

## Pathology Review Flash Cards GI, Liver

Spring 2009

### Esophagus Fistulas and Stenosis

- Tracheoesophageal Fistulas
  - upper esophagus ends in a blind pouch (atresia), lower esophagus connects to trachea near bifurcation
    - this is the most common variant (90%)
  - fistula may connect to upper blind pouch (2<sup>nd</sup> most common)
  - Atresia is associated with congenital heart disease and OTHER GI malformations – polyhydramnios in the fetus (can't swallow amniotic fluid)
- Stenosis-inflammatory, submucosal thickening with atrophy of the muscularis propria
  - causes-radiation, reflux, scleroderma, caustic injury

### Esophagus Diverticula

- Zenker's-above UES
  - assoc. w/ cricopharyngeus motor dysfunction
  - presents with regurgitation w/out dysphagia
  - Can complicate with aspiration → pneumonia
- Traction-middle of esophagus
  - thought to be due to congenital motor dysfunction
  - usually asymptomatic
- Epiphrenic-above LES
  - due to failure of LES to relax upon swallowing
  - presents with nocturnal regurgitation of fluid

### Esophagus Abnormalities

- Achalasia-lack of peristalsis, failure of relaxation and increased resting tone of LES
  - Esophagus will be dilated above LES, myenteric plexus will be absent
  - Seen secondarily to Chagas disease from T. cruzi infection
  - **predisposed to sq. cell carcinoma of esophagus (5%)**
- Sliding hiatal hernia-protrusion of cardia thru diaphragm
  - results in bell shaped dilatation above diaphragm
  - Paraesophageal hiatal hernia- greater curvature protrusion
    - esophagus is not dilated
  - symptoms-heartburn, reflux; complications-ulceration and perforation

### Esophageal Varices

- Esophageal varices
  - Collaterals form around lower esophagus and proximal stomach in the esophageal mucosa and submucosa secondary to portal HTN
  - Varices are tortuous vessels with increased intravenous pressure
  - seen in 90% of cirrhotic patients; assoc. w/ alcohol (US) and schistosomiasis (worldwide)
  - rupture results in massive hemorrhage (50% mortality)

### Mallory Weiss Tears

- longitudinal tearing of esophagus following severe retching
- usually occurs at gastro-esophageal junction or proximal gastric mucosa
- Seen in alcoholics and bulimia
- Bleeding usually not severe and self-limited

## Infectious Esophagitis

- *Associated with immunosuppression HIV/AIDS*
- Candida
  - Patched or diffuse involvement of mucosa
  - Gray-white pseudomembranes
- Herpes
  - Punched-out ulcers
  - *Intranuclear* inclusions seen in degenerating epithelial cells
- CMV
  - Punched-out ulcers
  - *Intranuclear and cytoplasmic* inclusions found in papillary endothelium and stromal cells at the base of the ulcer

## Reflux Esophagitis

- Most common cause of esophagitis; adults >40
  - assoc. w/ alcohol, tobacco, decreased LES tone, hiatal hernia, pregnancy, scleroderma
- 3 characteristic features:
  - 1. inflammatory infiltrate- neutrophils, eosinophils, lymphocytes
  - 2. basal zone hyperplasia
  - 3. Elongation of lamina propria papillae
- Presents w/ dysphagia, heartburn, regurgitation, hematemesis, or melena
- Complications: bleeding, stricture development, Barrett's esophagus

## Barrett's Esophagus

- Complication of long-standing esophagitis
- Metaplasia of the distal esophagus → squamous mucosa changed to columnar epithelium with intestinal goblet cells
- Metaplasia seen as red, velvet mucosa against a background of smooth, pale, squamous cell mucosa
- Begins near squamocolumnar junction and goes upward
- Associated with increased risk of adenocarcinoma in the bottom 1/3 of the esophagus

## Esophageal Neoplasms

- Squamous cell carcinoma
  - 90% of esophageal CA worldwide- 50% in US
  - Assoc. w/ alcohol, tobacco, and nutritional deficiencies
  - Distribution: 20% upper, 50% middle, 30% lower
  - Begin as small, gray-white plaque areas but can become protruded, flat, or excavated and are often large at Dx
- Adenocarcinoma:
  - Distal 1/3 of esophagus- assoc. w/ Barrett's esophagus
  - Mucin-producing glandular tumors with intestinal-type features
- Both present with dysphagia, weight loss, hematemesis
- Both spread by direct extension to adjacent structures

## Stomach – Congenital Lesions

- Gastric Heterotopia:
  - patches of ectopic gastric mucosa in duodenum or more distal sites
  - causes bleeding and ulcerations (esp. w/Meckel's diverticulum)
- Diaphragmatic Hernia:
  - weakness or partial-to-total absence usually on the left
  - herniation of abdominal contents in utero
  - results in respiratory insufficiency
- Pyloric Stenosis:
  - familial; 1/300-900 live births; 3-4x more common in boys
  - projectile vomiting in second or third week of life
  - palpable mass on exam
  - Results from hypertrophy/hyperplasia of pyloric muscularis propria

## Helicobacter Pylori Infection

- Most important cause of chronic gastritis
  - 90% of pts. w/*chronic gastritis of the antrum*
- Colonizes 50% of persons over age 50, most of which are asymptomatic
- Gram negative rod with flagella
  - elaborates *urease* to produce ammonia and buffer gastric acid
- Reside in superficial mucous layer among microvilli
  - they do not invade the mucosa
- May predispose to gastric carcinoma and lymphoma

### Autoimmune Gastritis (Pernicious Anemia)

- Accounts for <10% of chronic gastritis
- Autoantibodies to gastric gland parietal cells and intrinsic factor
  - Results in gland destruction and mucosal atrophy
- Assoc. w/achlorhydria and pernicious (megaloblastic) anemia
- Associated with other autoimmune diseases
  - Hashimoto's and Addison's
- Autosomal dominant- familial occurrence well-established
- Long-term risk of gastric carcinoma is 2-4%

### Acute Gastric Ulceration

- Assoc. w/ NSAID therapy & physiologic stress
- Stress ulcers seen in patients with shock, burns, sepsis, or severe trauma (5-10% of ICU patients)
- Ulcers are circular and small; anywhere in stomach, dark brown base ("cigarette burns")
- Surrounding mucosa is normal with no scarring or thickening of blood vessels
- **Cushings ulcers** → due to increased intracranial pressure or post-intracranial surgery
- **Curling's ulcers** → located in proximal duodenum

### Zollinger-Ellison Syndrome

- Hypersecretion of gastrin from gastrinoma (pancreatic, duodenal, or elsewhere)
- Ulcers present in 90-95%; most commonly found in duodenum but may occur in more distal gut
- >50% metastasized at time of diagnosis
- Ulcers intractable to usual modalities of therapy
- Diarrhea is common presenting symptom
- Treat with H2 blockers and surgical removal of tumor

### Stomach – Peptic Ulcer Disease

- Ulcers usually solitary → from chronic mucosal damage 2° to acid and pepsin secretion
- Location: duodenum (1<sup>st</sup> portion) > stomach (antrum) > gastroesophageal junction (GERD)
- Associated with:
  - H. pylori in 100% of duodenal and 70% of gastric ulcers
  - Chronic NSAID use suppresses prostaglandins
  - Corticosteroids & hypercalcemia also contribute
  - Tobacco impairs mucosal blood flow

### Peptic Ulcer Disease cont.

- Gross morphology:
  - Size doesn't differentiate benign from malignant
  - Punched-out lesion; no heaped-up margins as in malignant lesions; ulcer base is smooth & clean
  - Fibrosis of surrounding wall leads to spoke-like folds
- Microscopic morphology:
  - Non-specific inflammatory infiltrate w/neutrophils
  - deep-layer granulation tissue w/mononuclear cells
- Clinical:
  - Epigastric gnawing, burning, or aching pain; worse at night and 1-3 hrs. after a meal
  - Nausea & vomiting; pain may be referred to back

### Hypertrophy/Hyperplasia

- Menetrier disease
  - hypersecretion of mucus with no hyperacidity (glandular atrophy)
  - may result in protein-losing gastroenteropathy
  - infrequently, metaplasia of mucosa associated with increased incidence of gastric carcinoma
- Parallels between stomach and colon
  - Polyps can be hyperplastic or adenomatous
  - Adenomatous polyps associated with foci of carcinoma
  - Hyperplasia with atypia predisposes to cancer
    - In stomach, associated with chronic gastritis

## Gastric Polyps

- Any nodule or mass projecting above mucosa; uncommon (0.4%), 3-5% in Japan
- Majority are non-neoplastic (90%) and represent *hyperplastic lesions*
  - Due to chronic inflammation
  - Seen most commonly with chronic gastritis
- *True adenomas*: 5 to 10% of gastric polyps; have dysplastic epithelium and malignant potential
  - M:F ratio 2:1; up to 40% contain a focus of carcinoma
  - Autoimmune gastritis and colonic polyposis syndromes predispose to gastric adenomas

## Gastric Carcinoma

- Represent 90-95% of malignant gastric cancers; others are lymphomas, carcinoids, & stromal tumors
- Most prevalent in *Japan* (smoked salmon?)
- 5 yr. survival <20%
- ½ are *bulky tumors* resembling colonic adenocarcinoma
- ½ are *diffuse & infiltrative (signet ring cells)*
- Contributing factors: H. pylori w/ chronic gastritis, autoimmune gastritis, diet, cigarettes (NOT alcohol)

## Gastric Carcinoma

- Key feature is *presence of dysplasia*
- Lesser curvature of antropyloric region is favored
- *Depth of invasion* is most important for classification
- Growth pattern can be exophytic, flat/depressed (infiltrative), or excavated (mimics ulcers → but margins are heaped-up)
- Often metastasize to supraclavicular sentinel node
- Metastasis to both ovaries → *Krukenberg tumor*
- Insidious w/non-specific symptoms → late diagnosis

## Malabsorption Syndromes

- **Celiac Sprue** – immune mediated hypersensitivity reaction to gluten/gliadin; proximal small intestine
  - *Blunting of villi w/ hyperplastic crypts* and diffuse enteritis
  - Lymphocytes in lamina propria; linked to **HLA B8**; associated with *dermatitis herpetiformis*
  - **Increased risk of malignancy** (usually T cell lymphoma)
- **Tropical Sprue**
  - Caused by overgrowth of enterotoxigenic organisms
  - Affects all levels of small intestine (variable enteritis)
  - Occurs *days-weeks after diarrheal disease following trip to endemic area*
  - Treat w/ broad spectrum antibiotics

## Malabsorption Syndromes

- **Whipple's Disease**
  - Caused by gram+ actinomycete *Tropheryma whippeli*
  - Affects *intestine, CNS and joints*
  - Distended macrophages in lamina propria w/ PAS+ granules
  - Villi expansion → *"shaggy" appearance*
  - NO inflammation; YES lymphadenopathy and hyperpigmentation
- **Disaccharidase (Lactase) Deficiency**
  - *No morphological changes*
  - *Osmotic diarrhea*; ↑ H<sub>2</sub> production → abdominal pain/distention, bloating
  - Usually acquired, can be congenital; blacks > whites

## Malabsorption Syndromes

- **Abetalipoproteinemia**
  - Autosomal recessive (rare)
  - *Deficiency of apoprotein B* → unable to assemble chylomicrons and export lipoproteins → store triglycerides in cells with **lipid vacuolation**
  - Circulating *acanthocytes or burr cells*
  - Low LDL and VLDL
  - Results in *steatorrhea* or failure to thrive
- **Bacterial Overgrowth**
  - Associated with luminal stasis, achlorhydria, immune deficiencies
  - Malabsorption due to bacterial use of nutrients, breakdown of bile acids, and mucosal inflammation

### Nutritional Aspects of Malabsorption

- Almost all syndromes will cause weight loss, anorexia, abdominal distension, borborygmi, muscle wasting
- General endocrine: amenorrhea, impotence, infertility
- Fat malabsorption causes deficiencies of related vitamins
  - Vitamin A: dermatitis, hyperkeratosis, peripheral neuropathy
  - Vitamin D: hypocalcemia with osteopenia and tetany
  - Vitamin K: abnormal bleeding
  - Lipid membrane defects from essential fatty acid deficiency, leading to characteristic burr cells on peripheral blood smear as in abetalipoproteinemia
- Protein deficiency with retained carbohydrate absorption leads to low albumin with edema, as in pancreatic insufficiency

### Nutritional Aspects of Malabsorption

- B<sub>12</sub> and folate deficiencies lead to megaloblastic anemia; also neuropathy (subacute combined degeneration) with B<sub>12</sub>
  - B<sub>12</sub> deficiency is common in disease of the terminal ileum
  - Also isolated deficiency with lack of intrinsic factor, as in atrophic gastritis
- Iron deficiency leads to microcytic, hypochromic anemia
  - Must rule out colon cancer before diagnosing any other malabsorptive condition
- Electrolyte abnormalities and dehydration from protracted diarrhea

### Crohn's Disease

- f>m; mainly western population
- **smoking** is risk factor
- peaks in 20's-30's
- may involve **any part of bowel** (mouth→anus)
- **skip lesions**
- lesions coalesce into **linear ulcers**
- **non-caseating granulomas** found throughout bowel
- transmural involvement→fissures and fistulas
- **string sign**→narrowed lumen with thick wall
- 5-6x increase in GI cancer
- more skin and liver extraintestinal effects than UC

### Ulcerative colitis

- whites > blacks, found globally
- peaks 20-25 yo
- mucosa and submucosa of rectum and large intestines; lesions in continuous fashion without skip lesions
- involves rectum and extends proximally; rarely any ileum
- Inflammatory pseudopolyps—extensive ulceration and hemorrhage with areas of regeneration; no granulomas
- can have nerve damage leading to toxic megacolon
- Ulcers and crypt abscesses containing neutrophils
- bloody, mucoid diarrhea may last for days-months
- 20-30x incr risk for GI cancer
- Complications include: toxic megacolon, primary sclerosing cholangitis (HLA-B27 positive) and colon adenocarcinoma

#### Crohn's Disease

#### Ulcerative Colitis

Small intestine alone 40% Small intestine and colon 30% Colon alone 30%	Colon only (rarely terminal ileum, appendix)
Skip lesions with normal intervening bowel	Continuous from rectum proximally
Transmural including serosa and subserosa	Mucosa and submucosa; stops at muscularis
Linear ulcers and deep fissures Strictures and fistulas Thickened wall (except in colon)	Superficial ulcers Rare strictures Thin wall
Non-caseating granulomas Crypt abscesses Fibrosis	Pseudopolyps Inflammatory cell infiltrate Crypt abscesses
Malignant potential 5-6 fold Responds poorly to surgery; treat with immunosuppressive agents	Malignant potential 20-30 fold Good response to therapy

### Appendicitis

- Fecalith obstructs proximal lumen (50-80%)
- Continued secretion of mucinous fluid causes increased intraluminal pressure
- Collapse of venous drainage results in ischemia
  - Inflammatory edema and exudate result in more ischemia
- Secondary bacterial proliferation
- Histologic criteria→ neutrophilic infiltrate of muscularis
- Presents as RLQ pain, N/V, fever, high WBC

## Congenital Intestinal Disease

- Atresia and Stenosis
  - Uncommon, duodenum most common site, colon never involved, can occur from developmental failure/intrauterine vascular accidents/intussusceptions
  - Atresia can be a mucosal diaphragm or a string-like segment of bowel connecting normal pieces
  - Stenosis (more rare) can be either of those but with a partial opening

## Congenital Intestinal Disease

- Meckel Diverticulum
  - Failure of involution of the vitelline duct, antimesenteric side of bowel w/in 2' of ileocecal valve
  - contains all three layers of bowel wall
  - heterotopic rests of tissue often found (gastric, pancreatic)
- Congenital Aganglionic Megacolon (Hirschsprung Disease)
  - Lack of neural crest cell migration/premature death of ganglia (lack of submucosal and myenteric plexus)
  - RET gene may be involved
  - rectum always involved, more proximal colon is variable
  - colon proximal to lesion undergoes dilation and hypertrophy, eventual rupture, stercoral ulcers may be seen

## Adhesions/Volvulus/Intestinal Carcinoids

- Adhesions – usually from previous surgery (also endometriosis and radiation); #1 cause of small bowel obstruction.
- Volvulus – cecum in young adults, sigmoid in older; bowel twists around mesenteric root with strangulation and obstruction; Risk factors = chronic constipation, pregnancy, laxative abuse
- Carcinoids – malignant neuroendocrine tumors; bright yellow
  - #1 site is appendix, no mets from appendix; most common site producing liver mets is the terminal ileum.
  - Carcinoid syndrome only seen secondary to liver mets.
    - Flushing, diarrhea, 5-HIAA seen in urine

## Smooth Muscle Tumors

- **Leiomyoma**
  - Benign, often arise in uterus, also in erector pili muscles in skin, nipples, scrotum, and labia
  - Multiple lesions associated w/AD inheritance
  - No larger than 1-2cm, fascicles of spindle cells intersecting at right angles, blunt-ended elongated nuclei w/little atypia and mitotic figures
- **Leiomyosarcoma**
  - Most in skin and deep soft tissues of extremities and retroperitoneum, painless firm masses
  - Malignant spindle cells in interweaving fascicles, may have prominent myxoid stroma or epithelioid cells; >10 mitoses per high power field
  - stain with antibodies to vimentin, actin, smooth muscle actin, and desmin

## Diverticulosis/ Diverticulitis

- **Diverticulosis**
  - Common in elderly
  - Often multiple; outpouchings of mucosa from: 1) focal weakness in colonic wall and 2) increased intraluminal pressure
  - Most in sigmoid colon alongside taeniae coli
  - Most asymptomatic- some abdominal discomfort, constipation, distension
  - MCC of hematochezia- enlarged vessels often at apex of diverticulum just below the mucosa

## Diverticulosis/ Diverticulitis

- **Diverticulitis**
  - Presents as “left sided appendicitis”
  - Obstruction or perforation of diverticula→ inflammation, pain, bacterial overgrowth
  - Often resolves spontaneously- rarely causes fibrosis or generalized peritonitis

## Ischemic Bowel Disease

- Usually ACUTE occlusion of a major supply trunk
- Older individuals, usually with pre-existing abdominal disease (adhesions, torsion)
- Morphologic patterns
  - Transmural infarction = implies *mechanical compromise* of major mesenteric vessels
    - appears hemorrhagic due to blood reflow; arterial lesions are well demarcated; venous occlusions fade gradually
    - within 1 to 4 days, bacteria cause gangrene and perforation
  - Mucosal or mural infarction = results from *hypoperfusion* (either acute or chronic)
    - epithelial sloughing with ulceration, absence of inflammation
    - bacterial superinfection may result in pseudomembranous colitis
- Chronic ischemia has *fibrosis* that may lead to stricture formation
  - notoriously segmental and patchy

## Angiodysplasia

- occurs in elderly (after 6th decade)
- account for 20% of significant lower intestinal bleeding
- Pathology
  - ectatic nests of pre-existing veins, venules, and capillaries
  - tortuous dilatations of mucosal and submucosal vessels of the cecum and right colon
- Pathogenesis
  - focal dilatation and tortuosity of vessels from intermittent occlusion secondary to normal colonic contraction

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## Secretory Diarrhea: viral

- **Rotovirus** (11 segments dsRNA, non-enveloped, 2 layer capsid, core with complete transcriptional system)
  - 25-65% diarrhea infants small children (6-24 months), 140 million inf & 1 million deaths/yr
  - outbreaks in peds units and daycares
  - Path: 10 virions for infection, 2 day incubation → selectively infects and destroys enterocytes (villus cells) in small intestine, doesn't infect crypt cells → repopulation by secretory cells → massive loss water/electrolytes + osmotic diarrhea due to incomplete absorption → lots of virus shed in stools
  - Antibodies provide partial protection, in mother's milk (most common time infection is weaning)

## Secretory Diarrhea: viral

- **Caliciviruses = Norwalk** (pos ssRNA, non-enveloped icosahedral, fecal-oral)
  - Non-bacterial food-borne gastroenteritis epidemics in all ages
  - Exposure of individuals to common source
  - 2 day incubation → 12-60 hours nausea, vomiting, diarrhea, cramps
- **Adenovirus** (dsDNA, non-enveloped icosahedral capsid, fiber – attach hemagglutinin, no enzymes in core, released by cell lysis)
  - Enteric serotypes common cause of infant diarrhea
  - 1 week incubation → moderate gastroenteritis with vomit lasts 10 days
  - atrophy of villus and hyperplasia of crypts (as in Rotovirus) causes loss of fluids/electrolytes and malabsorption

## Secretory Diarrhea: viral

- **Astrovirus** (neg ssRNA, non-enveloped, filamentous and pleomorphic)
  - Children (4% all gastroenteritis)
  - Anorexia, headache, fever with diarrhea
- **Common Morphological Features:**
  - Small intestinal mucosa with shortened villi and lymphocytic infiltrate into lamina propria
  - Vacuolization and loss of microvillus brush boarder
  - Crypts are hypertrophied

## Secretory Diarrhea: enterotoxin mediated

- ***Vibrio cholera*** (g-, comma shaped, alkali tolerant, oxidase positive) fecal-oral, killed by stomach acid so need large inoculation
  - Path: Flagella attach to epi→secrete toxin→activate adenylate cyclase→cAMP formed→secretion of Cl- and bicarb→diarrhea
  - Cholera toxin: 5 B subunit binds ganglioside Gm1, A endocytosed, split A1, A2→A1 binds ARF→NAD+ARF-A1 ribosylates Gsalpha→ activates
  - Morph: proximal intestine, mucus depleted crypts

## Secretory Diarrhea: enterotoxin mediated

- ***E. coli (ETEC)*** g-, rod, oxidase neg, FA... "traveler's diarrhea"
  - Path: adhere to epi via pili→HL and HS enterotoxins→loss fluids and electrolytes
- ***Bacillus cereus*** (g+ rod, motile, endospore, FA, cat positive)
  - Path: enterotoxins, HL and HS
- ***Clostridium perfringens***
  - Path: necrotic enterocolitis (strain C)... enterotoxin superantigen Gastroenteritis (strain A).. food poisoning
  - Morph: similar to V. cholera, but with some epi damage, can be necrotizing

## Dysentery

- ***Shigella*** (g-, FA, non-motile, non-coliform, S. flexneri) fecal-oral, virulent
  - Path: invades epithelia→escapes phagolysosome→lysis cell
- Shigatoxin causes mucosal necrosis: fibrinosuppurative exudate + hemorrhagic colitis and **hemolytic uremic syndrome**
  - Sequelae: reactive arthritis: Reiter's syndrome (nongonococcal urethritis+reactive arthritis+conjunctivitis) 80% HLA-B27, one month following genitourinary (Chlamydia) or GI (Shigella, Salmonella, Yersinia, Campylobacter) low back, ankles, knees, feet asymmetrically
  - Morph: hyperemia, edema, enlargement of mucosal lymphoid nodules in distal colon→inflammation and erosion with thick purulent exudate

## Dysentery

- ***Salmonella*** (g-, flagellate, non-coliform, produce H2S) contaminated meats **NO TOXIN**
- **Typhoid fever** → Signs: "rose spots" - chest/abdomen, **hepatosplenomegaly, dysentery** Labs: **neutropenia**
  - Enteric fever: fever, bacteremia – associated with sickle cell and schistosomiasis
  - Food poisoning: vomiting + diarrhea, self-limited except for immunocomp
- blunted villi, vascular congestion, mononuclear infiltrate in ileum and colon→**peyer patch ulceration**→ with S. typhi get massive reticuloendothelial proliferation→**splenomegaly**→typhoid nodules in liver

## Dysentery

- ***Campylobacter*** (g-, comma, flagellate, oxidase and catalase positive) most common cause: diarrhea, gastritis, and dysentery... can develop to sepsis... bad for immunocompromised
  - C. jejuni Path: flagella binds epi→invades mucosa→causing diarrhea, dysentery, or enteric fever (when disseminates to mesenteric nodes with toxin/invasive lesion, crypt abscess)
  - Sequelae: reactive arthritis (with Shigella, Salmonella, Yersinia) and **Guillan Barre Syndrome**
    - C. festus = undercooked beef, grows 25, capsule S protein inhibits C3b binding
    - C. jejuni = chicken, grows 42

## Dysentery

- ***Clostridium difficile*** (g+, anaerobe, normal gut flora, sporulator) antibiotic-induced colitis
  - Path: long course broad spec antibiotics→overgrowth C. difficile→production apoptotic toxins: enterotoxin A and cytotoxin B →inflammatory cells over lesion form pseudomembrane
  - Clinical: acute or chronic diarrhea after surgery or antibiotics
  - Morph: formation of fibropurulent membrane
  - UNIQUE→ denuded epithelium with neutrophil infiltrate, fibrin thrombi in lamina propria, and mushrooming mucopurulent exudate from crypts



## Dysentery

- ***E. coli*** (g-, rods, green sheen on EMB, coliform, FA)
- **(O157H7) no fermentation sorbitol** + grows at 45, commensal in animals, contaminated meat and unpasteurized milk
  - Path: shiga-like toxins acts on receptor (only in humans) → mRNA translation stopped → mucosal invasion → damage cells causing abdominal pain and diarrhea
  - Sequelae: **hemolytic uremic syndrome** = hemolytic uremia, renal failure, and thrombocytopenia... mostly in young and old
- **(EIEC)** Path: attaches and invades colon → inhibits absorption → initiates inflammation → watery to bloody diarrhea

## Non-neoplastic colonic polyps

1. Hyperplastic polyps
  - Most common type of polyp
  - Can occur anywhere in the colon or small intestine
  - Clinically insignificant but may be mistaken for adenomatous polyp
2. Inflammatory polyps (2 types)
  - Benign lymphoid polyps and inflammatory pseudopolyps
  - Consist of granulation tissue and remnants of mucosa
  - Caused by chronic inflammatory bowel disease

## Non-neoplastic colonic polyps

3. Hamartomatous polyps (2 types)
  - Juvenile polyps
    - Only located in the rectum
    - Occur mostly in children (can also be seen in adults)
  - Peutz-Jehgers (PJ) Polyps
    - Part of PJ syndrome
    - PJ syndrome – polyps of colon and s.i., melanotic accumulation in mouth, lips, hands, and genitals
    - PJ polyps have no malignant potential, but PJ syndrome associated w/adenocarcinoma of colon and CA at other sites (stomach, breast, ovary)

## Familial Adenomatous Polyposis

- uncommon autosomal dominant disorders
- differs from Peutz-Jehgers syndrome in that polyps are adenomatous, instead of hamartomas
- onset of polyps 2nd-3rd decade, followed by cancer in 10-15 years
- Features
  - innumerable adenomatous polyps that carpet the mucosal surface (500-2500); minimum of 100 polyps necessary for diagnosis
  - frequency of progression to colon adenocarcinoma approaches 100%
  - vast majority of polyps are tubular adenomas
  - cancer prevention includes colectomy and early detection of disease in first-degree relatives

## Colon Cancer

- Vast majority are adenocarcinomas; generally arise from pre-existing dysplastic proliferation (adenomatous polyps)
- Predisposing factors include diet (low fiber, high fat, high refined carbohydrates), adenomatous polyps (especially villous), inherited multiple polyposis syndromes (familial polyposis, Gardner syndrome, and Turcot syndrome), long standing ulcerative colitis, and genetics.
- Most people affected are aged 60-70, M>F.
- Lesions are generally slow growing.

## Colon Cancer

- Genetics – APC mutations common, methylation errors, ras mutation (larger polyps), 18q deletions, 17p losses (p53 suppressor gene), p53 mutations, overexpression of Bcl-2.
- Right sided lesions grow as polyps or can fungate and cause fatigue, weakness, and iron deficiency anemia from blood loss.
- Left sided lesions occur as circular lesions around the colon (napkin ring) that cause occult bleeding, changes in bowel movements, and LLQ cramping pain.

## Colon Cancer

- The most important prognostic factor is depth of tumor invasion.
- Stage A – limited to mucosa, 100% 5 year survival.
- Stage B – invades muscularis but not lymph nodes, 50% 5 year survival.
- Stage C – spread to local lymph nodes, 25% 5 year survival.
- Spread is by local invasion into lymphatics and the bloodstream; common metastasis to lymph nodes, liver, lungs and bones.

## Hepatitis A

- RNA picornavirus
- Transmission: Fecal/oral, liver/bile/stools/blood
- Acute infection only with no carrier state
- May present with jaundice without other symptoms
- Diagnosis
  - 1) anti-HAV antibodies
  - 2) high IgM antibodies diagnostic; switches to IgG with convalescence

## Hepatitis B

- Double-stranded DNA hepdnavirus, "Dane particle"
- Transmission through all body fluids excluding stool, vertical transmission leads to infant carrier state
- Can develop acute (most cases) or chronic infection- *T-cell mediated immunity responsible for disease manifestations*
- Long incubation (3 months) with carrier state
- Necessary for Hepatitis D infection

## Hepatitis B

- Chronic infection -↑risk of hepatocellular carcinoma
- Acute Dx: HBsAg(hepatitis B surface Ag) and IgM anti-HBc (HepB core)
- Carrier Dx: HBsAg without anti-HBs AB
- Dx active viral replication: HBeAg
- "window period" is time between disappearance of HBs antigen and subsequent appearance of anti-HBs antibody; during this time period, anti-HBc and anti-HBe are the only markers

## Hepatitis C

- RNA flavivirus- HCV
- Blood borne transmission, post-transfusion hepatitis, post- tansplant, not (very rare) sex
- Chronic infection with progression to cirrhosis
- *Chronic infection with HCV is associated with the development of hepatocellular carcinoma*
- Persistent infection and chronicity hallmarks of HCV
- Similar disease course to HBV
- Dx: anti-HBC antibody (IgM or IgG due to chronicity) and PCR of viral DNA

## Hepatitis D & Hepatitis E

- Hepatitis D – delta agent, RNA virus
  - Africa, Middle East, southern Italy
  - Only able to replicate and cause infection when encapsulated by HBsAg
  - Acute coinfection – after exposure to serum containing both
    - HBV must establish first to provide HBsAg – mild to fulminant
  - Superinfection – Chronic HBV carrier with inoculation of HDV
    - 80% develop chronic, progressive dx, leading to cirrhosis
- Hepatitis E – water-borne, enteric transmission
  - Young adults in Asia, India, sub-Saharan Africa, Mexico
  - 6 week incubation, self-limiting disease (2-4 wks)
  - High mortality among pregnant women!

## Hepatitis morphology

- Acute Hepatitis: The portal tracts will be infiltrated with a mixture of inflammatory cells
  - ballooning degeneration of the cells. This can progress to rupture of the cell membrane and cytolysis.
  - CD8 Tcell induced apoptosis; cells to shrink and become intensely eosinophilic with fragmented nuclei (Councilman Bodies)
  - Severe loss of hepatocytes can lead to bridging necrosis connecting portal and central regions.
  - HBV infected - cytoplasm packed with spheres and tubules of HBsAg; finely granular eosinophilic cytoplasm "ground glass appearance"
- Chronic Hepatitis: smoldering loss of hepatocytes leads to bridging necrosis and fibrosis. This can progress to cirrhosis with fibrous septae surrounding regenerative nodules.

## Alcoholic Liver Disease- Fatty Liver

- **Steatosis**(Fatty Change/Perivenular Fibrosis)
  - Liver is grossly enlarged, soft, yellow and greasy
    - Accumulation of small (microvesicular) lipid droplets in hepatocytes which become macrovesicular deposits with chronic intake
  - excess NADH shunts towards fat synthesis
  - impaired assembly and secretion of lipoproteins
  - hepatomegaly with mild increase in bilirubin and alkaline phosphatase levels
  - With long standing disease, fibrosis occurs around central vein where damage become irreversible
  - Fatty liver changes are completely reversible

## Alcoholic Liver Disease- Hepatitis

- necrosis, inflammation, fibrosis, Mallory bodies
- Occurs after a binge- causes P450 induction and high acetaldehyde levels, both of which result in oxidative damage to membranes.
- malaise, anorexia, tender hepatomegaly
- high bilirubin and alkaline phosphatase
- may be reversible
- Fibrosis- sinusoidal and perivenular fibrosis
- Neutrophil reaction- accumulation around degenerating cells; also monocytic and lymphocytic infiltrates

## Alcoholic Liver Disease- Cirrhosis

- As necrotic tissue is lost, liver becomes shrunken and is replaced by fibrotic tissue
- Typical pattern: micronodular cirrhosis
  - nodule formation separated by fibrous tracts surrounding regenerating hepatocytes
  - Form of postnecrotic cirrhosis
- May occur with or without previous steatosis or hepatitis.
- chronic necrosis and inflammation leads to loss of liver tissue, nodular fibrosis, and portal hypertension.
- elevated bilirubin, aminotransferase and low proteins (albumin, clotting factors)
- causes: variceal hemorrhage, ascites, caput medusa, malaise, hepatocellular carcinoma

## Fetal Alcohol Syndrome

- Alcohol abuse during pregnancy
  - 1200 cases per year
- Growth retardation, microcephaly, facial dysmorphism, congenital anomalies
  - Fetal neurological tissue particularly susceptible to damage from alcohol
- Most common cause of preventable mental retardation in the US

## Hemochromatosis - General

- Lifelong iron overload
  - lack of negative feedback regulation of iron absorption with accumulation of 0.5-1.0g/year
  - Symptoms in 5<sup>th</sup>-6<sup>th</sup> decade with 50g accumulation (nl. 1-2g)
- Genetic susceptibility is autosomal recessive
  - Linked to HLA-H on chromosome 6
  - 2<sup>o</sup> forms from repeated transfusions or excess iron intake
- Male:Female ratio 7:1
  - Women protected by physiological iron loss (menstration)
- Classic triad: micronodular cirrhosis, brittle diabetes, skin hyperpigmentation
  - Hepatocellular carcinoma risk increased 200-fold

## Hemochromatosis - Pathology

- Deposition of ferritin and hemosiderin in organs
  - Free radicals form in Fenton reaction
  - Lipid peroxidation, stimulation of collagen formation, and DNA damage
- Hepatic hemosiderosis with micronodular cirrhosis
- Pancreatic iron deposition with fibrosis
- Myocardial iron deposition
  - arrhythmia, restrictive cardiomyopathy
- Iron deposition in many other organs
  - excess melanin production, arthralgia, hypogonadism, impotence

## Wilson's Disease

- (hepatolenticular degeneration)
- Autosomal recessive deficiency in hepatic canalicular copper transport protein
    - Liver cannot excrete copper in bile or load onto ceruloplasmin
    - First accumulates in liver, then spills into blood by age 5 and deposits in organs
    - Levels typically symptomatic in young adulthood (rarely younger than 5 or older than 30)
  - Deposits in liver with fatty change and chronic hepatitis with Mallory bodies
    - mixed cirrhosis and hepatic encephalopathy
    - deposits stain with rhodamine
  - Copper deposits in brain, especially basal ganglia
    - Parkinsonism, inappropriate behavior, and dementia
  - Kidney disease leading to osteoporosis, renal calculi
  - Kayser-Fleischer rings: copper deposits outside iris

## $\alpha$ -1 Antitrypsin Deficiency

- Autosomal recessive mutation of protease inhibitor synthesized in hepatocytes
  - Does not migrate to Golgi apparatus and precipitates in endoplasmic reticulum; 10% of homozygotes show liver dis.
  - Chronic hepatitis in childhood with micronodular cirrhosis or latent disease presenting in adulthood with macronodular cirrhosis
  - Can cause neonatal cholestasis and biliary tract fibrosis
  - PAS-positive, diastase resistant globular cytoplasmic inclusions
  - Infrequently fatty change and Mallory bodies
- 2-3% lifetime hepatocellular carcinoma risk

## Reye's Syndrome

- Rare, often fatal childhood illness (6 months-15 years)
  - Widespread mitochondrial injury with encephalopathy and liver injury
  - Pathogenesis unclear, but associated with viral infections (esp. influenza, chicken pox) treated with aspirin
  - Usually begins 3-7 days after viral illness presents
- Sudden onset of vomiting and lethargy with progressive rostral-caudal degeneration
- Microvesicular fatty liver
  - Anion-gap acidosis, hyperammonemia, hypoglycemia, elevated free fatty acids, hyperbilirubinemia, elevated liver enzymes
- Cerebral edema and swelling of astrocytes
- 25% progress to coma; 10-40% fatal

## Pharmaceutical Liver Toxicity

- Direct toxicity of metabolites to hepatocytes, immune-mediated, or hormonal injury
- Cholestasis—hyperbilirubinemia with pattern indicative of biliary obstruction
- Hepatocyte injury
  - Mild toxicity causes fatty liver change
  - Severe injury can result in fulminant necrosis
- Idiosyncratic reaction—risk does not change with dose
  - Cholestasis: typical antipsychotics
  - Hepatocellular injury: halothane, flurothane
- Dose-related—risk and severity increase with dose
  - Cholestasis: testosterone, oral contraceptives
  - Hepatocellular injury: carbon tetrachloride, acetaminophen

## Liver Labs: Bilirubin

- Byproduct of heme metabolism
  - Hemoglobin --> biliverdin --> unconjugated (indirect) bilirubin --> conjugated (direct) bilirubin --> urobilinogen
- Unconjugated: insoluble, albumin-bound form
  - Not secreted in urine
- Conjugated: soluble glucuronidated molecules
  - Physiologically secreted in bile
  - Presence in blood and urine is pathologic (indirect:direct normal 5-10:1)
- Urobilinogen (gut flora by-product) is H<sub>2</sub>O soluble
  - 80% excreted in feces
  - 20% reabsorbed; mostly enters enterohepatic circulation
  - small amount physiologically excreted in urine

## Liver Labs: Hyperbilirubinemia

- All forms cause jaundice, icterus (apparent at >2mg/dL)
- Unconjugated is neurotoxic, especially to infants (kernicterus)
- Hemolysis
  - Increased heme release leads to unconjugated hyperbilirubinemia
  - Normal liver function, so conjugated bilirubin is excreted, and does not appear in the blood
  - Increased delivery to intestine leads to increased urinary urobilinogen
  - Increased bilirubin delivery to gallbladder leads to pigmented gallstones

## Liver Labs: Hyperbilirubinemia (Continued)

- Biliary obstruction
  - Conjugated bilirubin is not excreted in feces, and levels increase in blood and urine (>50% conjugated bilirubinemia suggests obstruction)
  - Decreased intestinal delivery leads to decreased urinary urobilinogen
  - Bile salts not excreted in stool, resulting in increased blood levels and deposition in skin; causes acholic stool and pruritis

## Liver Labs: Hyperbilirubinemia (Continued)

- Hepatocellular injury
  - Liver cannot properly conjugate bile, leading to unconjugated hyperbilirubinemia
  - Injured hepatocytes lose membrane integrity, so conjugated bilirubin spills into blood; however, levels of conjugated bilirubin are still much lower than levels of unconjugated bilirubin
  - Appears with increase in liver enzyme levels and signs of liver failure

## Liver Enzymes

- **Aspartate aminotransferase (AST/SGOT), Alanine aminotransferase (ALT/SGPT)**
  - Necrosis of tissue releases enzymes into blood
  - Highest levels in acute necrosis; persistent elevation in chronic disease
  - ALT more specific for liver than AST
- **Alkaline Phosphatase**
  - Increase signifies injury or proliferation of bile duct epithelium
  - Electrophoresis separates from bone remodeling isoform
- **$\gamma$ -glutamyltransferase (GGT)**
  - Highest in extrahepatic obstruction(5-30X); mild elevation with infectious hepatitis(2-5X)
  - Extremely sensitive for hepatobiliary disease
  - Earliest to increase and remains elevated

## Liver Labs – Other Markers

- Increase in PT and/or aPTT can be due to EITHER
  - Decreased vitamin K absorption due to fat malabsorption (bile deficiency, intestinal damage) or intestinal flora derangement
  - Decreased clotting factor synthesis (severe liver damage)
- Decreased albumin
  - Normally synthesized by liver to increase plasma oncotic pressure
  - Decrease causes anasarca and is a poor prognostic sign
- Hyperammonemia
  - Impaired urea cycle metabolism
  - Leads to hepatic encephalopathy, hyperreflexia, asterixis
- Elevated serum lipids (cholesterol, TGs)
  - Impaired hepatic lipid metabolism

## Liver failure, liver infarction

- 2 most common causes – viral hepatitis and ethanol
- Can occur acutely or gradual accumulation of damage
  - Need to lose 80-90% of function before “failure”
- Loss of protein synthesis
  - Serum albumin, coagulation components
  - Can measure with PTT, CBC
- Loss of metabolic functions
  - Hyperestrogenism – most common cause of gynecomastia
  - Palmar erythema, telangiectasias, weight loss, muscle wasting, hypoglycemic, fetor hepaticus
- Hepatorenal failure - no intrinsic renal damage

### Liver failure, liver infarction

- Hepatoencephalopathy – CNS, neuromuscular system
  - Buildup of toxic products, shunting of blood
- Ischemia rare – dual blood supply
- Infarctions generally localized
- Typically anemic and pale-tan, can be hemorrhagic
- Associated with hepatic artery thrombosis, PAN, embolism, neoplasia or sepsis
- Portal vein thrombosis – abdominal pain, ascites, portal hypertension, bowel obstruction, bowel infarction
- Extrahepatic – cancers, sepsis, post surgical
- Intrahepatic – infarct of Zahn – sharp line of red/blue discoloration

### Liver Disease in Pregnancy

- **Pre-eclampsia** causes periportal necrosis (hepatic hematoma when severe) and the subclinical HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
- **Acute fatty liver** of pregnancy is microvesicular steatosis during third trimester, due to metabolic defects...can cause hepatic failure
- **Intrahepatic cholestasis** often causes pruritis (bile salts in skin)...benign except gallstone risk
- Termination of pregnancy cures all three

### Hepatocellular Carcinoma

- In US, alcoholic cirrhosis, HCV, hemochromatosis biggest factors... HBV worldwide
- Gross: may be unifocal, multifocal, or diffuse
- Well-differentiated tumors form nests with central lumen, or carcinoma may be anaplastic
- Strong propensity for vascular invasion... intrahepatic and IVC metastasis
- Symptoms masked by underlying hepatitis/cirrhosis... $\alpha$ -fetoprotein elevated 50-75%, imaging most important diagnostically

### Cholangiocarcinoma

- Malignancy in biliary tree, arising either intra- or extrahepatic
- Increased risk with primary sclerosing cholangitis, Caroli disease, and choledochal cysts
- Sclerosing well-differentiated adenocarcinomas that invade lymph and sinusoids, causing extensive intrahepatic metastasis...like normal biliary epithelium, do not stain for bile
- Late symptomology (bile obstruction; lung, vertebral, adrenal, brain metastasis) and poor prognosis

### Portal HTN, Congestive Liver Disease

- Pressure difference of 5mmHg b/w Portal and hepatic vv.
- Causes:
  - Prehepatic—portal and splenic vv. thrombosis
  - Intrahepatic—CIRRHOSIS, schistosomiasis (3<sup>rd</sup> world)
  - Posthepatic—R Heart failure, Budd-Chiari syndrome
- Sx—collaterals (caput medusa, esophageal varicies, hemorrhoidal plexus), ascites, hepatic encephalopathy

### Intrahepatic Congenital Biliary Disease

Condition	Description	Clinical Importance
Von Meyerburg's Plexes	incomplete involution of embryonic bile duct	clinically insignificant; mildly dilated ducts
Caroli's Syndrome	segmentally dilated ducts that may contain bile	cholangitis, hepatic abscesses, and portal hypertension, assoc. w/ congenital hepatic fibrosis
Polycystic Liver Disease	AD; cysts <i>detached</i> from biliary tree (NO BILE)	adult form of renal polycystic disease
Congenital Hepatic Fibrosis	AR; cysts <i>connected</i> to biliary tree	childhood form of renal polycystic disease; liver failure common cause of death
Paucity of BD (Alagille Syndrome)	AD; portal tract bile ducts <i>completely absent</i> ; also have CV, vertebral, facial abnormalities	risk for hepatic failure and *** <u>hepatocellular carcinoma</u> (NOT cholangiocarcinoma), fat malnutrition

## Congenital Hyperbilirubinemia

- **Unconjugated**
  - Gilbert syndrome is most common: defect in uptake/conjugation of unconjugated bilirubin
    - Usually mild or asymptomatic
  - Crigler-Najjar syndrome: decreased conjugating enzymes
    - Type 2 is fatal
- **Obstructive (Conjugated)**
  - Dubin-Johnson: defect in secretion into intrahepatic ducts, see black pigment in hepatocytes
  - Rotor's Syndrome, like Dubin-Johnson but no black pigment

## Extrahepatic Congenital Biliary Disease

- **Biliary Atresia**: complete obstruction of bile flow due to destruction of all/part of extrahepatic bile ducts
  - born with normal ductal system, destroyed over weeks to months
  - periductal inflammation and fibrosing stricture of hepatic/common bile duct
  - causes multiple: viruses, toxins, autoimmune, genetics
  - leads to cholestasis & rapidly progressing secondary biliary cirrhosis
  - ↑ bilirubin, modest ↑ transaminase & ALP
  - #1 cause of death due to liver disease in early childhood

## Extrahepatic Congenital Biliary Disease

- **Choledochal cysts**: congenital dilations of common bile duct
  - present before age 10 w/ jaundice, recurrent colicky abdominal pain
  - may exist in conjunction with cystic dilations of intrahepatic biliary tree (caroli's disease)
  - multiple forms: segmental cylindrical dilations; diverticuli; choledochoceles (cystic lesions protruding into duodenum)
  - ↑ risk for stones, stenosis, stricture, intrahepatic ductal disease, bile duct carcinoma

## Primary Biliary Cirrhosis

- Autoimmune destruction of the intrahepatic bile ducts
- Females >> males, middle-age, insidious onset
- Symptoms from bile obstruction: pruritis, jaundice, dark urine, light acholic stools, xanthomas, hepatosplenomegaly
- Laboratory:
  - Conjugated hyperbilirubinemia
  - increased serum alkaline phosphatase, bile acids & cholesterol
  - Elevated serum anti-mitochondrial IgM antibodies
- May be symptom free for many years, but w/ time (2 or more decades) destruction of liver architecture & portal tract fibrosis leads to cirrhosis and portal HTN

## Primary Biliary Cirrhosis

- associated w/ **hepatocellular carcinoma** in 3-4%
- treatment = liver transplant
- Morphology:
  - Dense **lymphocytic** infiltrate in portal tracts w/ **noncaseating granulomatous destruction** of medium sized intrahepatic terminal & conducting bile ducts (non-suppurative inflammation)
  - Proliferation of bile duct epithelium in portal tracts upstream from the damaged bile ducts (florid ductal lesions)
  - Periportal inflammation and necrosis of hepatic parenchyma; bile stasis stains hepatic parenchyma green
  - Over years to decades, portal tract scarring and bridging fibrosis occur, leading to micronodular cirrhosis

## Secondary Biliary Cirrhosis

- Intrahepatic biliary destruction secondary to long-standing extra-hepatic biliary tree obstruction:
  - Gallstones, strictures, carcinoma of pancreatic head, biliary atresia (kids)
- Same symptoms and lab values as primary biliary cirrhosis but w/out the increase in serum IgM
- Morphology:
  - Prominent bile stasis in bile ducts & formation of bile lakes
  - Green bile pigment staining of hepatic parenchyma
  - Proliferation of ductal epithelium with surrounding **neutrophilic** infiltrate, portal tract edema and feathery hepatocyte degeneration
  - Eventual periportal fibrosis & micronodular cirrhosis

## Primary Sclerosing Cholangitis

- Inflammation and obliterative fibrosis of both intrahepatic & extrahepatic bile ducts
- Male > female, 3<sup>rd</sup>-5<sup>th</sup> decades, possibly autoimmune, 50-70% associated w/ **ulcerative colitis**, "Walter Payton disease"
- Same insidious onset, same symptoms and labs as primary biliary cirrhosis, but with autoantibodies in <10%
  - Over time, leads to cirrhosis & portal HTN like 1° & 2° biliary cirrhosis
- increased risk of **cholangiocarcinoma**
- Morphology
  - Concentric periductal portal tract fibrosis → **onion-skinning**
  - Lymphocytic infiltrate
  - segmental stenosis of extra & intrahepatic bile ducts → "beading" on xray

## Gallbladder Cholelithiasis

- clinical correlations
  - obesity, genetic predisposition, high caloric diet, high cholesterol, GI disorders (cystic fibrosis), female sex hormones, age, diabetes
  - increasing incidence with age: significant proportion of women in their 80's have stones at autopsy
- symptomology: fatty food intolerance, colic, infections, mucosal erosions with perforation and fistula formation
- cholesterol stone formation
  - cholesterol stones: radiolucent, large (several cm.)
  - bile must be supersaturated with cholesterol
- pigmented gallstones: increased hemolysis and delivery of unconjugated bilirubin to liver
  - jet black ovoids; associated with Oriental race, chronic hemolysis, ETOH

## Gallbladder Cholecystitis

- **Cause:** 90% are due to gallstones; ischemia
- **Pathogenesis:**
  - Protective mucus layer is disrupted > dysmotility > distention and increased intraluminal pressure > decreased blood flow; may later develop infection
- **Pathology:**
  - Empyema of the gallbladder: lumen filled with pus
  - Hydrops of the gallbladder: atrophic chronically obstructed gallbladder containing clear secretions
  - Mild: wall is thickened, edematous, hyperemic
  - Severe: gangrenous with perforations
- **Clinical:**
  - RUQ pain, fever, nausea, vomiting, leukocytosis
  - Complications: ascending cholangitis, perforation and abscess formation, rupture and peritonitis, biliary enteric fistula

## Biliary Cancers

- Cholangiocarcinoma
  - adenocarcinomas of the ductules; <10% of hepatic carcinomas
  - clearly defined glandular and tubular structures; markedly desmoplastic with mucus in cells
  - Associated with primary sclerosing cholangitis, inflammatory bowel disease (particularly ulcerative colitis), and choledochal cysts
  - NOT associated with cirrhosis or chronic hepatitis
  - hematogenous spread to lungs, bone, adrenals, brain; lymph nodes in 50%

## Biliary Cancers

- Ductal Carcinoma
  - M>F; assoc. with chronic inflammation; ascaris and liver flukes, Oriental pop.
  - Also associated with primary sclerosing cholangitis, inflammatory bowel disease, or choledochal cysts
  - uncommon tumors, extremely insidious
  - gallstones present only in 1/3
  - 75% metastasize before discovery
    - due to development of jaundice, may be relatively small at diagnosis
    - however, most not resectable at time of surgery

## Acute Pancreatitis

- Autodigestion of the pancreas by pancreatic enzymes
- Cause: alcohol (65% of cases; men) and gallstones/biliary disease (35-60%; women) are primary risk factors
- Pathology
  - Edema, fat necrosis, inflammation, proteolytic destruction of parenchyma, destruction of blood vessels with hemorrhage, pseudocyst formation
  - No fibrosis
- Clinical
  - Serum amylase and lipase will be increased
  - Jaundice, severe abdominal pain
  - Hypocalcemia can result due to Ca<sup>++</sup> collecting in Ca<sup>++</sup> soaps



## Chronic Pancreatitis

- Chronic pancreatitis is usually secondary to repeated exacerbations of *subclinical* acute pancreatitis
- Almost always associated with alcohol abuse. Also biliary disease, elevated  $Ca^{++}$ , elevated lipids
- Pathology
  - Inflammation with destruction of exocrine pancreas, fibrosis, and later destruction of endocrine parenchyma
  - Calcification (often visible on x-ray)
  - Dilated ducts with protein plugs
- Clinical
  - Fat malabsorption may occur (Vit A, D, E, K)
  - Clinical signs: variable, but include abdominal/back pain and steatorrhea
  - May have repeated exacerbations or remain subclinical until the development of pancreatic insufficiency or diabetes mellitus
  - Amylase and lipase may not be elevated due to destruction of acini

## Pancreatic Pseudocysts and Islet Cell Tumors

- Pseudocysts
  - Occur at locations of inflammation, necrosis, or hemorrhage (e.g. acute pancreatitis)
  - Usually solitary and located at tail (unilocular = cyst, multilocular = cancer)
  - Necrotic, hemorrhagic material rich in pancreatic enzymes surrounded by granulation tissue
  - No epithelial lining or communication with ducts
  - Usually spontaneously resolve; Can cause abdominal pain, peritonitis, and hemorrhage
- Benign tumors of islet cells can cause insulinoma, gastrinoma (Zollinger-Ellison), glucagonoma, pancreatic carcinoid tumor, etc...

## Pancreatic Cancer

- Almost always adenocarcinoma. >99% ductal.
- Associated w/ smoking, diet, industrial toxins, not alcohol
- clinical
  - Often arises in pancreatic head → jaundice
  - Involvement of pancreatic tail → 2° diabetes
  - abdominal pain radiating to back, anorexia, migratory thrombophlebitis (Trousseau sign), distended gall bladder
- Histology
  - ranges from well-differentiated glandular adenocarcinomas to anaplastic cuboidal epithelium
  - Deeply infiltrative growth
  - Strong desmoplastic response
- Silent and widespread dissemination (massive hepatic metastasis). <1 yr survival.