Learning Objectives
- Describe normal structure and functions of the liver in relation to the major diseases of the liver
- Describe causes of liver injury and the effects on hepatic function
- Differentiate three major types of viral hepatitis (pathogenesis, incubation period, incidence of complications, frequency of carriers, diagnostic tests)
- Explain adverse effects of alcohol intake on liver structure, function
- Explain formation of gallstones, causes and effects
- Compare three major causes of jaundice

The Liver, the Biliary System, and Pancreas

Chapter 16

The Liver (1 of 2)
- Largest organ in body, right upper abdominal area, beneath the diaphragm
- Main functions
  - Metabolism: carbohydrates, protein, and fat delivered through the portal circulation
  - Synthesis: plasma proteins, clotting factors
  - Storage: vitamin B12 and other materials
  - Detoxification and excretion: various substances

The Liver (2 of 2)
- Has a double blood supply
  - Portal vein: 75% of blood, drains spleen and GI tract, rich in nutrients absorbed from intestines, low in oxygen
  - Hepatic artery: rest of blood, high in oxygen, low in nutrients
  - Both blood mix in the liver eventually collecting into right and left hepatic veins that drain into inferior vena cava
- Portal triad, portal tracts travel together
  - Hepatic artery branches
  - Portal vein
  - Bile ducts
  - Lymphatic vessels

The Liver and Biliary System
Bile (1 of 2)

- From the breakdown of red blood cells
- When red blood cells break down, iron is reused and iron-free heme pigment or bilirubin is excreted in the bile
- Small quantities of bile are continually present in blood
- When blood passes through liver, bilirubin is removed by conjugation or by combining bilirubin with glucuronic acid
- Bile: aqueous solution with various dissolved substances
  - Conjugated bilirubin
  - Bile salts: major constituent of bile; derivatives of cholesterol and amino acids; emulsify fat; function as detergents

Bile (2 of 2)

- Other substances present in bile
  - Lecithin: lipid that also functions as a detergent
  - Cholesterol
  - Water
  - Minerals
- Bile is secreted continually
  - Concentrated and stored in gallbladder
  - During digestion, gallbladder contracts, releasing bile into the duodenum
  - Bile does not contain digestive enzymes, but acts as a biologic detergent

Types of Liver Injury

- Manifestations
  - Cell necrosis
  - Fatty change
  - Mixed necrosis and fatty change
- Common types of liver injury
  - Viral hepatitis
  - Fatty liver
  - Alcoholic liver disease or alcoholic hepatitis
  - Cirrhosis

Hepatitis A

- RNA-containing virus
- Incubation period: 2 to 6 weeks
- Excreted through nose, throat, stools
- Transmission
  - Person-to-person contact
  - Fecal contamination of food or water
- Self-limited; no carriers; no chronic liver disease
- Prevention
  - Hepatitis A vaccine
  - Hepatitis A immune globulin: given after exposure
Acute viral hepatitis

Hepatitis B
- DNA-containing virus
- Incubation period: 6 weeks to 4 months
- Transmission: blood or body fluids
- Diagnosis: antigen-antibody test results
  - Infected persons: HBsAg positive; lack anti-HBs
  - Immune persons: presence of anti-HBs
  - 10% become carriers and may develop chronic liver disease
- Prevention
  - Hepatitis B vaccine
  - Hepatitis B immune globulin: given after exposure

Electron photomicrographs of complete virus particles (arrows) and excess surface antigen in blood of patient with hepatitis B.

Acute HBV Infection and recovery

Hepatitis C (1 of 2)
- RNA virus
- Incubation period: 3 to 12 weeks
- Transmission: blood and body fluids
- Antigen-antibody test results
  - HCV RNA: presence of virus in blood and active infection
  - Anti-HCV: infection but does not confer immunity
- 75% become carriers and many develop chronic liver disease
- No prevention of disease after exposure
- No immunization available
Hepatitis C (2 of 2)

- Testing for asymptomatic HCV infection
- Recommendations
  - Persons who have injected illegal drugs
  - Persons who received antihemophilic globulin or other clotting factor concentrates before 1987
  - Persons who received blood transfusions before 1992
  - Health care personnel who have been exposed to blood or body fluids

Hepatitis D: Delta Hepatitis

- Small, defective RNA virus
- Only infects persons with acute or chronic HBV infection
- Delta virus is unable to produce its own virus coat and uses HBsAg produced by HBV
- Most U.S. cases from sharing needles

Hepatitis E

- RNA-containing virus
- Transmission
  - Oral-fecal
  - Contaminated water
- No prevention of disease after exposure
- No immunization available

Hepatitis Outcomes

Fatty Liver

- Fat accumulates in liver secondary to injury
- Common in heavy drinkers and alcoholics
- May be caused by chemicals and solvents
- Impaired liver function but injury is still reversible
Alcoholic Liver Disease

- Refers to a group of structural and functional changes in the liver resulting from excessive alcohol consumption
- Severity depends on amount and duration of alcohol consumption
- 3 stages of progression
  - Alcoholic fatty liver: mildest form
  - Alcoholic hepatitis: causes degenerative changes and necrosis of liver cells
  - Alcoholic cirrhosis: most advanced, diffuse scarring, disturbed liver function

Cirrhosis (1 of 3)

- Diffuse scarring of the liver from any cause with derangement of liver function and regeneration
  - Alcoholic liver disease
  - Chronic hepatitis
  - Severe liver necrosis
  - Repeated liver injury: drugs and chemicals
  - Longstanding bile duct obstruction
- Manifestations
  - Liver failure
  - Portal hypertension
  - Ascites, collateral circulation formation

Cirrhosis (2 of 3)

- Manifestations
  - Bypass routes connect systemic-portal venous systems
  - Anastomoses develop between branches of portal and system veins
  - Blood shunted away from high pressure portal system into low pressure veins of systemic circulation
    - Esophageal veins become distended
    - Risk of fatal hemorrhage from esophageal varices
  - Inability to inactivate estrogen in males
    - Testicular atrophy, loss of sex drive, breast hypertrophy

Cirrhosis (3 of 3)

- Advanced hepatic cirrhosis illustrating elevated nodules of liver tissue surrounded by depressed areas of scar tissue. Exterior of liver.
A low-magnification photomicrograph of cirrhotic liver illustrating nodules of liver cells circumscribed by dense scar tissue (blue-green stain).

**Cirrhosis (3 of 3)**

- Surgical procedures
  - Portal-systemic anastomoses to control varices
    - Splenorenal shunt
    - Portacaval shunt
    - Intrahepatic portosystemic shunt
  - Transjugular intrahepatic portosystemic shunt (TIPS)
    - An alternative to an open operative procedure
    - Intrahepatic shunt between hepatic and portal vein branches
- Materials in ascitic fluid may cause intravascular coagulation syndrome, other complications

**Ascites**

A comparison of normal blood flow pathways with those in cirrhosis.
Biliary Cirrhosis

• Primary biliary cirrhosis
  – Autoimmune disease attacking small intrahepatic bile ducts
  – No specific treatment, may lead to liver failure
  – Require liver transplant
• Secondary biliary cirrhosis
  – Obstruction of large extrahepatic bile ducts
  • Gallstone, carcinoma in pancreas, cancer from common bile duct
  – Treatment: relieve or bypass duct obstruction

Cholelithiasis (1 of 2)

• Formation of stones in the gallbladder
• Incidence
  – Higher in women than men
  – Higher in women who have borne several children
  – Twice as high in women who use contraceptive pills
  – Higher in obese women
• Factors influencing solubility of cholesterol in bile
  – Cholesterol is insoluble in aqueous solution
  – Dissolved in micelles composed of bile salts and lecithin
  – Solubility of cholesterol depends on ratio of cholesterol to bile salts and lecithin

Cholelithiasis (2 of 2)

• Complications
  – Asymptomatic
  – Biliary colic if stone is extruded into ducts
  • Common duct obstruction: obstructive jaundice
  • Cystic duct obstruction: no jaundice, acute cholecystitis may occur if preexisting infection in gallbladder
• Treatment
  – Cholecystectomy
  – Chenodeoxycholic acid dissolves gallstones

Cholecystitis

• Inflammation of gallbladder
  – Chronic infection is common
  – Gallstones may predispose to cholecystitis
  – Impaction of a stone in neck of gallbladder may cause acute cholecystitis

Reye’s Syndrome

• Pathogenesis
  – Evidence suggests the combined effect of viral illness and use of acetylsalicylic acid (aspirin)
  – Aspirin may increase injurious effects of virus
  – Liver damage
  – Brain damage
• Characteristics
  – Affects infants and children
  – Fatty liver with liver dysfunction
  – Cerebral edema with neurologic dysfunction
  – No specific treatment
Liver Tumors

• Benign adenomas: uncommon, occur in women taking contraceptive pills
• Primary carcinoma
  – Uncommon in U.S. and Canada but common in Asia and Africa due to high incidence HBV carriers
  – HBV carriers have a high risk for developing liver disease and primary liver carcinoma
• Metastatic carcinoma
  – Common in developed countries
  – Spread from primary sites such as GI tract, lung, breast
  – Tumor cells carried in the blood and delivered to the liver via hepatic artery

Jaundice

• Yellow discoloration of skin and sclera from accumulation of bile pigment in tissues and body fluids
• Causes of accumulation
  – Hemolytic jaundice: increased breakdown of red cells
  – Hepatocellular jaundice: liver injury impairing conjugation of bilirubin
  – Obstructive jaundice: bile duct obstructed by tumor or stone impairing delivery of bile into duodenum

Liver Biopsy

• Indications
  – To determine cause of liver disease
  – To evaluate extent of liver cell damage in persons with chronic hepatitis
• Needle inserted through abdominal skin directly into liver
• Biopsy specimen examined histologically by pathologist
  – Provides specific diagnosis
  – Provides basis for treatment

Discussion

• What groups of people are considered at risk for hepatitis C?
• What is anicteric hepatitis?
• What is subclinical hepatitis?
• Chronic liver disease is a complication of which types of viral hepatitis?

Pancreas (1 of 2)

• Two glands in one
  – Digestive gland
  – Endocrine gland
• Exocrine function: exocrine tissue of the pancreas
  – Concerned solely with digestion
  – Secretes alkaline pancreatic juice rich in digestive enzymes into the duodenum through the pancreatic duct to aid digestion

Duct System of Pancreas

• Gall bladder
• Right and left hepatic ducts
• Common hepatic duct
• Common bile duct
• Accessory pancreatic duct
• Main pancreatic duct
• Duodenal papilla
Pancreas (2 of 2)
• Endocrine function: endocrine tissue of the pancreas
• Consists of multiple small clusters of cells scattered throughout the gland as pancreatic islets or Islets of Langerhans
  – Discharge secretions directly into the bloodstream
  – Each islet is composed of different types of cells
    • Alpha cells: secrete glucagon; raise blood glucose
    • Beta cells: secrete insulin; lower blood glucose
    • Delta cells: secrete somatostatin; inhibit secretion of glucagon and insulin

A photomicrograph of pancreatic islet surrounded by exocrine pancreatic tissue

Acute Pancreatitis (1 of 3)
• Pathogenesis
  – Escape of pancreatic juice from the ducts into the pancreatic tissue
  – Pancreatic digestive enzymes cause destruction and severe hemorrhage
  – Involves active secretion of pancreatic juice despite an obstructed pancreatic duct at its entrance into the duodenum
  – Resulting build-up of pancreatic juice increases pressure within the duct system, causing ducts to rupture

Acute Pancreatitis (2 of 3)
• Predisposing factors
  – Gallbladder disease/gallbladder stones
    • Common bile duct and common pancreatic duct enter the duodenum via the ampulla of Vater
    • Impacted stone in ampulla obstructs pancreatic duct
  – Excessive alcohol consumption
    • Potent stimulus for pancreatic secretions
    • Induces edema, spasm of pancreatic sphincter, in ampulla of Vater
    • Results in high intraductal pressure, duct necrosis, and escape of pancreatic juice

Acute Pancreatitis (3 of 3)
• Clinical manifestations
  – Severe abdominal pain
  – Seriously ill
  – High mortality rate

Chronic Pancreatitis
• Repeated episodes of mild inflammation of pancreas
• Each bout destroys some pancreatic tissue
• Inflammation subsides and damaged pancreatic tissue is replaced by scar tissue, leading to progressive destruction of pancreatic tissue
• Manifestations
  – Difficulty digesting and absorbing nutrients
  – Not enough surviving pancreatic tissue to produce adequate enzymes
  – Destruction of pancreatic islets may lead to diabetes
Cystic Fibrosis (1 of 3)
- Serious hereditary disease, autosomal recessive trait
- Mutation of a normal gene, CF gene, on long arm of chromosome 7
- Manifests in infancy and childhood
- Incidence in whites: 1 in 3,000
- Incidence in blacks and other races: rare
- Mortality, more than 50% die before age 32
- Pathogenesis:
  - Defective transport of chloride, sodium, and H₂O across cell membrane
  - Deficient electrolyte and H₂O in the mucus secreted by the pancreas, bile ducts, respiratory tract, and other secretory cells

Cystic Fibrosis (2 of 3)
- Pathogenesis:
  - Mucus becomes abnormally thick, precipitates, and forms dense plugs that obstruct the pancreatic ducts, bronchi, bronchioles, and bile ducts
  - Obstruction of pancreatic ducts: causes atrophy and fibrosis
  - Obstruction of bronchi: causes lung injury
  - Obstruction of biliary ducts: causes liver scarring
  - Abnormal function of sweat glands: unable to conserve sodium and chloride with excessively high salt concentration in sweat; basis of diagnostic test

Cystic Fibrosis (3 of 3)
- Treatment:
  - Oral capsules containing pancreatic enzymes to compensate for lack of pancreatic digestive enzymes
  - Various treatments to preserve as much pulmonary function as possible
  - Vigorous treatment of pulmonary bacterial infections
  - Lung transplant may eventually be required if lungs are severely damaged

Diabetes Mellitus
- Very common and important metabolic disease
- Two major groups depending on cause:
  - Type 1 diabetes
    - Insulin deficiency
    - Occurs primarily in children and young adults
  - Type 2 diabetes
    - Inadequate response to insulin
    - Typically an adult-onset diabetes
    - More common than Type 1
    - Becoming more common in children
- Manifestation: Increased glucose levels in blood or hyperglycemia

Diabetes Mellitus
- Comparison of two major types of diabetes mellitus:

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<thead>
<tr>
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<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
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<tr>
<td>Liquid level of onset</td>
<td>Childhood</td>
<td>Middle age or later</td>
</tr>
<tr>
<td>Body type</td>
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<td>Obese</td>
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<tr>
<td>Plasma insulin</td>
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<td>Complications</td>
<td>Ketoacidosis</td>
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<td>Response to insulin</td>
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<tr>
<td>Response to oral antidiabetic drugs</td>
<td>Unresponsive</td>
<td>Responsive</td>
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Type 1 Diabetes Mellitus

- Results from damage to pancreatic islets leading to reduction or absence of insulin secretion
- Often follows a viral infection that destroys the pancreatic islets
- Abnormal immune response may play part: production of autoantibodies directed against islet cells
- With a hereditary predisposition
- Complication
  - Diabetic ketosis

Type 2 Diabetes Mellitus (1 of 2)

- Complex metabolic disease
- Occurs in older, overweight, or obese adults
- Increasingly seen among younger people who are overweight or obese
- Insulin secretion is normal or increased
- Reduced response of tissues to insulin
- Cause is not completely understood but weight reduction restores insulin responsiveness
- Islet function is not completely normal as pancreas is not able to increase insulin output to compensate for the insulin resistance

Type 2 Diabetes Mellitus (2 of 2)

- Hereditary disease
- Children of parents with diabetes are at a significant risk
- Incidence in some populations as high as 40% (Pima Indians of Arizona)
- Complication
- Hyperosmolar nonketotic coma due to marked hyperglycemia

Complications of Diabetes

- Increased susceptibility to infection
- Diabetic coma
- Ketoacidosis
- Hyperosmolar coma
- Arteriosclerosis
- Blindness
- Renal failure
- Peripheral neuritis

Ketone Bodies (1 of 2)

- Glucose is absorbed normally but is not used properly for energy due to insulin deficiency or insensitivity
- Body turns to fat as a source of energy
- Fat is broken down into a fatty acid and glycerol
- Fatty acid broken down further into 2 carbon fragments combined with carrier molecule, acetyl coenzyme A
- Some acetyl-CoA are converted by the liver into ketone bodies
- More acetyl-CoA molecules are produced than can be oxidized as a source of energy
- Ketosis: accumulation of ketone bodies in blood and excreted in the urine together with H₂O and electrolytes
Ketone Bodies (2 of 2)

- Acetoacetic acid: from condensation of 2 acetyl-CoA molecules
- Beta-hydroxybutyric acid: from addition of a hydrogen atom to an oxygen atom and converted into a –OH group
- Acetone: from removal of a carboxyl group of acetoacetic
- Type 1 diabetes complication
- Ketoacidosis: overproduction of ketone bodies
  - Buffer systems cannot maintain normal pH
  - May lead to coma

Hyperosmolar Hyperglycemic Nonketotic Coma

- Type 2 diabetes complication
- Severe hyperglycemia
  - Blood glucose increases 10 to 20 x normal value
- Absence of ketosis
  - Less insulin is required to inhibit fat mobilization than is needed to promote entry of glucose into cells
  - Patients have enough insulin to prevent ketosis, not enough to prevent hyperglycemia
- Results in coma due to extreme hyperosmolality of blood
  - H₂O moves out of the cells into the extracellular fluid
  - Cells become dehydrated disturbing functions of neurons leading to coma

Insulin

- Influences carbohydrate, protein, and fat metabolism on liver cells, muscle, and adipose tissues
- Main stimulus for release: high glucose in blood
- Promotes
  - Entry of glucose into cells
  - Utilization of glucose as source of energy
  - Storage of glucose as glycogen
  - Conversion of glucose into triglycerides
  - Storage of newly formed triglyceride in fat cells
  - Entry of amino acids into cells and stimulates protein synthesis

Hyperglycemia in Diabetes (1 of 2)

- Pancreas regulates the glucose in blood by adjusting its output of insulin
  - Hypoglycemia: low blood sugar
  - Adrenal medulla: responds by discharging epinephrine that raises blood glucose
- Neurologic manifestations appear if blood glucose continues to fall
- Other causes of hypoglycemia
  - Oral hypoglycemic drugs in type 2 diabetics
  - Self-administration of oral hypoglycemic drugs or insulin by emotionally disturbed person
  - Islet cell tumor

Hypoglycemia in Diabetes (2 of 2)

- Must adjust dose of insulin to match the amount of ingested carbohydrate
  - Insufficient insulin, glucose levels increase
  - Too much insulin, glucose levels decrease
- Conditions predisposing to hypoglycemia in a diabetic patient taking insulin
  - Skipping a meal: carbohydrate intake is insufficient in relation to amount of insulin and blood glucose falls
  - Vigorous exercise: with high physical activity there is high glucose utilization; excess insulin
  - Too much insulin causes a precipitous drop in glucose leading to insulin reaction or insulin shock
Treatment of Diabetes

- Diet
- Type 1 diabetes: requires insulin; dosage adjusted to control level of blood glucose
- Type 2 diabetes
  – Management: weight reduction and diet
  – Oral hypoglycemic drugs if patient does not respond adequately to diet and exercise regimen

Monitoring Control of Diabetes

- Goal: achieve control of blood glucose as close as possible to normal
  – Frequent periodic measurements of blood glucose
  – Urine test: detects glucose spilling into the urine when blood glucose is too high
  – Measurement of glycosylated hemoglobin: serves as an index of long-term control of hyperglycemia

Tumors of the Pancreas

- Carcinoma of the pancreas
  – Usually develops in the head of the pancreas
    – Blocks common bile duct
    – Causes obstructive jaundice
  – Tumors elsewhere in pancreas: no specific symptoms, usually far advanced when first detected
- Islet cell tumors
  – Benign
  – Beta cell tumors produce hyperinsulinism and hypoglycemia

Discussion

- Insulin performs all of the following functions EXCEPT
  A. It promotes entry of amino acids into the cells
  B. It promotes storage of glucose in muscle and liver cells
  C. It promotes entry and absorption of glucose into cells for use as energy
  D. It promotes the breakdown of fat
  E. It lowers blood glucose