

Section 14

LECTURE

Pathology of the Pancreas and Biliary Tract

Anatomy and Pathology of the Pancreas and Biliary Tract

Part I: Functional Anatomy

I. Biliary Tract

A. Anatomy and histology

Within the liver, the bile canaliculi (between hepatocytes) anastomose and drain to pre-ductules (canals of Hering), ductules and interlobular bile ducts in the portal areas (Figure 1). These ducts repeatedly fuse to form the right and left hepatic bile ducts which leave the liver, fuse to form the common hepatic duct, and join the cystic duct from the gallbladder to form the common bile duct. This duct enters the duodenal wall, is joined by the pancreatic duct, and both enter the duodenal lumen via the ampulla of Vater, where a smooth muscle sphincter (of Oddi) regulates bile flow. Variations in the union of the cystic with the pancreatic duct are common.

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The bile ducts are lined by a single layer of cuboidal to low columnar epithelium. The luminal plasma membrane of these cells has microvilli and the cytoplasm contains numerous mitochondria. In the larger ducts, a few goblet cells are interspersed in the epithelium and smooth muscle appears in the connective tissue wall. This smooth muscle helps to regulate bile flow.

The gallbladder is a hollow organ, roughly 10 cm long and 4 cm in diameter. The gallbladder is continuous with the cystic duct at the neck region where the wall forms prominent folds containing smooth muscle (so-called spiral valve). The gallbladder wall contains the following layers:

1. *Mucosa*: Columnar epithelium similar to that in the bile ducts. The mucosa forms folds which smooth out when the organ is distended. There is a lamina propria but no muscularis mucosae.
2. *Submucosa*: Absent.
3. *Muscularis*: Irregular array of smooth muscle fibers interspersed with many elastic fibers.
4. *Serosa*: Absent where gallbladder rests against the liver.

B. Functions

1. The biliary epithelium of the intra- and extrahepatic biliary tree is not an inert conduit for the passage of bile. Rather, there may be extensive modification of the biliary contents, primarily through exchange of water and inorganic and organic ions. In particular, the biliary tree may contribute up to 40% of bile volume as a sodium bicarbonate-rich fluid. During periods of biliary obstruction, there may be considerable reabsorption of solutes and fluid by the biliary tree.

2. The gallbladder stores bile and concentrates it by removing inorganic ions and water. The mechanism of this is believed to be the active transport of solute (Na^+ , Cl^-) across the lateral cell membranes of the mucosal cells into the intercellular space. A concentration gradient is established across the mucosal cell membrane, resulting in the movement of solutes and water from the lumen, through the mucosal cells, and into the intercellular spaces. Fluid and solute then move across the basement membrane into capillaries of the lamina propria as a result of elevated hydrostatic pressure in the intercellular spaces. The gallbladder mucosa also elaborates a rich mucinous glycoprotein, which covers the mucosal surface. The luminal environment plays a critical, but as yet poorly understood, role in gallstone pathogenesis.

3. When gastric contents, particularly fat, enter the duodenum, they cause the release of two enzymes from the duodenal mucosa which directly affect biliary function: (grossly simplified)
 - a. *Cholecystokinin* (same molecule as pancreaticozym) causes contraction of the gallbladder and relaxation of the sphincter of Oddi. The gallbladder empties into the duodenum; bile salts become available for digestion.
 - b. *Secretin* causes secretion by the bile duct mucosal cells of isotonic fluid rich in HCO_3^- .

II. Pancreas

A. Anatomy

1. The pancreas is a 20-25 cm elongate, lobulated, pink-white gland which lies transversely in the retroperitoneum at the level of the upper lumbar vertebrae. The *head* of the pancreas lies in close proximity to the duodenum, while the *body and tail* extend to the left, with the tail adjacent to the spleen.
2. The blood supply is from the celiac and superior mesenteric arteries and drains into the portal or splenic veins. Sympathetic nerve fibers from the celiac plexus and myelinated fibers from the vagus terminate on the acini.
3. The pancreas has two distinct functional components:
 - a. *Exocrine* function: Digestion; involves ducts and acini.
 - b. *Endocrine* function: Carbohydrate homeostasis; involves the islets.

B. The Exocrine Pancreas

1. The exocrine pancreas is a complex tubuloacinar gland. The terminal portions of the multiple branching duct systems are called *acini*, it is here that the zymogenic secretions are synthesized (see below). The acini are formed by a semilunar arrangement of columnar cells which release their secretions into the central (luminal) portion of the acinus (Figure 2). From the acinus, the secretions are carried to the duodenum by the anastomosing and enlarging duct system.

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2. The pancreatic acinar cell is the prototype of the protein-producing exocrine glandular cell, and as such has been extensively studied by radioactive isotope labelling, histochemistry, and electron microscopy. Synthesis of secretory product is rapid, with precursor labelled amino acids appearing in secretory vacuoles within one hour of injection. These cells maintain a basal secretory rate which in turn is modified by the needs of the digestive process (see below).

3. *Pancreatic ductal system.* The acinar lumen is continuous with a small terminal duct lined by cuboidal pale centroacinar cells which are currently thought to be important in secretion of electrolytes and water. These join with the intralobular or intercalated ducts; the latter join to form larger interlobular ducts which empty into the main pancreatic ducts (Wirsung; Santorini) leading into the duodenum at the ampulla of Vater. The larger ducts are lined by pale-staining columnar cells containing few organelles in a low density

cytoplasm; they are interspersed with goblet cells and argentaffin cells.

4. Correlation of function with pancreatic exocrine structure (more detail in lecture on physiology):

a. Food in the duodenum stimulates release of two hormones from duodenal mucosal endocrine cells which stimulate the exocrine pancreas:

- *Secretin*: Stimulates water and HCO_3^- flow from the ductal cells.
- *Cholecystokinin-pancreozymin*: Stimulates zymogen release from acinar cells. Morphologically, this is manifested by a depletion of granules in the apical acinar cell cytoplasm.

b. The ductal cells contain an active carbonic anhydrase system for HCO_3^- production. The ductal cells also produce most of the pancreatic secretion volume of 1-2 liters per day. The HCO_3^- helps to neutralize the acid gastric pH and thus provides a pH medium (neutral or alkaline) compatible with pancreatic digestive enzyme activity.

c. The acinar zymogen vacuoles contain a variety of digestive enzymes, over a dozen of which have been identified, and some of which (lipases and proteases) are produced nowhere else in the gastrointestinal tract.

- The acinar cells have three mechanisms to protect themselves from autodigestion by these potent enzymes:
 1. Some of the most potent enzymes, such as the proteases, are present in the acinar cells as catalytically inert precursors called proenzymes. After release from the cells, these proenzymes are not activated until they reach the duodenal lumen. For example, enterokinase released from the duodenal mucosa (plus Ca^{2+}) converts inactive trypsinogen to active trypsin. In turn, other pancreatic proenzymes in the duodenal lumen are activated by trypsin.
 2. Prior to secretion, the enzymes are segregated in membrane-enclosed vacuoles in the acinar cells.
 3. Enzyme inhibitors are present in pancreatic tissue and in pancreatic secretions. Specifically, trypsin and ribonuclease inhibitors have been identified.
- Amylase and lipase appear to be present in "active" form in acinar cells and can be assayed directly. They have no known proenzyme forms and no known intracellular inhibitors. As such, they serve as useful serum markers of pancreatitis, in which pancreatic enzymes are released into the general circulation.
- The major pancreatic enzymes may be summarized as follows:
 - a. *Proteases*: proenzymes in acinar cells; activated in duodenum.
 1. Trypsin: cleaves polypeptides at aromatic amino acids.
 2. Chymotrypsin: cleaves polypeptides at basic amino acids.
 3. Carboxypeptidase: removes single amino acids sequentially from the carboxy ends of polypeptide chains.
 - b. *Lipase*: splits triglycerides into fatty acids and monoglyceride. Requires pancreatic colipase to function.
 - c. *Elastases; collagenases; phospholipase*
 - d. *DNA-ase and RNA-ase*
 - e. *Amylase*: breaks amylose, amylopectin and glycogen to yield disaccharides. Salivary glands also produce amylase and can assist pancreatic function in this regard.

- The pancreas can alter the types of digestive enzymes it synthesizes according to the type of diet ingested.
 - a. Rats fed a high carbohydrate diet have high amylase and low protease activities in pancreatic tissue and secretions.
 - b. Change to a high protein diet reverses these ratios, with adaptation to change in diet taking about four days. However, the mechanisms involved in adaptation are unknown.
- Factors in the control of pancreatic enzyme secretion: CCK-PZ, gastrin, and vagal release of acetylcholine all play a role in stimulating secretion at the time of food ingestion. These substances appear to exert their effect on the basal plasma membrane of the acinar cells, and their effects are probably mediated via cyclic-AMP.

Part II: Pathology of the Exocrine Pancreas

- I. The major disease processes involving the pancreas are congenital, inflammatory, and neoplastic. As we shall see, pancreatic cancer is an almost universally lethal disease; this is partly related to the anatomic location of the pancreas, which permits extensive growth of tumors in the body and tail without development of clinical symptoms.
- II. **Cystic Fibrosis**
 - A. A congenital disease of autosomal recessive type characterized by (1) increased viscosity of mucous secretions throughout the body (pancreas, gut, respiratory tract) and (2) an electrolyte defect of eccrine sweat glands resulting in high sodium and chloride concentrations in the sweat.
 1. This is the most common potentially lethal genetic disease of white races. Occurs in about 1 in 3,000 live births; 5% carrier rate in Caucasians in the US. Rare in African Americans.
 2. About 50% of patients live only to their tenth birthday; another 3-5% to their 20th birthday; and a few live to age 30 and beyond. Life-span lengthening with improved supportive care (see below).
 - B. Etiology and pathogenesis
 1. The gene responsible for the defect in cystic fibrosis was cloned and described in 1989, and is located on chromosome 7 at q31. This single gene codes for the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel which is activated by cAMP. Although this is one of two chloride channels in many epithelia, the loss of chloride transport capacity from mutation of this particular channel is sufficient to cause a substantial decrease of chloride transport. All disease manifestations can be traced to this defect.

The most frequent mutation of this 1480 residue glycosylated molecule is a deletion of a phenylalanine residue in the 508 position of the protein encoded by the gene (denoted as delta-F508). The mutant protein is synthesized, but in mammalian cells at 37°C cannot be exported from the endoplasmic reticulum. Thus, this disease falls into the category of diseases due to defective protein trafficking. When expressed in *Xenopus* oocytes at 25°C, the protein is successfully delivered to the cell membrane, and does show some minor transport defects.
 2. The transport defect is an impermeability to the Cl⁻ ion, characterized as a polyexocrinopathy affecting sweat glands, airway epithelia and intestinal and pancreatobiliary ducts, with 90% of the

mortality due to pulmonary infections and complications. The fundamental pathology is an alteration in physiologic secretions, resulting in production of a viscous, mucoid secretion which plugs normal passages for the movement of luminal fluid. Thus, the clinical manifestations of cystic fibrosis are mostly secondary to obstruction.

- a. Chronic pulmonary disease due to bronchial obstruction; leading cause of death
 - b. Pancreatic insufficiency secondary to duct obstruction; maldigestion
 - c. Bowel obstruction due to inspissated luminal contents
3. The defect in eccrine sweat glands is the result in inadequate chloride absorption: eccrine glands initially generate a fluid isosmotic with plasma. Cells of the sweat gland duct resorb NaCl, and with it, water. Defective chloride conductance by the apical CFTR transporter leads to the elaboration of "salty sweat", a phenomenon known to mothers and wet nurses of these sickly children since the 17th century. Measurement of elevated sweat electrolytes (Na⁺, Cl⁻ and K⁺) is the major diagnostic test in this disease. This defect may lead to massive salt depletion in hot weather.
- C. Pathology - changes secondary to outflow obstruction.
1. Pancreas
 - a. Ducts dilated; often filled with mucous concretions
 - b. Atrophy of acini with replacement fibrosis
 - c. Islets relatively resistant to destruction; diabetes develops late in clinical course.
 2. Gastrointestinal tract
 - a. Meconium ileus: inspissated meconium obstructing the ileum. Occurs in 10-15% of newborns with cystic fibrosis. Can cause:
 - 1) Ileal atresia secondary to inflammatory reaction to meconium
 - 2) Volvulus
 - 3) Perforation with peritonitis
 - b. Intestinal obstruction by viscous fecal masses can occur throughout life.
 - c. Inflammation and fibrosis of the liver secondary to bile duct obstruction.
 3. Respiratory system
 - a. Acute and chronic bronchitis
 - b. Development of obstructive lung disease and recurrent pulmonary sepsis
- D. Clinically, the bowel problems related to inspissated meconium occur at birth. Later, in infancy and childhood, respiratory problems dominate the clinical picture. Evidence of pancreatic insufficiency is usually relatively late in developing. Treatment of all phases of this disease is symptomatic and supportive (antibiotics, inhalation therapy, etc.) but has prolonged life considerably. Exciting advances are being made experimentally in efforts to correct the defect by directed gene therapy, and/or correct the regulatory defect by pharmacologic intervention.

III. Pancreatitis

A. Acute (hemorrhagic) pancreatitis

1. A disease of adults (majority between ages 40 to 70) characterized clinically by severe abdominal pain, prostration, shock and death in 15-25% of cases despite vigorous supportive therapy.
2. Etiology: Although the precise cellular mechanisms by which a defined insult induces acute

pancreatitis are unclear, there are several factors which have the capacity to initiate this disease:

- a. Alcoholism - most common factor
- b. Biliary tract disease - specifically, cholelithiasis
- c. Trauma
- d. Tumors
- e. Vascular insufficiency - such as that induced by thrombosis
- f. Hyperparathyroidism
- g. Infection - some viruses, such as mumps, have a tropism for pancreatic tissue
- h. Hyperlipidemia
- i. Drugs: azathioprine, estrogens, furosemide, methyldopa, pentamidine, procainamide, sulfonamides, thiazide diuretics

None of the above factors are present in 12-40% of patients with acute pancreatitis (idiopathic pancreatitis).

3. Pathogenesis:

- a. The pancreas produces a variety of enzymes, often in inactive forms, which have potent degradative functions (see below). The tissue destruction occurring in pancreatitis appears to be due to autodigestion by these enzymes. However, it is presently unclear how such enzymes are activated within the pancreatic ducts. One theory suggests that reflux of duodenal contents into the duct activates these enzymes; alternatively, intrinsic defects in the barrier function of pancreatic epithelial cells might lead to leakage of enzymes into the interstitium with activation. Finally, the formation of concretions in pancreatic ducts (as can be seen in alcoholism) might predispose to extrusion of pancreatic enzymes.
- b. Enzymes produced by the pancreas which may play a destructive role in pancreatitis:
 - i. Trypsin - may activate other enzymes capable of damaging the pancreas (phospholipase A₂, elastase, colipase)
 - ii. Elastase - may damage elastic tissue of blood vessels
 - iii. Kallikrein - liberates bradykinin and kallidin which increase vascular permeability and promote leukocyte infiltration. (Note: the above enzymes could thus explain the hemorrhage, edema, and leukocyte infiltration seen in acute pancreatitis.)
 - iv. Lipase - if activated by colipase in presence of bile salts, can produce fat necrosis
 - v. Phospholipase A₂ - in its active form, produces necrosis of adipose tissue and pancreatic tissue. (Note: Thus, these latter enzymes could explain the pancreatic and fat necrosis seen in acute pancreatitis.)

4. Pathology:

- a. Early: congestion and edema of pancreas, then vascular thrombi and necrosis; hemorrhages
- b. Development of tissue and fat necrosis with acute inflammation, extending into surrounding tissues in severe cases
- c. Healing with fibrosis, if patient survives; formation of pseudocysts (see below)
- d. Complications:
 - Peritonitis - fluid loss, shock, etc.
 - Hypocalcemia - may cause tetany
 - Fat necrosis at a distance, due to circulating lipases

5. Clinical features: Outlined in other lectures.

- B. *Focal pancreatitis*: As the name implies, the pathology here is focal areas of tissue and fat necrosis with inflammation. The lesions are usually small and asymptomatic, being discovered at autopsy when the patient dies for other reasons. Etiology: some cases associated with infection (e.g., mumps) and some cases to ischemia.
- C. *Chronic pancreatitis*
1. Also a disease of middle age characterized by recurrent episodes of pancreatitis. Often terminates in exocrine pancreatic insufficiency and diabetes mellitus due to loss of functioning parenchyma and islets.
 2. Etiology and pathogenesis:
 - Etiology often unclear. Felt in many cases to result from recurrent bouts of acute pancreatitis. May rarely be secondary to hyperparathyroidism or occur in a hereditary form having its clinical onset in childhood.
 - Most commonly associated with chronic alcoholism and with biliary tract disease.
 - About 1/3 of patients with acute pancreatitis who survive will have recurrent acute attacks; some cases seem to progress to chronic pancreatitis (? recurrent exposure to etiologic factor, ? development of autoimmunity).
 3. Pathology: progressive atrophy and fibrosis of gland, often with focal areas of acute pancreatitis and fat necrosis. Ductal ectasia, focal calcification, and pseudocyst formation common.

IV. Cysts and Pseudocysts

- A. The majority of pancreatic cysts are acquired, developing as long-term sequelae in acute and chronic pancreatitis. They may arise from ducts dilated secondary to obstruction (retention cysts) or from walled-off accumulations of pancreatic necrotic debris, enzymes, and hemorrhage that have ruptured through the pancreatic surface, usually into the lesser sac (traumatic, inflammatory, or "pseudo"-cysts). The term "pseudo"-cysts recognizes the fact that, unlike true cysts, these cysts are not lined by an epithelium.
1. The cysts may become quite large, containing two or more liters of fluid.
 2. Cysts may become clinically palpable, and enter the differential diagnosis of epigastric masses (although they may be palpable at other sites in the abdomen as well).
- B. A few cases of pancreatic cyst formation are congenital. These cysts are usually small, multiple, and associated with cysts in other organs, especially cerebellum, kidneys, and liver (i.e., polycystic kidney disease).

V. Neoplasms of exocrine pancreas

- A. Benign tumors of ductal origin (adenomas, solid or cystic) are rare.
- B. Stromal tumors and lymphomas are likewise very rare; occasionally, tumors may metastasize to the pancreas.
- C. *Carcinoma*: most important pancreatic neoplasm
1. General features:
 - a. Majority arise from ductal epithelium; a few from acini
 - b. Incidence: about 6% of all abdominal neoplasms; #4 cause of fatal carcinoma in USA

- c. Majority occur after age 50; rare under age 40. Slight male preponderance.
 2. Pathology
 - a. The majority of pancreatic carcinomas are firm masses that histologically are adenocarcinomas of variable degrees of differentiation.
 - b. About 70% arise in the head of the pancreas. In this area, they tend to invade the common bile duct, resulting in relatively early obstructive jaundice. The remainder arise in the body and tail, where they may remain asymptomatic until late in their natural history.
 - c. Natural history:
 - Direct extension outside pancreas, especially into retroperitoneal soft tissue, where nerve sheath invasion is common.
 - Local lymph node metastases.
 - Distant metastases (liver, lung, etc.) usually late.
 - Pancreatic carcinoma may be associated with the syndrome of multiple superficial venous thrombi; mechanism unclear.
 3. Symptomatology
 - a. Pain - epigastric or back; often (but not always) related to neural invasion.
 - b. Jaundice - due to common bile duct obstruction.
 - c. Maldigestion and malabsorption - if sufficient acinar tissue is destroyed by tumor, or more commonly, if pancreatic duct is obstructed by tumor.
 - d. Weight loss; migratory venous thrombosis.
 4. Diagnosis: a variety of diagnostic procedures are in use (see clinical lectures), including use of fine needle aspiration biopsy. Often laparotomy with needle biopsy is necessary to make the diagnosis. Even then, the gross (and, sometimes, microscopic) differentiation of a desmoplastic carcinoma from chronic pancreatitis can be difficult.
 5. Prognosis: Dismal. Without therapy, most patients are dead of their disease within 12 months of the onset of their clinical symptoms. With radical surgery (pancreatectomy and removal of surrounding tissue), the 5 year survival is still very small due to the extensive growth of these tumors before they become clinically evident.
- D. Lesions of the endocrine pancreas are discussed in the Endocrinology class. However, one lesion of the islets is worth mentioning in the GI course. This lesion is non-beta cell tumor that gives rise to the Zollinger-Ellison syndrome.
1. Clinical features of syndrome:
 - a. Gastric acid hypersecretion
 - b. Often, atypical peptic ulcer development: unusual locations (distal duodenum, esophagus) and refractory to therapy
 - c. Non-beta cell tumor(s) in the pancreas
 2. The pancreatic tumors are thought to be formed of delta cells that are producing gastrin which in turn stimulates gastric acid production. Lesions are often multiple and some are malignant.
 3. About 1/3 of these patients have adenomas in other endocrine organs, particularly the pituitary and parathyroids (multiple endocrine adenoma syndrome).

Part III: Pathology of the Biliary Tract

I. Inflammation

A. Acute cholecystitis

1. A disease of relatively sudden onset, occurring chiefly in adults, characterized by right upper quadrant abdominal pain and evidence of peritoneal irritation, and requiring surgical intervention.

- The incidence of disease is greater in females than in males (2:1 F:M ratio at age 40).
2. Etiology
 - a. Most cases related to presence of gallstones and presumed obstruction of cystic duct.
 - b. Some cases due to bacterial infection, either secondary due to hematogenous spread from another organ or due to ascending infection up the biliary tree (cholangitis).
 - c. Some cases related to vascular ischemia:
 - Low-flow syndromes; thrombosis
 - Vasculitis
 - Sickle-Cell Disease
 - d. Acute acalculous cholecystitis is a potentially fatal complication in the severely ill patient (post-surgical, debilitated, burn/trauma patients).
 3. Pathology
 - a. Swollen dusky gallbladder, with acute inflammation and edema throughout the wall; variable amount of infarction.
 - b. Changes usually progressive, resulting in extensive necrosis with rupture of the viscus and/or peritonitis.

B. Chronic cholecystitis (repetitive acute cholecystitis with healing between episodes)

1. A chronic illness characterized by recurrent acute right upper quadrant discomfort, nausea, and vomiting. The patient is at risk for an episode of superimposed acute cholecystitis and its complications. Acute cholecystitis is more common in association with healed (i.e., chronic) cholecystitis and gallstones than in an otherwise normal gallbladder.
2. Etiology: Most cases associated with gallstones. Some cases secondary to smoldering bacterial sepsis in biliary tract (e.g., Salmonella).
3. Pathology
 - a. Gross: fibrotic contracted gallbladder
 - b. Microscopic:
 - Coarsening and ulceration of mucosa; Rokitansky-Aschoff sinuses.
 - Muscular hypertrophy
 - Fibrosis and chronic inflammation, usually involving all layers.

II. Cholelithiasis (Gallstones) - see Dr. Carey's lectures for physical biochemistry

- A. Gallstones are a tremendous public health problem and the cause of much morbidity (and appreciable mortality) in the USA.
 1. An estimated 15,000,000 people in this country have stones; about 500,000 persons undergo biliary tract surgery for stones each year, for the removal of several tons of gallstones per year.
 2. Stones more common in females (2:1); reason for sex prevalence unclear (? hormonal influences).
 3. Obesity is a common factor in stone formation, as is parity.
- B. Etiology: Epidemiologic and biochemical investigations suggest a multifactorial process.
 1. Imbalance in the secretory rates of major constituents of bile (bile salts decrease, cholesterol increase) results in precipitation of cholesterol.
 2. Gallbladder bile contains mucoproteins which primarily inhibit (but some may promote) the formation of gallstones. Imbalances may lead to nucleation events.
 3. Abnormal prostaglandin balance may inhibit gallbladder motility, leading to stasis.

4. Rarely, precipitation of cholesterol from change in bile composition due to presence of foreign material (bacteria) in gallbladder.
- C. Stones are classified according to their major chemical components as cholesterol stones or calcium bilirubinate stones (<10% cholesterol, related to hemolytic states). Principles of stone composition and formation are covered in detail in the Biliary Secretion lecture by Dr. Carey. Stones may be associated with cholesterosis of gallbladder: the accumulation of cholesterol esters in macrophages in the lamina propria of the gallbladder. Grossly, the gallbladder shows yellow mucosal striae, the so-called "strawberry" pattern. However, cholesterosis is also often present in gallbladders that contain no stones.
- D. Effects of stones
1. None (~80%)
 2. Predispose to pain (misnamed "colic") and/or cholecystitis (obstruction of cystic duct).
 3. Small stones may enter biliary tree causing: RUQ pain, "colic", Impaction, Obstructive jaundice, Retrograde sepsis, suppurative cholangitis
 4. Large stones may erode from gallbladder into adjacent organs, e.g.: Colon, Duodenum, giving rise to mechanical obstruction, termed "gallstone ileus". Fistula thus formed may allow organisms to ascend into gallbladder.
 5. Carcinoma of the gallbladder occurs in 1-2% of patients with cholelithiasis who are over age 60. Stones are found in 75-85% of cancerous gallbladders.
- E. Therapy: expectant (i.e., monitor with no treatment), surgical or medical (pharmaceutical dissolution of cholesterol stones only).

III. Neoplasms

- A. Benign epithelial and stromal tumors - rare.
- B. Majority of malignant tumors are carcinoma (sarcomas very rare), most (over 90%) arise in gallbladder, the rest throughout the biliary tree.
1. In the gallbladder, carcinomas are associated with the presence of gallstones.
 2. Pathology:
 - a. Majority are adenocarcinomas, well- or poorly-differentiated; rest are squamous cell carcinomas (probably arise from areas of squamous metaplasia).
 - b. Usually arise in fundus or neck of the gallbladder and tend to infiltrate the wall extensively; local spread to liver, metastases to regional lymph nodes.
 3. Symptomatology
 - a. Pain (and sometimes a palpable mass) - right upper quadrant of abdomen
 - b. Jaundice - due to biliary tract obstruction
 - c. Perforation
 - d. Ascites - due to peritoneal metastases.
 4. Prognosis: excellent if discovered incidentally in a gallbladder removed for stones; poor otherwise. Surgery is usually too late to be curative. 95% of patients are dead within one year of surgery.

IV. Non-Neoplastic Occlusive Disease of the Extrahepatic Biliary Tree

- A. Stones most common cause (see above)
- B. Biliary atresia of infancy: Rare syndrome of unknown etiology. Jaundice in early postnatal life. Surgical correction is possible, but difficult (Kasai procedure - portal-jejunal anastomosis).

- C. Primary sclerosing cholangitis: Rare progressive inflammatory sclerosing lesion of unknown etiology occurring predominantly in adults. Approximately 30% of cases occur in patients with ulcerative colitis.
 Note: Any chronic form of occlusive disease of the extrahepatic biliary tree will lead to secondary biliary cirrhosis if uncorrected.

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