Pancreatic secretions and bile are required for digestion

- Bile: Emulsification of fat
- Pancreatic secretions: Digestion of proteins, carbohydrates and fat
GALLSTONES

Bile

- Secreted by hepatocytes
- Transported through the biliary system
- Stored and concentrated in the gallbladder
- Released into duodenum after ingestion of food (mediated by CCK)
**Bile composition**

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Salts (Lecithin)</td>
<td>12%</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>4%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.7%</td>
</tr>
<tr>
<td>Miscellaneous (Pigment, Protein)</td>
<td>1%</td>
</tr>
<tr>
<td>Water (H₂O)</td>
<td>84.3%</td>
</tr>
</tbody>
</table>

**Formation and secretion of bile acids**

1. **Synthesis (0.3-0.6g)**
   - Cholesterol
   - Cyp7a
   - Bile acids

2. **Enterohepatic circulation (5-10x daily)**
   - ABCG11
   - ABCG11

**Fecal loss 0.3-0.6g**
(equals hepatic synthesis)
FXR is bile acid sensor of bile acids and lowers intracellular bile acid levels (to prevent toxicity)

Secretion of cholesterol

Cholesterol

- Cyp7a
- Bile acids
- FXR
- ABCG11
- Hepatocyte

Synthesis

Cholesterol

- HDL
- LDL
- LDL-R

Export into Periphery (VLDL)

Bile acids

- ABCG5/8
LXR is a cholesterol sensor and lowers intracellular cholesterol levels

Cholesterol requires bile salts for solubilization
Excess cholesterol precipitates to form cholesterol crystals and stones

Composition of Gallbladder bile

- Healthy controls
- Patients with Gallstones
**Cholesterol stones:**
- Great majority of all stones in the US (>70%)
- either pure cholesterol stones or mixed stones (more than 50% cholesterol content)

**Pigment stones:**
- contain pigment = bilirubin
- usually due to increased hemolyis
- or due to decreased bilirubin conjugation

---

**x-Ray Appearance of Gallstones**

<table>
<thead>
<tr>
<th>Radio-opaque</th>
<th>Radioluscent</th>
</tr>
</thead>
<tbody>
<tr>
<td>27% = Cholesterol Stones</td>
<td>83% = Cholesterol Stones</td>
</tr>
<tr>
<td>73% = Pigment Stones</td>
<td>17% = Pigment Stones</td>
</tr>
</tbody>
</table>
Factors Favoring Cholesterol Gallstones

- Hepatic Production of Lithogenic Bile
  
  **A. Decreased Secretion of Bile Acids**
  1. Fasting (pooling of bile salts in gallbladder)
  2. Decreased bile salt synthesis despite diminished pool
  3. Cyp7a mutations (rare)
  4. Decreased bile acid return to liver (ileal resection)

  STASIS

  - NUCLEATION

  SUPERSATURATION

- Gallbladder Factors
  
  1. Stasis (TPN, progestins, crash diet)
  2. Nucleation (increased mucoproteins)

  • Excess cholesterol secretion
  1. Obesity
  2. Estrogens
  3. Genetic factors/Ethnicity (Pimas)
• 80% of all gallbladder stones will never cause symptoms

• 1-4% of gallbladder stones/year cause symptoms (e.g. colic, pancreatitis)

**Natural History of Gallstones**

**Ultrasound**

**Dilated Duct**

**Intraductal stone** (not always present)

**ERCP**

**Schematic diagram for the management of gallstone disease**

- **Asymptomatic**
  - **Follow-up**
  - **Laparoscopic Cholecystectomy +/- ERCP**
  - **Complicated**
  - **Uncomplicated**

- **Symptomatic**
  - **Only if contraindications for surgery:**
    - Observation
    - Ursodiol
    - Possibly emergency
PANCREAS PHYSIOLOGY

Pancreas macro- and microanatomy

Gall bladder
Common bile duct
Pancreas
Pancreatic duct
Duodenum
Duct
Acini
Islet of Langerhans
Pancreatic acini
Delta cell
Alpha cell
Beta cell
PP cell
Vessel/NBC
Major functional units

- **ACINUS**
  - Digestive enzyme secretion

- **DUCTULE**
  - Water, bicarbonate secretion

---

**HC0₃ concentration and pH increase with increased pancreatic secretion**

Meal-stimulated secretion

The increase in HC0₃ serves to buffer the acidic pH of food after it passes into the duodenum.
Bicarbonate secretion is regulated through hormonal and neural mechanisms

**Cephalic phase**
- Food cues

**Gastric phase**
- Distention

**Intestinal phase**
- pH sensitive secretin-releasing factor
- Secretin
- Secretin S-cells
- duodenal pH<4.5
- pH sensitive secretin-releasing factor
- Secretin S-cells

**Hormonal Mechanism**
- Secretin
- Secretin-releasing factor
- Secretin S-cells

**Neural Mechanism**
- Vagal afferents
- Vagal efferents
- Ach (Acetylcholine)
- Dorsal Vagal Complex

**Regulation Sites**
- Dorsal Vagal Complex
- Vagal afferents
- Vagal efferents

**Secretion Factors**
- H₂O, NaHCO₃
- Secretin
- Secretin-releasing factor
- Secretin S-cells
Regulation of Enzyme Secretion

Cephalic phase
Food cues

Gastric phase
Distention

Intestinal phase
CCK-sensing Vagal Afferents
Proteins, AA, FA

Dorsal Vagal Complex
Vagal Efferents

Chymotrypsinogen
Enterokinase
Trypsinogen
Trypsin
Trypsin
Chymotrypsinogen
Chymotrypsin
Proelastase
Elastase
Procarboxypeptidase
Carboxypeptidase
Prophospholipase
Phospholipase
Procolipase
Colipase

Activation of pancreatic enzymes in the intestine
PATHOGENESIS OF PANCREATITIS

Classification of pancreatitis

**Functional and morphologic changes**

- **CHRONIC**
  - e.g. ETOH, hereditary
  - **Outcome:**
    - Pain
    - Endocrine insufficiency
    - Exocrine insufficiency

- **ACUTE RECURRENT**
  - e.g. sludge, SOD
  - **Outcome:**
    - Recovery or death

- **ACUTE**
  - e.g. stone, drug, toxin
  - **Outcome:**
    - Recovery or death
Etiology of Acute Pancreatitis

- Alcoholic
- Idiopathic
- Biliary
- Other
- Autoimmune
- Drug-induced
- Iatrogenic
- IBD-related
- Infectious
- Inherited
- Metabolic
- Neoplastic
- Structural
- Toxic
- Traumatic
- Vascular

Cellular Injury through Activated Enzymes

1. Blockage of Secretion
2. Activation of Zymogens in Lysosomes (Cathepsin B)
3. Organelle Damage and Cell Injury by Activated Enzymes

Increased pressure
Perturbed environment

RER
Lysosome
Golgi Complex
Local effects of inflammation and pancreas injury

- Third space losses
- Fat necrosis
- Pancreatic and peripancreatic necrosis

Cytokines Play an Important Role in Pancreatic Injury

- Insult
- Pancreatic Acinar Cell
- Cytokine production
- Chemoattraction and activation
- Neutrophil
- Macrophage
- Inflammation Cell Death
Cytokines Mediate Systemic Complications

Liver failure
Liver

ARDS
Lungs
Shock, Organ failure
Microcirculation

TNFa
IL-1b
IL-61

ICAM-1
PAF
Endothelin
INOS
ICAM-1

Etiology of Chronic Pancreatitis

Alcoholic
Other
Idiopathic

Cystic fibrosis
Hereditary pancreatitis
Hypertriglyceridemia
Autoimmune
Fibrocalcific (Tropical)
**Effects of Chronic Alcohol on the Pancreas**

- Calcification
- Fibrosis
- Decreased blood flow
- Altered protein synthesis
- Cytotoxic lymphocytes
- Direct toxic effects

**Hereditary Pancreatitis**

- Mutations in cationic trypsinogen
- Autosomal dominant
- Incomplete penetrance
- Early onset
- Frequent calcification
- Increased pancreatic cancer

*affected*
PANCREATITIS
CLINICAL CONSIDERATIONS

Other causes of hyperamylasemia and hyperlipasemia:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amylase</th>
<th>Lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotitis</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Tumors</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Biliary disease</td>
<td>yes</td>
<td>slight</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Renal failure</td>
<td>yes</td>
<td>slight</td>
</tr>
<tr>
<td>Intestinal obstruction, ulceration, ischemia</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Macroamylasemia</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Perforated viscus</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
IMAGING DIAGNOSIS

Interstitial pancreatitis

Necrotizing pancreatitis

Higher rate of complications (bacterial infection, organ failure) and mortality

If CT is performed within 24h of first symptoms, findings may be normal

PROGNOSIS OF ACUTE PANCREATITIS

Ranson’s severity score & mortality

Admission
- Age > 55 years
- WBC > 16,000 mm³
- Glucose > 200 mg/dl
- LDH > 350 IU/L
- AST > 120 IU/L

During first 48h
- Hct decrease >10%
- BUN increase > 5 mg/dl
- Ca²⁺ < 8 mg/dl
- PaO₂ < 60 mm Hg
- Base deficit > 4 mEq/L
- Negative fluid balance > 6L

Most patients with severe pancreatitis

Score

% Mortality
Acute Pancreatitis Complications

Grey-Turner sign

Obstructing Pseudocyst

ARDS

Acute Pancreatitis Complications

Infected Necrosis

Treatment

Antibiotic
### PANCREATIC FLUID COLLECTION NOMENCLATURE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute collection</td>
<td>A.P./ trauma, &lt;48 hrs, no wall</td>
</tr>
<tr>
<td>Pancre. Necrosis (early)</td>
<td>A.P., 1-2 wks &gt;30% necr., no wall</td>
</tr>
<tr>
<td>Organized necrosis</td>
<td>A.P., &gt;2-4 wks, partially walled necrotic debris &amp; panc. juice</td>
</tr>
<tr>
<td>Acute pseudocyst</td>
<td>A.P., &gt;4 wks, walled juice</td>
</tr>
<tr>
<td>Chronic pseudocyst</td>
<td>C.P., walled juice/”retention”</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
<td>A.P./C.P./ trauma, peripanc. collection of pus, no debris</td>
</tr>
</tbody>
</table>

Adapted from Bradley et al Atlanta Symposium, Arch Surg 1993 & Baron et al GIE 2002

### Chronic Pancreatitis: Diagnostic tests

x-ray and fecal fat have a low sensitivity to detect CP!

Amylase and Lipase are often within the normal range!!
Chronic Pancreatitis: Diagnostic tests

**Imaging**
- ERCP/EUS
- CT Ultrasonogram
- Abdominal x-ray

**Functional**
- Secretin test
- Fecal chymotrypsin
- Serum trypsinogen
- Fecal fat
- Blood glucose

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**Imaging of Chronic Pancreatitis**

- Abdominal X-ray
- Abdominal Ultrasound
- CT scan
- ERCP
Chronic Pain is a Common Symptom of Chronic Pancreatitis

Exogenous proteases may decrease CCK release and pain in chronic pancreatitis