Inflammation
Proliferative Lesions

Hepatocellular Lesions
- Foci of cellular alteration
- Hyperplasias
  - Regenerative hyperplasia
  - Focal hyperplasia
- Hepatocellular adenoma
- Hepatocellular carcinoma
- Hepatoblastoma

Oval Cell Lesions
- Oval cell hyperplasia
- Oval cell neoplasia

Biliary Lesions
- Cholangioma
- Cholangiocarcinoma

Combined Lesions
- Hepatocholangioma
- Hepatocholangiocarcinoma

Questionable Lesions
- Cholangiofibrosis vs. “Cholangiocarcinoma”
- Ito cell “proliferations”
Proliferative Lesions

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Foci of Cellular Alteration
Foci of cellular alteration occur spontaneously in older rodents and when induced by treatment may occur in younger rodents.
Relationship of Foci and Liver Tumors in F344 Rat 2-Year Bioassays

- Liver tumor negative studies
  - No increased incidence of foci at study termination
- Liver tumor positive studies – genotoxic agent
  - 3 to 10-fold increase in multiple foci
  - Eosinophilic (3-10X); Clear (2-9X); Mixed (3x); Basophilic (4-8X)
- Liver tumor positive studies – non-genotoxic agent
  - 2 to 15-fold increase in foci
  - Eosinophilic (4-15X); Mixed (2-5X)
Proliferative Lesions

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**Oval Cell Lesions**
- Oval cell hyperplasia
- Oval cell neoplasia
Regenerate: Hyperplasia; Nodular hyperplasia
Liver plates merge with surrounding hepatocytes but have a mild compression.

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Portal triads

C.V.

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Portal triads

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Another Similar Lesion Located Beneath the Hepatic Capsule

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Proliferative Lesions

Hepatocellular Lesions
• Foci of cellular alteration
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Hepatocellular Adenoma
Carcinoma Arising in Adenoma
Hepatocellular Carcinoma
Hepatocellular Carcinoma
Hepatoblastoma
Proliferative Lesions

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Oval Cell Hyperplasia
Proliferative Lesions

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Questionable Lesions
• Cholangiofibrosis vs. “Cholangiocarcinoma”
• Ito cell “proliferations”
Cholangioma
Cholangiocarcinoma
Hepatocholangioma
Hepatobiliary carcinoma
Controversial Proliferative Lesions

- Cholangiofibrosis vs. cholangiocarcinoma
- Ito cell hyperplasia vs. Ito cell tumor
Cholangiofibrosis vs. Cholangiocarcinoma
Cholangiofibrosis
Cholangiofibrosis
Cholangiofibrosis
Cholangiofibrosis vs. Cholangiocarcinoma
Cholangiofibrosis  

Cholangiocarcinoma
Ito Cell Tumor
Ito Cell “Tumor”
Some Summary Points

- Liver has remarkable reserve capacity
- Responses can be adaptive or adverse
- Adverse effects often occur together
- Rat liver has a secondary lobular structure that may explain unusual distribution of lesions
- Nodular lesions and aggressive proliferative changes in the liver are not necessarily neoplasms