Pathology of Liver Diseases I

Hepatic Injury
Morphologic Patterns of Hepatic Injury

• Degeneration and Intracellular Accumulations
  – Ballooning degeneration
  – Hepatic steatosis or fatty change
• Apoptosis
• Necrosis
Ballooning Degeneration

- Toxic injury
- Hepatitis
- Often in a centrilobular distribution

From Rubin and Farber, Fig. 1-2
Fatty Change

- A REVERSIBLE LESION
- Microvesicular hepatic steatosis
  - Alcoholic liver disease and other intoxications
  - Reyes syndrome
  - Acute fatty liver of pregnancy
- Macrovesicular hepatic steatosis
  - Alcoholic liver disease and other intoxications
  - Diabetes (metabolic syndrome)
    - Can progress to inflammatory liver disease and cirrhosis
  - Obesity

From Sherlock and Summerfield, Fig. 355
Apoptosis

• Apoptotic bodies
• Councilman bodies

From Robbins Basic Pathology, 10th ed. Fig. 16.3
Patterns of Necrosis

- Focal Necrosis
- Zonal Necrosis
  - Centrilobular
  - Midzonal
  - Portal
- Submassive Necrosis
  - Bridging Necrosis
- Massive Necrosis

From Sherlock and Summerfield, Fig. 123
Bridging Necrosis

- Portal-portal
- Portal-central

From Rubin, Fig. 14-22
Responses to Injury

• Regeneration
• Inflammation
• Fibrosis
<table>
<thead>
<tr>
<th>Test Category</th>
<th>Serum Measurement*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatocyte integrity</strong></td>
<td>Cytosolic hepatocellular enzymes†</td>
</tr>
<tr>
<td></td>
<td><em>Serum aspartate aminotransferase (AST)</em></td>
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<tr>
<td></td>
<td><em>Serum alanine aminotransferase (ALT)</em></td>
</tr>
<tr>
<td></td>
<td>Serum lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td><strong>Biliary excretory function</strong></td>
<td>Substances normally secreted in bile†</td>
</tr>
<tr>
<td></td>
<td><em>Serum bilirubin</em></td>
</tr>
<tr>
<td></td>
<td><em>Total</em>: unconjugated plus conjugated</td>
</tr>
<tr>
<td></td>
<td><em>Direct</em>: conjugated only</td>
</tr>
<tr>
<td></td>
<td><em>Delta</em>: covalently linked to albumin</td>
</tr>
<tr>
<td></td>
<td>Urine bilirubin</td>
</tr>
<tr>
<td></td>
<td>Serum bile acids</td>
</tr>
<tr>
<td></td>
<td>Plasma membrane enzymes (from damage to bile canaliculus)†</td>
</tr>
<tr>
<td></td>
<td><em>Serum alkaline phosphatase</em></td>
</tr>
<tr>
<td></td>
<td>Serum γ-glutamyl transpeptidase</td>
</tr>
<tr>
<td></td>
<td>Serum 5'-nucleotidase</td>
</tr>
<tr>
<td><strong>Hepatocyte function</strong></td>
<td>Proteins secreted into the blood</td>
</tr>
<tr>
<td></td>
<td><em>Serum albumin</em></td>
</tr>
<tr>
<td></td>
<td><em>Prothrombin time</em>† (factors V, VII, X, prothrombin, fibrinogen)</td>
</tr>
<tr>
<td></td>
<td>Hepatocyte metabolism</td>
</tr>
<tr>
<td></td>
<td>Serum ammonia†</td>
</tr>
<tr>
<td></td>
<td>Aminopyrine breath test (hepatic demethylation)†</td>
</tr>
<tr>
<td></td>
<td>Galactose elimination (intravenous injection)†</td>
</tr>
</tbody>
</table>

* The most common tests are in italics.
† An elevation implicates liver disease.
‡ A decrease implicates liver disease.

From Robbins and Cotran
Pathologic Basis of Disease, 8th Edition
Jaundice and Cholestasis

- Bilirubin metabolism
  - Hemoglobin degradation is the main source of bilirubin
  - Unconjugated bilirubin is water insoluble, bound to albumin, and is not secreted in urine
  - Hepatocytes take up bilirubin and conjugate it to glucouronic acid
  - Conjugated bilirubin is secreted into bile
  - Bacteria break down bilirubin to colorless urobilinogens
Cholestasis

- Hepatocellular vs Obstructive
- Symptoms
  - Jaundice
  - Pruritis
  - Xanthomas
- Morphology
  - Bile pigment in parenchyma
  - Dilatation of biliary tree upstream of obstruction
  - Bile duct proliferation, foamy degeneration, apoptosis, inflammation, bile lakes, fibrosis

Robbins Basic Pathology, 7th Ed., Fig. 16-2
Cholestasis

From Sherlock and Summerfield, Fig. 231
Hepatic Failure

- Liver has enormous reserve functional capacity - 80-90% destruction before hepatic failure supervenes
- Mortality is 70-90%
- Acute liver failure –occurs within 26 weeks of the initial insult
- Chronic liver failure typically occurs in the setting of chronic liver disease and cirrhosis
- Morphology
  - Acute - Massive hepatic necrosis
  - Acute - Massive hepatic dysfunction without necrosis
  - Chronic - Cirrhosis
Hepatic Failure

• Can be chronic or acute
• Clinical picture
  – Jaundice
  – Hypoalbuminemia
    • Edema, Ascites
  – Coagulopathy
  – Hyperammonemia
  – Fetor hepaticus
  – Palmar erythema
  – Spider angiomas
  – Muscle wasting/weight loss

From Sherlock and Summerfield, Fig. 27
Complications of Hepatic Failure

• Hepatic encephalopathy
  – Signs and symptoms
  – Hyperammonemia is key factor
  – Reversible

• Ascites
  – Portal hypertension and hypoalbumenemia

• Hepatorenal syndrome
  – Na+ retention, decreased GFR, and free-water excretion
  – Peripheral vasodilation and decreased renal perfusion
  – Drop in urine output with increase in BUN and serum creatinine

• Hepatopulmonary syndrome
  – Hypoxemia and pulmonary vasodilation
Cirrhosis - Defining Characteristics

• Injury and resulting fibrosis are diffuse
• Normal lobular architecture is disrupted
• Fibrosis
  – Delicate bands
    • Portal-portal
    • Portal-central
    • Central-central
  – Broad scars replacing multiple adjacent lobules
• Regenerating parenchymal nodules
  – Primarily proliferating hepatocytes rather than regeneration from hepatic stem cells
  – Required for diagnosis
  – Can be large or small
  – Balance between regeneration and scarring
Cirrhosis - Important Points

• Generally a result of repetitive, episodic liver cell death
• The vascular architecture is remodeled by parenchymal damage and scarring
  – Formation of abnormal connections resulting in shunting from vascular inflow to hepatic vein outflow
  – Loss of fenestration by endothelial cells
• Although potentially reversible through hepatic remodeling, this has been difficult to achieve in practice. This is in spite of the presence of large amounts of collagenase and matrix metalloproteinases (MMPs) present in cirrhotic livers.

Robbins and Cotran, 9th ed., Fig 18-4
Cirhosis-Child-Pugh Classification

- Three classes of cirrhosis
  - Class A - well compensated
  - Class B – partially decompensated
  - Class C – decompensated
- Narrow bands of densely compacted fibrous septa separated by large islands of intact hepatic parenchyma are associated with less portal hypertension and thus are better compensated
- Broad scars with dilated lymphatic spaces have more portal hypertension and are less well compensated
Cirrhosis - Morphologic Classification

• Based on nodule size
  – Micronodular, < 3 mm
  – Macronodular, > 3 mm
  – Mixed

• Classification based on etiology and stage is much more useful
Micronodular Cirrhosis

From Sherlock and Summerfield, Fig. 132
Macronodular Cirrhosis

From Sherlock and Summerfield, Fig. 134

From Sherlock and Summerfield, Fig. 1
Mixed Micronodular and Macronodular Cirrhosis

From Sherlock and Summerfield, Fig. 137
Diseases Leading to Cirrhosis

- Alcoholic liver disease
- Viral hepatitis
- Non-alcoholic steatohepatitis (NASH)
- Extrahepatic biliary obstruction
- Primary biliary cirrhosis
- Hemochromatosis
- Wilson’s disease
- Alpha-1 antitrypsin deficiency
- Cystic fibrosis
- Other inherited metabolic defects
- Drug-induced
- Cryptogenic (unknown etiology)
Changing Epidemiology of Cirrhosis

- Death rates due to cirrhosis and cirrhosis associated hepatocellular carcinoma have been increasing as much as 3% per year since 2009
- Death rate from cirrhosis has increased in younger age groups
- Associated with three disease states
  - Alcohol abuse
  - Nonalcoholic steatohepatitis (NASH)
  - Chronic Hepatitis C
Pathogenesis of Cirrhosis

• Proliferation and activation of hepatic stellate reticular cells (Ito cells)

• Collagen remodeling
  – Space of Disse normally contains a loose network of Type IV collagen
  – Degradation of Type IV collagen by matrix metalloproteinases. Inflammatory disruption of the extracellular matrix.
  – Type I and Type III collagens are laid down by stellate reticular cells. Maturation of collagen produces contraction and additional vascular obstruction
Pathogenesis of Cirrhosis

The stellate reticular, or Ito, cell

From Cotran, Kumar, Collins, 5th Ed. Fig. 18-2

From Robbins Pathologic Basis of Disease, 7th ed., Fig. 18-2
Pathogenesis of Cirrhosis

- Chronic Inflammation
  - Most hepatic chronic inflammatory conditions have an increased risk of cirrhosis
  - IL-1, IL-6, TGF-beta, TNF, PDGF, and other cytokines secreted by hepatocytes, Kupffer cells, and endothelial cells
    - PDGF and TNF-alpha stimulate Ito cell proliferation
    - TGF-beta stimulates collagen I & III synthesis
    - TNF-alpha is toxic to hepatocytes

Reactive Oxygen Species

Oxidative Stress

Lipid Peroxidation

Ito cells

Kupffer cells

TGF-β, TNF-α, PDGF

Collagen

Hepatocyte death
Portal Hypertension

• Pre-hepatic
  – Thrombosis of portal vein with splenomegaly

• Post-hepatic
  – Cardiac
  – Hepatic vein outflow obstruction

• Hepatic
  – Cirrhosis
  – Schistosomiasis
  – Granulomatous diseases (TB, sarcoid)
Portal Hypertension and Cirrhosis

• Pathogenesis
  – Sclerosis of sinusoidal vascular bed
  – Dilation of the splanchnic arterial circulation due to increased arterial NO. This is thought to be secondary to decreased clearance of bacterial DNA by Kupffer cells
  – Arterial-venous anastomoses
  – Central vein compression by regenerating nodules and bands of fibrosis
Portal Hypertension and Cirrhosis

• Ascites
  – Pathogenesis
    • Increased sinusoidal and lymphatic pressures
    • Increased splanchnic circulation
    • Decreased synthesis of albumen plus sequestration of albumen in ascitic fluid with loss of plasma oncotic pressure
    • Secondary hyperaldosteronism with sodium retention
  – Complications
    • Secondary infection (spontaneous peritonitis)
    • Decreased serum albumen, edema
    • Respiratory embarrassment
Portal Hypertension and Cirrhosis

- Porto-systemic shunts
  - Esophageal varices and hemorrhage
  - Abdominal wall
  - Hemorrhoidal varices
  - Hepatic encephalopathy
- Splenomegaly
  - Hypersplenism
- Testicular atrophy
- Gynecomastia

From Sherlock and Summerfield, Fig. 139
Viral Hepatitis
Viruses That Cause Hepatitis

- Hepatitis A Virus
- Hepatitis B Virus
- Hepatitis C Virus
- Hepatitis D Virus
- Hepatitis E Virus
- Hepatitis G Virus
- Transmissible Transfusion Virus
- Epstein-Barr Virus
- Cytomegalovirus
- Herpes Simplex Virus
- Rubella Virus
- Enteroviruses
- Yellow Fever Virus
- Lasa Fever Virus
- Many others
Clinical Spectrum

• Subclinical disease
• Acute hepatitis
• Fulminant hepatitis with acute hepatic failure
• Chronic hepatitis
  – Clinical, biochemical, or serologic hepatitis for greater than 6 months duration with histologic documentation of inflammation and necrosis
Acute Hepatitis

• Morphologic appearance is generally similar for all of the hepatitis viruses.

• Evidence of liver cell injury, necrosis, apoptosis
  – Fatty change (Hepatitis C)
  – Ballooning degeneration and necrosis
  – Councilman (acidophilic) bodies (apoptosis)
  – Foci of regenerating cells
  – Changes are often more prominent in centrilobular zone

• Inflammation
Acute Hepatitis

- **Inflammatory Response**
  - Mononuclear (primarily lymphocytic) infiltrate
  - PMNs may be present, particularly in areas of necrosis
  - Inflammation most prominent in portal region and around central vein
  - Limiting plate around portal region is usually intact
- **Other Changes**
  - Cholestasis may be present - cholestatic hepatitis
  - Prominent Kupffer cell and endothelial cell swelling

From Robbins Basic Pathology, 7th Ed., Fig. 16-9A
Acute viral hepatitis showing disruption of lobular architecture, inflammatory cells in the sinusoids, and hepatocellular apoptosis (arrow).
Fulminant Hepatitis

• Confluent hepatic necrosis
  – Typically affects whole regions of the lobule

• Submassive hepatic necrosis
  – Involves entire lobule or groups of lobules
  – More severe clinical course

• Massive hepatic necrosis (acute yellow atrophy)
  – Liver is shrunken
  – Majority of hepatocytes are dead
  – Acute liver failure
  – High mortality, but hepatic function recovers without cirrhosis if patient survives
Massive hepatic necrosis

**Figure 16-11**
Massive necrosis, cut section of liver. The liver is small (700 g), bile stained, and soft. The capsule is wrinkled.

**Figure 16-12**
Massive necrosis, microscopic section. Portal tracts and central veins are closer together than normal, owing to necrosis and collapse of the intervening parenchyma. The rudimentary ductal structures are the result of early hepatocyte regeneration. An infiltrate of chronic inflammatory cells is present.

From Robbins Basic Pathology, 7th Ed., Fig. 16-11

From Robbins Basic Pathology, 7th Ed., Fig. 16-12
Chronic Hepatitis

- Greater than 6 months duration
- HBV and HCV
- Range of histologic changes
- Can progress to cirrhosis
- Liver biopsy is most important diagnostic tool
- Clinical activity may not correlate well with the histologic picture
- However the rate of change in the histologic picture over time is a good prognostic indicator

From Robbins Basic Pathology, 7th Ed., Fig. 16-9B
Chronic Hepatitis

• Less severe changes - obsolete term was chronic persistent hepatitis
  – Inflammation limited to portal tracts
  – Limiting plate is intact
  – Hepatocyte apoptosis and necrosis are minimal
  – HBV and HCV
  – Ground glass hepatocytes may be present (HBV only)

• More severe changes - obsolete term was chronic active hepatitis
  – Inflammatory infiltrate extends beyond portal tracts, penetrating limiting plates. Infiltrate surrounds single hepatocytes and groups of hepatocytes, particularly in portal region
  – Hepatocyte apoptosis and necrosis are evident
**Chronic Hepatitis**

**FIGURE 14-24**

Chronic persistent hepatitis. A photomicrograph shows the portal tract infiltrated by mononuclear inflammatory cells. The lobular parenchyma is essentially intact.

From Rubin and Farber
Chronic Hepatitis

FIGURE 14-26
Chronic active hepatitis. A photomicrograph shows a mononuclear inflammatory infiltrate in an expanded portal tract. The inflammation penetrates the limiting plate and surrounds groups of hepatocytes on the border of the portal tract.
Suddenly, Professor Liebowitz realizes he has come to the seminar without his duck.