

Principles of Liver Pathology

Liver anatomy	<ul style="list-style-type: none"> • Largest organ in the body. Covered by Glisson's capsule. Right (including quadrate (inferior), and caudate (posterior)) and left lobes. • Dual blood supply: portal vein and hepatic artery. • Portal venous pressure is normally low (7 mm Hg). • Cirrhosis is most common cause of portal hypertension. 	<p>(A) Classic microanatomic unit is the lobule: hexagon with central vein in center and peripheral portal tracts. Limiting plate on periphery and is damaged in chronic hepatitis. Liver plates are normally one cell thick.</p> <ul style="list-style-type: none"> • Portal tracts contain branches of the hepatic artery, portal vein, and interlobular bile ducts. • Canal of Hering is intermediate cell population between hepatocytes and the bile ducts. Cells lie in outer third of lobule. Also in this area are hepatic stem cells (oval cells). These may form bile duct structures in obstruction. • Sinusoids made from fenestrated endothelial cells with no basement membrane are between liver cords. Endothelial cells secrete NO and endothelin. • Kupffer cells within vascular space: clear organisms from incoming portal blood, make cytokines, and digest dead hepatocytes. • Pit cells are large granular lymphocytes that function like natural killer cells. Also within vascular space. • Between sinusoidal endothelium and hepatocytes is the space of Disse. Contains collagen fibrils and stellate cells (Ito cells). These are elongated cells with lipid vacuoles that store vitamin A and can transform into cells that secrete collagen and can contract. These cells cause the fibrosis in chronic liver disease. Also secrete NO and endothelin. <p>(B) Alternative unit is the acinus. Portal vein and hepatic arteriole perfuse at center and terminal hepatic venules (central veins) lie at periphery. Indicates oxygenation of regions. From most oxygenated to least is periportal (zone 1), midzone (zone 2), and centrilobular (zone 3). Different zones have different functions. e.g. zone 3 has lots of P-450 and gets most affected by drug toxicities. Also, zone 3 is vulnerable to ischemia. Zone 1 synthesizes the most bile salts.</p> <ul style="list-style-type: none"> • Bile canaliculus formed by tight junctions between 2 liver cells. Actin myofilaments provide contractions for propelling bile. Canalicular membranes contain bile salt transport proteins. These become mutated in various jaundice diseases (e.g. Progressive Familial Intrahepatic Cholestasis (PFIC), Dubin-Johnson Syndrome, Benign Recurrent Cholestasis). • Bile secretion into canaliculus by bile salt-dependent (osmotic) and independent (ATP) flow. Independent flow inhibited by endotoxin in sepsis which causes cholestasis.
Acute Hepatitis	<ul style="list-style-type: none"> • Diffuse hepatocellular damage and death by apoptosis associated with portal and lobular inflammation. • Infiltrates of mononuclear cells within sinusoids and portal tracts. • Ballooning degeneration and apoptosis of hepatocytes with formation of intrasinusoidal acidophilic bodies (apoptotic bodies). 	<ul style="list-style-type: none"> • Common causes include infection by Hep A-E and drug hepatotoxicity. • Disease of cell-mediated immunity.
Chronic Hepatitis	<ul style="list-style-type: none"> • Inflammation of the liver continuing without improvement for 6 months or longer. • Continued lymphocytic and plasma cell infiltrates within portal tracts and lobules. Varying degrees of hepatocyte damage and apoptosis, though less than with acute. 	<ul style="list-style-type: none"> • Major causes are (1) viral Hep B-D, (2) autoimmune hepatitis, (3) drug toxicity, and (4) metabolic diseases (g.g. α1-anti-trypsin deficiency and Wilson's disease).

	<ul style="list-style-type: none"> • Piecemeal necrosis (interface hepatitis) is a special form of chronic portal and periportal inflammation. Infiltrates of lymphocytes and plasma cells extend into the limiting plate region with resultant apoptosis of hepatocytes. Usually associated with fibrosis and can eventually lead to cirrhosis. 	
Fatty Liver	<ul style="list-style-type: none"> • The presence of lipid vacuoles within hepatocytes. Also called steatosis. • Associated with inflammation and fibrosis in steatohepatitis. Major pathologic features include large droplet fat, liver cell ballooning, fibrosis around central veins and in the perisinusoidal region, Mallory bodies within hepatocytes, and PMN infiltrates around affected hepatocytes. May lead to cirrhosis. 	<ul style="list-style-type: none"> • Abnormal lipid and lipoprotein metabolism. • 2 types: <ul style="list-style-type: none"> (1) Large droplet (macrovesicular). Most common. Large lipid vacuoles displace nucleus to periphery of cell. Associated with major causes of fatty liver, like alcohol, obesity, diabetes, and corticosteroids. (2) Small droplet (microvesicular). Uncommon. Finely divided lipid vacuoles throughout cytoplasm. Nucleus remains at center of cell. Usually reflects disturbed mitochondrial β oxidation of fatty acids. Causes include Reye's syndrome, tetracycline toxicity, acute fatty liver of pregnancy, and toxicity of nucleoside analogues and of valproic acid.
Cholestasis	<ul style="list-style-type: none"> • The presence of stagnated bile in the liver. • Jaundice when serum total bilirubin at 2-3 mg/dl. • Bile can be seen within hepatocytes and bile canaliculi. • Surgical jaundice is large bile duct obstruction and might be cured by surgery. e.g. Gallstones, biliary strictures, carcinoma of head of pancreas. • Medical jaundice refers to an intrahepatic disease. e.g. Drug-induced cholestasis and acute hepatitis. • Try to determine where bile is obstructed. Use serum liver tests, autoantibodies, ultrasound, endoscopy, cholangiography, and CT. Also, liver biopsy. • Major pathologic legions: <ul style="list-style-type: none"> (1) Cholestasis alone: Bile visible on histology within hepatocytes or canaliculi. Typical of drug-induced jaundice or gram-negative septicemia. (2) Cholestasis and portal tract changes of edema, PMNs and bile ductular proliferation: Typical of acute large bile duct obstruction (e.g. gallstones, biliary stricture, carcinoma of head of pancreas). If ascending infection of bile ducts also present, then have acute cholangitis with PMNs. Chronically leads to portal fibrosis which leads to biliary cirrhosis. (3) Damage to interlobular bile ducts: Specifically affect the intrahepatic bile ducts. Leads to bile duct epithelial damage, inflammation, and loss of the bile ducts. Primary biliary cirrhosis is the prototype disease. Also, acute liver transplant rejection, graft vs. host, and some drug hepatotoxicity. 	<ul style="list-style-type: none"> • Due to disturbed bile flow at any level, from hepatocyte to ampulla of Vater. • Distinguish between bile duct diseases and intrahepatic cholestasis: <ul style="list-style-type: none"> (1) Bile duct diseases: e.g. gallstone in common bile duct, pancreatic/ampullary carcinoma, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), metastases in porta hepatis lymph nodes. (2) Intrahepatic cholestasis: e.g. viral hepatitis, drug hepatitis, endotoxic shock/gram-negative sepsis. • With chronicity, develop portal fibrosis, portal-to-portal bridging fibrosis, and then biliary cirrhosis.
Cirrhosis	<ul style="list-style-type: none"> • Diffuse fibrosis surrounding architecturally abnormal regenerative nodules. • Micronodular (<3 mm nodules) usually alcohol, chronic Hep C, and hemochromatosis. • Macronodular usually chronic Hep B, Wilson's, and α1-anti-trypsin. • Biliary cirrhosis not either category with a sandpaper-like surface. • Histologic features useful e.g. ground-glass hepatocytes in HBV cirrhosis; fat, PMNs, and Mallory bodies in alcoholic cirrhosis. 	<ul style="list-style-type: none"> • End result of chronic liver diseases that cause irreversible damage to liver architecture. • Causes include alcoholic liver disease (60-70%), viral hepatitis (10%), biliary disease (5-10%), hereditary hemochromatosis (5%), Wilson's disease (rare), α1-anti-trypsin deficiency (rare), and cryptogenic cirrhosis (10-15%). • Consequences are altered liver cell metabolic and synthetic function, Kupffer cell phagocytic function, bile secretion, and blood flow patterns. • 2 most important consequences are liver cell failure and portal

		<p>hypertension.</p> <ul style="list-style-type: none"> • Cirrhosis is the most common cause of portal hypertension.
Portal Hypertension	<ul style="list-style-type: none"> • Most common cause is cirrhosis. • Enlarged spleen single most important diagnostic sign of portal hypertension. • Varices occur. 3 common sites: (1) Esophageal varices, (2) middle and inferior hemorrhoidal varices, and (3) para-umbilical veins (caput medusae). • Wedged pressure is normal in pre-hepatic hypertension and is elevated in post-hepatic and some intrahepatic portal hypertension like cirrhosis. 	<ul style="list-style-type: none"> • Pressure can be measured using wedged hepatic venous pressure. • Divided into 3 types: <ol style="list-style-type: none"> (1) Pre-hepatic: e.g. Thrombosis of portal vein or splenic vein. (2) Intrahepatic: Divided into (a) pre-sinusoidal, lesions in portal tracts or obstruction of portal vein branches e.g. schistosomiasis; (b) sinusoidal; and (c) post-sinusoidal, in central veins e.g. bush tea ingestion. (3) Post-hepatic: obstruction within hepatic veins or IVC (e.g. thrombosis, congenital web of IVC).

Hepatic Secretory Function and Jaundice

Bilirubin	<ul style="list-style-type: none"> • Elevated serum bilirubin one of the hallmarks of liver dysfunction. • Bilirubin results in jaundice at 2 mg/dl. • Arises from metabolism of heme. Heme cleaved to biliverdin IXα, Fe, and CO. Biliverdin reduced to bilirubin IXα. Bilirubin is an involuted molecule which makes it insoluble in water. • Bilirubin is transported from reticuloendothelial system (spleen and bone marrow) to the liver bound to albumin. Only a little bit is free. • Bilirubin in bile goes from bile duct to small intestine to colon. In colon, gets changed into colorless urobilinogen. 20% absorbed by intestine and taken up by liver and secreted into bile. Small amount bypasses liver and excreted into urine. If not absorbed, then oxidized to urobilin which makes stool brown. 	<ul style="list-style-type: none"> • Most (75%) derived from RBC destruction in reticuloendothelial system. • Minor sources are cytochrome P450s (22%) and premature destruction of RBCs. • Minor source bilirubin called “early labeled fraction” because of early peak of radiolabeled bilirubin. Later peak is at 120 days (life span of RBC).
Hepatocyte metabolism of bilirubin	<p>(1) Uptake by hepatocytes: Unconjugated bilirubin arrives bound to albumin and is separated from albumin when entering the cell.</p> <p>(2) Transport to the endoplasmic reticulum: Binds to ligandin (protein Z) within hepatocyte. Some associates with fatty acid binding protein (protein Y). Some transferred directly to smooth endoplasmic reticulum.</p> <p>(3) Conjugation: Occurs in the ER. Catalyzed by UDP-glucurono-syltransferase (UGT) family. UGT1 family contains two bilirubin conjugating forms. Four UGT1 isoforms expressed by alternative splicing from single gene, <i>UGT1</i> on chromosome 2q37. The 2 bilirubin conjugating forms termed B-UGT1 and B-UGT2. Activity stimulated by phenobarbital. Glucuronic acids attached to propionic groups of bilirubin. Conjugated to mono- and then diglucuronide. Conjugation makes it not involuted so that it is soluble in water.</p> <p>(4) Secretion: Secreted across canalicular apical membrane and into bile ductules. Carrier mediated and can be inhibited but uses different transporter than bile acids. Rate limiting step in bilirubin metabolism. 1-2% of bile and almost all conjugated.</p>	
Bilirubin pathophysiology	<ul style="list-style-type: none"> • Increased concentrations indicate abnormal hepatic function, overproduction of bilirubin, or bile duct obstruction. Usually < 1 mg/dl. • Conjugated (direct) serum bilirubin >30% of total is abnormal. • Bilirubin toxic when 15-20x normal. • In infants, see kernicterus which is severe unconjugated hyperbilirubinemia with deposition in the cerebellum, brain stem, and basal ganglia. Due to lipid-solubility of unconjugated bilirubin and immature blood-brain barrier. Very rare in adults. 	<ul style="list-style-type: none"> • Unconjugated bilirubin lightly bound to albumin in blood. Conjugated is less tightly bound and more is free. Free unconjugated never found in urine. Free conjugated excreted in urine. In disease states, conjugated bilirubin can be covalently bound to albumin. • High serum conjugated bilirubin found in hepatitis and obstruction of bile ducts. Secretion of bilirubin (rate limiting step in metabolism) is often abnormal. Unconjugated bilirubin rises a bit from mass action inhibition of conjugation and release of unconjugated bilirubin from damaged hepatocytes. • Isolated unconjugated hyperbilirubinemia usually due to extrahepatic overproduction or inherited defects in bilirubin conjugation (e.g. mutations in the <i>UGT1</i> gene).

<p>Disorders causing unconjugated hyperbilirubinemia</p>	<p>(1) Overproduction</p> <ul style="list-style-type: none"> • Hemolysis: Intravascular (hemolytic anemia, transfusion reactions) and extravascular (resorption of hematoma). • Ineffective erythropoiesis: Megaloblastic anemia and thalassemias. <p>(2) Impaired Uptake</p> <ul style="list-style-type: none"> • Fasting • Sepsis • Gilbert syndrome (possibly, see below) • Drugs e.g. probenecid <p>(3) Impaired Conjugation</p> <ul style="list-style-type: none"> • Neonatal (physiologic) jaundice: Mostly due to decreased UGT1 activity. Decreased ligandin, increased bilirubin from ineffective erythropoiesis, decreased RBC survival, and degradation of RBC mass. Treatment with phototherapy with visible light (photoisomers). • Crigler-Najjar syndrome: Autosomal recessive mutations in <i>UGT1</i> gene leading to decreased to absent bilirubin conjugation. Type 1: absent activity. Type 2: decreased activity with serum bilirubin from 8 to 20 mg/dl. • Gilbert syndrome: Mildly decreased UGT1 activity. Mutations in the UGT1 gene promoter. Unconjugated serum bilirubin from 1.5-6.0 mg/dl. Decreased uptake may contribute. Exacerbated by stress, fasting, and infection. Concentrations decreased by phenobarbital. Fairly common and runs in families. 	
<p>Disorders causing conjugated hyperbilirubinemia</p>	<p>(1) Impaired secretion of conjugated bilirubin</p> <ul style="list-style-type: none"> • Hepatocellular diseases: Most common in acquired diseases such as viral, drug, and alcoholic hepatitis and cirrhosis. • Pregnancy: Jaundice in 3rd trimester in 1% in US. Estrogen sensitivity like jaundice induced by birth control pills. • Dubin-Johnson syndrome: Autosomal recessive. Very rare except in Persian Jews. Dark pigment in hepatocytes. Benign course. • Rotor syndrome: Autosomal recessive. Rare. Benign course. <p>(2) Intrahepatic/Extrahepatic biliary tree obstruction and cholestasis</p> <ul style="list-style-type: none"> • Obstruction to flow of bile: Strictures, gallstones, tumor, autoimmune bile duct destruction (primary biliary cirrhosis, primary sclerosing cholangitis), and drugs. • Benign recurrent intrahepatic cholestasis and familial intrahepatic cholestasis 1: Mutations in P-type ATPase on chromosome 18q21 probably a bile salt transport protein. Decrease bile flow can lead to jaundice. Progressive form leads to serious liver disease. 	
<p>Other tests of hepatic function and disease</p>	<p><u>Biochemical</u></p> <ul style="list-style-type: none"> • Bilirubin • Albumin: Synthesized in hepatocytes and secreted into blood. $t_{1/2} \sim 20d$. Hypoalbuminemia can occur with synthetic dysfunction in chronic liver disease, especially in advanced cirrhosis. • Prothrombin time: Blood clotting factors synthesized in liver, most with $t_{1/2}$ between 6-96 hrs. Will be prolonged within 1-2 d of synthetic dysfunction in severe acute liver disease. Can also be prolonged in advanced chronic liver disease. • Glucose: Glycogenolysis and gluconeogenesis take place in the liver. Hypoglycemia can occur in severe liver dysfunction. • Cholesterol: Synthesized in liver and secreted as complex with lipoproteins. Serum cholesterol low in severe hepatocellular dysfunction. Biliary obstruction leads to elevations in cholesterol. Abnormal lipoprotein X. • ALT (alanine aminotransferase): Specific for hepatocytes. In cytosol. Catalyzes transamination between amino and α-keto acids. Serum concentration elevated when hepatocytes are damaged or destroyed. • AST (aspartate aminotransferase): In mitochondria and cytosol of hepatocytes. Also in heart and skeletal muscle. Catalyzes transamination 	<p><u>Imaging</u></p> <ul style="list-style-type: none"> • Ultrasound: Visualize gallstones, dilated bile ducts, and intrahepatic and extrahepatic masses. Can see features of cirrhosis. Combined with Doppler to examine blood flow. Reversal of portal flow suggests hypertension. • CT: Information about intrahepatic and extrahepatic masses and liver size and shape. • Liver-spleen scan: Based on reticuloendothelial cell uptake of ⁹⁹Tc-labeled colloid. Image from emitted γ-rays. Increased splenic and bone marrow uptake of label seen in portal hypertension, usually secondary to cirrhosis. • Oral cholecystography: Visualize gallbladder. Lipid-soluble dye given orally, removed from blood by liver, conjugated, and secreted into bile. Dye concentrates in gallbladder and stone can be seen by x-ray. Non-visualization of gallbladder suggests hepatic secretory dysfunction or cystic duct obstruction. • Radionuclide biliary scans: ⁹⁹Tc-labeled compounds taken up by liver and secreted into bile to image gallbladder and biliary tree by using a γ-ray camera. If cystic duct obstructed (e.g. cholecystitis), gallbladder will not visualize. Not reliable in presence of severe secretory dysfunction.

	<p>between amino and α-keto acids. Serum concentration elevated when hepatocytes are damaged or destroyed. Also elevated in muscle damage (e.g. MI).</p> <ul style="list-style-type: none"> • Alkaline phosphatase: Predominantly near microvilli of the bile canaliculi. Also in bone and placenta. Serum activity elevated with intrahepatic cholestasis, extrahepatic biliary obstruction, or invasion of the liver (e.g. tumor, mycobacterial infections). Also may be elevated in bone diseases. • γ-glutamyltranspeptidase (GGT): Specific for liver. Serum activity rises under same conditions as rise in alkaline phosphatase. Can help differentiate biliary disease from bone disease. 	<ul style="list-style-type: none"> • Endoscopic retrograde cholangiopancreatography (ERCP): Endoscopic annulation of the ampulla of Vater and injection of x-ray contrast medium into common bile duct and pancreatic duct. Image of biliary tree obtained by x-ray. Can be performed in the presence of severe hepatic dysfunction. Also used therapeutically e.g. extract stones in common bile ducts, dilate strictures, or place stents). • Transhepatic cholangiography: Needle through liver parenchyma into a dilated intrahepatic bile duct. Injection of contrast medium to take x-ray images. Can be performed only if intrahepatic bile ducts are dilated.
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Viral and Autoimmune Hepatitis

<p>Acute Hepatitis</p>	<ul style="list-style-type: none"> • Hep A-E produce an early episode of malaise, nausea, and anorexia (d-wks) followed by jaundice (1-4wk) and elevated AST and ALT (10-20x normal). • Incidence of viral hepatitis in U.S. in 1990s was: HAV 40%, HBV 32%, HCV 21%, HDV 2%, HEV 3% (patients who travel to endemic area), and unidentified 2%. • Hepatocyte degeneration and death with inflammation. Hepatocyte death (spotty necrosis) occurs in the form of ballooning (lytic) degeneration and apoptosis. • Acidophilic bodies are present (densely eosinophilic apoptotic cells). • Infiltrate of lymphocytes within sinusoids and portal tracts. • If severe, spotty necrosis may become confluent to give bridging hepatic necrosis (between portal tracts or between portal tracts and central veins), multilobular necrosis, and, the worst form, massive hepatic necrosis (pathologic correlate of fulminant hepatitis). • In massive hepatic necrosis, both lobes are severely affected with few residual hepatocytes. Liver is shrunken and has wrinkled capsule from parenchymal loss. Mortality high. Only develops in 1-3% of cases of acute viral or drug hepatitis. 	<ul style="list-style-type: none"> • All the hepatitis viruses are RNA except HBV which is a DNA virus. • CMV, Epstein-Barr Virus (EBV), and Herpes Simplex Virus (HSV) may also infect the liver. • Immune mediated injury rather than cytopathic. Three-pronged immune response: <ol style="list-style-type: none"> (1) Non-specific immune effects: INFs bind to targeted cells and stimulate cytokine cascade; complement may bind to virion envelope proteins; and NK cells can bind to infected hepatocytes. (2) Antibody synthesis: Neutralizing Abs opsonize live virions which are removed by PMNs and macrophages. (3) T-cell response: Clearance ultimately linked to T-cells.
<p>Chronic Hepatitis</p>	<ul style="list-style-type: none"> • Inflammation of the liver continuing without improvement for >6 months. • Base diagnosis on abnormal AST and ALT over long period of time. Levels abnormal (2-5x increase) but not as bad as in acute hepatitis. • Many patients asymptomatic while fatigue is most common symptom in others. • May be present for decades. <29% lead to cirrhosis. • The liver biopsy essential to classify. Can indicate grade of necroinflammatory activity and stage of fibrosis. • Some histological features indicative of causitive factor: chronic HBV, ground-glass inclusions; chronic HCV, lymphoid aggregates or follicles in portal tracts, fat in hepatocytes, and bile duct damage; autoimmune hepatitis, interface hepatitis, plasma cell-enriched portal infiltrates, and liver cell rosettes; α1-anti-trypsin deficiency, PAS-positive, diastase- 	<ul style="list-style-type: none"> • Causes of chronic hepatitis: HBV, HCV, HDV, autoimmune hepatitis, drugs, and metabolic diseases (α1-anti-trypsin and Wilson's). • Once cirrhosis occurs, may be well compensated with good synthetic function (normal albumin and clotting parameters). • When decompensated, can develop bleeding diathesis with elevated prothrombin time and bleeding form esophageal varices and ascites. • In more advanced forms, get palmar erythema, spider angiomas on the chest and upper extremities, and ascites. • Carrier is someone with chronic hepatitis virus infection but no symptoms. Either have findings or little or no histologic findings on biopsy. • 2 major pathways of chronic hepatitis are necroinflammation and fibrosis (cirrhosis). • Portal tracts and lobular parenchyma may be affected. Lymphocytic and

	<p>resistant globules in periportal hepatocytes; and Wilson's disease, stainable copper and copper-binding protein.</p>	<p>plasma cell infiltrates and scattered acidophilic bodies.</p> <ul style="list-style-type: none"> • Some patients show piecemeal necrosis (interface hepatitis) where infiltrates go beyond portal tract into the periportal region with death of hepatocytes there. Usually associated with portal and periportal fibrosis. • The patients who eventually develop cirrhosis usually had a combination of continued piecemeal necrosis, lobular necroinflammation, architectural remodeling of the liver, and progressive deposition of fibrosis. Liver cell dysplasia may develop and are associated with later development of hepatocellular carcinoma. 										
<p>Hepatitis A Virus (HAV)</p>	<ul style="list-style-type: none"> • RNA picorna virus transmitted by oral-fecal route. • Contaminated shellfish and food handlers common sources. • Elderly and poor health do worse. • Mostly children and young adults are affected. • Gammaglobulin and hepatitis vaccine for prophylaxis. • Diagnostic acute serum test is IgM anti-HAV. Later, IgG develops. 	<ul style="list-style-type: none"> • Incubation 15-50 days and illness lasts 6 weeks. • Does not lead to chronic hepatitis or cirrhosis. 										
<p>Hepatitis B Virus (HBV)</p>	<ul style="list-style-type: none"> • dsDNA virus, member of the HEPADNA virus group. • Transmitted sexually, by IV drugs, or vertically. • Endemic regions in Asia and S. Africa. • Outer envelope is hepatitis B surface antigen (HBsAg). • Detection of HBsAg in serum is the diagnostic hallmark of acute and chronic infection. • HBsAg synthesized in hepatocyte ER with excess leaking into serum. • HBsAg comes in 4 varieties: adw, adr, ayw, and ayr. • Hepatitis B core antigen (HBcAg) surrounded by HBsAg. Mutant forms of HBcAg exist and are found to be responsible for certain cases of fulminant hepatitis. • A portion of HBcAg is cleaved off and detectable in serum early in infection and is called early antigen or hepatitis B early antigen (HBeAg). Marker for particularly infectious patients. • Also, HBxAg which is involved in transactivation process of viral replication and associated with hepatocarcinogenesis. • Following acute HBV infection, the normal host synthesizes anti-HBs (neutralizing Ab) to clear the infection. Resultant anti-HBs long-lived and protective against new infections. • HBV vaccine is a synthetic HBsAg. • In acute infection, IgM anti-HBc is also positive. Later converts to IgG anti-HBc which is long-lived. • High infectivity indicated by serum HBeAg, HBV DNA, and DNA polymerase. • 4% fail to clear the virus after infection and become HBsAg carriers. They do not develop anti-HBs. Show positive serum HBsAg and IgG anti-HBc. HBeAg is present until seroconverts to anti-HBe. Quiescent phase of chronic HBV ensues. 	<ul style="list-style-type: none"> • Incubation period is 50-160 days. • Entire HBV particle called DANE particle. • Serologic events in HBV infection <table border="1" data-bbox="1186 649 1990 901"> <thead> <tr> <th>Condition</th> <th>Serum HBV Ag or Ab present</th> </tr> </thead> <tbody> <tr> <td>Acute HBV</td> <td>HBsAg, IgM anti-HBc, HBV DNA</td> </tr> <tr> <td>Chronic HBV</td> <td>HBsAg, HBeAg, IgG anti-HBc, HBV DNA (HBeAg to anti-HBe seroconversion may occur at some point)</td> </tr> <tr> <td>Convalescent HBV infection (immune patient)</td> <td>anti-HBs, IgG anti-HBc</td> </tr> <tr> <td>Vaccinated subject</td> <td>anti-HBs</td> </tr> </tbody> </table>	Condition	Serum HBV Ag or Ab present	Acute HBV	HBsAg, IgM anti-HBc, HBV DNA	Chronic HBV	HBsAg, HBeAg, IgG anti-HBc, HBV DNA (HBeAg to anti-HBe seroconversion may occur at some point)	Convalescent HBV infection (immune patient)	anti-HBs, IgG anti-HBc	Vaccinated subject	anti-HBs
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<p>Hepatitis C Virus (HCV)</p>	<ul style="list-style-type: none"> • RNA virus closely related to flaviviruses like arbovirus (yellow fever). • Transfusion most recognized form of infection. • Also, IV drugs, tatoos, sexual, and vertical transmission. 	<ul style="list-style-type: none"> • Incubation period relatively short (weeks). • 6 different genotypes with different geographic distributions are known. • 3 factors associated with high rate of chronic hepatitis (75-80%) after 										

	<ul style="list-style-type: none"> • Also, by needlestick. • High rates from hemodialysis. • Most cases asymptomatic except maybe fatigue. • Of those with chronic hepatitis, 20% get cirrhosis and 25% of those get hepatocellular carcinoma. • No vaccine. • Ab testing to HCV or anti-HCV is by ELISA for core protein and several non-structural proteins. • Serum testing for HCV RNA most specific diagnostic test. • Periods of normal AST and ALT punctuated by abrupt rises i.e. fluctuations. Usually discovered because of these abnormal levels. 	<p>acute infection:</p> <ol style="list-style-type: none"> (1) Abs to HCV are not neutralizing Abs. (2) High rates of HCV mutation with evolution of quasispecies are found (3) T-helper cell response in many individuals is insufficient for viral clearance.
Hepatitis D Virus (HDV or δ agent)	<ul style="list-style-type: none"> • ssRNA virus with outer coat of HBsAg. Core protein is HDAg (δ Ag). • Drug addicts and multiply transfused at increased risk. • Should be suspected in any patient admitted with fulminant hepatitis and HBsAg-(+) or in patients with chronic HBsAg-(+) hepatitis who suddenly deteriorate. • Diagnosis based on finding positive serum HBsAg and anti-HDV antibodies. δ Ag can also be stained immunohistochemically. 	<ul style="list-style-type: none"> • Patient must have HBV infection in order to have HDV infection. • HDV hepatitis worse than HBV hepatitis alone.
Hepatitis E Virus (HEV)	<ul style="list-style-type: none"> • Water-borne RNA virus. • Epidemic outbreaks in India and Somalia. • Mode of transmission and epidemic nature resemble HAV. • Mortality is 20% in pregnant women. • Does not lead to chronic hepatitis. • If found in US, patient usually has travel history to endemic areas. • Serum anti-HEV can be tested for diagnosis. 	
Autoimmune Hepatitis (AIH)	<ul style="list-style-type: none"> • Liver is the target of a cell-mediated attack by plasma cells and lymphocytes. Goes to cirrhosis if untreated. • 3 major types (I, II, and III). Type I most common. • In US, Type I autoimmune hepatitis most common after chronic viral. • Type I mainly in young women <40 yo with serum anti-smooth muscle antibodies (SMA), anti-nuclear antibodies (ANA), or both. Sometimes present as acute hepatitis. Hypoalbuminemia, thrombocytopenia, ascites, and varices may be present. AST and ALT increased. • Type II mainly in children (2-14 yo) with Ab to liver/kidney microsomes (anti-LKM). Rare in US. • Type III in adults with Ab to soluble liver Ag (anti-SLA). Ag is hepatocellular cytokeratins 8 and 18. • Corticosteroid therapy treatment of choice. Forestall development of cirrhosis. • Liver biopsy shows chronic hepatitis with active interface hepatitis, plasma cell-enriched portal and peri-portal infiltrate, and clusters of periportal hepatocytes in liver-cell rosettes. Cirrhosis may or may not be present. 	<ul style="list-style-type: none"> • Occurs in setting of other autoimmune phenomena such as: <ol style="list-style-type: none"> (1) Presence of serum autoantibodies (2) Hypergammaglobulinemia (3) Concurrent immunologic disorders (e.g. autoimmune thyroiditis, RA) (4) HLA positivity for A1, A8, and DR3 or Dr4 (5) Responsiveness to corticosteroid therapy

Alcohol, Drug Hepatitis, Metabolic Diseases

<p>General Features of Drug Metabolism</p>	<ul style="list-style-type: none"> • Oxidoreductases, hydrolases, and transferases. • Phase I reactions: oxidoreductases and hydrolases. • Phase II reactions: transferases. • Phase I & II reactions work to increase the polarity and water solubility of a molecule for excretion. • P450 system on ER membrane most important. • P450 concentrated in centrilobular (zone 3) hepatocytes. Injurious effects of alcohol and other drugs seen here. • Other drugs selective for other parts of liver e.g. phosphorous poisoning which causes periportal fat and necrosis and allopurinol which causes hepatic granulomas. 	
<p><u>Alcoholic Liver Disease</u></p>	<ul style="list-style-type: none"> • Leading cause of liver disease in West. Dose and duration dependent. • Alcohol abuse 5th leading cause of death. 	
<p>(A) Alcoholic Biochemistry</p>	<ul style="list-style-type: none"> • Legions in acinar zone 3. • Acetaldehyde is the major biochemical culprit in the disease. Covalently bind to hepatocyte proteins and messes with synthetic and metabolic function. • Most serious effect is steatohepatitis. 	<ul style="list-style-type: none"> • Metabolized by alcohol dehydrogenase (ADH). • Some contribution from P450 microsomal ethanol oxidizing sytem (MEOS), particularly from P450 2E1 (CYP 2E1). Gets induced with chronic ingestion. CYP 2E1 generates oxygen free radicals by lipid peroxidation in zone 3 and resulting metabolites cause fibrosis and inflammation (malondialdehyde and 4-hydroxynonenal). Combine to cause steatohepatitis. • Malondialdehyde activates NF-κB which causes increased TNF-α and IL-8 (proinflammatory). Also activates hepatic stellate cells (Ito), causing fibrosis. Also cross-links cytokeratins leading to Mallory bodies. • 4-OH-nonenal attracts PMNs.
<p>(B) Acetaldehyde</p>	<ul style="list-style-type: none"> • Induction of MEOS responsible for increased tolerance to barbiturates and other sedatives in sober alcoholics. Also responsible for increased risk of liver damage due to Tylenol at therapeutic doses (more toxic metabolite produced). • Increased ketone production, hyperlipidemia, triglycerides, and fatty liver from decreased fatty acid oxidation and citric acid cycle activity. 	<ol style="list-style-type: none"> (1) Binds to cell proteins, damaging macromolecules. (2) Depletes cellular glutathione (which is cytoprotective). (3) Damages mitochondria which decreases oxidation of fatty acids, decreases cytochrome oxidase activity, and decreases oxidative phosphorylation. (4) Binds to microtubules to impair protein secretion (cell swelling with retained proteins).
<p>(C) Pathologic Consequences of Alcoholic Injury: fatty liver, steatohepatitis, and cirrhosis</p>	<p>(1) <u>Fatty liver (steatosis):</u></p> <ul style="list-style-type: none"> • Alcohol most common cause in US. Also, obesity, diabetes, corticosteroids, and malnutrition. • May be no clinical or biochemical evidence of disease in those with fatty liver. Hepatomegaly with elevated ALT, AST, or alkaline phosphatase may be present. • When present, may take 6 weeks of abstinence to remove fat. • From generation of excess reduced nicotinamide-adenine dinucleotide by ADH and acetaldehyde DH. Normal substrates shunted away from catabolism and toward lipid biosynthesis. • Impaired assembly and secretion of lipoproteins plus increased peripheral catabolism of fat also cause triglyceride vacuoles in hepatocytes. • Liver is enlarged, yellow, and grey. Large triglyceride vacuoles (macrovesicular fat) in hepatocytes. Vacuoles compress nuclei to periphery of cell. • Microvesicular fat (small droplet) NOT characteristic of alcohol toxicity. Seen in patients with Reye's syndrome, tetracycline toxicity, acute fatty 	<p>(2 and 3) <u>Steatohepatitis and Cirrhosis:</u></p> <ul style="list-style-type: none"> • Serious forms of liver injury with lots of morbidity and mortality. • Genetic predisposition, polymorphism of ADH, immune system, and sex (lower gastric metabolism of EtOH in women) determine probability of serious liver injury. • At >80 g/d of alcohol consumption, risk of liver injury is serious. • Cirrhotic dose is 160 g/d. • Steatohepatitis characterized by fat, liver cell ballooning, fibrosis surrounding central veins and extending into sinusoids and around hepatocytes, Mallory bodies, and PMN infiltrates. Fibrosis from stellate cells transforming into myofibroblasts. • Alcoholic hepatitis is syndrome of nausea, vomiting, fever, abdominal pain, jaundice, and leukocytosis in peripheral blood associated with steatohepatitis. Aminotransferases are elevated with AST>ALT. • Nonalcoholic steatohepatitis (NASH) from obesity, amiodarone, tamoxifen, and nifedipine. • Fibrosis from centrilobular regions bridging to portal tracts and

	<p>liver of pregnancy (3rd trimester), and valproic acid and nucleoside analogue toxicity.</p>	<p>regeneration of hepatocytes into nodules results in cirrhosis in alcoholics with steatohepatitis.</p> <ul style="list-style-type: none"> • Liver surface becomes finely nodular, resulting in micronodular cirrhosis as regenerative nodules begin to develop. • Heptocellular carcinoma develops in 15% with alcoholic cirrhosis. • Risk increased with concomitant chronic hepatitis C infection. • Alcoholics also at risk of pancreatitis and rupture of esophageal varices. • Incidence of changes in chronic alcoholism: 25% normal, 30% fatty liver, 20% steatohepatitis without cirrhosis, 25% cirrhosis. 																		
<p>Drug Hepatitis</p>	<ul style="list-style-type: none"> • Acute and chronic hepatitis. Chronic occurs only with continued use. • Predictable (intrinsic) hepatoxins cause damage in a dose-related fashion. e.g. Acetaminophen and CCl₄. Usually affects acinar zone 3. • Unpredictable (idiosyncratic) hepatotoxins cause damage in a small number of patients follow even a small dose. Cannot be predicted from patient to patient. e.g. Isoniazid and α-methyl dopa hepatitis. • Acetaminophen is a predictable hepatotoxin resulting in centrilobular (zone 3) necrosis of hepatocytes due to the metabolite N-acetyl-p-benzoquinoneimine. The metabolite usually removed by intracellular glutathione, but once glutathione is depleted, it causes severe damage. Either from overdose of increased P450 in alcoholics. May be delayed symptoms, though nausea, vomiting, abdominal pain, and hepatic tenderness may develop. Symptom-free period important because gastric lavage and N-acetylcysteine may be life-saving during this period. Aminotransferases begin to rise 12-24 hrs later. Oliguric renal failure, encephalopathy, and cerebral edema follow. 	<ul style="list-style-type: none"> • Examples of selective drug hepatitis: <table border="1" data-bbox="1186 402 1990 690"> <tr> <td>zone 3 necrosis</td> <td>acetaminophen, CCl₄</td> </tr> <tr> <td>panlobular hepatitis</td> <td>isoniazid, aldomet</td> </tr> <tr> <td>chronic hepatitis</td> <td>isoniazid, nitrofurantoin</td> </tr> <tr> <td>cholestasis</td> <td>oral contraceptives</td> </tr> <tr> <td>portal fibrosis</td> <td>methotrexate</td> </tr> <tr> <td>granulomas</td> <td>allopurinol, phenylbutazone</td> </tr> <tr> <td>veno-occlusive disease</td> <td>pyrrolizidine alkaloids (bush tea)</td> </tr> <tr> <td>liver-cell adenoma</td> <td>oral contraceptives</td> </tr> <tr> <td>angiosarcoma</td> <td>thorotrast, vinyl chloride</td> </tr> </table>	zone 3 necrosis	acetaminophen, CCl ₄	panlobular hepatitis	isoniazid, aldomet	chronic hepatitis	isoniazid, nitrofurantoin	cholestasis	oral contraceptives	portal fibrosis	methotrexate	granulomas	allopurinol, phenylbutazone	veno-occlusive disease	pyrrolizidine alkaloids (bush tea)	liver-cell adenoma	oral contraceptives	angiosarcoma	thorotrast, vinyl chloride
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<p>α-1-antitrypsin (AAT) Deficiency</p>	<ul style="list-style-type: none"> • Major serum inhibitor of neutrophil elastase. • Synthesized in hepatocytes and macrophages. • Diagnosis made when evidence of liver disease in presence of PAS-positive globules on liver biopsy. Serum AAT level should be taken and patient should be phenotyped. • Most important pathologic lesion in adults is chronic hepatitis with or without cirrhosis. Rarely, hepatocellular carcinoma. • In children, AAT deficiency may be manifested by neonatal hepatic (giant cell) or destruction of intrahepatic bile ducts. 	<ul style="list-style-type: none"> • Many alleles of AAT gene. The PiMM phenotype provides a normal serum AAT level. • A mutation of AAT gene leads to conformational changes that prevents normal signalling for secretion from liver. Most common variant is the Z gene (Glu replaced by Lys). • Patients with the PiZZ phenotype have liver disease and emphysema. Liver contains periportal purple-staining PAS-positive, diastase-resistant globules from retention of the enzyme. Have less than 10% of normal levels. • In PiMZ (heterozygotic) patients, may be liver disease. About 60% of normal AAT levels. • Other gene variants include S, Mmalton, and Mduarte types. 																		
<p>Wilson's Disease (hepatolenticular degeneration)</p>	<ul style="list-style-type: none"> • Autosomal recessive disorder of Cu overload from mutant ATP7B gene on chromosome 13. Results in Cu overload. • Clinical presentation may be neurologic, psychiatric, ophthalmologic, hepatic, or hematologic (hemolysis). • Characteristic Wilson's disease triad includes (1) basal ganglia degeneration, (2) liver damage, and (3) Kayser-Fleischer ring (which is a ring of brown pigment at the corneal margin or Descemet's membrane). • Low serum level of ceruloplasmin. • Early phase, liver shows only fat and glycogen in hepatocyte nuclei. 	<ul style="list-style-type: none"> • Normal gene product is a Cu-transporting ATPases on trans network of Golgi of hepatocytes. Excrete Cu into bile canaliculi. • ATPases mutation also causes defective incorporation of Cu into ceruloplasmin (which is a Cu transporter). Ceruloplasmin gets degraded as a result and there is a low serum level of ceruloplasmin. 																		

	<p>Mitochondrial abnormalities (dilated cristae, vacuolar inclusions) by EM.</p> <ul style="list-style-type: none"> • Later, chronic hepatitis, Mallory bodies, and cirrhosis. Some get fulminant hepatitis. • Stainable copper on biopsy may be present, though variable over liver. • Increased quantitative liver copper >250 µg/g dry wt most specific diagnostic assay. • Also, can use increased serum Cu levels and increased 24 hr urinary Cu excretion as diagnostic assays. • Treatable disorder, so should be excluded in any patient <30 yo with liver disease. Penicillamine for therapy. 	
Hereditary Hemochromatosis (HHC)	<ul style="list-style-type: none"> • Autosomal recessive disorder of Fe storage from HFE gene on chromosome 6. Excess Fe deposited in parenchymal cells of many organs. • Most common genetic disorder among whites with carrier rate of 1 in 9. • Estimated disease prevalence of 1 in 300. • Classical clinical triad of (1) hepatomegaly, (2) diabetes, and (3) skin pigmentation (“bronzed diabetes”). • Cardiac failure, arthropathy, and hypogonadism other multiorgan effects. • Asymptomatic patients indentified through screening serum Fe or family screening of probands. • Currently, most common symptoms at time of diagnosis are weakness, arthralgias, impotence, and loss of libido. At presentation there is commonly hepatomegaly, skin pigmentation, and arthritis. Cirrhosis and diabetes mellitus are becoming less common are less frequent symptoms. • Imperative that diagnosis of HHC is made early—before cirrhosis—so that phlebotomy therapy can be instituted. • Therapy includes 1-2x weekly phlebotomies until serum ferritin <200 ng/ml or deferoxamine or some other chelating agent. • <u>Major diagnostic tests</u> (1) Determine serum iron indices: Serum transferrin saturation (>45% suspicious, >60% highly specific for disease) and elevated serum ferritin. (2) Serum test for HFE gene. (3) Liver biopsy: Iron staining, determination of stage of disease, and determination of hepatic [Fe] and hepatic Fe index. Also look for other pathology such as alcoholic liver disease and chronic viral hepatitis. 	<ul style="list-style-type: none"> • Normally hemosiderosis is found mostly in Kupffer cells. • Missense mutation in homozygous form of HHC (82-100%) is known as C282Y (Cys to Tyr). Also a H63D mutation. Only C282Y/C282Y homozygotes and possibly C282Y/H63D heterozygotes found in clinical HHC. • Wild type HFE gene product expressed on small intestinal epithelium and acts as the gatekeeper for Fe absorption so that only physiologic amounts of Fe enter the circulation. The C282Y product does not adequately control iron absorption by small intestinal epithelium resulting in Fe overload of liver and other organs. • <u>Pathologic changes</u> (1) Iron overload: Hepatocytes absorb increased Fe as cytosolic ferritin and lysosomal hemosiderin. Iron stainable with Prussian blue iron stain. Kupffer cells and macrophages are devoid of hemosiderin (though you would think they would have it). Hepatic [Fe] is increased; can get hepatic iron index when incorporate it with patient’s age. (2) Portal Fibrosis: Eventually Fe becomes stored in portal macrophages resulting in free radical generation, activation of stellate cells, and fibrosis. (3) Cirrhosis: Progressive bridging fibrosis between port tracks plus nodular regeneration of Fe-laden hepatocytes result in cirrhosis. There is a 250x increased risk of hepatocellular carcinoma.
Other Diseases	<ul style="list-style-type: none"> • Many inherited metabolic disorders involved the liver such as lysosomal storage disorders with abnormal storage in Kupffer cells, hepatocytes, or both. • The porphyrias are a category of diseases resulting from deficiencies of enzymes that synthesize heme. 2 specific ones are porphyria cutanea tarda and protoporphyrria that involve the liver, with abnormal porphyrin storage. 	

Biliary & Vascular Diseases, Tumors, and Transplantation

Cholestasis	<ul style="list-style-type: none"> • Cholestasis is a stagnation of bile flow within the liver. • Golden-brown bile seen on histologic sections. 	<ul style="list-style-type: none"> • Most common cause is obstruction of the large bile ducts (gallstones or choledocholithiasis).
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	<ul style="list-style-type: none"> • Grossly, liver is brown or green. • Associated with jaundice, dark urine, and pale (acholic) stools. • Diseases of bile ducts amenable to surgical intervention called surgical jaundice. • Intrahepatic bile duct or parenchymal liver disease called medical jaundice. • “Cholestatic” serum liver tests: Elevated serum conjugated bilirubin , bile acids, alkaline phosphatase, and cholesterol. These are normally excreted in bile and obstruction causes regurgitation into serum. • Bile acids can lead to pruritis. • Copper may accumulate in hepatocytes since it is normally excreted in bile. 	<ul style="list-style-type: none"> • Primary biliary cirrhosis (PBC), a disease of small intrahepatic bile ducts, may lead to cholestasis, though signs and symptoms would occur late in disease due to reserve of unaffected ducts.
<u>Diseases of the Large Bile Ducts (Large Bile Duct Obstruction)</u>	<ul style="list-style-type: none"> • Cholestasis combined with a portal lesion comprising edema, bile ductular proliferation, and PMN infiltration. • Liver cells containing bile show feathery degeneration from leaching action of retained bile salts. • Bile infarcts, extravasates, and lakes. • If unrelieved, portal fibrosis develops leading to cirrhosis over years. 	<ul style="list-style-type: none"> • Stagnant bile a good medium for bacterial growth and ascending infection, that is, cholangitis. <i>E. coli</i> most common organism. Liver abscesses may result. Acute infective cholangitis characterized by PMNs in portal tracts and bile ducts. Abscesses often found in subdiaphragmatic region.
(1) Gallstones	<ul style="list-style-type: none"> • 90% of gallstones a mixture of 3 varieties. • When in common bile duct, cause choledocholithiasis and often obstructive jaundice with elevated serum bilirubin and alkaline phosphatase. 	<ul style="list-style-type: none"> • 3 varieties: <ul style="list-style-type: none"> a. cholesterol b. Ca bilirubinate (pigment stones) c. CaCO₃
(2) Carcinoma	<ul style="list-style-type: none"> • Head of pancreas, ampulla, or bile ducts (cholangiocarcinoma). • All are adenocarcinomas that incite desmoplasia. • Cholangiocarcinomas may develop in extrahepatic and intrahepatic ducts. • In Asia, bile duct carcinomas are associated with liver fluke. 	
(3) Common bile duct stricture	<ul style="list-style-type: none"> • Uncommon outcome following cholecystectomy or surgery in the porta hepatis region. 	
(4) Primary sclerosing cholangitis (PSC)	<ul style="list-style-type: none"> • Chronic fibrosing disorder. • Affects extrahepatic and intrahepatic ducts. • Cholangiogram with strictures and dilatations (“beading and stricturing”). • Often affects young adults and is an indication for liver transplantations. 	<ul style="list-style-type: none"> • 70% associated with inflammatory bowel disease (mostly ulcerative colitis, sometimes Crohn’s disease). • 80% have positive serum pANCA (peripheral anti-neutrophil cytoplasmic Ab) with unknown cause. • Bile ducts with dense, concentric onion skin fibrosis.
(5) Enlarged porta hepatis LNs	<ul style="list-style-type: none"> • May contain lymphoma or metastatic carcinoma. 	
(6) Extrahepatic biliary atresia	<ul style="list-style-type: none"> • Neonatal disease. • Persistent jaundice beyond 2 weeks. • Surgical treatment to remove fibrotic segment of bile duct plus anastomosis of a loops of small intestine to the surgical resection margin in the hilum of the liver (hepatic portoenterostomy or Kasai procedure) must be performed by 8 weeks to prevent biliary cirrhosis. • 60% of treated patients develop complications: disease progresses to involve intrahepatic bile ducts or recurrent cholangitis or portal hypertension develop. • Liver transplants ultimately required in many children with disease. Most common reason for liver transplant in children. 	<ul style="list-style-type: none"> • Obliteration of the extrahepatic biliary tree by fibrosis and inflammation of unknown etiology. Maybe intrauterine/perinatal viral infection.

(7) Choledochal cyst	<ul style="list-style-type: none"> • Congenital weakness in wall of common bile duct with saccular dilatation leading to obstructive jaundice. 	
<u>Diseases of the Small Intrahepatic Bile Ducts</u>		
(1) Primary biliary cirrhosis (PBC)	<ul style="list-style-type: none"> • 90% women, usually 30-60 yo. • Many asymptomatic, others have pruritus. • Progresses slowly. Leads to cirrhosis and liver failure. • Many patients do not have cirrhosis at the beginning of the disease. • May take decades for late complications and cirrhosis to happen. • Associated with other immune disorders such as Sjogren's, Raynaud's, autoimmune thyroiditis, arthropathies, and celiac disease. • Frequently discovered due to elevated alkaline phosphatase on routine blood test. • Serum bilirubin remains normal due to uninvolved intrahepatic bile ducts and lack of large bile duct involvement. • Serological diagnosis based on positive serum anti-mitochondrial Abs (AMA). • Immune attack results in the florid bile duct lesion, a diagnostic liver biopsy sign. Bile duct is infiltrated by lymphocytes, plasma cells, and eosinophils. Granulomas sometimes formed. • Most common complications are pruritis, fatigue, bone pain, deformities, and fractures (2° to osteoporosis). Pruritis may be caused by bile salts. Endogenous opioids also may mediate pruritis (CNS) involvement. Cholestasis contributes to osteoporosis for unknown reasons. • No cure for PBC. • Therapy includes ursodeoxycholic acid which provides a choleric effect (improvement in flow), improves liver function tests, and may delay progression on disease towards need for liver transplantation. • Pruritis treated with (i) non-absorbable resins (e.g. cholestyramine), (ii) rifampicin (unknown mechanism), and (iii) with opiate antagonists. 	<ul style="list-style-type: none"> • Segmental destruction of intrahepatic bile ducts by lymphocytes and plasma cells, aka chronic non-suppurative destructive cholangitis (CNSDC). Results in ductopenia and cholestasis. • Anti-mitochondrial Abs directed against 2-oxo-acid dehydrogenase complex (2-OADC) found on the inner membrane of mitochondria (commonly the E2 subunit of pyruvate dehydrogenase complex). Immune attack on bile ducts by coordinated interplay of 2-OADC/MHC-II display, synthesis of anti-mitochondrial Abs, and T-cell attack response. • 4 histological stages: <ul style="list-style-type: none"> Stage 1: Florid bile duct lesion: Scattered interlobular and septal bile ducts surrounded and damaged by immune cell infiltrates. Stage 2: Bile ductular proliferation: Ducts destroyed and have been replaced by proliferating small duct-like structures within portal tracts. Stage 3: Portal tract scarring: Loss of portal tracts leads to fibrosis. Portal hypertension may be present (before cirrhosis) and early signs of cholestasis and Cu retention. Stage 4: Biliary cirrhosis: Bridging fibrosis between portal tracts with nodules of regenerative hepatocytes in thickened plates. Portal hypertension, cholestasis, and Cu. Late PBC with liver failure or portal hypertension an indication for liver transplant.
(2) Paucity of intrahepatic bile duct syndromes	<ul style="list-style-type: none"> • In neonates, may be syndromic and nonsyndromic forms of bile duct paucity. • Liver biopsy shows loss of bile ducts from portal tracts with varying degrees of cholestasis. 	<ul style="list-style-type: none"> • Syndromic paucity of bile ducts (Alagille syndrome): Unusual disorder where affected neonates or children show an entire syndrome including abnormal facies (wide-spaced eyes, small, triangular chin), pulmonic stenosis, butterfly-shaped vertebrae, and posterior embryotoxin on ophthalmologic exam. Mutations in the JAGGED protein with binds to NOTCH receptor have been found. • Nonsyndromic paucity of bile ducts: None of the anomalies of syndromic. Intrauterine CMV and α-1-antitrypsin deficiency are 2 possible causes. • Drug-induced bile duct damage: Usually in adults. Chlorpromazine and augmentin (amoxicillin-clavulanic acid) implicated. • Acute liver transplant damage: Foreign MHC-II Ags.
(3) Embryologic abnormalities of bile ducts (Fibropolycystic)	<ul style="list-style-type: none"> • Bile duct plate in embryo is the precursor to bile ducts. • If portions of plate persist, can become cystically dilated and cause problems. 	<ul style="list-style-type: none"> • Simplest disease is the solitary bile duct malformation (von Meyenburg complex). Small white nodule sometimes found incidentally during surgery on surface of liver. Irregular dilated bile duct structure within portal connective tissue.

diseases)		<ul style="list-style-type: none"> • More significant is congenital hepatic fibrosis. Many irregular portal tract bile duct malformations embedded in fibrosis. Portal-to-portal bridging fibrosis. May present as portal hypertension in childhood. • Caroli's disease a form of massive dilatation of bile duct malformations. Recurrent episodes of cholangitis due to loculation of bile in dilated biliary structures. • Polycystic liver associated with polycystic kidneys in about 1/3 of patients. Multiple cysts from bile duct malformations.
(4) Hereditary chronic hyperbilirubinemias	<ul style="list-style-type: none"> • e.g. Gilbert's disease, Crigler-Najjar syndrome, Rotor syndrome, Dubin-Johnson syndrome, progressive familial intrahepatic cholestasis (PFIC), and benign recurrent cholestasis. 	<ul style="list-style-type: none"> • Elevated serum conjugated or unconjugated bilirubin results from abnormalities in bilirubin or bile acid uptake, conjugation, and excretion by hepatocytes. • Demonstrate mutations in bile acid transport proteins of the bile canaliculus resulting in cholestasis.
Vascular Disorders	<p>(A) <u>Central Veins / Hepatic Veins / Sinusoids</u></p> <ul style="list-style-type: none"> • Right-sided heart failure: Centrilobular congestion and nutmeg liver. If chronic, may be fibrosis around central veins, called cardiac sclerosis. • Hepatic venous outflow obstruction (Budd-Chiari syndrome): Blocked venous return to heart. May be in the IVC (webs, tumors, thrombosis), hepatic veins (thrombosis like is p. vera or with oral contraceptives), or in central veins (veno-occlusive disease from bush tea). Liver becomes suddenly enlarged and tender with purple, congested surface. Ascites. • Peliosis hepatis: Pools of blood dilating the sinusoids. Liver grossly mottled purple with cyst-like collections of blood. Related to use of anabolic steroids and oral contraceptives. Seen in TB and AIDS. 	<p>(B) Arteries: Infarcts rare due to dual blood supply. Infarcts only occur after occlusion or ligation of the hepatic artery. The major disease is polyarteritis nodosa (PAN): transmural inflammation and fibrinoid necrosis. Hepatitis B infection in 1/3 of patients.</p> <p>(C) Portal Vein Occlusion: From invasion by malignant tumors (frequently hepatocellular carcinoma), thrombosis from clotting disorders, or thrombosis with infection (pylphlebitis) following an abdominal infection or perforated viscus.</p>
<u>Liver Tumors</u>	<ul style="list-style-type: none"> • Most important tumor is METASTASIS (GI tract, pancreas, lung, breast). • Most common primary benign tumor is the hemangioma. • Hepatocellular carcinoma (HCC) is the most common malignant tumor of hepatocytes. 	
(1) Hemangioma	<ul style="list-style-type: none"> • Benign. Most common benign tumor. • Well-circumscribed tumor of blood vessels filled with blood. • Usually discovered <u>incidentally at surgery or with imaging</u>. 	
(2) Liver-cell adenoma	<ul style="list-style-type: none"> • Benign. Well-circumscribed tumor of hepatocytes growing in broad sheets. • Oral contraceptive use. Can regress with cessation of contraceptives. • May cause abdominal pain and ruptures into peritoneum. 	
(3) Focal nodular hyperplasia (FNH)	<ul style="list-style-type: none"> • Benign. Probably more of a malformation than a true neoplasm. • Central stellate scar containing an arterial malformation and proliferating bile ductules. • Liver parenchyma regenerates in cirrhosis-like nodules. Surround liver normal. • Usually an incidental finding at surgery or by imaging. 	
(4) Hepatocellular carcinoma (HCC)	<ul style="list-style-type: none"> • Hepatocellular carcinoma (HCC) is the most common malignant liver tumor and one of the most common human malignancies due to prevalence in Africa and Southeast Asia. • 70% have underlying cirrhosis with HBV and HCV infections as major risk factors. Other settings are alcoholic cirrhosis and the cirrhotic 	<ul style="list-style-type: none"> • Multistep pathway to HCC involved with expression of various oncogenes plus possible exposure to aflatoxin, hepatitis virus, and inflammation and necrosis of the liver with regeneration. • Subtype called fibrolamellar carcinoma in young patients (20-50 yo)

	<p>stage of HHC.</p> <ul style="list-style-type: none"> • Note not to use “hepatoma” for HCC. • Grows as disorganized thickened cords. • Grow as unifocal masses within cirrhosis or as multiple disseminated foci. • Invades portal and hepatic veins. • May produce bile. • 3/4 have elevated serum alphafetoprotein (AFP) levels. • Prognosis really bad unless tumor is small and resectable. 	<p>who do not have cirrhosis or usual risk factors. Histologically, there are lamellae of fibrosis separating malignant hepatocytes. Prognosis is better than standard HCC since tumor amenable to surgical resection or liver transplant and the liver is not cirrhotic.</p>
(5) Hepatoblastoma	<ul style="list-style-type: none"> • Malignant tumor of childhood, associated with positive serum AFP. 	
(6) Bile duct carcinoma (Cholangiocarcinoma)	<ul style="list-style-type: none"> • Malignant. • In extra- or intrahepatic bile ducts. • In Asia, liver fluke infestation is the causative factor. In the West, cause unknown. 	
(7) Angiosarcoma	<ul style="list-style-type: none"> • Malignant. • Exposure to thorotrast (old school contrast agent), vinyl chloride, and arsinic compounds. 	<ul style="list-style-type: none"> • Derived from endothelial cells.
(8) Malignant lymphomas	<ul style="list-style-type: none"> • Malignant. Non-Hodgkin’s and Hodgkin’s lymphomas. Rarely primary in liver. 	<ul style="list-style-type: none"> • Diffuse infiltration of portal tracts or solitary masses of lymphoma.
(9) Leukemias	<ul style="list-style-type: none"> • Malignant. 	<ul style="list-style-type: none"> • Infiltrate hepatic sinusoids. Sometimes there is portal tract involvement.
Liver Transplantation	<ul style="list-style-type: none"> • Can use lobes of living donor livers in addition to cadaveric livers. • Most common reason for dysfunction following transplantation is ACUTE REJECTION. Major targets are HLA-II Ags on bile duct epithelium and on endothelium of portal veins (sometimes central veins or sinusoids). • Classical pathologic triad of acute rejection consists of a (1) cellular infiltrate of lymphocytes, eosinophils, and other immune cells; (2) bile duct damage; and (3) endotheliitis of the portal veins. • Preservation injury occurs several weeks after transplantation when there has been a prolonged “ischemic” time between harvest and transplant as well as reperfusion injury. • Intercurrent problems include bile duct anastomotic obstruction, hepatic arterial thrombosis, or opportunistic infections like CMV of graft. • Long-term, worry about recurrence (like Hep B and C) and chronic rejection. 	<ul style="list-style-type: none"> • Indications for adults: cirrhosis from Hep B or C, autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Also, chronic liver diseases or fulminant hepatitis. • Indications for children: extrahepatic biliary atresia. Also, metabolic disorders.

Systemic Consequences of Cirrhosis

Overview		
Portal hypertension		
(1) Varices		
(2) Hypersplenism		
(3) Hepatorenal syndrome		
(4) Disordered hemostasis		
(5) Gonadal failure		

and feminization of men		
(6) HCC		
(7) Bone disease		
Pathogenesis of Ascites		
(1) Local circulatory factors		
(2) Role of Kidney		
(3) Meaning of "effective plasma volume"		
(4) Differential diagnosis		
Hepatic Encephalopathy		
(1) Pathogenesis		
(2) Therapy		

Gallstone Formation

Overview	<ul style="list-style-type: none"> • Physiochemical properties of bile. • Kinetics of salt metabolism. • Mechanisms of bile formation. • Consequences of hepatic secretory failure. • Pathogenesis of cholesterol gallstone formation. 	
Secretion and Function of Bile	<ul style="list-style-type: none"> • In aqueous solution of organic and inorganic compounds. • Physiochemical properties make micellar solubilization of lipid possible in environment of both bile and intestinal fluid. • About a liter of bile is secreted daily in adults. 	
Composition of Hepatic Bile	<u>Water and solids</u> <ul style="list-style-type: none"> • Mostly water (97.5%). • Bile salts (0.9%), soluble salts (0.7%), mucin and pigments (0.5%), fatty acids, cholesterol, lecithin, neutral fat, and insoluble salts. 	<u>Electrolytes</u> <ul style="list-style-type: none"> • Na, K, Ca, Cl, and HCO₃
Bile Salt Metabolism and Kinetics	<ul style="list-style-type: none"> • Synthesized from cholesterol. Major excretory pathway for cholesterol. • Normally, 0.3-0.6 g bile salts synthesized daily and can increase 5-10x. • Normal bile salt kinetics depend on hepatic synthesis, secretion into bile, an appropriate intestinal milieu, and an intact enterohepatic circulation. • Primary bile salts directly from cholesterol: sodium cholate and sodium chenodeoxycholate. Regulated through feedback inhibition from portal venous blood during enterohepatic circulation. • Inhibition at site of 7α-hydroxylase microsomal enzyme, which is rate-limiting in synthesis of bile salt from cholesterol. • Also inhibition at HMG-CoA reductase which is the rate-limiting step in cholesterol synthesis. • Factors effecting level of bile salts in the portal blood will affect rate of both bile salt and cholesterol synthesis. • In hepatic cell, bile salts undergo conjugation via amide bond to Gly or taurine (3:1). Extremely strong bond only cleaved by bacterial cholyl amidases. Lowers the pKa of bile acids (taurine more). Therefore, remains in solution even at low pH. • Conserved by enterohepatic circulation. Reabsorbed through Na-coupled transport mechanism in the ileum and some passively (fraction of Gly conjugates are nonpolar). • >90% of bile salts reabsorbed. Actual pool of bile salts becomes a physiologic pool of 15-30 g (vs. 2-3 g in the intestines at one time). 	

	<ul style="list-style-type: none"> • In intestinal lumen, bile salts may be (1) deconjugated (cholyl amidases) and (2) dehydroxylated by anaerobes like bacteroides to produce the secondary bile salts: (1) sodium deoxycholate from cholate conjugates and (2) sodium lithocholate from chenodeoxycholate conjugates. • After 1 enterohepatic circulation, 10-20% of portal venous bile acids are no longer conjugated. Reconjugated upon uptake by liver. • Secondary bile salts undergo enterohepatic circulation. Bile is a mixture of primary and secondary bile salts. • Normal distribution of bile salts: cholate 40%, chenodeoxycholate 40%, deoxycholate 20%, and lithocholate (13%)? • Increased colonic concentration of bile salts can induce water and electrolyte secretion and watery diarrhea.
(1) Coordinate regulation of bile salt metabolism by nuclear hormone receptors	<ul style="list-style-type: none"> • Nuclear hormone receptors are transcription factors activated by ligands. • FXR activated by bile salts at physiologic concentrations. Acts as a heterodimer with RXR to upregulate expression of bile salt transporters on both the basolateral and canalicular hepatocyte membranes. Upregulates expression of ileal bile acid binding protein. • Conversely, bile salt activation of FXR represses cholesterol 7α-hydroxylase. Indirect mechanism
(2) Integration of cholesterol homeostasis and biliary metabolism	<ul style="list-style-type: none"> • LXR (with RXR) coordinates reverse cholesterol transport from peripheral tissues to the liver. Also, helps to convert cholesterol into bile acids and excrete cholesterol in the small intestine. • Activated LXR increases expression of phospholipid/cholesterol transporter ABCA1 in cholesterol-loaded cells. Leads to enhanced efflux of free cholesterol. LXR activated when accumulating sterols converted to oxysterols. • Syllabus becomes really difficult to follow at this point. pg. 66
Physicochemical Properties of the Constituents of Bile	<ul style="list-style-type: none"> • Solubility of lipid constituents determined by number of hydrophilic vs. hydrophobic groups. Further enhanced by ionization of each polar group. • All lipids in bile are amphiphiles. • Micelles form when hydrophilic properties dominate. • To form micelles, need to exceed the CMC (about 2-3 mM for bile). • Micelles allow solubilization of lipid. • Lecithin, a polar lipid, can help form mixed micelles. Mixed micelles have a larger lipid-soluble core than a pure bile salt micelle. Mixed micelles crucial in solubilization of cholesterol. Also crucial to solubilize dietary fat.
Secretion of Bile	<ul style="list-style-type: none"> • Active transport of bile salts and other organic anions at the canaliculus appears to be the major impetus for bile flow. • Biliary ductules capable of both reabsorption and secretion (secretin stimulates release of an alkaline solution thought to originate in distal bile ducts). • Secretion of cholesterol and lecithin in bile occurs at level of the hepatocyte. But at low rates of bile salt secretion, can get cholesterol gallstones.
Gallbladder Function	<ul style="list-style-type: none"> • Mucosa capable of concentrating bile salts, pigments, and lipid constituents of bile. Active transport of Na, Cl, and HCO₃ and water follows. • Bile secretion by the liver is continuous. Primarily diverted to gallbladder in fasting state. • With feeding, fatty acids and AAs stimulate release of CCK-PZ from the small intestine to relax the sphincter of Oddi and induce contraction of the gallbladder.
Disorders of Bile Secretion	<ul style="list-style-type: none"> • With reduced bile secretion or cholestasis, there are increases in plasma concentrations of bilirubin, alkaline phosphatase, or bile salts. • When acquired, damage usually results in both hepatocellular dysfunction and cholestasis. • In hepatitis and EtOH cirrhosis, all secretory processes decreased. • In chronic cholangitides, bile salt secretion especially affected. • Obstruction of the common bile duct causes failure of secretion. • Sign and symptoms depend on the duration and severity of the underlying liver disease.
Gallstone Formation	<ul style="list-style-type: none"> • Solubilization of bile depends on relative concentrations of cholesterol, lecithin, and bile salts. • In saturated zone, a 2-phase system of cholesterol crystals and saturated micellar solution coexist. The crystals may aggregate to form gallstones. • Nucleation important in determining which patients with supersaturated bile will get gallstones. Someone already with gallstones will more easily get more than someone without any. • Normal bile has promoters and inhibitors of nucleation. Balance is key. • Oral feeding of chenodeoxycholic acid (CDCA) to increase rate of bile salt secretion, enhance cholesterol solubility, and dissolve gallstones.
	<ul style="list-style-type: none"> • Most prevalent disease of the biliary system is cholelithiasis. • 75% of gallstones in U.S. are cholesterol stones (pure or mixed). • All remaining stones are pigment stones (mostly Ca and bilirubinate). • Gallstones form when [cholesterol] or [bilirubin] too great. • Only defects in bile acid or cholesterol secretion have been identified as causes of lithogenic bile formation. • During normal fasting, solubility of cholesterol in newly formed bile is decreased. Many patients with gallstone have less bile salts. • Estrogens increase cholesterol secretion into bile, 2° to upregulation of hepatic LDL receptors. May explain why more gallstones in women.

	<p>Mechanism of action may be inhibition of HMG-CoA reductase, though.</p> <ul style="list-style-type: none"> • Ursodeoxycholic acid shown to be as effective as CDCA. Decreases biliary secretion of cholesterol and unsaturates bile. Can promote solubilization of cholesterol in liquid crystals to promote dissolution. • Ursodeoxycholic acid and CDCA can only be given to patients with (1) radiolucent stones, (2) functioning gallbladder on oral cholecystogram, and (3) stones <2 cm in diameter. • Cholecystectomy remains the treatment of choice. Low rate of stone formation after this surgery due to (1) formation of less lithogenic bile due to more rapid and continuous circulation of the bile salt pool and (2) removal of nucleation-promoting factors in the gallbladder. • If not fit for surgery, try dissolution therapy with or without sound shock wave therapy. 	<ul style="list-style-type: none"> • Obese over-secrete cholesterol into bile. • During active weight-loss, cholesterol saturation in bile increases more. <p><u>Factors favoring cholesterol gallstone formation</u></p> <p>Hepatic production of lithogenic bile</p> <p>A. Decreased secretion of bile acids</p> <ol style="list-style-type: none"> 1. Fasting in normals (pooling of bile salts in gallbladder) 2. Low synthesis despite diminished bile salt pool 3. Decreased bile acid return to liver-ileal resection <p>B. Excess cholesterol secretion</p> <ol style="list-style-type: none"> 1. Obesity 2. Estrogens 3. Clofibrate 4. Pima Indian women <p>C. Combo of above factors</p> <p>Gallbladder factors</p> <p>A. Stasis, nucleation (mucous), infection</p> <p>B. Effect of removing gallbladder.</p>
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Pancreatitis

Pancreatic Physiology	<ul style="list-style-type: none"> • Exocrine secretes digestive enzymes and bicarbonate. Exocrine pancreas: acinar cells secrete digestive enzymes, ductal cells secrete fluid and electrolytes, particularly HCO₃⁻. • Endocrine for overall cell metabolism in the body. 	
(1) Acinar cell function	<ul style="list-style-type: none"> • Digestive enzymes stored in secretory granules (zymogen granules) at apical domain of the cell. • Enzymes released into centroacinar lumen under appropriate neurohumoral stimuli. • Pancreas protects itself from autodigestion by (1) synthesizing and separating inactive precursors from lysosomal granules and (2) packaging a trypsin inhibitor with trypsinogen so that the small amount of trypsin normally activated is quickly inactivated. 	<ul style="list-style-type: none"> • Proteases: Trypsinogen, chymotrypsinogen, procarboxypeptidase, and proaminopeptidase stored and released in inactive form. Enterokinase converts trypsinogen into trypsin by cleaving off the trypsinogen activation peptide (TAP). Trypsin converts other inactive proteases into active forms. • Amylase: Only pancreatic enzyme that digests carbohydrates. Secreted in active form and cleaves the inner 1-4 links of starch and glycogen. Also produced in the salivary gland. • Lipase: Major lipolytic enzyme from pancreas. Optimal saponification requires presence of bile, neutral pH, and co-lipase.
(2) Duct cell functions	<ul style="list-style-type: none"> • Electrolyte secretion arises in ductal cells. • HCO₃⁻ derived from (1) conversion of blood-borne CO₂ to HCO₃⁻ by carbonic anhydrase and (2) cell extrusion of H⁺ across basolateral membrane by an H-ATPase or a Na/H exchanger with HCO₃⁻ secretion across the apical membrane by a H/HCO₃⁻ exchanger. Cl⁻ then taken into the cell and pumped back out into the lumen via the CFTR channel (cAMP-activatable Cl⁻ channel). Na, K, and water follow into the lumen. The fluid remains isosmotic with plasma. 	
(3) Regulation of exocrine function	<p><u>Diet</u></p> <ul style="list-style-type: none"> • Short-term changes in diet do not change digestive enzyme ratios. • Long-term, there may be an change in enzyme ratios. e.g. Diet high in carbohydrates lead to relative increase in amylase secretion. In protein deficiency, protease increases and amylase decreases, in terms of proportions. • In extreme malnutrition, pancreas losses almost all secretory function. <p><u>Stimulation of pancreatic secretion</u></p> <ul style="list-style-type: none"> • Food cues, acid (H⁺), AAs, fatty acids, hyperosmolarity, and gastric distension. These act through the vagus nerve (ACh) or local release of secretin and CCK). 	

	<ul style="list-style-type: none"> • Secretin is the main stimulus for pancreatic fluid and HCO₃ secretion from duct cells. Gastric acid causes its release from the upper small bowel. Secretin binds to its receptor on duct cells which causes an increase in cAMP and stimulation of fluid secretion. ACh and CCK are synergistic (via a different pathway). In diseases that damage the small bowel mucosa (e.g. celiac disease), there may be a failure to release secretin and CCK, causing a suboptimal pancreatic response to a meal. • Cholecystokinin (CCK) is the main stimulus for pancreatic enzyme secretion and contraction of the gallbladder. Amino acids and fatty acids cause its release from the mucosa of the upper small bowel. Atropine completely blocks its pancreatic action. Activates cholinergic neurons in the pancreas. ACh via M3 receptors on acinar cells is the faster activator of enzyme secretion. • Vagus nerve is the main neural influence on the pancreas. Vagotomy and anticholinergics reduce enzyme secretory response. Release of secretin and CCK from duodenal mucosa not affected by cholinergic block. ACh acts directly on pancreatic acinar cells to stimulate enzyme secretion. <p><u>Inhibition of pancreatic secretion</u></p> <ul style="list-style-type: none"> • Pancreatic juice in duodenum suppresses pancreatic secretion. • Trypsin suppresses CCK release from the mucosa. Denatures the CCK-releasing factor that normally triggers its release. • Glucagon, somatostatin, and pancreatic polypeptide (PP) inhibit pancreatic secretion.
Acute Pancreatitis	<ul style="list-style-type: none"> • 80% due to gallstones and alcohol. 10% other and 10% idiopathic. • 10% other includes drugs, scorpion toxin, infection, trauma, hypertriglyceridemia, hypercalcemia, pancreatic cancer, and ischemia. • Sometimes in children, mostly due to trauma, idiopathic, biliary disease, drugs, and infections. Cystic fibrosis another major cause.
(1) Pathophysiology	<ul style="list-style-type: none"> • Not well understood. • Gallstones: Passage of a causes edema of the distal pancreatic duct with resultant ductal hypertension. Increased pancreatic intraductal pressure is sufficient to develop acute pancreatitis. • Earliest cellular abnormality found in acute pancreatitis is the coalescence of zymogen granules with lysosomes. Cathepsin B may be responsible for converting trypsinogen to trypsin in those organelles. • Trypsin activates phospholipase A2 and elastase. These are capable of digesting surrounding tissue. Also, lipase leads to fat necrosis. The liberated fatty acids can bind Ca and lead to hypocalcemia. • Pancreatic proteases can make it into the circulation and cause organ damage. Phospholipase A2 degrades surfactant. Trypsin activates complement, kinin, and kallikrein leading to vascular collapse.
(2) Variable course and complications	<ul style="list-style-type: none"> • Sudden onset with unpredictable course. • Obesity a risk factor for severity. <p><u>When >1 of the following findings are present, a more severe course is expected</u></p> <p><i>Early complications (1-2 weeks)</i></p> <ol style="list-style-type: none"> Pancreatic Necrosis. Greater than 50%. Shock. Due to blood loss from pancreas, increased vascular permeability, and vasodilation. Hypoxia. Capillary permeability in the lung. Can develop ARDS. Hypocalcemia. Formation of insoluble Ca-fatty acid complexes. Hyperglycemia. Release of glucagon from pancreas. Also, decreased insulin release if pancreas damaged enough. Acute Renal Failure. Usually due to ATN 2° to hypotension. Jaundice. Inflammation causing obstruction of the common bile duct. <p><i>Late complications (>2 weeks)</i></p> <ol style="list-style-type: none"> Pancreatic Pseudocysts. Pancreas has no capsule and so pancreatic fluid can be released more easily into surrounding areas, causing these things. Pancreatic Ascites. When disrupted pancreatic duct in communication with the peritoneal cavity. Pancreatic Abscess.
(3) Diagnosis	<ul style="list-style-type: none"> • Combine clinical assessment, lab tests, and imaging studies. • Classically present with epigastric pain, often radiating to the back, vomiting, and low-grade fever. In severe cases, can present in shock, respiratory failure, or psychosis, delirium, or coma. • On PE, local epigastric tenderness. Ecchymoses in the flanks (Grey Turner sign) or in the navel area (Cullen sign) with severe hemorrhagic pancreatitis. • Elevation of serum amylase in the right clinical setting is the hallmark of pancreatitis. Can also be due to other causes. Tricky. • Amylase may be missed if there is delay in going to the hospital. Serum lipase may be diagnostic in these cases.

	<ul style="list-style-type: none"> • Magnitude of amylase elevation NOT predictive of severity. TAP levels might be predictive, however. • Abdominal sonogram good for stones and duct dilatations. • Abdominal CT scan best for imaging pancreas and identify pancreatic necrosis. • ERCP performed when no etiology found or for emergent extraction of an obstructing gallstone in the distal common bile duct. 	
(4) Treatment	<ul style="list-style-type: none"> • Treatment mainly supportive. • Stop oral intake, use IV, analgesics, and intubation if needed. • Management of fluid and electrolytes important to maintain BP. 	<ul style="list-style-type: none"> • Nasogastric suctioning may provide relief to some patients. • Emergent extraction of an obstructing gallstone and prolonged peritoneal lavage in severe necrotizing pancreatitis may decrease mortality.
Chronic Pancreatitis	<ul style="list-style-type: none"> • Poorly understood. Most common causes are alcohol and malnutrition. • Other causes include hereditary, CF, and idiopathic. • Gallstone disease NEVER causes chronic pancreatitis. • <u>Alcohol</u>: 70-80% of cases. High fat and protein diet at increased risk. • Earliest change is in the small ductules where a protein-rich fluid accumulates and leads to obstruction. Later, calcified stones are found in the large pancreatic ducts. • May cause obstruction in 2 ways: (1) Increase digestive enzyme secretion and potentiate effects of CCK on enzyme secretion. Leads to unusually proteinaceous pancreatic fluid. (2) Decreased [lithostatin] (it normally prevents Ca deposition) • <u>Tropical (nutritional)</u>: Not known whether it is due to a nutrient-deficient diet, cassava (found in tropical rootstock), or both. • <u>Hereditary</u>: Familial pancreatitis, hyperlipidemia, and CF. 	
(1) Clinical features	<ul style="list-style-type: none"> • Abdominal pain, malabsorption, and diabetes. • Abdominal pain from increased intraductal pressure and neural inflammation. Occurs after eating, but sometimes constant. • Malabsorption (especially fat from decreased lipase) and diabetes do not occur until >90% of pancreas has been destroyed. • Weight loss from avoidance of food more than malabsorption. • <u>Diagnosis</u> • Diagnosis best made by history and imaging. No good labs for diagnosis. • Diffuse pancreatic calcifications in 30-40% and is diagnostic. • Sonogram or CT may show a dilated pancreatic duct, a classical finding. • ERCP and endoscopic ultrasonography when there is high suspicion for chronic pancreatitis but that imaging is negative. • <u>Complications</u> • Can be complicated by pseudocysts and pancreatic ascites. • Also, splenic vein thrombosis (presenting as upper GI hemorrhage 2° to gastric varices). Treatment in this case is splenectomy. 	<p><u>Treatment</u></p> <ul style="list-style-type: none"> • Analgesics and pancreatic enzyme replacement are mainstays of treatment. • Pain requires narcotics. Enzyme replacement also helps pain by decreasing pancreatic secretions. If these fail, try surgery. • Pancreaticojejunostomy when duct is dilated provides pain relief in 80% of cases. Partial pancreatectomy in diffuse pancreatic disease without ductal obstruction provides pain relief in 50% of cases. • Malabsorption treated with pancreatic enzyme replacement. Improves fat absorption. Use coated delivery system to prevent denaturing of enzymes in certain cases. • Small doses of insulin provide adequate control when endocrine deficiencies are present
(2) Carcinoma	<ul style="list-style-type: none"> • Incidence of adenocarcinoma rising. • Usually incurable by the time symptoms arise. • Painless jaundice when head of pancreas involved with bile duct obstruction. • Can cause diabetes (1-2 year before tumor detected), pancreatitis, and pancreatic insufficiency. • 5 year survival rate <1% but improved survival when tumor is <2cm. • Sonogram nor CT reliable in detecting tumors <2cm. • ERCP with cytology helps in diagnosis and endoscopic ultrasonography is promising in detecting small tumors. But tests usually ordered too late. • Serum markers would be useful to have. CA19-9 is associated with pancreatic cancer but is not sensitive. • K-ras oncogene (codon 12) and DPC4 (on chromosome 12) are frequently mutated. 	

Pathology of Gallbladder and Pancreas

Cholecystitis	<u>Acute</u>	<u>Chronic</u>
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	<ul style="list-style-type: none"> • 95% from obstruction of cystic duct by a stone. Sometimes from trauma, surgery, severe dehydration, or polyarteritis nodosa. • Gallbladder distended and mucosa disrupted. • Concentrated bile seeps into gallbladder way, producing irritation. • Presence of bacteria in wall and lumen. Normal fecal flora. Bacteria not normally found in large numbers in biliary tree. Existing bacteria probably come from portal vein. Lots of bacteria in 30% of gallbladders with stones, probably since the bacteria cling to the stones and are not cleared. • Grossly, gallbladder shows variable degrees of erythema. Wall is thick and boggy from edema. • Histologically, there is acute inflammation and necrosis. • 80% can be treated with bed rest, nothing by mouth, nasogastric suction, atropine or other antispasmodics, narcotics for pain, and broad-spectrum antibiotics. Usually stone dislodges and everything goes back to normal. • 20% do not respond to initial therapy and things get worse. Concern about abscess, gangrene, perforation, and bile peritonitis. Do a cholecystectomy. 	<ul style="list-style-type: none"> • Most gallbladders resected for symptomatic gallstones show chronic cholecystitis. • Grossly, gallbladder wall shows variable thickening and fibrosis. • Histologically, see Rokitansky-Aschoff sinuses, hypertrophy of the muscularis, fibrosis, and infiltrates of chronic inflammatory cells. • Most have had previous attacks of acute cholecystitis that caused previous damage to gallbladder.
Hydrops	<ul style="list-style-type: none"> • Cystic duct orifice persistently obstructed by a stone but there is no infection. • Over months, gallbladder distends and fills with watery fluid (bile resorbed through mucosa). • On PE, a large, distended gallbladder can be palpated but no pain and tenderness. 	
Mucocele	<ul style="list-style-type: none"> • Variant of hydrops. • Gallbladder filled with mucous. • When cystic duct occluded, mucoid secretions accumulate. 	<ul style="list-style-type: none"> • Mucous secretory glands usually found in the gallbladder near the cystic duct. Also near ampulla of Vater. Serve as lubrication.
Gallbladder Carcinoma	<ul style="list-style-type: none"> • Infrequent. Found in <1% of resected gallbladders. • Often elderly with long history of gallbladder disease. • <5% alive at 5 years. The cured patients have small carcinomas. • Poor prognosis. Usually, tumor cannot be resected because it has invaded nearby structures such as the liver, porta hepatis, common duct, biliary tree, lymph nodes, or omentum. Need radical surgery. • Grossly, diffuse thickening of wall which looks like that of chronic cholecystitis. Sometimes, produces polypoid mass. • Histologically, are adenocarcinomas with varying degrees of differentiation. 	<ul style="list-style-type: none"> • 90-95% from gallbladders containing stones. • Cholelithiasis and 2° inflammatory changes may be important. • Signs and symptoms mimic cholelithiasis and cholecystitis. So, gallbladder carcinoma usually incidental finding from resection for another presumed cause.
Adenomyoma	<ul style="list-style-type: none"> • Most common benign tumor of gallbladder, though probably not a tumor. • Usually asymptomatic and found incidentally on gallbladder resection for an unrelated matter. • Lesions produce firm, rubbery, well-circumscribed nodules in fundus. • Composed of multiple diverticulum-like structures surrounded by whorls of smooth muscle. 	<ul style="list-style-type: none"> • Other benign tumors found only rarely in gallbladder and biliary tree.
Cholesterosis (Strawberry Gallbladder)	<ul style="list-style-type: none"> • Frequently found in stone-containing gallbladders. Usually incidental finding. • Grossly, thin yellow streaks in mucosa. • Histologically, foamy macrophages (lipids) in lamina propria. 	<ul style="list-style-type: none"> • Controversy over whether cholesterosis alone can produce symptoms.
Choledocholithiasis	<ul style="list-style-type: none"> • Common bile duct stones found in 5-25%. 	<ul style="list-style-type: none"> • Small stones tend to make it to the cystic and common bile ducts and

	<ul style="list-style-type: none"> • No pain in 20-25%. • Frequently obstruct duct and produce obstructive jaundice. May be intermittent. But no jaundice >25% since stones not big enough. • Most common extrahepatic cause of obstructive jaundice. • Can also lead to ascending cholangitis with fever, chills, and leukocytosis. Infection usually produced by bowel flora occurs proximal to obstruction and extends to the liver causing intrahepatic duct trouble. • Ultrasonography to ID common duct stones and dilation of duct. Rarely use IV or transhepatic cholangiography. • Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice. Fiberoptic endoscope in duodenum, ampulla cannulated, and radioopaque dye injected into ducts. 	produce pain on the way, though small stones less painful than the larger ones.
Gallstone Ileus	<ul style="list-style-type: none"> • Uncommon. • One large stone that gradually erodes through the gallbladder wall. • Usually becomes attacked by adhesions, usually the duodenum. • Rarely, the stone erodes through ileal wall to produce acute peritonitis. 	<ul style="list-style-type: none"> • Cholecystoduodenal fistula from erosion. Stone propelled through fistula and through small bowel. If lucky, it is small enough to go out with feces. If it measures >2-3 cm, then it might become lodged in distal ileum and cause intestinal obstruction.
Acute Pancreatitis	<ul style="list-style-type: none"> • Serious, potentially lethal disease. Cause of death of 0.5% of autopsies. • Various degrees of swelling, edema, necrosis, fat necrosis, and hemorrhage. • Fat necrosis from lipase leaking from pancreas. Adipose tissue of omentum, mesentery, and retroperitoneum may contain 0.1-0.3 cm yellow flecks which are foci of fat necrosis. • Histologically, outline of fat cells seen, but fat has been hydrolyzed. Fatty acids combine with Ca, producing Ca soap. May be hypocalcemia. 	<ul style="list-style-type: none"> • Future lectures deals with this in detail.
Pancreatic Pseudocyst	<ul style="list-style-type: none"> • Unilocular fluid-filled cyst that forms in areas of extensive necrosis. • May complicate acute pancreatitis or trauma to pancreas. • Do not regress spontaneously. • Treated by opening into adjacent structure to drain, collapse, and go away. 	<ul style="list-style-type: none"> • Occurs in pancreas but more often in the lesser sac between the pancreas and stomach, colon, or liver.
Chronic Relapsing Pancreatitis	<ul style="list-style-type: none"> • Chronic alcoholics. • 2 forms of inherited type (5-10%): cystic fibrosis and hereditary pancreatitis. • Cystic fibrosis form manifested by pancreatic insufficiency but rarely presents with pain. • Hereditary pancreatitis characterized by recurrent acute pancreatitis. Gene not known. Predisposes towards ductal carcinoma (5%). 	<ul style="list-style-type: none"> • Long history of multiple, mild attacks of abdominal pain from bouts of overeating and heavy alcohol use. Probably have recurrent attacks of mild acute pancreatitis. • With time, develop chronic pancreatitis and pancreatolithiasis (CaCO₃ in pancreatic ducts). Stones associated with severe pain and patients become narcotic addicts. Cause of stone formation unknown, though there are theories. • In the late stage, develop malabsorption from lack of pancreatic enzymes and develop diabetes (destruction of islets).
Pancreatic Carcinoma	<ul style="list-style-type: none"> • 5th most common cause of cancer death (after lung, colon, breast, and prostate). • Majority in head of pancreas (70%). • Prognosis is poor. 2% alive at 5 years. 90% have unresectable tumor. Fewer than 5% have a resectable tumor, usually in head of pancreas. • May have persistent unexplained weight loss. • 50% with abdominal pain, often radiating to the back. • 50% of patients have obstructive jaundice which occurs when carcinoma is in head of pancreas. 	<ul style="list-style-type: none"> • Little know about its pathogenesis. • Courvoisier's Law: When the common bile duct is obstructed by a stone, the gallbladder is rarely dilated (since the gallbladder is fibrotic as a result of chronic cholecystitis). • Pancreas extremely difficult to investigate and diagnosis made only when cancer is too large and invasive to be curable. • Most common primary tumor is adenocarcinoma (>95%). Originate within pancreatic ducts. Feel hard on palpation. Elicit desmoplastic stromal

	<ul style="list-style-type: none"> • Steatorrhea when tumor obstructs pancreatic duct. • Rarely is there acute pancreatitis • Diabetes if carcinoma destroys body and tail of pancreas. • On PE, distended and palpable gallbladder in about 50%. • When cancer in body or tail, mass palpable in upper or mid-abdomen since it's usually large at time of diagnosis. • Enlarged, nodular liver may be palpable due to metastases. • Ascites from metastatic deposits in the peritoneal cavity. • Migratory thrombophlebitis (Trousseau's sign) found in 5%. • Whipple's resection for resectable tumors in head of pancreas. • Palliative options include cholecystojejunostomy or gastrojejunostomy to relieve obstructions. 	<p>reaction. Histologically, varying degrees of differentiation. Atrophy and fibrosis of adjacent pancreatic tissue. Difficult to identify borders of tumor on gross exam. Also, perineural invasion which may cause pain. Metastases in peripancreatic LNs. Tumor spreads to periduodenal, perigastric, and mesenteric nodes. Frequently metastasize liver and peritoneum.</p> <ul style="list-style-type: none"> • Islet cell tumors uncommon. • Cystadenomas (benign) uncommon.
Cystadenomas	<ul style="list-style-type: none"> • Benign and rare. Not precancerous. • Produce localized masses of multiple cystic structures lined by benign ductal epithelium. 	<ul style="list-style-type: none"> • 2 types: (1) Cysts lined by mucin-producing cells. (2) (Glycogen rich) serous cystadenoma. Lined by benign epithelial cells that contain lots of glycogen in cytoplasm.
Ectopic Pancreas	<ul style="list-style-type: none"> • Can be found in stomach, duodenum, and less commonly in small bowel. • Associated with hypertrophied muscularis propria. Nodule in gastric or small bowel that can seem like a tumor on palpation. 	<ul style="list-style-type: none"> • Islet cells usually not present. • Incidental finding in 2% of autopsies.
Pancreatic Endocrine Neoplasms	<ul style="list-style-type: none"> • Islet cell tumors. • That's it. Look in Kumar for more. 	

GI Motility and Esophageal Disease

Physiology of Alimentary Tract Motility	<ul style="list-style-type: none"> • 3 functions: (1) propulsion, (2) mixing, and (3) reservoir. • Nerves and smooth muscle except for striated muscle of mouth, pharynx, proximal esophagus, and external anal sphincter. • Enteric NS is the neuronal plexuses between the 2 smooth muscle layers (Auerbach's and Meissner's). Receives input from local neuronal complexes and the ANS. • Brain-gut peptides in both organs: vasoactive intestinal peptide (VIP), 5HT, and cholecystokinin (CCK). • Sphincter is a segment of bowel with a resting pressure greater than that of surrounding bowel. • Basic propulsive activity is called peristalsis. Major stimulus is gut distension. 	<ul style="list-style-type: none"> • Motor activity controlled by myogenic, neurogenic, and endocrine: (1) Myogenic: Primary control. Basic electrical rhythm (GER), or slow waves, is the intrinsic rhythm of smooth muscle membrane potential. Thought to be generated by a Na pump. Propagated from cell to cell through low R nexuses and move longitudinally in a caudally. Each gut segment has its own BER. Stomach slow wave frequency is 3/min. Duodenum is 11/min. Ileum is 8/min. Colon is 3-6/min. None in esophagus. Determine time, direction, and speed of alimentary tract contractions. (2) Neurogenic: CNS and ENS. CNS through ANS. Reflex arcs through celiac, superior, and inferior mesenteric ganglia. ENS equally important and can function independently of CNS. ENS neurons in ganglia and many interconnecting fibers between Auerbach's and Meissner's plexus. Complex interactions within the ENS. Substances of the ENS include: ACh, somatostatin, NE, VIP, 5HT, enkephalins, substance P, dopamine, neurotensin, and bombesin. See pg. 91 in syllabus for table.
Normal Mechanism of Swallowing	<ul style="list-style-type: none"> • Proximal third of esophagus is striated muscle. Remainder smooth muscle. • Esophagus with UES and LES. • 2 phases of swallowing, oropharyngeal and esophageal (1) Oropharyngeal: Initial phase. Regulated in medulla (swallowing center). Directs ingested food and liquid and prevents aspiration. Initiation 	<ul style="list-style-type: none"> (2) Esophageal: Downward peristaltic wave initiated. LES relaxes at onset, prior to arrival of wave. It closes after the bolus has been cleared from the esophagus. Three types of peristaltic waves: (a) Primary initiated by the act of swallowing and is a continuation of the wave from the pharynx. (b) Secondary initiated by food remaining in esophagus after the primary

	of swallowing is voluntary, then medullary swallowing center takes over. Nasopharynx closes, UES relaxes, and the airway closes. Sequential contraction of the pharyngeal constrictors push the food bolus from pharynx into the esophagus. Then inhibition of respiration terminated and UES allowed to close.	wave. The stimulus is esophageal distension. Considered to be important in prevention of reflux esophagitis since it clears refluxed gastric acid. (c) Tertiary are nonpropulsive, nonintegrated, abnormal contractions in patients with the dysmotility syndrome called esophageal spasm. Often associated with chest pain.
The Lower Esophageal Sphincter (LES)	<ul style="list-style-type: none"> • 3-5 cm segment of distal esophagus provides an anti-reflux barrier. • If there were no LES, there would be constant reflux due to the esophageal-gastric pressure differential. • Normally closed and can maintain a relative pressure of 12-30 mm Hg. 	<ul style="list-style-type: none"> • 3 considerations: (1) Factors controlling LES strength: Adapts to pressure changes in the gastric fundus (no constant strength). (2) Factors acutely altering LES strength: Increase: Gastrin, alkalization, and some cholinergics. Protein meal stimulates gastrin release. Decrease: Secretin, CCK, glucagon, acidification, and vagal stimulation. (3) Factors that control LES relaxation in response to swallowing.
Esophageal Dysmotility and Disease		
(1) Symptoms of Esophageal Dysfunction: Dysphasia, Pain, Regurgitation of Food	<p><u>Dysphagia:</u> Sensation that a bolus is not passing normally.</p> <ul style="list-style-type: none"> • Not to be confused with odynophagia. • Oropharyngeal: Unable to propel bolus out of mouth. Nasal regurgitation and pulmonary aspiration. Neurologic and striated muscle diseases like CVA, myasthenia gravis, bulbar palsy, dermatomyositis, and polymyositis. Mechanical lesions like tumors, abscesses, or cricopharyngeal achalasia. • Esophageal: Failure of bolus to reach stomach. "Gets stuck" in chest. Mechanical narrowing or a motility disorder. In general, mechanical obstruction complains of dysphagia with solids only. Motor disorder complains of both solid and liquid dysphagia. 	<p><u>Pain:</u> Odynophagia which is pain on swallowing.</p> <ul style="list-style-type: none"> • Lesion that interrupts integrity of esophageal mucosa. • Often short lived pain caused by contact of bolus with lesion. • Esophagitis most common cause. • May be an early symptom of carcinoma. • Often develop aversion to eating due to pain. • Odynophagia is not "noncardiac" chest pain. Noncardiac chest pain can mimic angina or MI and is deeper and more visceral than odynophagia. Noncardiac is longer lasting and thought to have something to do with an esophageal motility disorder. May be a result of reflux. • Acid perfusion (Bernstein test), edrophonium provocation test, and esophageal manometry helpful in distinguishing odynophagia from noncardiac chest pain.
(2) Diseases That Cause Esophageal Dysphagia	<p><u>Mechanical (obstructive) dysphagia</u></p> <p>(a) Esophageal Carcinoma: Most common cause is squamous cell carcinoma (smoking and alcohol associated). 10% are adenocarcinomas which arise from Barrett's esophagus. Surgical resection, chemotherapy, and palliative measures like radiotherapy, laser ablation, and stents. 5 year survival <10%.</p> <p>(b) Peptic Stricture: Recurrent reflux can cause ulcerative esophagitis leading to scarring and stricturing of the distal esophagus. Use endoscopic biopsy to rule out malignant strictures. Dilate benign ones.</p> <p>(c) Caustic Stricture: From ingestion of lye. Increased risk of cancer. Either dilation or surgery.</p> <p>(d) Esophageal Rings and Webs: Benign mucosal duplications that cause intermittent solid food dysphagia. Dilate to treat.</p>	<p><u>Motor dysphagia</u></p> <p>(a) Achalasia: Gradual onset and progression of dysphagia from solids to liquids and finally regurgitation. On CXR, mediastinum enlarged from esophageal dilation. Failure of LES to relax during swallowing and absence of peristalsis in esophagus. Treat with nitrates or nifedipine (works 30% of time). Definitive treatment is through pneumatic dilation of LES or surgical myotomy.</p> <p>(b) Scleroderma: If have cutaneous symptoms, usually will also have esophageal involvement. Smooth muscle atrophy and fibrosis. Failure of muscle contraction in the distal esophagus and LES incompetency. Symptoms of dysphagia and GERD.</p>
(3) Gastroesophageal Reflux Disease (GERD)	<ul style="list-style-type: none"> • Heartburn. Often from increased gastric volume from meal, obesity, etc. • Prompt relief from antacid. • Usually esophagitis in those with GERD. • Progress to erosive esophagitis and sometimes peptic stricture formation. 	<ul style="list-style-type: none"> • Normals do not notice when acid is dripped into esophagus whereas GERDs do (Bernstein test). • Secondary peristalsis, gravity, and neutralization with saliva decrease the contact time of acid with the mucosa.

	<ul style="list-style-type: none"> Histological damage is cumulative and depends on the duration of the reflux episodes (as well as the frequency to a certain extent). 											
(4) Diagnostic Procedures in the Study of the Esophagus	<p>(1) X-ray: Barium swallow important. Rate of progression, narrowing, dilatation, mucosal irregularity, abnormal peristalsis, reflux, or spasm of LES can be seen. e.g. Carcinoma is an irregular, "rat tail" stricture. Achalasia shows a symmetrical, smooth narrowing at cardia with proximal dilatation. A videosophagram on a patient with oropharyngeal dysphagia to reveal abnormalities in slow motion.</p> <p>(2) Endoscopy: Direct inspection of esophageal mucosa. Most important diagnostic tool for esophagitis, strictures, and neoplasia. Biopsies.</p> <p>(3) Manometry: Helpful in diagnosis of nonmechanical dysphagia, severe reflux, and noncardiac chest pain.</p> <p>(4) Acid perfusion test (Bernstein): Good to distinguish reflux symptoms from nonreflux.</p> <p>(5) Edrophonium test (Tensilon): Test for noncardiac chest pain. Edrophonium is a cholinesterase inhibitor. Normals have an increase in the amplitude and duration of peristaltic contractions with no chest pain. Positive test is chest pain after injection.</p> <p>(6) pH monitoring: 24-hr ambulatory pH monitoring is the best: can document number of episodes and total time pH<4</p>											
Disorders of Gastric Emptying (general) and treatment	<ul style="list-style-type: none"> 3 functions: (1) reservoir for food, (2) fractionates food into chyme, and (3) delivers chyme to the duodenum at a good rate. Gastric emptying studied using Technetium-99. After ingestion of radiolabeled food, the stomach is scanned with a gamma camera. The T_{1/2} is calculated. Regulation of gastric motility by hormones and neurotransmitters: <table border="1" data-bbox="346 617 1155 779"> <thead> <tr> <th>Contracting agents</th> <th>Relaxing agents</th> </tr> </thead> <tbody> <tr> <td>ACh</td> <td>VIP</td> </tr> <tr> <td>Gastrin</td> <td>Secretin</td> </tr> <tr> <td>CCK</td> <td>Glucagon</td> </tr> <tr> <td>Motilin</td> <td></td> </tr> </tbody> </table>	Contracting agents	Relaxing agents	ACh	VIP	Gastrin	Secretin	CCK	Glucagon	Motilin		<ul style="list-style-type: none"> Proximal stomach: As food enters, undergoes adaptive relaxation. Modulated by vagal dopaminergic neurons. Distal stomach: Breaks down food into small particles. Contractile activity controlled by pacemaker cells generating a slow wave and peristalsis. Smooth muscle cells modulated by hormones and neurotransmitters. Speed of propagation increased by stretch in the smooth muscle fibers. As contractile wave approaches pylorus, the pylorus closes. Serves to prevent large particles from entering duodenum and serves to retroperpel food so that there can be a to-and-fro motion in the stomach. Emptying of indigestible fiber: The 4-phase interdigestive migratory motor complex (IMMC) appears to clear the stomach of indigestible solid food between meals.
Contracting agents	Relaxing agents											
ACh	VIP											
Gastrin	Secretin											
CCK	Glucagon											
Motilin												
(1) Accelerated Gastric Emptying	<ul style="list-style-type: none"> After ulcer surgery, especially vagotomy and pyloroplasty. Worse after large meals. Responsible for the dumping syndrome after ulcer surgery. Includes early satiety, nausea and vomiting, sweats, syncope, diarrhea, and flushing. 	<ul style="list-style-type: none"> Rapid emptying into proximal small intestine causes distension and release of gut hormones, especially serotonin. If emptied content is hyperosmolar, further distension may occur due to influx of water from blood into lumen. 										
(2) Diabetic Gastroparesis	<ul style="list-style-type: none"> Delayed gastric emptying. Longstanding type I diabetes. Presents with nausea, vomiting, and early satiety. Improvement of diabetic control seems to decrease symptoms early on. 	<ul style="list-style-type: none"> Cause is probably autonomic neuropathy. Solid emptying delayed longer than liquid emptying. Make control of diabetes more difficult with frequent episodes of hypoglycemia. Due to decreased IMMC activity, bezoars may develop. 										
(3) Postoperative Gastric Atony	<ul style="list-style-type: none"> Delayed gastric emptying. In 5% of patients undergoing gastric surgery. 	<ul style="list-style-type: none"> Loss of vagal tone seems to be the cause. 										
(4) Gastric Dysrhythmias	<ul style="list-style-type: none"> Delayed gastric emptying. Abnormally slow firing pacemakers. 	<ul style="list-style-type: none"> Some cases where removal of the offending portion of stomach improves symptoms. 										
Acute Megacolon (pseudoobstruction type)	<ul style="list-style-type: none"> Acute toxic megacolon can develop during severe bowel inflammation from IBD or infection. Life-threatening and an indication for emergency colectomy. 	<ul style="list-style-type: none"> Ogilvie's syndrome another form of acute megacolon. Seen following orthopedic or abdominal surgery, metabolic disturbances, or in neurologic disorders. Etiology unclear, but usually responds to decompression. Surgery sometimes necessary. 										
Chronic Intestinal Pseudoobstruction (CIP)	<ul style="list-style-type: none"> Care and heterogeneous clinical syndrome. Recurrent episodes of signs and symptoms of intestinal obstruction in the absence of a lumen-obstructing lesion. Can be caused by a bunch of things. Can be congenital and run in families. e.g. Hirschsprung's disease is an intrinsic disorder of the enteric nervous system due to colonic aganglionosis. Implicated drugs include anticholinergics, phenothiazines, 	<ul style="list-style-type: none"> Myopathic variety associated with progressive systemic sclerosis and amyloidosis. Neuropathic variety a manifestation of autonomic neuropathy as in diabetes mellitus. Bacterial overgrowth common in pseudoobstruction and can result in malabsorption of bile salts and nutrients. 										

antihypertensives, narcotics, and tricyclics.

See table 5 on page 99 for drug options.

Esophageal Pathology (Non-Neoplastic and Neoplastic)

Esophagitis	<ul style="list-style-type: none"> • Common lesion. World-wide distribution, though prevalence high in Northern Iran and parts of China. • In U.S., 7% have daily symptoms. 7% of this group have pathologic change on endoscopy and biopsy. 44% of all have monthly symptoms. • Many possible causes, but most frequently a result of gastric reflux into distal esophagus. 	<ul style="list-style-type: none"> • Causes of esophagitis: <ol style="list-style-type: none"> (1) Gastric reflux (acid and pepsin) and sometimes duodenal reflux (bile and pancreatic secretions) (2) Trauma (intubation) (3) Irritants (lye, alcohol, smoking, hot fluids, tetracycline) (4) Uremia (5) Infections: viral (CMV, HSV), fungal (Candida), bacteria (rare) (6) Radiation (7) Cancer chemotherapy (8) Graft-versus-host disease (9) Systemic conditions with decreased LES tone: hypothyroidism, scleroderma, pregnancy (10) Skin diseases: pemphigus, pemphigoid, epidermolysis bullosa
(1) Reflux esophagitis	<ul style="list-style-type: none"> • Production of epophagitis depends on volume, duration, and composition of reflux. Depends on adequacy of clearing mechanisms. • Sliding hiatal hernia commonly seen with reflux esophagitis. Most people with esophagitis have these hernias, but not vice versa. 	<ul style="list-style-type: none"> • Hyperplasia of basal layer, elongation of stromal papillae, and infiltration with inflammatory cells, often with eosinophils. • Complications include ulceration, bleeding, stricture, and replacement of squamous epithelium with columnar epithelium. Leads to Barrett's.
(2) Barrett's esophagus	<ul style="list-style-type: none"> • Precancerous condition. RR is 30-40 for esophageal adenocarcinoma. • Acquired from reflux esophagitis. • Replacement of normal squamous mucosa of distal esophagus by metaplastic columnar (glandular) epithelium with goblet cells. • Intestinal type mucosa. • Occurs in 10% of patients with long-standing gastro-esophageal reflux. • Majority of cases are undetected. For every known case, there are 20 unknowns. 	<ul style="list-style-type: none"> • Dysplasia is a step between metaplasia and carcinoma and can develop in patients with Barrett's. Patients are periodically checked for dysplasia by endoscopy. Treatment is variable. Local resection and laser therapy. Esophagectomy for high grade dysplasia but has high morbidity.
(3) Infectious esophagitis	<ul style="list-style-type: none"> • CMV and HSV esophagitis cause punched-out ulcers in immune-deficient patients. • CMV produces intranuclear and intracytoplasmic inclusion bodies and infects stromal cells like endothelium. More common in AIDS patients. • HSV produces intranuclear inclusion bodies, molding and ground-glass appearance of nuclei, and multiple nuclei. Squamous cells affected. 	<ul style="list-style-type: none"> • Fungal esophagitis usually caused by <i>Candida albicans</i> though other fungi like <i>Mucor</i> and <i>Aspergillus</i> can also do their thing. • Immunosuppression and broad-spectrum antibiotic therapy predispose. • Common in AIDS patients. • Candidiasis produces an erosive esophagitis with necrosis of superficial epithelium and infiltration by fungal hyphae. • Grossly, white pseudomembrane seen.
Developmental defects	<ul style="list-style-type: none"> • Atresia (segmental absence), fistula, and stenosis. • Rarely get agenesis. 	
Acquired anomalies	<ul style="list-style-type: none"> • Secondary to inflammation and scarring. 	<ul style="list-style-type: none"> • Stenosis, webs, and rings (Schatzki's rings at or just above the squamocolumnar junction).
Diverticula	<p>(1) Outpouchings at the weak junctional area or between the pharyngeal constrictor muscle and proximal esophagus (Zenker's diverticulum, pulsion diverticula).</p>	<p>(2) Outpouchings at sites of mediastinal scarring in the distal esophagus (traction diverticula).</p>
Hiatal hernia	<ul style="list-style-type: none"> • Parts of stomach above the diaphragm. • Most are sliding (95%). 	<ul style="list-style-type: none"> • Paraesophageal hernia is rare. Noncontiguous part of stomach along the greater curvature enters thorax. Usually due to previous surgery.

Achalasia	<ul style="list-style-type: none"> • Dilatation of esophagus due to failure of LES to relax. • Complications include reflux esophagitis, <i>Candida</i> esophagitis, lower esophageal diverticula, and squamous cell carcinoma (5%). • Aspiration leads to pneumonia. 	<ul style="list-style-type: none"> • Cause of failure not evident, though may be due to decreased or absent intramural ganglion cells, destruction of the ganglion by infection with <i>Toxoplasma cruzi</i> (Chagas disease), destruction of vagal motor nuclei (polio), diabetic neuropathy, or infiltrative disorders (cancer, sarcoidosis).
Varices	<ul style="list-style-type: none"> • Dilated veins in distal esophagus in patients with portal hypertension. • Rupture produces massive hemorrhage. 	<ul style="list-style-type: none"> • Portal blood diverted through the coronary veins of stomach into the plexus of esophageal subepithelial and submucosal veins. Then from there to the azygos vein and SVC.
Mallory-Weiss Syndrome	<ul style="list-style-type: none"> • Laceration of the gastroesophageal junction due to excessive vomiting. 	
Esophageal Tumors	<ul style="list-style-type: none"> • Majority are malignant epithelial (carcinoma). • If left untreated, squamous and adenocarcinoma with invade the wall, spread into adjacent organs, and metastasize, especially to liver. • Classification of esophageal carcinomas related to extent of invasion into esophageal wall. • T1 have 90-100% survival. But only 10% diagnosed at this early stage. • T2 have 45% survival. • 0% survival is spread to adjacent organs. 	<p>T0 Carcinoma in situ T1 Lamina propria or submucosal invasion T2 Muscularis propria invasion T3 Adventitial invasion T4 Invasion into adjacent structures. (trachea, mediastinum, lung) N0, N1, M0, and M1 as usual.</p>
(1) Esophageal squamous cell carcinoma (SCC)	<ul style="list-style-type: none"> • Carcinomas from epithelium of mucosal lining. • Arises from normal squamous mucosa. Any level. • Constitute 90% of esophageal carcinomas worldwide. Unusually common in China and Iran (accounts for 20% of cancer deaths there). • Usually present with pain and difficulty swallowing. • Invasive SCC produces intraluminal polypoid masses, strictures, or ulcers that can erode. • Endoscopy and biopsy needed for diagnosis. • May be well or poorly differentiated. • If left untreated, will spread to lymph nodes, etc. and produce metastases, primarily to liver. 	<ul style="list-style-type: none"> • Risk factors include esophagitis, achalasia, alcoholism, smoking, vitamin deficiencies (A, C, riboflavin, thiamine, pyridoxine, Zn, Mo), exposure to nitrates/nitrosamines, and fungal contamination of food. • Begins with squamous dysplasia with no symptoms but can be detected on biopsy. Then carcinoma-in-situ (CIS) and invasive carcinoma. • Rare subtypes are verrucous carcinoma (unaggressive), spindle cell carcinoma (carcinosarcoma), and small cell carcinoma (highly malignant).
(2) Esophageal adenocarcinoma	<ul style="list-style-type: none"> • From Barrett's mucosa and ultimately a complication of GERD. • Most common esophageal carcinoma in U.S. Has been rapidly increasing in incidence. 21% increase in incidence among white, U.S. men. • Always arise in distal esophagus. • Gross appearance similar to SCC. Raised patches, nodular masses, ulcers, or strictures. • Histologic features similar to gastric carcinoma. Irregular glands lined by pleomorphic columnar or cuboidal cells replacing mucosa and invading deep into esophageal wall. • Dysplastic intestinal glands and Barrett's-type mucosa at tumor edge (look benign). 	<ul style="list-style-type: none"> • Rarely, carcinoma is the diffuse type, composed of poorly differentiated mucinous cells with intracytoplasmic mucin. The mucin displaces the nucleus to the periphery making signet-ring cells. • Rarely, adenocarcinomas arise from submucosal mucinous glands and resemble salivary gland carcinomas.
(3) Rare esophageal tumors	<ul style="list-style-type: none"> • Mucosa can give rise to squamous papillomas, inflammatory polyps, fibrovascular polyps, and inflammatory fibroid polyps. • Melanomas from scattered melanocytes at base of squamous epithelium. • Submucosa can give rise to various fibrous, vessel, lymphatic, and nerve tumors. 	<ul style="list-style-type: none"> • Muscle tumors from muscularis propria like leiomyomas and leiomyosarcomas. • Lymphomas from anywhere in the GI tract. Esophagus is the rarest primary site.

Peptic Ulcer Disease

Peptic Ulcer	<ul style="list-style-type: none"> • Punched-out mucosal defect penetrating deeper than muscularis. • Occurs partly as a consequence of acid and pepsin. • In the stomach, esophagus, duodenum, jejunum, and Meckel's. 	<ul style="list-style-type: none"> • Peptic ulcer disease (PUD) refers to a tendency to recurrent injury. • Gastric may be malignant. Duodenal almost never are.
Gastritis	<ul style="list-style-type: none"> • Inflammation of gastric mucosa which may be acute or chronic. 	<ul style="list-style-type: none"> • Causes include acid-peptic disease, drugs, infections, EtOH, bile, corrosives, and ischemia.
Dyspepsia	<ul style="list-style-type: none"> • Abdominal or substernal discomfort, especially after eating, "indigestion." 	
Melana	<ul style="list-style-type: none"> • Tarry-black stools. • Source of bleeding can be as low as the proximal colon, though typically a sign of upper GI bleeding. 	<ul style="list-style-type: none"> • May indicate GI bleeding but also from iron, spinach, Pepto-Bismol, other bismuth, charcoal, or licorice. • Develops when lots of hemoglobin (100 ml blood) converted by bacteria to hematin or other hemochromes.
Hematemesis	<ul style="list-style-type: none"> • Vomiting of blood. 	<ul style="list-style-type: none"> • Appears bright red, maroon, or as "coffee grounds."
Epidemiology and Risk Factors of Peptic Ulcer Disease	<ul style="list-style-type: none"> • 1-year point prevalence of 2%. • Life-time prevalence 11-14% in men and 8-11% in women. • In U.S. duodenal ulcer (DU) 5-10x more common than gastric ulcer (GU). • In Japan, GU more common than DU. • Can occur at any age. Significant incidence of DU in childhood. Incidence of GU increases with age. Not so for DU. 	<ul style="list-style-type: none"> • <i>H. pylori</i> infection believed to be the major cause of DU. • NSAIDs are frequent causes of GU but not DU. • <i>H. pylori</i> and NSAIDs account for >90% of ulcers. • Arterial hypotension such as from shock can lead to acute gastric ulceration with hemorrhage. Called a stress ulcer and is 2° to ischemia of the gastric wall. • Family history. 3x greater incidence in 1° relatives with either DU or GU. Unclear how this relates to <i>H. pylori</i>. • Smoking causes a 2x greater incidence. Ulcer healing also delayed. • Associated diseases. Increased incidence of DU in patients with gastronomas (Z-E syndrome), mastocytosis, COPD, reflux esophagitis, renal failure, and cirrhosis. • Non-factors. Diet, stressful life, personality type, EtOH, coffee, and corticosteroids do not contribute.
Natural History and Clinical Features	<ul style="list-style-type: none"> • Most heal spontaneously. In absence of treatment, most recur. • Serious complications are hemorrhage, perforation, and pyloric obstruction. • Surgery may be required if medicine fails or complications occur. • Acid secretion inhibitors and use of antibiotics reduce recurrence. • Surgery for PUD is now rare. • Present with epigastric or vague abdominal pain or discomfort. Others present with a complication without preceding symptoms. • GU can be malignant and DU almost never are malignant. Multiple biopsies in GU to exclude cancer. 	<ul style="list-style-type: none"> • Basal acid output usually 15% of maximal acid output. • Circadian rhythm to basal acid output. Peak at 10pm. Nadir at 8am. • Variations in gastric pH vs. time depend on: (1) rate of acid secretion, (2) buffering capacity of food, and (3) rate of gastric emptying. • After meal, rate of acid secretion is highest, but pH is not especially low due to buffering by food. As rate declines, pH paradoxically falls since most of the buffering food has been used up and the stomach is emptying. • Acid in duodenum rapidly neutralized by duodenal and pancreatic secretions.
Cellular Mechanism of Acid Secretion and its Regulation	<ul style="list-style-type: none"> • Acid secretion initiated by Ca and cAMP-mediated opening of K and Cl channels in apical membrane. K/H ATPase exchanger in apical membrane secretes H. Basolateral Cl/HCO₃ exchanger extrudes HCO₃. • Also involves cAMP and Ca mediated fusion of intracellular vesicle membranes with the apical membrane. 	<ul style="list-style-type: none"> • Histamine, gastrin, and acetylcholine are the principle activators of HCl secretion. Histamine and gastrin work synergistically. A block of one will effectively block the other. • Histamine from small endocrine-type epithelial cells (ECL cells) throughout fundus of the stomach. Released in response to gastrin and ACh. On parietal cell, H₂ receptor coupled via a G protein to adenylate cyclase. • Gastrin from G cells of the antral epithelium. Released in response to oropharyngeal (feeding), central neural (hypoglycemia), and luminal (antral distention and aromatic amino acids) stimuli. Local neural activation mediated by gastrin-releasing peptide (GRP). Release inhibited by luminal

		<p>acid and somatostatin. Gastrin receptors on both ECL and parietal cells. Activation increases cell Ca. Also a growth factor for ECL cells and parietal cells. When serum gastrin levels remain elevated (form a K/H pump inhibitor or a gastrinoma), proliferation of both parietal and ECL cells develops and acid secreting capacity increases.</p> <ul style="list-style-type: none"> • Acetylcholine released from nerve endings. Muscarinic receptors on G cells, D cells, ECL cells, and parietal cells. Binding stimulates G, ECL, and parietal cells and inhibits D cells. H2 receptor antagonists block almost all cholinergic stimulation of acid secretion. Like gastrin, ACh increases parietal cell [Ca] • Somatostatin inhibits acid secretion. Released in the antrum and fundus by D cells and from nerve fibers. Release from antrum suppresses gastrin release. Release stimulated by luminal acid, gastrin, CCK, secretin, and VIP. Inhibited by ACh. Receptors on G cells, ECL cells, and parietal cells.
The Gastric Mucosal Barrier	<ul style="list-style-type: none"> • Prevention of back secretion of 0.1M HCl. (a) Intrinsic Epithelial Resistance to Ion Diffusion. Gastric epithelium relatively tight. (b) Mucosal Blood Flow. Buffers and carries away back-diffusing H. As long as H is being secreted, there should be enough HCO₃ to buffer. When acid-secretion ceases, HCl slowly back-diffuses and removal requires lots of capillary circulation. Mucosal ischemia with arterial hypotension to stress erosions in the ICU. (c) Cell Proliferation. Gastric and duodenal epithelium turns over every 4-6 days. Reduction in turnover rate (chemotherapy and uremia) predispose to ulcers or failure healing. (d) Gastric Mucus. Gastric surface cells and cells in upper region of gastric glands secrete a high-viscosity, glycoprotein mucous gel covering the entire epithelium. These cells also secrete HCO₃, creating a pH gradient across the gel from a surface pH>7 to a luminal mucous pH2. Acid pooled in gastric lumen sits on top of the gel, but acid secreted by parietal cells in crypts penetrates through discrete channels. Prevents back-diffusion. (e) HCO₃ Secretion. Cells in stomach and duodenum secrete to protect mucosa from acid injury. (f) Prostaglandins. Defends in 3 ways: (1) stimulation of HCO₃ secretion, (2) stimulation of mucus secretion, and (3) inhibition of acid secretion. NSAIDs inhibit protaglandin synthesis and are ulcerogenic. 25% of chronic NSAID-takers develop ulcers. 30% of upper GI bleeding due to NSAIDs. COX-2 inhibitors better (inhibit inducible but not constitutive COX). 	
Role of <i>Helicobacter pylori</i> in Peptic Ulcer Disease, Chronic Gastritis, and Gastric Cancer	<p><u>PUD</u></p> <ul style="list-style-type: none"> • Considered an infectious disease. <i>H. pylori</i> is the responsible agent. • Koch's postulates fulfilled. • Work done by a medical student and a pathologist. 	
(1) Bacteriology	<ul style="list-style-type: none"> • <i>H. pylori</i> is a spiral-shaped, motile gram-negative rod. • Found in between the gastric epithelial cell surace and the overlying mucous gel. • Found only where gastric epithelium found. In the stomach and at sites of gastric metaplasia such as the esophagus, duodenum, and Meckel's. 	<ul style="list-style-type: none"> • Survives in stomach acid due to urease activity which generates ammonia from urea and maintains a pH-neutral microenvironment. • Slightly greater prevalence in blood group O individuals due to adherence to a particular Ag of the O antigen complex. • Some <i>H. pylori</i> proteins adhere to sialic acid residues on glycoproteins on the gastric epithelial surface.
(2) Epidemiology	<ul style="list-style-type: none"> • Prevalent. Lives in symbiosis with host. • >1/3 of world infected. 	<ul style="list-style-type: none"> • In U.S. incidence increases with age: 10% <30 and 80% >80 have it. • Incidence may be decreasing in U.S.
(3) Pathogenesis	<ul style="list-style-type: none"> • Initial infection associated with intense and transiently bacterial proliferation and gastric inflammation. Immune response generated. Inflammation leads to hypochlorhydria for up to several months. Gradually, inflammation reduced to a stable state (chronic diffuse superficial gastritis), normal gastric pH restored, and disappearance of symptoms; however, 	<ul style="list-style-type: none"> • Almost all with DU and 80% with GU are infected with <i>H. pylori</i>. • Antibiotic treatment leads to rapid resolution of the gastritis. • <i>H. pylori</i> has several properties that facilitate persistence in the host: (1) microaerophilic metabolism for survival under gel, (2) spiral shape, motility, and ability to adhere to gastric epithelia and resist peristalsis, (3)

	humoral immune response insufficient to eliminate the organism. This state, asymptomatic, can last for decades or even a lifetime. Only a subset develop peptic ulceration and a much smaller number get lymphoma. Some get a gradual progression of inflammation until gastric glands disappear and atrophic gastritis ensues. Atrophic gastritis (with intestinal metaplasia) represents a premalignant lesion. Patients with gastric cancer have a high proportion of <i>H. pylori</i> infection vs. control.	urease ability, and (4) SOD and catalase to protect them from phagocytes. <ul style="list-style-type: none"> • Mechanisms to inflammation not understood. It is noninvasive. Maybe urease has something to do with it. Some uremic patients develop gastritis. • Has a marked genetic diversity. Three properties identified: (1) <i>cagA</i> in infected ulcer patients, (2) <i>vacA</i> that causes vacuolation of eukaryotic cells, and (3) some unknown thing that activates PMNs without opsonins. • <i>H. pylori</i> not typically found in duodenum, but associated with DU probably because of some gastric metaplasia in duodenum. Also, may be because of increased postprandial gastrin release leading to increased acid production. <i>H. pylori</i> might injure somatostatin-secreting D cells, too.
(4) Pathology	<ul style="list-style-type: none"> • Organism and inflammation found mainly in the antrum except when drugs are used to suppress acidity. In drugged patients, the organism and inflammation extend into the gastric fundus. 	
(5) Diagnosis	<ul style="list-style-type: none"> • Breath test is noninvasive and highly sensitive and specific. • Also, biopsy, urease (aspirate), serology, and culture. 	
NSAID-Induced Peptic Ulceration	<ul style="list-style-type: none"> • Most are in the stomach. Unclear whether NSAIDs increase the incidence of DU. 	
Gastrinoma and Zollinger-Ellison Syndrome	<ul style="list-style-type: none"> • Arise from pancreatic ductular epithelium (NOT islet cells). • Rare tumor/syndrome. Slow-growing. • Recurrent and often multiple duodenal ulcers. • Diarrhea in >1/2 of patients from sheer volume of concentrated gastric acid and malabsorption due to pancreatic enzymes inactivation by low pH. • Some patients have only a modest increase in gastrin. Use secretin infusion test for diagnosis (as opposed to gastrin test). • Acid suppression in ZE possible with high dose K/H pump inhibitor. • Tumor resection only chance for cure. 	<ul style="list-style-type: none"> • Functions of gastrin in Z-E syndrome symptoms: (a) stimulation of existing parietal cells to secrete acid and (b) proliferation of parietal cells (trophic effect on gastric epithelium). • All symptoms due to gastric hypersecretion from increase in serum gastrin level. • Hypochlorhydria (as in anti-acid therapy) also elevates serum gastrin but not as much as in Z-E syndrome. • In Z-E patients, secretin increases gastrin a lot. In G cell hyperfunction, secretin does not increase gastrin.

Gastric Pathology

Gastritis	<ul style="list-style-type: none"> • Very common. • 1/3 of asymptomatic U.S. adults have chronic gastritis on biopsy. • 3 problems of gastritis: (1) Poor correlation between clinical and pathologic diagnosis, (2) pathogenesis of many forms poorly understood, and (3) no universally accepted system of classification. • Descriptively, can distinguish: <ol style="list-style-type: none"> (1) Acute gastritis (PMNs) (2) Hemorrhagic gastritis (fresh blood) – EtOH, stress, aspirin (3) Erosive gastritis (destruction of parts of the mucosa) (4) Granulomatous gastritis (granulomas) – Crohn’s disease, sarcoid (5) Eosinophilic gastritis (eosinophils) (6) Chronic gastritis (most common form) – lots of etiologies 	<ul style="list-style-type: none"> • Most cases caused by <i>H. pylori</i>. Other factors include: <ol style="list-style-type: none"> (1) Heavy use of NSAIDs, especially aspirin. (2) Excessive alcohol (3) Heavy smoking (4) Cancer chemotherapy (5) Uremia (6) Systemic infections (Salmonella, CMV) (7) Severe stress (8) Ischemia and shock (9) Suicide attempts with acids or alkali (10) Irradiation (11) Mechanical trauma (12) Distal gastrectomy
Types of Chronic Gastritis	<ul style="list-style-type: none"> • Type A and B both lead to chronic atrophic gastritis. 	
(1) Autoimmune gastritis (type A)	<ul style="list-style-type: none"> • Uncommon. Often seen with other autoimmune disorders. • Diffuse. Corpus of stomach. 	<ul style="list-style-type: none"> • Ab against acid-producing parietal cells and IF (absorption of B₁₂). • Leads to pernicious anemia.

	<ul style="list-style-type: none"> • Histologically, mucosa infiltrated by PMNs and plasma cells. Fundic glands gradually replaced by intestinal-type epithelium. • Intestinal metaplasia an intermediate step in some gastric carcinomas. 	<ul style="list-style-type: none"> • Leads to mucosal atrophy (chronic atrophic gastritis) and loss of acid production (hypochlorhydria).
(2) Chronic antral gastritis (type B)	<ul style="list-style-type: none"> • More common than type A. • Most cases due to <i>H. pylori</i> and affects corpus and antrum but is worse in antrum. • In West, most common complication is duodenal ulcer. • In the developing world, gastric carcinoma is most common complication. • Histologically, <i>H. pylori</i>-associated gastritis produces a chronic active gastritis with an infiltrate of lymphocytes, plasma cells, and PMNs. • <i>H. pylori</i> can be seen on H&E and other staining. Absent over intestinal metaplasia since can only survive on neutral gastric mucus. 	<ul style="list-style-type: none"> • Initially, superficial gastritis, then inflammation of full thickness of antral mucosa, gland destruction, atrophy, and intestinal metaplasia. Then chronic atrophic gastritis. • <i>H. pylori</i> gastritis linked to gastric carcinoma and lymphoma. Lymphoid follicles develop (not normal). • <i>H. pylori</i> is an S-shaped, gram-negative, urease-producing rod found in 50% of asymptomatic U.S. adults >50 yo. Ingestion of large doses causes acute symptomatic gastritis which usually goes away. Unclear why chronic gastritis develops in some.
(3) Chemical gastritis (type C)	<ul style="list-style-type: none"> • Repeated chemical or toxic injury to gastric mucosa (reflux of bile acids and other duodenal secretions). • Histologically, foveolar hyperplasia, edema, and mild chronic inflammation. • Mainly found in patients post gastrectomy and post cholecystectomy. 	<ul style="list-style-type: none"> • Similar histological changes seen in patients ingesting lots of NSAIDs.
Hypertrophic Gastropathy	<ul style="list-style-type: none"> • Rugal enlargement not caused by inflammation but by hyperplasia. 	<ul style="list-style-type: none"> • 3 variants (although only 2 in notes): (a) Menetrier's disease is most common and characterized by hyperplasia of foveolar and surface mucous cells. Can lead to protein loss and peripheral edema (protein-losing gastroenteropathy). (b) Zollinger-Ellison syndrome is characterized by hyperplasia of parietal cells resulting in hyperacidity and peptic ulceration. Associated with gastrinoma.
Gastric Varices	<ul style="list-style-type: none"> • Develop in proximal stomach in patients with portal hypertension. 	<ul style="list-style-type: none"> • Esophageal varices usually present.
Gastric Ulcers	<ul style="list-style-type: none"> • Less common than duodenal ulcers and most often located in the antrum. • Can occur anywhere in the stomach. • Causes include: <i>H. pylori</i> infection, NSAIDs, Motility disturbances, and interference with blood supply. With compromised circulation as in shock, acid back-diffusion can quickly lead to ulceration. 	<ul style="list-style-type: none"> • Ulcer means tissue destruction with penetration beyond the mucosa. • In contrast, gastric erosions implies loss of epithelium but not penetration to deeper levels of stomach wall.
Gastric Tumors	<ul style="list-style-type: none"> • Majority arise from mucosa. A minority from gastric wall. 	
(1) Gastric Polyps	<ul style="list-style-type: none"> • Benign mucosal tumors. • >90% are non-neoplastic. Background of chronic gastritis. 	<ul style="list-style-type: none"> • Hyperplastic polyps composed of dilated and cystic gastric pits lined by bland mucous cells. Antral or fundal glands at the base. Smooth muscle between the glands. Stroma usually edematous and inflamed. Rarer in stomach than in colon. • Foveolar hyperplasia are polyps solely composed of elongated pits. • Fundic gland polyps arise only in the fundus or body and have no edematous stroma. The glands are hyperplastic and some are cystic. Usually multiple and seen in patients taking omeprazole. Occurs in FAP, but most seen clinically not related to FAP. • Adenomatous polyps, also called adenomas, are 5-10% of gastric polyps. Precursors to gastric carcinomas. Usually single, in older patients with gastritis and intestinal metaplasia and may be associated with polyposis syndromes. Rarer in stomach than in colon. About 40% contain foci of carcinoma and 1/3 associated with carcinoma elsewhere in stomach.
(2) Gastric Carcinoma	<ul style="list-style-type: none"> • Most common malignant neoplasm of stomach (90% of total). • Incidence has been decreasing and is now 6th most common cause of 	<ul style="list-style-type: none"> • Factors responsible for decrease in disease: (1) better refrigeration and decreased use of smoked foods, (2) decreased use of nitrite preservatives

	<p>cancer death. Especially high incidence in Japan and Costa Rica.</p> <ul style="list-style-type: none"> • Decrease in incidence of gastric carcinoma due to decrease of distal gastric carcinoma. Cardiac carcinoma has increased in incidence. • In Japan, a high incidence of atrophic gastritis and gastric carcinoma. • Chronic atrophic gastritis (intestinal metaplasia) found in over 90% of carcinoma-stricken stomachs. • 50-60% arise in distal stomach, especially in lesser curvature (“Magenstrasse”), 25% in cardia, and the rest in body and fundus. 	<p>(converted to nitrosamines and nitrosamides in stomach), and (3) increased intake of Vitamin C which counteracts nitrosamines and nitrosamides.</p> <ul style="list-style-type: none"> • Most gastric cancers arise in areas of intestinal metaplasia. • Chronic atrophic gastritis with intestinal metaplasia frequently in presence of <i>H. pylori</i>. • Pernicious anemia patients have extensive intestinal metaplasia in stomachs and a greater incidence of carcinoma. Intestinal metaplasia most common in antrum along lesser curvature, where carcinoma is found. 	
(3) Classification of gastric carcinomas	<p><u>By Growth Pattern</u></p> <p>(1) Ulcerating, penetrating type. Most common. Deeply excavating mass with heaped up edges.</p> <p>(2) Fungating usually a well-differentiated adenocarcinoma. Polypoid mass.</p> <p>(3) Superficial spreading only in mucosa and superficial submucosa. Superficially ulcerated lesion. Mimics a benign ulcer. Best prognosis.</p> <p>(4) Linitis plastica poorly differentiated carcinoma. Diffusely infiltrates wall with desmoplastic reaction. Leads to the “leather bottle stomach.” The worst prognosis.</p>	<p><u>By Depth of Invasion</u></p> <p>(1) Early gastric carcinoma confined to mucosa and submucosa. 35% of all gastric cancer in Japan. 10% in U.S. 90% 5-year survival.</p> <p>(2) Advanced gastric carcinoma invades into muscularis or beyond. Less than 10% 5-year survival.</p>	<p><u>Histologically</u></p> <p>(1) Intestinal type have glands resembling colonic adenocarcinoma. Growth expanding and produces ulcerating and fungating masses. Metastases to lymph nodes and liver.</p> <p>(2) Diffuse type have no glands or poorly-formed glands of signet ring cells. Growth pattern is infiltrating. Linitis plastica most common presentation. Metastases to lymph nodes and peritoneum.</p> <p>(3) Mixed types.</p> <p>(4) Rare carcinomas: Undifferentiated, small-cell, mixed endocrine-exocrine.</p>
(4) Gastric Carcinoids	<ul style="list-style-type: none"> • ECL carcinoids are small and multiple with hypergastrinemia. • ECL carcinoids single and sporadic without increased gastrin. • Non-functioning and slow growing. • Grossly, carcinoids present as nodules or polyps. • Histologically, composed of monomorphous epithelial cells without mitotic activity or necrosis. Arranged in well-defined nests, ribbons, or trabeculae. 	<ul style="list-style-type: none"> • Derived from enterochromaffin-like (ECL) cells in mucosa of fundus and body or from gastrin-producing (G) cells of the antrum. • Gastrin has a trophic effect on ECL cells. ECL carcinoids found with hypergastrinemia (type A gastritis, Z-E syndrome, multiple endocrine neoplasia type I). 	
(5) Gastric Lymphomas	<ul style="list-style-type: none"> • Malignant. Mostly B-cell type. • 10% of all gastric malignancies. • Most are low-grade and associated with <i>H. pylori</i> (62-77%). MALT may regress after eradication of <i>H. pylori</i> with antibiotics. • High grade ones do not respond to antibiotics. 	<ul style="list-style-type: none"> • Lymphomas associated with immunosuppression (acquired, HIV, or congenital) often present first in the stomach and are of large cell or Burkitt-like type. 	
(6) Gastrointestinal Stromal Tumors (GISTs)	<ul style="list-style-type: none"> • Arise in wall of stomach or intestine. • Grossly, intramural nodular masses that either project into lumen, ulcerate, and bleed or project into peritoneal cavity and compress adjacent structures. • Histologically, composed of spindle cells (resembling smooth muscle cells) or oval or round cells (resembling epithelial cells, hence, “epithelioid”). • Malignant GISTs metastasize via blood to liver. 	<ul style="list-style-type: none"> • Derived from cells of Cajal, the pacemaker cells, at the junction of internal and external muscle layers. • Cells contain KIT (CD117) Ag and respond to Gleevec. • Most express CD34 in addition to c-KIT and sometimes smooth muscle markers. • May be benign, uncertain malignant, or malignant. Distinction based on tumor size and histologic features like pleomorphism, cellularity, mitotic count, necrosis, and mucosal invasion. 	

Diarrheal Diseases

Permeabilities and Ion Transport	<ul style="list-style-type: none"> • Normal colon can absorb up to 5 liters per day. Small intestine can absorb even more. • Small intestines and colon can actively secrete and absorb. Secretion from crypts, absorption from villi and surface cells.
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Mechanism	<ul style="list-style-type: none"> • Small intestine low resistance tight junctions. Colonic junctions even tighter, resistance increasing from proximal to distal. • Water flow passive. Passive permeability of cations greater than anions. • Active transport of cations. • Na pumped out across the basolateral membrane by Na/K ATPase. At the apical membrane: In distal colon, diffuses through aldosterone-regulated channels; in proximal to distal colon, transported via Na/H exchanger; and in small intestine, transported through Na/glucose and Na/AA cotransporters. • In ileum and colon, Cl/HCO₃ exchanger brings Cl in against its gradient and pumps HCO₃ out due to Na/H exchange. Also, HCO₃ secreted due to a reverse gradient for Cl (low [Cl]_{intra} and high [Cl]_{extra}). • Cl actively secreted by crypt cells throughout. Involves (1) electrically neutral Na-K-2Cl cotransporter in the basolateral membrane, (2) Na pump, and (3) an anion channel like CFTR. CFTR activated by cAMP or cGMP. 5% of infants with CF develop meconium ileus (an intestinal obstruction) due to abnormal intestinal secretion. • HCO₃ absorbed in jejunum (Na/H exchange) and secreted in duodenum, ileum, and colon. Complex mechanism. • K transport in small intestine is passive. In colon, passive, active secretion, and active absorption. 	
Electrolyte Composition of Stool	<ul style="list-style-type: none"> • In small intestine, usually similar to plasma. • In ileum, HCO₃ may be high. • In colon, usually differences between it and plasma. Increases K excretion and absorbs Na. Replaces Cl and HCO₃ with organic anions. In cholera, however, this doesn't happen, and excreted stool looks a lot like plasma electrolyte composition. 	
Intracellular Mediators of Secretion	<ul style="list-style-type: none"> • cAMP and cGMP contribute to fluid secretion. Activate CFTR (Cl secretion) and inhibit Na/H and Cl/HCO₃ exchangers. • Elevation in intracellular Ca also stimulates secretion. Activates PKC and K channels to increase electrical driving force for Cl extrusion. 	
Extracellular Regulators of Intestinal Ion Transport	<ul style="list-style-type: none"> • Enteric NS with sympathetic and parasympathetic inputs. • Parasympathetics release substance P, vasoactive intestinal polypeptide (VIP), and acetylcholine. All stimulate Cl secretion and inhibit NaCl absorption. • Sympathetics release norepinephrine, neuropeptide Y, and somatostatin. All inhibit secretion and promote fluid and electrolyte absorption. Attach to receptors (1) on enterocytes (NE, α2-adrenergic receptors) and (2) on cholinergic neurons (inhibitory receptors). • Neurotensin, 5HT, and somatostatin release by APUD cells (amine-precursor uptake and decarboxylation). Neurotensin and 5HT stimulate secretion. Somatostatin has opposite effect. • Other specialized cells release guanylin which activates the brush border enzyme guanylate cyclase. Increase in cGMP stimulates secretion. • Prostaglandins, leukotrienes, platelet-activating factor, histamine, and oxygen free radicals from mesenchymal cells in lamina propria. Secretory. • Aldosterone enhances Na absorption in the colon. • Glucocorticoids enhance salt absorption in colon and small intestine. Inhibit phospholipase A2 to inhibit prostaglandins and leukotriene production. 	
Pathophysiology	<ul style="list-style-type: none"> • "Diarrhea" is (1) an increase in stool mass, (2) stool liquidity, and (3) an increase in stool frequency. • Diseases with a decrease in nutrients or fluids might not cause diarrhea. • Diarrhea may occur without a change in absorption. It may be secretory. 	<u>4 principle mechanisms of diarrhea:</u> (1) Osmotic (2) Secretory (3) Exudative (4) Altered motility
(1) Osmotic Diarrhea	<ul style="list-style-type: none"> • Follows ingestion of large amounts of poorly absorbable, low MW aqueous solutes. Osmotic force pulls water and ions into lumen. • Can develop in normal intestine e.g. with lactulose, a disaccharide of fructose and galactose, sorbitol, and Mg (in antacids, laxatives, etc.). • Also seen in intestinal disorders such as lactase deficiency and gluten-sensitive enteropathy (celiac disease). • Maldigestion causes a colonic osmotic diarrhea. 	<u>Tests</u> <ul style="list-style-type: none"> • Give nothing by mouth for 24-48 hrs. If diarrhea resolves, osmotic. If it doesn't resolve, probably secretory. • Stool Na and K to determine osmotic gap. Abnormally high implies osmotic diarrhea because there are unabsorbed ionic oligosaccharides, oligopeptides, or Mg. Absence of gap does not exclude osmotic diarrhea e.g. moderate carbohydrate malabsorption leading to ionic short chain organic acids in colon with no Na or K depression. • Stool pH. pH<5.5 suggests carbohydrate malabsorption, familial chloridorrhea, or gastrinoma.
(2) Secretory	Characterized by:	<ul style="list-style-type: none"> • Stimulate secretion and cause diarrhea: bacterial enterotoxins, bile acids,

Diarrhea	(1) Large stool volumes: several-24 L/day (2) No RBC's or WBC's in stool (3) Absence of fever or systemic symptoms (except from dehydration) (4) Persistence of diarrhea with fasting (though volume may diminish) (5) No stool osmotic gap	hydroxylated fatty acids (e.g. castor oil), tumor hormones, and inflammatory mediators. • Maximal secretory stimulation: >1L/hr in rehydrate adult. • Vascular collapse will occur without fluid replacement. • Excessive K and HCO ₃ loss in stool.
A. Bacterial Enterotoxins	• Also Yersinia, Shigella, Salmonella, pseudomonas	
a. Cholera toxin	<ul style="list-style-type: none"> • No histologic abnormality seen. Does not invade epithelium. • Cholera organism releases it. • Protein with a dimeric A subunit linked by S-S and 5 identical B subunits. • The B subunits bind to GM₁ on intestinal brush border membrane. Complex is endocytosed. Upon acidification of the vesicle, the A₁ subunit repositions on the vesicle surface and targets the α subunit of G_s. Freezes α-G_s in activated state leading to lots of activated adenylate cyclase. Persistent elevation of [cAMP] causes persistent secretion. • B subunits bind tightly and irreversibly. Eradication of organism does not immediately stop the diarrhea. 	
b. <i>E. coli</i> enterotoxins (LT and ST)	<ul style="list-style-type: none"> • Traveler's diarrhea. • Heat-labile toxin (LT) related to cholera toxin. Binds to GM₁. Same mechanism of action as cholera toxin. • Heat-stable toxin (ST_a) is a cysteine-rich low MW peptide. Brush border receptor for ST_a is a guanylate cyclase. Resulting increase in cGMP activates the enterocyte brush border anion channel via a cGMP-dependent protein kinase (e.g. phosphorylation of Cl channel). Resulting changes similar but not as extreme as those caused by cAMP agonists. • Guanylin is a naturally occurring ligand for the ST_a receptor. From goblet cells and used to moisten mucoid secretions. 	
B. Tumor Hormones		
a. VIP-secreting neoplasms	<ul style="list-style-type: none"> • Pancreatic islet neoplasms ("pancreatic cholera," ganglioneuromas, and pheochromocytomas. • VIP binds to enterocyte receptors coupled to G_s, activating adenylyl cyclase. 	
b. Carcinoid syndrome	<ul style="list-style-type: none"> • Cutaneous flushing and profuse diarrhea when metastasize to liver (bypass hepatic detoxification). • Very rarely, brochogenic carcinoids. • Can secrete 5HT, bradykinin, substance P, and prostaglandins. 	
c. Medullary carcinoma of the thyroid	<ul style="list-style-type: none"> • Secretes calcitonin (secretory). • Diarrhea in 30% with this tumor. 	
d. Gastrinoma	<ul style="list-style-type: none"> • Elevates gastric acid production causing both diarrhea and peptic ulceration (Z-E syndrome). • Diarrhea is partially malabsorptive. • Increase in acid production leads to large volume load for reabsorption and inactivates pancreatic digestive enzymes. Precipitates bile acids. 	
C. Bile acids and Fatty Acids	<ul style="list-style-type: none"> • Most do not reach the colon. • If they reach the colon, tend to stimulate fluid secretion. Bile acids deconjugated in colon. Gets inserted into brush border membrane. Activates membrane phospholipases and leads to secretion. Fatty acids undergo bacterial hydroxylation, membrane insertion, phospholipase activation, etc. • Diarrhea from celiac disease or with damaged ileum sometimes due to malabsorbed bile acids or fatty acids. • Can feed cholestyramine to bind bile acids and reduce diarrhea, though can result in worsening of diarrhea in cases of severely reduced bile acid pool. 	
D. Inflammation	<ul style="list-style-type: none"> • Inflammatory cells in lamina propria release prostaglandins, leukotrienes, PAF, and oxygen free radicals that stimulate secretion. • With acute inflammation, secretory diarrhea occurs. • With chronic inflammation, there is downregulation and secretion is not so bad. But absorption is affected and this causes diarrhea. 	
(3) Exudative Diarrhea	<ul style="list-style-type: none"> • When there's necrosis, can get exudation of mucus, protein, blood, and pus into the lumen. • Occurs in ulcerative colitis and invasive enteric infections like shigellosis. • Ulcerative colitis: protein loss leads to hypoalbuminemia. • Intestinal lymphectasia: Lymphatic obstruction increases interstitial hydrostatic pressure. Disrupts junctions and increases permeability. Lose lots of protein-rich fluid and cause diarrhea. Low fat diet may help. 	
(4) Altered Motility	<ul style="list-style-type: none"> • Increases or decreases of motility may cause diarrhea. 	

	<ul style="list-style-type: none"> • e.g. In thyrotoxicosis, motility increases with increase in stool frequency. In severe cases, diarrhea and steatorrhea ensue. • Bacterial overgrowth from ineffectual motility from large diverticula, smooth muscle damage, or autonomic neuropathy. Causes diarrhea and sometimes steatorrhea.
Congenital Diarrhea	<ul style="list-style-type: none"> • Abnormal fluid absorption begins in utero as polyhydramnios. <p><u>Congenital chloride diarrhea</u></p> <ul style="list-style-type: none"> • Defect in brush border Cl/HCO₃ exchange in ileum and colon. • Absorptive defect. • Less rare than Congenital sodium secretory diarrhea. • Stool electrolyte analysis: high [Cl] and low pH. Metabolic alkalosis ensues (only other times is in carbohydrate malabsorption and Z-E syndrome). • Nutrients absorbed normally and small intestine histologically normal. • Defective gene on chromosome 7 and of the sulfate transporter family. Transports Cl, HCO₃, and SO₄. • Ileum and colon involved. Jejunum spared. <p><u>Congenital sodium secretory diarrhea</u></p> <ul style="list-style-type: none"> • Defect in brush border Na/H exchange in jejunum. • Absorptive defect (secretory is a misnomer). • Rare. • Jejunum involved and others may be involved. <p><u>Other: all rare</u></p> <ul style="list-style-type: none"> • Congenital sucrase-isomaltase deficiency • Congenital glucose-galactose malabsorption • Lysinuric protein intolerance: Defect in dibasic amino acid transport across the enterocyte basolateral membrane. • Acrodermatitis enteropathica: Defect in Zn absorption. • Microvillus inclusion disease: Severe villus atrophy and crypt hypoplasia with the characteristic finding of microvilli contained within vesicles inside the enterocytes. Gene defect unknown.
Diarrhea in Chronic Diabetes Mellitus	<ul style="list-style-type: none"> • Nocturnal diarrhea with rectal incontinence an occasional complication of long-standing, insulin-dependent diabetes mellitus. • Typically occurs with peripheral and autonomic neuropathy and poor control. • Biopsies are usually normal. • Usually secondary to adrenergic nerve degeneration. Adrenergic nerves usually enhance absorption and inhibit secretion of water and electrolytes.
Sprue Syndromes (Tropical Sprue and Celiac Disease)	<p>4 reasons for profuse diarrhea in these patients:</p> <ol style="list-style-type: none"> (1) Unabsorbed solutes exert an osmotic force pulling water and electrolytes into the intestinal lumen. (2) The villus atrophy and crypt hypertrophy adversely alters the balance between absorption and secretion. (3) Unabsorbed bile acids and fatty acids stimulate fluid secretion in the colon. (4) The inflammatory response generates secretion-stimulating inflammatory mediators and eventually causes downregulation of all ion transport in involved gut segments.
Invasive microorganisms	<ul style="list-style-type: none"> • Enteric infection. • Common causes are <i>Shigella</i>, <i>Salmonella</i>, <i>Yersinia</i>, enteroinvasive <i>E. coli</i>, and <i>Campylobacter</i>. • Invade the epithelium and multiply intracellularly. Extensive damage to the surface with inflammation. • Diarrhea from epithelial damage and shift in ion transport from inflammation. • Some <i>Shigella</i> strains produce enterotoxins. Shiga toxin is cytolytic and inhibits protein synthesis in enterocytes. • Viruses like rotavirus, adenoviruses, and the Norwalk agent cause enterocyte destruction, inflammation, and temporary sprue-like syndrome. • Rotavirus is probably the most common cause of infant diarrhea worldwide.
Noninvasive but enterocyte-destructive microorganisms	<ul style="list-style-type: none"> • Enteric infection. • Do not penetrate beyond surface of the epithelial brush border (<i>C. difficile</i>, <i>Vibrio parahemolyticus</i>, <i>C. perfringens</i>, enteroadherent and enterohemorrhagic <i>E. coli</i>, <i>G. lamblia</i>). • Secrete cytolytic toxins. • <i>C. difficile</i> toxin A alters enterocyte cytoskeletal structure leading to epithelial destruction and inflammation. • Enterohemorrhagic <i>E. coli</i> from contaminated meat. Also affects vascular endothelium and can cause renal failure. • <i>Cryptosporidia</i> in AIDS patients. Adhere to the luminal surface of small intestine epithelial cells, membranes often fusing, and kills the enterocyte.
Food poisoning	<ul style="list-style-type: none"> • Enteric infection. • Term refers to toxins accumulating in food or water.

	<ul style="list-style-type: none"> • Typical organisms: <i>S. aureus</i>, <i>B. cereus</i>, <i>C. perfringens</i>, and <i>C. botulinum</i>. 	
Diarrhea in immuno-compromised patients	<ul style="list-style-type: none"> • Frequent complaint in AIDS. • <i>Cryptosporidium</i> most frequent pathogen. • Others are <i>microsporida</i>, <i>Isospora</i>, and <i>Cyclospora</i>. • Sometimes a sprue-like syndrome is found. • Also may be due to CMV, mycobacterium tuberculosis, or MAC. 	
Principles of Management	<u>Oral Rehydration Therapy</u> <ul style="list-style-type: none"> • Secretory agonists like cholera toxin inhibit all nutrient-independent salt absorption by stimulating active Cl secretion and inhibit Na/H and Cl/HCO₃ exchanges. • Intestinal glucose absorption involves coupled uptake of glucose and Na via the Na-glucose cotransporter in the villus cell brush border membrane. This cotransporter is not affected by cholera toxin. • By putting glucose in oral rehydration solutions (in addition to electrolytes), you take advantage of the Na-glucose cotransporter and increase absorption of Na (with water and Cl following passively) in spite of active Cl secretion from the diarrhea. 	<u>Pharmacologic</u> <ul style="list-style-type: none"> • Antibiotics should NOT be used for mild cases. When hemorrhagic, seriously dehydrating, associated with systemic signs and symptoms, or >5 days, antibiotics might be good. Fluoroquinolones commonly used. <i>C. difficile</i>-induced diarrhea should be treated by removing offending antibiotic and giving, orally, metronidazole or vancomycin. • Antidiarrheals in mild diarrheas lessen stool frequency and volume. Contraindicated in severe diarrhea due to pooling of large volumes. In secretory diarrheas, somatostatin analogues good (e.g. octreotide). In hormone-secreting tumors, somatostatin and its analogues good because (1) they block hormone production by the tumor and (2) they have a direct anti-secretory effect on the gut epithelium.

Inflammatory Bowel Disease and other Colitides

Idiopathic Inflammatory Bowel Disease	<ul style="list-style-type: none"> • Ulcerative colitis (UC) and Crohn's disease (CD). • Incidence rising. • Jews have higher incidence. • Smoking has higher incidence in CD but lower in UC. • Frequency of IBD in 1° family members are 30-100x normal. • CD more genetically predisposed than UC. • HLA types associated with disease. • Loci on chromosomes 12 (CD and UC) and 16 (CD) found. • May be immune-mediated. • Multifactorial disease. 	Pathological and Clinical Features of IBD			
			<i>Localization</i>	<i>Pathology</i>	<i>Clinical Correlates</i>
		CD	<ul style="list-style-type: none"> • Anywhere in GI tract • Most commonly in terminal ileum & proximal colon. • Skips areas. 	<ul style="list-style-type: none"> • Transmural inflammation. • Mainly lymphocytes and monocytes. • Granulomas. 	<ul style="list-style-type: none"> • Fistulas, abscesses, obstruction, malabsorption (if SI. involved). • Protein loss. • Diarrhea.
		UC	<ul style="list-style-type: none"> • Colon only. • Distal to proximal. 	<ul style="list-style-type: none"> • Mucosal inflammation. • Ulceration. • Mixed WBC response. • Cryptabscesses. 	<ul style="list-style-type: none"> • Bloody diarrhea. • Protein loss. • Toxic megacolon. • Colon cancer.
(1) Pathogenesis	<u>Epithelial Factors</u> <ul style="list-style-type: none"> • If barrier function breaks down, get a large influx of protein antigens (as opposed to a normally small trickle) and get an immune response causing chronic inflammation. • Depends on structural proteins as well as the repair process. • Intestinal trefoil factors (ITFs) facilitate repair from injury and normal cell turnover. TGFα is another repair molecule. Deficiency doesn't cause IBD by itself, but it does if coupled to mild injury. 	<u>Immune System Factors</u> <ul style="list-style-type: none"> • Always a little bit of inflammation in normal intestines. Greater in colon. • APCs produce and secrete IL-12 to make Th1 cells and IL-6 for Th2 cells. • Th1 secrete IL-2, INF-γ, and lymphotoxin. Cell-mediated response. Downregulates Th2 (IFN-γ). IFN-γ activates macrophages. Macrophages then secrete TNFα, IL-1β, and more IL-12. TNFα also induced apoptosis. • Th2 secrete IL-4, IL-5, IL-10, and IL-13. IL-4 is like IL-6. Th2 activate B cells to produce IgG1, IgA, and IgE for humoral response. Activates eosinophils (IL-5). Downregulates Th1 cells (IL-10, IL-4, and IL-13). • Normally a balance between Th1 and Th2. If either predominates, destructive inflammation ensues. 			
(2) Crohn's Disease	<ul style="list-style-type: none"> • Th1 response. Increased IL-12 and IFN-γ. Decreased IL-4 and IL-5. • TNFα antibody used to treat. 	<ul style="list-style-type: none"> • Histologically characterized by granulomatous inflammation (60%). Begin as microgranulomas. Never necrotizing. Can be found in LNs. 			

	<ul style="list-style-type: none"> • Used to be thought of as intestinal TB. • Affects the terminal ileum, typically. Also, colon and proximal GI tract. • Rectum often spared. • Typically segmental. • Cobblestone mucosa. • Transmural inflammation with thickened and stiff walls. May develop strictures. • Mucosal ulcers may lead to fistulae. 	<ul style="list-style-type: none"> • Necrosis of individual epithelial cells leading to aphthoid ulcers. • Also necrosis of axons in the bowel wall. • In fully established cases, get creeping of fat adherent to the bowel wall. • Extensive inflammation with PMNs in crypt lumen (crypt abscess). • Repeated crypt damage leads to Paneth cell and pyloric metaplasia. • After many years of CD, get crypt dysplasia which predisposes to cancer. • Often knife-like ulcers that more fissures. • Complications include fistulae, bleeding, and, rarely, toxic dilatation and perforation. Risk of carcinoma 4-20x normal.
(3) Ulcerative Colitis (UC)	<ul style="list-style-type: none"> • Th2 response. Increased IL-5. Unchanged IL-12 and IFN-γ (and IL-4). • Typically diffuse. No skip areas. <p>3 forms may be identified.</p> <p>(1) Ulcerative proctitis and proctosigmoiditis (80%) limited to distal colon. Pain and bleeding, no diarrhea. No additional cancer risk.</p> <p>(2) Left-sided colitis extends to the mid transverse colon or less.</p> <p>(3) Pancolitis (10%) involves entire colon or up to the hepatic flexure. Pain and bloody diarrhea. Rectum involved in almost all cases, histologically.</p> <ul style="list-style-type: none"> • Primarily a mucosal disease. Diffusely red, swollen, friable, and granular. • Ulcers in severe disease and are broad-based. • Pseudopolyps from regenerating mucosa between ulcers. • In pancolitis, terminal ileum may become involved (backwash ileitis). 	<ul style="list-style-type: none"> • Histologically most marked distally. • Diffuse inflammation with varying numbers of PMNs in crypts (cryptitis). Crypt abscesses more common than in CD. Rupture leads to ulcers which may extend into submucosa. • Crypts eventually undergo atrophy or regeneration leading to irregular-looking and distributed crypts. • Paneth cell metaplasia, pyloric metaplasia, and increase in endocrine cells may be seen. • Muscularis mucosae hypertrophic and submucosa obliterated by fibromuscular tissue. • No transmural inflammation. No granulomas. • Complications include toxic megacolon (2-4%), usually early. Most serious is colon carcinoma. Duration and extent determine risk.
(4) Extra-intestinal manifestations	<p>Severity correlates with severity of bowel disease</p> <ul style="list-style-type: none"> • Colitic arthritis: Migratory and transient. Not deforming. Knees, hips, ankles, elbows, and wrists. • Skin lesions: Pyoderma gangrenosum and erythema nodosum. • Ocular lesions: Uveitis and episcleritis. • Calcium oxalate kidney stones: In extensive S.I. CD or CD with severe ileal involvement. Fat malabsorption develops from diminution of absorptive surface area or bile salt malabsorption. Dietary oxalates—which are normally precipitated and not absorbed—are not precipitated and are instead absorbed. This is because unabsorbed bile salts precipitate with Ca instead. The oxalate tends to precipitate in the acidic renal collecting duct. 	<p>Severity does not correlate with severity of bowel disease</p> <ul style="list-style-type: none"> • Sacroiliitis and ankylosing spondylitis: Progressive and crippling. Not ameliorated by colectomy or improvement of bowel disease. • Sclerosing cholangitis: Leads to biliary cirrhosis. Not improved by colectomy.
Infectious Enterocolitis	<ul style="list-style-type: none"> • Involve small and large intestinal mucosa. <p><u>Viral enterocolitis</u></p> <ul style="list-style-type: none"> • Invade epithelial cells and some (like CMV) produce typical inclusion bodies in nuclei or cytoplasm. • Rotavirus infects mostly children. • Norwalk virus responsible for most foodborne infections. • CMV common cause of colitis in immunocompromised, especially HIV. <p><u>Bacterial enterocolitis</u></p> <ul style="list-style-type: none"> • Most common are <i>E. coli</i>, <i>Salmonella</i>, <i>Shigella</i>, <i>Campylobacter</i>, <i>Yersinia</i>, and <i>C. difficile</i>. • <i>E. coli</i> species invade, damage by toxins, or damage by attachment. • <i>Salmonella</i>, <i>Shigella</i>, <i>Campylobacter</i>, and <i>Yersinia</i> invade epithelium. • <i>Clostridium</i> produces cytotoxin but does not invade. • <i>Salmonella typhimurium</i> produce systemic infection (typhoid fever) resulting in chronic infection of biliary tree, joints, bones, and meninges. • Most bacteria damage the surface epithelium, cause crypts to proliferate, and cause the lamina propria to be infiltrated by PMNs. 	

	<ul style="list-style-type: none"> • More severe damage by <i>Salmonella</i> or <i>Shigella</i> leads to erosion and ulceration. • <i>C. difficile</i> colitis from broad-spectrum antibiotics. Mucosa damaged by toxins and damaged areas are covered with a pseudomembrane of cell debris, mucus, and acute inflammatory exudate. Pseudomembranous colitis also occurs in other infections and in ischemia. <p><u>Amebiasis</u></p> <ul style="list-style-type: none"> • Caused by <i>Entameba histolytica</i>. Affects 500 million in developing countries. • Attach to colonic epithelium, lyse epithelial cells, and invade the bowel wall. • Cecum and ascending colon affected preferentially. • Ulcers are flask-shaped with a narrow neck and broad base. • Mucosal necrosis accompanied by relatively little inflammation (liquefactive necrosis).
Ischemic Colitis	<ul style="list-style-type: none"> • Increased in frequency due to longer life. • Affects older patients with chronic vascular insufficiency to the intestine, most frequently the splenic flexure. • Patchy mucosal inflammation and ulceration may mimic IBD and infectious colitis. • Submucosal inflammation may lead to stricture.
Radiation-induced colitis	<ul style="list-style-type: none"> • In men after radiotherapy for prostate cancer. • In women after radiotherapy for uterine cancer. • Histologically resembles ischemic colitis, but includes cytologic atypia of epithelial and stromal cells and telangiectasia.
Lymphocytic/ microscopic colitis	<ul style="list-style-type: none"> • Watery diarrhea and endoscopically normal colon. • Lymphocytic infiltration of surface and crypt epithelium. Increase in chronic inflammatory cells in the lamina propria. • Crypt architecture remains normal. • Collagenous colitis is subepithelial collagen increased. • Both types found with increased frequency in patients with celiac disease.

Differential Diagnosis of CD, UC, and Infectious Colitis

	<i>Chrohn's Disease</i>	<i>Ulcerative Colitis</i>	<i>Infectious Colitis</i>
<u>Macroscopic</u>			
Ileum	+	+/-	+/-
Colon	+	+	+
Skip lesions	+	-	+/-
Stricture	+	+/-	-
Thickened wall	+	+/-	-
Shortened bowel	-	+/-	-
Cobblestone	+	+/-	-
<u>Microscopic</u>			
Aphthoid ulcer	+	-	+
Ulcers	+	+	+/-
Pseudopolyps	+/-	+	-
Transmural inflammation	+	-	-
Granulomas	+	-	+
Fistulae	+	-	-
Serositis	+	-	-

Malabsorption

General		
Intraluminal Stage		

<u>(Digestion)</u>		
(1) Carbohydrate and Protein Digestion		
(2) Fat (Triglyceride) Digestion		
a. Intra-gastric emulsification and lipolysis		
b. Small intestinal lipolysis		
c. Micellar solubilization of fat		
<u>Mucosal Stage</u>		
(1) Selective Carbohydrate Malabsorption		
(2) Selective Protein Malabsorption		
(3) Mucosal Defect in Lipid Absorption		
(4) Intestinal Mucosal Diseases		
a. Celiac Disease		
b. Tropical Sprue		
c. Vitamin B₁₂ (Cobalamin) Deficiency		
d. Folic Acid		
e. Iron		
f. Calcium		
<u>Removal Stage</u>		
Protein-Losing Enteropathy		

Small Intestinal Pathology (Non-neoplastic and neoplastic)

Malabsorptive Disorders	<ul style="list-style-type: none"> • Mucosal biopsy usually needed to differentiate between diseases. • If absorption is at fault, morphologic changes likely. • If inadequate digestion, morphologic feature may be lacking. 	
(1) Celiac Disease	<ul style="list-style-type: none"> • Also known as gluten-sensitive enteropathy (GSE), nontropical sprue, and celiac sprue. • Common among whites, rare in Africans and Asians. • Genetic predisposition. Familial clustering and association with HLAs. 	<ul style="list-style-type: none"> • Diagnosis requires (1) documentation of malabsorption, (2) demonstration of villous atrophy by small bowel biopsy, (3) improvement of symptoms and mucosal histology after gluten withdrawal. • Most pronounced in the proximal small intestine (where gluten is).

	<ul style="list-style-type: none"> • Sensitivity to gluten, in particular gliadin. Intestinal injury. • Dermatitis herpetiformis cause histopathologic changes similar to celiac sprue. Malabsorption usually not present. Gluten-free diet usually cures. • Recurring cases, despite gluten-free diet are classified as refractory or unclassified sprue. Long term complications include intestinal lymphoma and GI and extraintestinal carcinoma. Both prefer the small intestine. • Sprue-related are T-cell type. Develop after 10-20 years of malabsorption. Prognosis poor. In contrast, 95% of GI lymphomas are B type. 	<ul style="list-style-type: none"> • Iron, Ca, folate, and pyridoxine absorption affected. • Histologically, total or subtotal loss of villi. Flattening of mucosal surface and reduction of the absorptive surface area. Loss of brush border. • Elongation of crypts (crypt hyperplasia) and increased crypt mitoses. • Plasma cells. Other cells also seen. • Surface epithelium with increased T-cells and vacuolization.
(2) Tropical Sprue (Post-infectious Sprue)	<ul style="list-style-type: none"> • Celiac-like disease. • Caught in the tropics. Common in the Caribbean (except Jamaica), Central and S. Africa, India, S.E. Asia, and Central and S. America. • Specific causal agent unknown. • Bacterial overgrowth by enteropathic organisms (<i>E. coli</i>, <i>Hemophilus</i>) plays a role. Good clinical response to antibiotics. • Microscopic changes similar to celiac sprue, though villous atrophy usually subtotal and atrophic. Also, distal small intestine involved as well as proximal. • B₁₂ often malabsorbed (normally absorbed in ileum). Pernicious anemia and megalocytosis of intestinal epithelial cells ensues. 	
(3) Whipple's Disease	<ul style="list-style-type: none"> • Rare cause. Systemic. • Linked to infection with <i>Tropheryma whipplei</i>. Gram+ actinomycete. • Principally affect the intestine, the CNS, and joints. • Small intestinal mucosa infiltrated with large distended macrophages: Whipple macrophages. Cause blunting and flattening of surface. • Distinguish from MAI. Whipple's responds to antibiotics. MAI does not. 	
(4) A-β-lipoproteinemia	<ul style="list-style-type: none"> • Malabsorption due to enterocyte failure of proper conversion of absorbed nutrients. • Inability to synthesize apolipoprotein B results in no chylomicrons. • Dietary fat stored in absorptive cells as triglycerides. Produce vacuolization. • In circulation, an absence of lipoproteins containing apolipoprotein B (chylomicrons, VLDL, and LDL). • Lipid abnormality leads to membrane abnormalities in RBCs which are acantholytic burr cells. 	
(5) Lymphangiectasia	<ul style="list-style-type: none"> • Rare. • Transport of lipids into the circulation abnormal due to primary congenital lymphangiectasia (defective formation of lymphatics). • Secondary lymphangiectasia from heart disease or an inflammatory or infiltrative lesion that interferes with lymphatic circulation. • Fistulas may form into gut lumen with hypoproteinemia and edema. 	
(6) Others	<ul style="list-style-type: none"> • Collagenous sprue • Lymphoma • AIDS enteropathy • Infections: CMV, MAI, cryptosporidiosis, microsporidiosis, isosporiasis • Eosinophilic gastroenteritis • Radiation enteritis • Microvillus inclusion disease (rare congenital disorder) 	
Other Small bowel Pathologies		
(1) Duodenal Ulcer	<ul style="list-style-type: none"> • Majority found in the first portion of the duodenum. 	<ul style="list-style-type: none"> • By definition, it is a necrotic lesion that extends beyond the mucosa.
(2) Meckel's Diverticulum	<ul style="list-style-type: none"> • Persistence of the vitelline duct. • 2% of normal population, 30 cm from ileocecal valve. 	<ul style="list-style-type: none"> • Complications: ulceration, bleeding, intussusception, and perforation.
(3) Intussusception	<ul style="list-style-type: none"> • Telescoping of one segment of bowel into another. • Spontaneous in children. 	<ul style="list-style-type: none"> • In adults, secondary to other lesions, usually tumors. • Complications: obstruction and infarction.
(4) Volvulus	<ul style="list-style-type: none"> • Twisting of a loop of bowel around its mesenteric base. • Most frequent in sigmoid colon. 	
Tumors of Small Intestine	<ul style="list-style-type: none"> • Account for only 3-6% of GI tumors (even though it accounts for 75% of the length of the GI tract). 	

(1) Secondary Tumors	<ul style="list-style-type: none"> • Malignant tumors from elsewhere frequently seed the serosal surface. Commonly from carcinomas in the colon, stomach, pancreas, or ovary. • Serosal metastases often associated with ascites and a fibrotic reaction leading to adhesions. • As frequent as primary small intestinal tumors. 	
(2) Primary Tumors	<ul style="list-style-type: none"> • Often asymptomatic and found incidentally. These are usually benign. • Malignant tumors produce symptoms. 	<ul style="list-style-type: none"> • Two important patterns: Intestinal obstruction and intestinal bleeding.
a. Adenocarcinoma	<ul style="list-style-type: none"> • Most frequent in duodenum, though rare in small bowel. • Histologically, show varying degrees of differentiation. • Grossly and histologically similar to adenocarcinomas of the large intestine. 	<ul style="list-style-type: none"> • Carcinomas of the ampulla of Vater produce obstructive jaundice early. 5 year survival is 25%. • Arise in 2nd and 3rd portions of duodenum (rare in 1st). Produce symptoms later so have a poorer prognosis. 5 year survival 25-35%.
b. Adenomas	<ul style="list-style-type: none"> • Most common in duodenum, though rarely found in small intestine. • Grossly and histologically similar to colonic adenomas. 	<ul style="list-style-type: none"> • My occur at ampulla to produce obstructive jaundice. • Probably give rise to adenocarcinomas. • FAP predisposes to adenomas leading to adenocarcinomas.
c. Hamartomatous Polyps	<ul style="list-style-type: none"> • Seen in Peutz-Jeghers syndrome, a rare familial disorder: Patients exhibit (1) mucocutaneous pigmentation, frequently of lips and oral mucosa, and (2) multiple hamartomatous polyps of the GI tract. • Most commonly found in the small intestine, primarily jejunum. Also in colon and least in stomach. • Hamartoma is a malformation with a mass of normal tissues of the area arranged in an abnormal way. • Peutz-Jeghers polyps composed of mature glandular structures mixed with bunches of muscle. Histologically not like a neoplasm, though may be hyperplastic. • Rarely, young patients with Peutz-Jeghers get invasive carcinomas especially in the stomach and duodenum. • Most with Peutz-Jegher's are hospitalized frequently over many years with GI bleeding or obstruction. Multiple operations. 	
d. Carcinoid Tumor	<ul style="list-style-type: none"> • Endocrine neoplasm. • The argentaffin cell (aka enterochromaffin or Kulchitsky cell) is a GI endocrine cell. Can be stained by silver. • Appendix most common site (50%). Next common is small intestine, rectum, or lung. • Better prognosis than ordinary adenocarcinomas. • 50% of symptomatic patients have non-resectable tumors. Since it is slow growing, resection and then re-resection later on is practical. • Extensive liver metastases leads to the carcinoid syndrome. Cutaneous flushing, profuse diarrhea, bronchospasm, and right heart failure. Excise the metastases. Elevated 5HIAA in urine (5HT metabolite). 	<ul style="list-style-type: none"> • Grossly, small, firm, yellow-tan nodules. • Reactive fibrosis when tumor invades. Maybe from 5HT from tumor. • Obstruction or volvulus from matted LNs in the mesentery. • Metastasis from 2-80% incidence depending on size of tumor. • Microscopically, typical endocrine pattern. Appearance correlates with slow growth rate.
e. Lymphoma	<ul style="list-style-type: none"> • Secondarily involve GI tract or mesenteric LNs. • Also, may arise in extra-nodal sites like stomach and small intestine (40%). • Most common in ileum where more lymphoid tissue found. • Produce diffuse thickening of bowel wall or obstructing masses. • Mucosal frequently ulcerated and bleeding. • Occasionally perforation with acute peritonitis. • Malabsorption may develop. 	<p>3 major types:</p> <p>(1) Sporadic lymphoma: aka Western type lymphoma. B-cell lymphoma. Arises from MALT so also called a MALToma. Surgical resection. If recur, often only in GI tract. Often show c-myc rearrangements. 10 year survival is 85%.</p> <p>(2) Enteropathy or Sprue-associated lymphomas: Celiac disease usually after many years of malabsorption. T-cell lymphomas. Poor prognosis.</p> <p>(3) Mediterranean lymphoma: B-cell lymphoma. Children and young adults. Usually involves the jejunum. History of enteric infections with recurrent diarrhea. Jejunum with marked hyperplasia of lymphoid and plasma cells. Have an abnormal serum protein called α heavy-chain disease protein.</p>
f. GI Stromal Tumor (GIST)	<ul style="list-style-type: none"> • 2/3 arise in stomach. The rest are in the jejunum and ileum. Rarely duodenum. • Arise from interstitial cells of Cajal. 	<ul style="list-style-type: none"> • Immunoreactivity for c-kit. Rare GISTs have no reactivity (v. malignant). • Tumor size, mitotic count, dense cellularity, and mucosal invasion correlate to degree of malignancy.

Colorectal Tumors

General	<ul style="list-style-type: none"> • One of the leading cancers. • Lifetime risk is 5%. • FAP and HNPCC • Precursor to the adenocarcinoma is the adenoma. 	<ul style="list-style-type: none"> • 2 main pathways: (1) Genetic alteration of APC/βcatenin/Tcf-4 signaling, known as the suppressor pathway since APC is a tumor suppressor gene. (2) Alteration of DNA mismatch repair genes with microsatellite instability, or the mutator pathway.
Diet	<ul style="list-style-type: none"> • Western-type diet. Meat, smoking, and alcohol risk factors. • Vegetables, NSAIDs, and physical activity protective. 	
Chronic Inflammation	<ul style="list-style-type: none"> • A risk factor for colorectal adenocarcinomas. • Chronic UC 10X greater risk of colorectal adenocarcinoma. Extent and duration of disease important. Severity not important. Disease limited to rectum has no increased risk of carcinoma. Pancolitis greatest risk. Risk of dysplasia increases with duration. • Prognosis from IBD similar to sporadic, stage for stage. 	
Adenoma-Carcinoma Sequence	<ul style="list-style-type: none"> • Adenoma associated with colorectal carcinoma. • Distributions within colorectum similar. • Peak incidence of adenomas precede the peak for carcinomas. • Adenomatous epithelium often co-existent with adenocarcinoma. • Screening for adenomas with removal reduce incidence of cancer. 	
Molecular genetic pathways of colorectal carcinogenesis	<p>(1) <u>APC/β-catenin and Adenoma-Carcinoma Sequence</u></p> <ul style="list-style-type: none"> • 80% of sporadic colorectal carcinoma. • Suppressor pathway. • APC anti-proliferative effect. • APC regulates intracellular levels of β-catenin. • β-catenin binds E-cadherin and also activates cell proliferation. WNT signaling pathway. • When APC is knocked out, β-catenin sticks around and causes growth. 	<p>(2) <u>DNA Mismatch Repair Gene Pathway leading to microsatellite instability (MSI)</u></p> <ul style="list-style-type: none"> • 10-15% of sporadic colorectal carcinoma. • Mutator pathway. • Hallmark of defective mismatch repair is MSI. Propensity to develop mutations at these microsatellites.
Familial adenomatous polyposis (FAP)	<ul style="list-style-type: none"> • Germline mutation of the APC gene. Rare. • Develop lots and lots of adenomatous polyps early on. • Earliest precursor lesions are aberrant crypt foci. 	
HNPCC	<ul style="list-style-type: none"> • Germline mutation of a mismatch repair gene resulting in a microsatellite instability (MSI). Rare. • Predominantly right-sided colon tumors in young patients. • Not a lot of polyps. But the few polyps there quite likely to develop cancer. Accelerated tumorigenesis. So need colonoscopy every 1-2 years. • Mutations most commonly seen in hMSH2 gene on chromosome 2p, hMLH1 gene on chromosome 3p. • Also at increased risk of extracolonic cancers. • Better prognosis than with sporadic colon cancers, stage for stage. 	
Clinical Criteria for HNPCC		
Staging		

Head and Neck crap