Case 1

Febrile with T 100.7 F, pulse 100, BP 150/90
Abdomen: RUQ and epigastric tenderness to light palpation, with inspiratory arrest and increased pain on deep palpation. (Murphy’s sign)

Labs: WBC 12,500; (normal bilirubin, Alk phos, AST, ALT).

Ultrasound shows normal liver, normal pancreas without duct dilatation and a distended thickened gallbladder with a stone in cystic duct.

DIAGNOSIS???

Acute Cholecystitis

Epigastric, RUQ pain
Radiate to shoulder
Fever, chills
Nausea, vomiting
Mild Jaundice
RUQ guarding, tenderness
Tender Mass (50%)
Culture Normal Biliary Tree:
No Bacteria
Bacteria Normally Cleared

In G.B. with cholelithiasis
Bacteria cling to stones
If stone obstructs cystic duct orifice
G.B. distended
Mucosa Disrupted
Bacteria invade G.B. Wall

**Gallstones**  
(Cholelithiasis)

- 10 - 20% Adults
- 35% Autopsy: Over 65

- Over 20 Million
- 600,000 Cholecystectomies
- #2 reason for abdominal operations

**Gallstones**  
(Cholelithiasis)

- Two major types- classified by composition
  – Cholesterol (mixed) and pigment stones
  – Mixed stones - cholesterol with (bilirubin, calcium salts, protein, bile acids, fatty acids)
- Western nations: 90% stones are cholesterol/mixed stones; 10% pigment stones
- Mixed stones – associated with high cholesterol
- Pigment stones – associated with hemolysis, biliary tract infections
Cholelithiasis

- 50 - 70% Asymptomatic
- Pain:
  - Biliary colic
  - Epigastric, RUQ
  - Abrupt, may last hours
  - Sudden obstruction:
    - Cystic Duct, CBD
    - Pain relieved
    - Stone back into G.B. or passes thru CBD
- Fatty Food Intolerance:
  - Indigestion, N. and V.

Choledocholithiasis
(Stones in the common bile duct)

- 5 - 25% of pts. with G.B. stones
- Pain: Epigastric, RUQ
- Stones may be passed
- Obstructive Jaundice
  - May be intermittent
- Ascending Cholangitis
  - Infection: to liver
- 20%: No pain; 25% no jaundice

Chronic Cholecystitis

- Associated with calculi in 95% of cases.
- Multiples episodes of inflammation cause GB thickening with chronic inflammation/ fibrosis and muscular hypertrophy.
- Rokitansky - Aschoff Sinuses (mucosa herniates through the muscularis mucosae)
- With longstanding inflammation GB becomes fibrotic and calcified “porcelain GB”
Rokitansky-Aschoff sinuses

Chronic Cholecystitis

- Fibrosis
- Chronic Inflammation
- Rokitansky - Aschoff Sinuses
- Hypertrophy: Muscularis

Cholesterolosis

Focal accumulation of cholesterol-laden macrophages in lamina propria of gallbladder (incidental finding).

Adenomyoma of Gall Bladder
Carcinoma: Gall Bladder

Uncommon: 5,000 cases / year
Fewer than 1% resected G.B.
Sx: same as with stones
5 yr. survival: Less than 5%
(survival relates to stage)

90%: Stones
Long Hx: symptomatic stones
Stones: predispose to CA., but uncommon complication

Case 2

56 year old woman presents to ER in shock, following rapid onset of severe upper abdominal pain, developing over the previous day.

Hx: heavy alcohol use.

LABs: Elevated serum amylase and elevated peritoneal fluid lipase
Case 2 - clinical course

Patient developed rapid onset of respiratory failure necessitating intubation and mechanical ventilation.

Over 48 hours, she was increasingly unstable, with evolution to multi-organ failure, and she expired 82 hours after admission.

An autopsy was performed.

Acute pancreatitis

- Edema, congestion
- Advanced hemorrhagic pancreatitis, fat necrosis
- Necrotic abscess, gangrene

Pathophysiology of acute pancreatitis

<table>
<thead>
<tr>
<th>Severity</th>
<th>Stage 1: Pancreatic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid</td>
<td>Edema, inflammation, fat necrosis, variable necrosis of pancreatic secretory cells</td>
</tr>
<tr>
<td>Severe</td>
<td>Local (peripancreatic) effects, retroperitoneal edema, extensive fat necrosis, leuko with &quot;third-spacing&quot; of fluid and electrolytes</td>
</tr>
</tbody>
</table>

Stage 2: Systemic complications
- Hypotension/shock, metabolic disturbances, organ failure, sepsis
**Acute Pancreatitis**

US: 45% of cases have gallstones and choledocholithiasis; 35% associated with heavy alcohol ingestion.

Pathology: Enzyme release is triggered with digestion of pancreas, necrosis of fat and lobules, hemorrhage from damaged blood vessels.

Variable severity: may lead to liquefactive necrosis, hemorrhage. Mild cases – may have local complications: abscess, pseudocyst.

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**ETIOLOGIES**
- Obstructive
- Toxins/drugs
- Metabolic
- Infection
- Vascular
- Trauma
- Idiopathic

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**Acute pancreatitis—initiation of autodigestion**

Enzymatic cleavage

Trypsinogen (inactive)

Trypsin (active)

Trypsinogen activation peptide (TAP)

Cleavage site

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**Activation cascade for pancreatic enzymes in acute pancreatitis**

- Zymogen
  - Chymotrypsinogen
  - Trypsinogen

- Proenzymes
  - Trypsinogen
  - Procarboxypeptidase A and B
  - Prophospholipase A

- Active enzymes
  - Chymotrypsin
  - Elastase
  - Carboxypeptidase A and B
  - Phospholipase A
  - Trypsin

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**Protection against autodigestion**

- Pressure gradient favoring unidirectional flow out of gland into duodenum

- Presence of trypsin inhibitors in pancreatic tissue and secretions

- Secretion of most enzymes as inactive precursors (zymogenes)

- Packaging of enzymes in membrane-bound zymogen (secretory) granules

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**Possible role of secretory block in genesis of pancreatitis**

- Intracellular activation of trypsinogen due to:
  - Lysosomal enzymes
  - Autoactivation related to change in zymogen granule pH or redox state

- Block in enzyme secretion due to:
  - Gallstone impacted at duodenal papilla
  - Excessive acinar use
  - Metabolic disturbance (e.g., T2D, T2 hypercoag)
  - Drugs (Aspirin, d-di)

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**Chronic Pancreatitis**

Continuing inflammation with irreversible changes in architecture, structure and function.

Fibrosis of parenchyma with distortion of duct architecture, loss of exocrine secretory function.

Changes may be focal or widespread.
Complications of Chronic Pancreatitis

Chronic abdominal pain, severe and unremitting, radiating to back.

- Malabsorption due to reduced enzyme secretion. (After 90% of pancreas is fibrotic, reduced lipase and trypsin secretion lead to steatorrhea).
- Pancreatic diabetes associated with decreased islets.
- Pancreatic pseudocysts with extension or rupture in adjacent organs.
- Risk factor for development of carcinoma of pancreas.

Case 3

67 year old woman with recent onset painless jaundice.

- History of 15lb weight loss over last 3 months.
- She smoked 1 pack per day x 35 years.
- Physical exam: palpable GB
- ERCP was performed with Endoscopic Ultrasound (EUS) evidence of a large mass in the head of the pancreas.
- An endoscopic FNA was performed.

Carcinoma of Pancreas

- Weight loss: 70%
- Pain: Abdominal 50%, Back 25%
- Persistent jaundice
- Anorexia
- Loose stools
- Nausea, vomiting

Courvoisier’s Sign:
Dilated palpable GB often reflects tumor obstructing the common bile duct.
Carcinoma of Pancreas
Enlarged, palpable G.B.: 50%
Mass in upper abdomen
Enlarged, nodular liver
Ascites
Jaundice
Migratory thrombophlebitis
(Trousseau’s sign)

Adenocarcinoma: Pancreas
60 - 70% Head
20 - 30% Body
5 - 10% Tail
Pancreatic adenocarcinoma – Lymph node metastases

Pancreatic adenocarcinoma – perineural invasion

Prognosis:
Adenocarcinoma: Pancreas

100 Patients
90 - 95 unresectable tumor
5 - 10 resection
1 - 2% 5 year survival
Most pts. die: 6 - 12 months

Pancreas Cancer Genetics

5-10% of cases are familial, some with defined genetic syndromes

Hereditary Pancreatitis: germline mutations in trypsinogen gene on 7q35 with 40% lifetime risk of developing pancreatic cancer.

Pancreatic cancers described in BRCA2 mutations in familial breast cancer kindreds.

Associated with germline p16 mutations, and HNPCC.

Role of oncogenes: KRAS-90%, p16-95%, p53-75%

Pancreatic Cystic Lesions

- Pseudocyst (benign – NOT a NEOPLASM)
- Serous cystadenoma (benign)
- Mucinous cystic neoplasm (benign, borderline or malignant)
- Intraductal papillary mucinous neoplasm (benign, borderline or malignant)

In-situ progression to Cancer
Pancreatic Pseudocyst

Pancreatic serous cystadenoma

NOT NEOPLASTIC - RESULT OF ACUTE PANCREATITIS

BENIGN

Mucinous cystic neoplasm

Intraductal mucinous neoplasm

Not associated with the pancreatic duct
Clinical spectrum: benign to malignant

Associated with the pancreatic duct
Clinical spectrum: benign to malignant

Pancreatic Endocrine Neoplasms

- 5% of pancreatic neoplasms
- “Islet cell Tumors” – inaccurate; arise from pluripotential ductal cells that differentiate along neuroendocrine lines.
- All have malignant potential except microadenomas (<5mm); No definite criteria to distinguish between benign and malignant (except for mets)

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Pancreatic Endocrine Tumors

Pancreatic Endocrine Neoplasms

Functional - recognizable syndrome; detect hormone in serum.
- Insulinoma (most common); hypoglycemia; 10% malignant
  - 10% assoc with MEN1
- Gastrinoma; duodenal ulcers; 75% malignant
  - 25% assoc with MEN1

Nonfunctional - no syndrome; normal serum hormone levels (except Pancreatic Polypeptide).
- Incidental; Obstructive Sx- head of pancreas; 50 – 90% malignant.

Pancreatic Endocrine Neoplasms

Classification:
Neuroendocrine neoplasm, well differentiated
  - Low grade: 0-1 mit/50HPF; no necrosis
  - Intermediate grade: >2mit/50 HPF; +/- necrosis

Neuroendocrine carcinoma, high grade
Small cell carcinoma / large cell neuroendocrine
  - High grade: >10mit/10 HPF; widespread necrosis

Pancreatic Endocrine Neoplasms

- Usually occur in body/tail
- Hypervascular, circumscribed
- Highlighted with Octreotide Scan (somatostatin receptors)
- Usually slow growing, mets to LNs, liver, bone (recommend resection of mets)