Pathophysiology of Gallstone Formation and Pancreatitis

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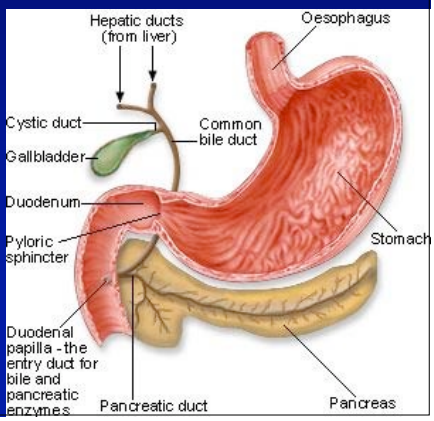
Pancreatic secretions and bile are required for digestion

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



GALLSTONES

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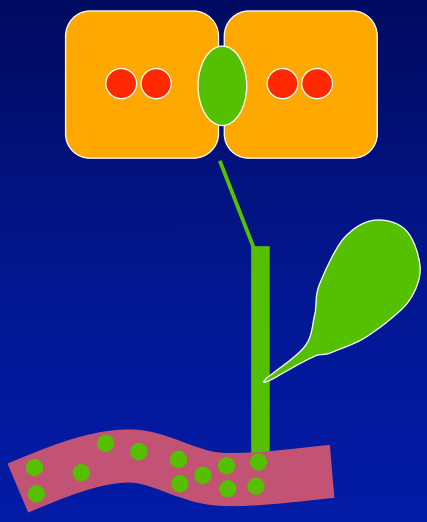
Bile



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

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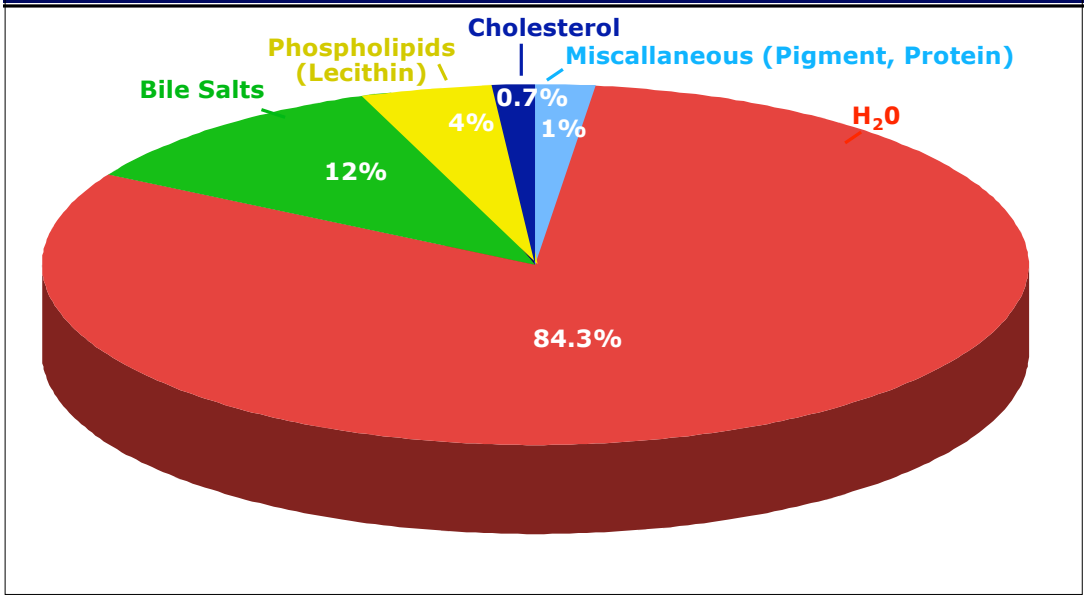
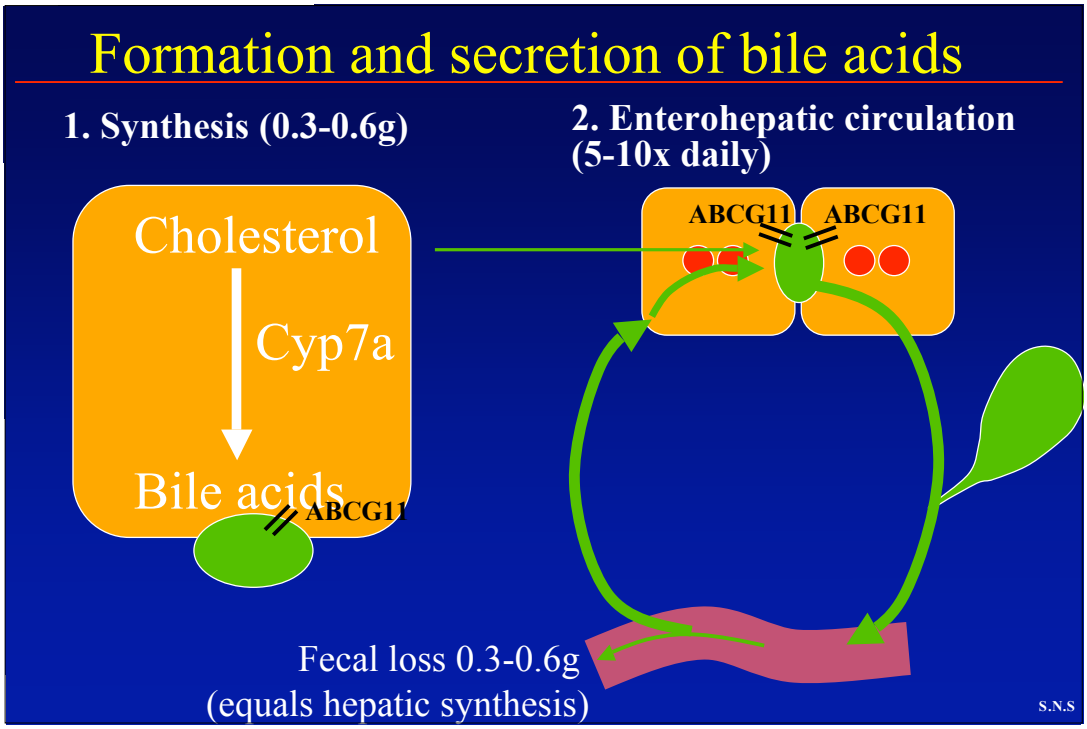
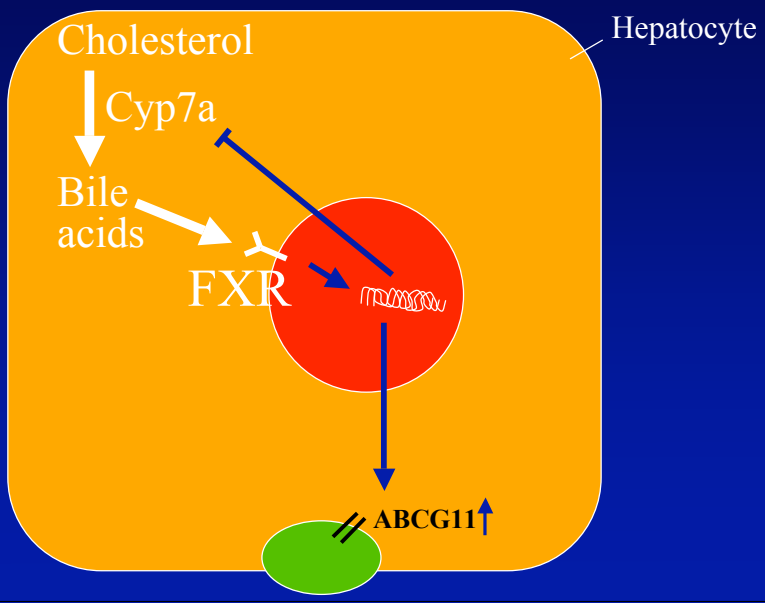
Bile composition



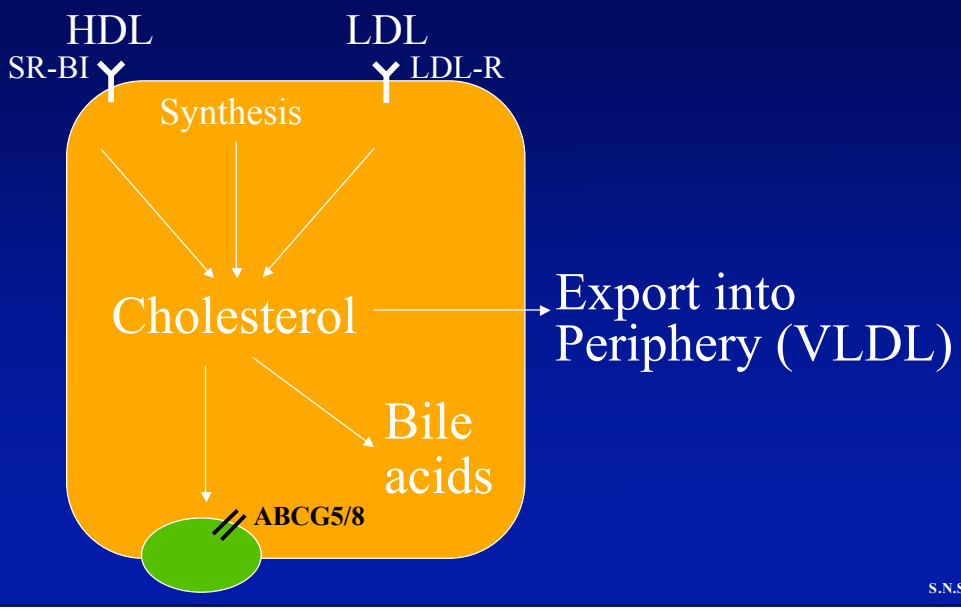
Formation and secretion of bile acids



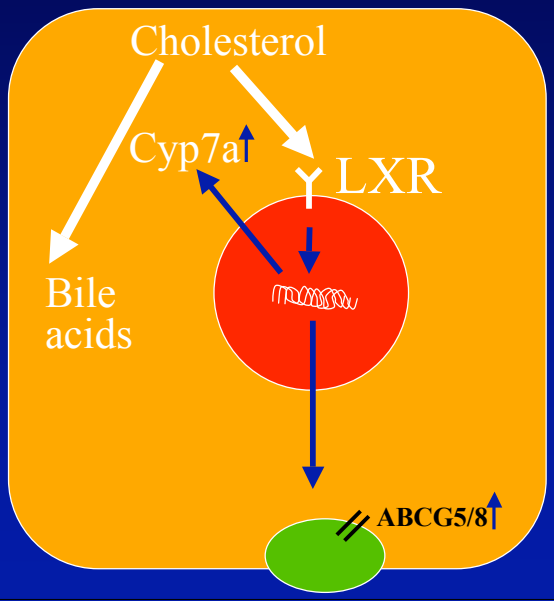
FXR is bile acid sensor of bile acids and lowers intracellular bile acid levels (to prevent toxicity)



Secretion of cholesterol



LXR is a cholesterol sensor and lowers intracellular cholesterol levels



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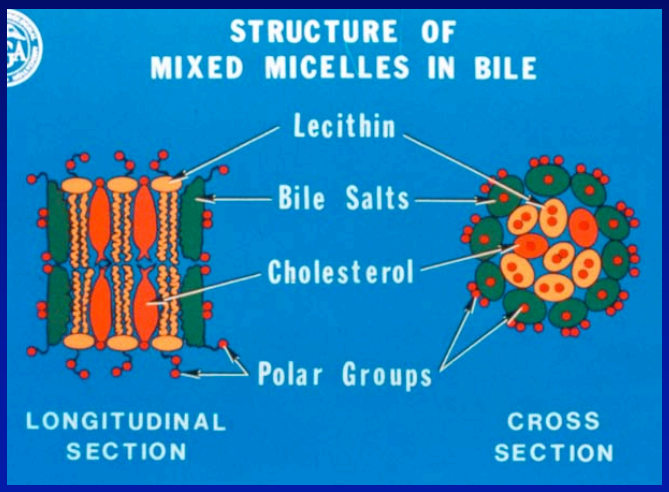
Cholesterol requires bile salts for solubilization



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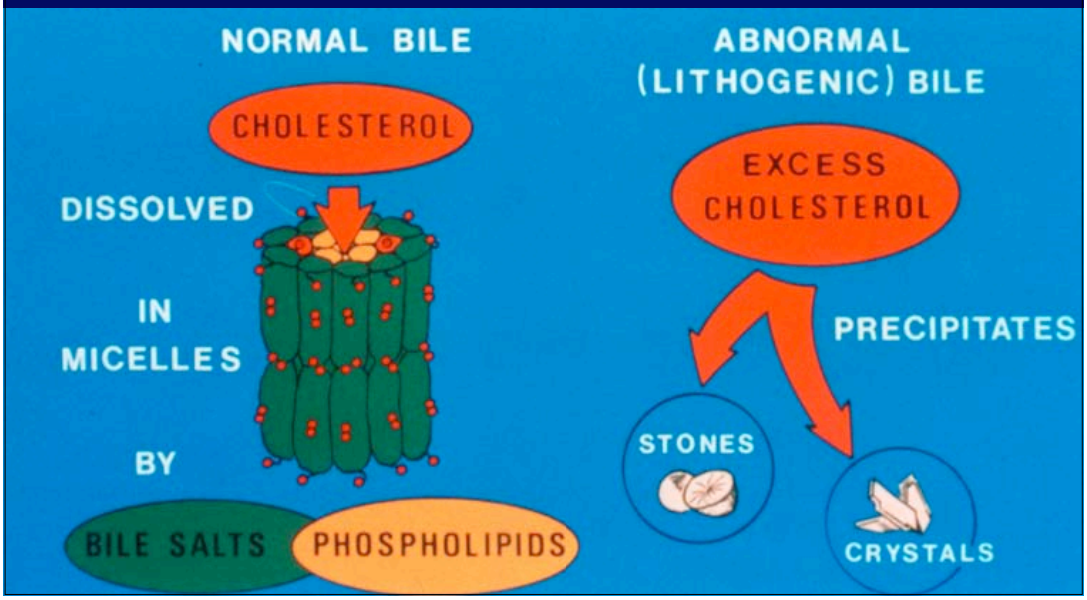
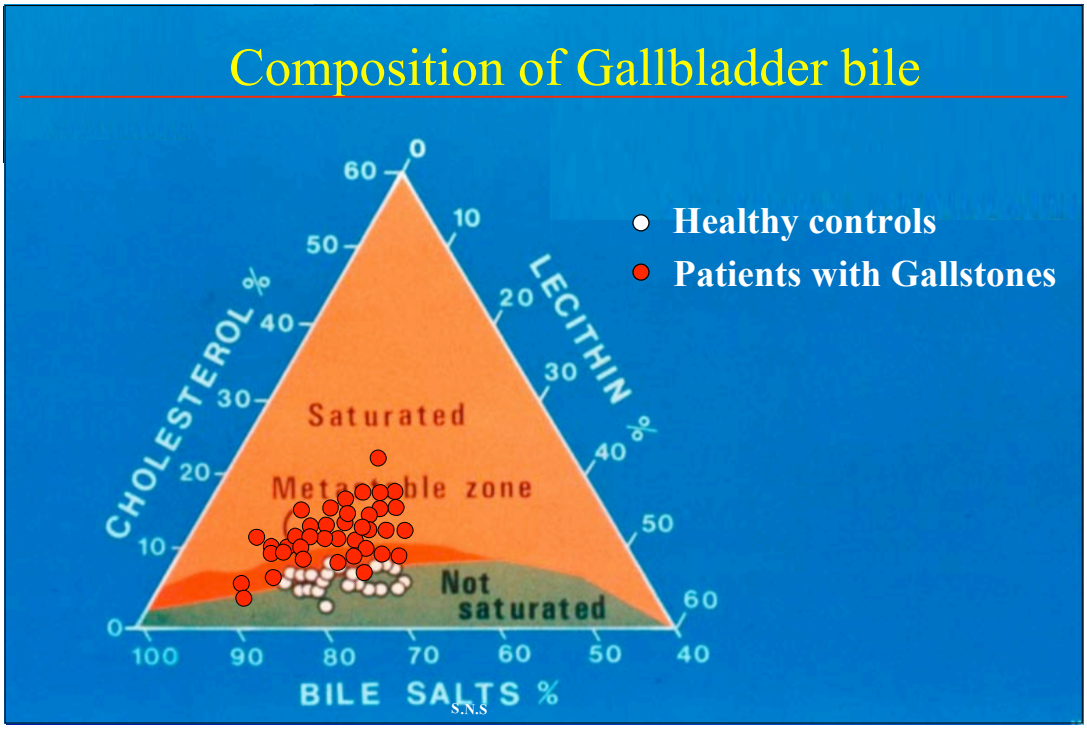
Excess cholesterol precipitates to form cholesterol crystals and stones



Composition of Gallbladder bile



Cholesterol stones:

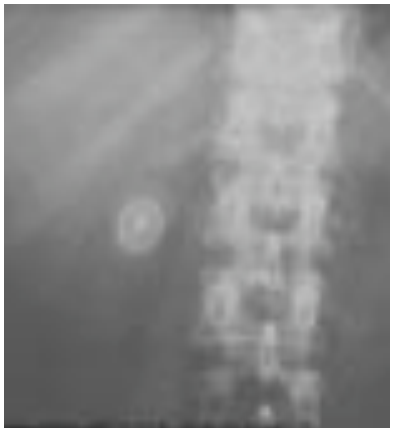
- Great majority of all stones in the US (>70%)
- either pure cholesterol stones or mixed stones (more than 50% cholesterol content)

Pigment stones:

- contain pigment = bilirubin
- usually due to increased hemolyis
- or due to decreased bilirubin conjugation

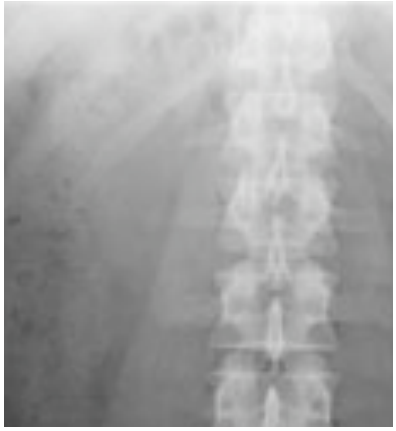
x-Ray Appearance of Gallstones

Radio-opaque



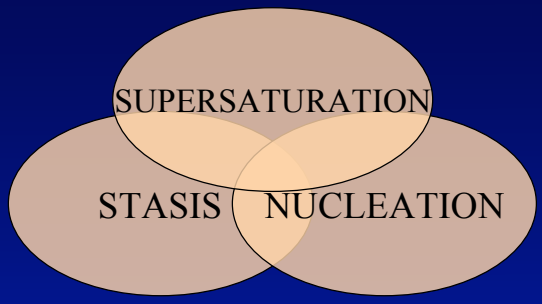
27% = Cholesterol Stones
73% = Pigment Stones

Radioluscent



83% = Cholesterol Stones
17% = Pigment Stones

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)

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Factors Favoring Cholesterol Gallstones

- **Hepatic Production of Lithogenic Bile**

B. Excess cholesterol secretion

1. Obesity
2. Estrogens
3. Genetic factors/Ethnicity (Pimas)

- **Gallbladder Factors**

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

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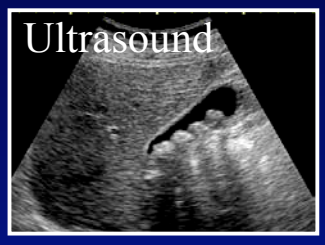
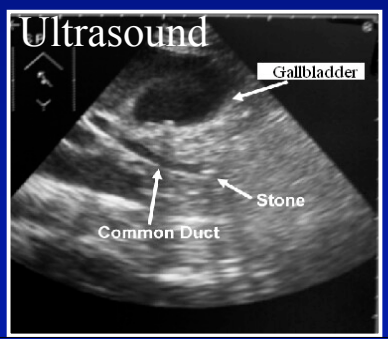
Natural History of Gallstones

- 80% of all gallbladder stones will never cause symptoms

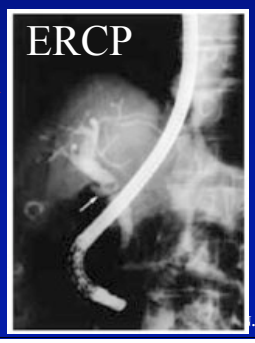


- 1-4% of gallbladder stones/year cause symptoms (e.g. colic, pancreatitis)

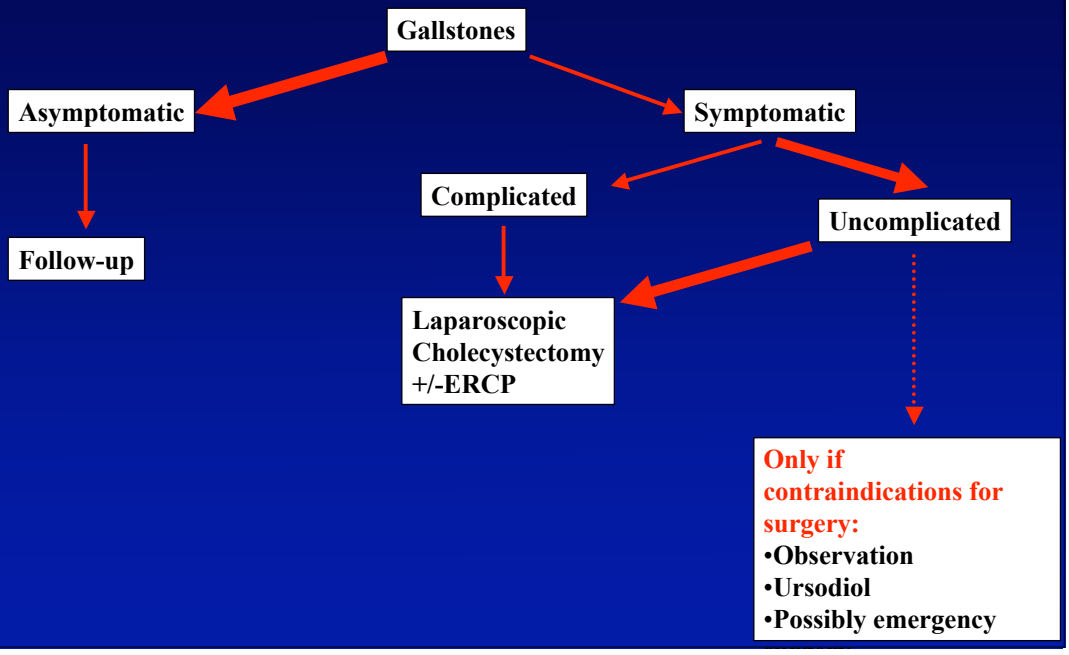


Dilated Duct

Intraductal stone
(not always present)



Schematic diagram for the management of gallstone disease



PANCREAS PHYSIOLOGY

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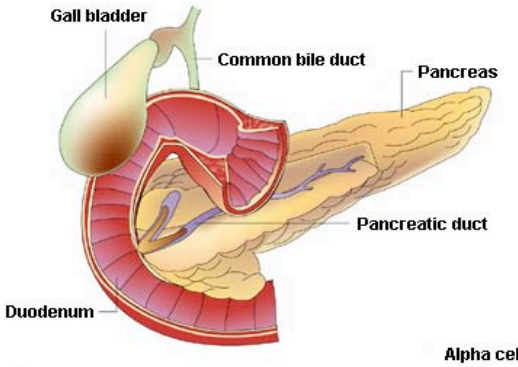
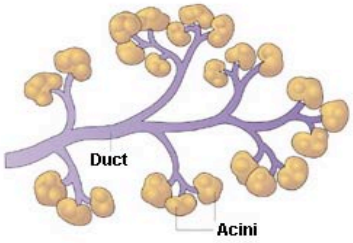
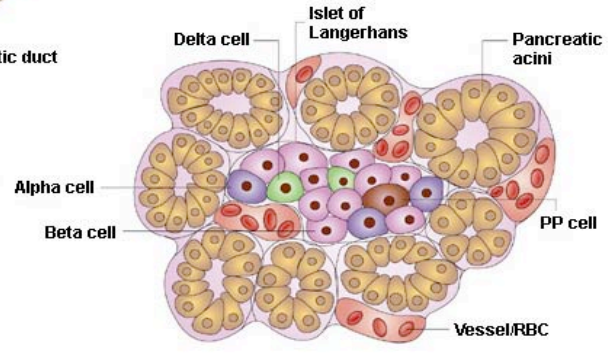
Pancreas macro- and microanatomy



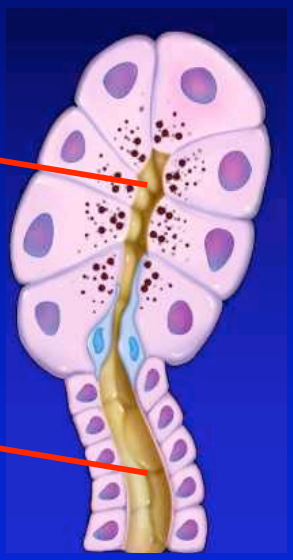




Major functional units

ACINUS
Digestive enzyme secretion

DUCTULE
Water, bicarbonate secretion



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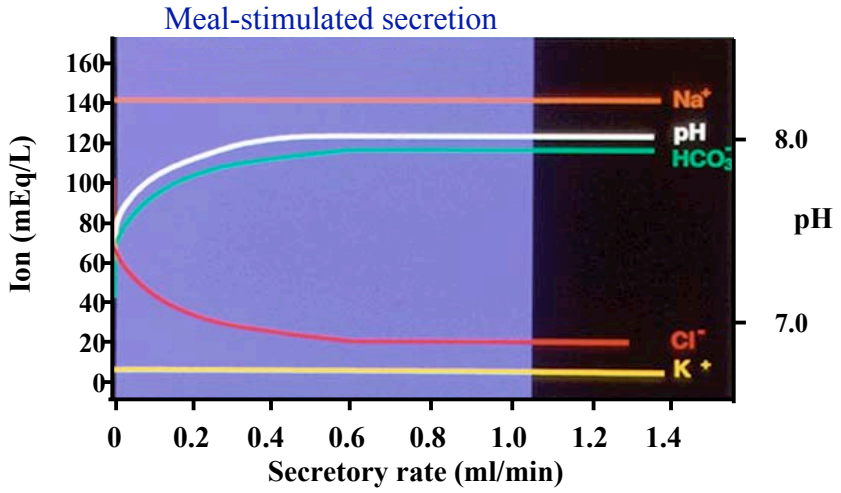
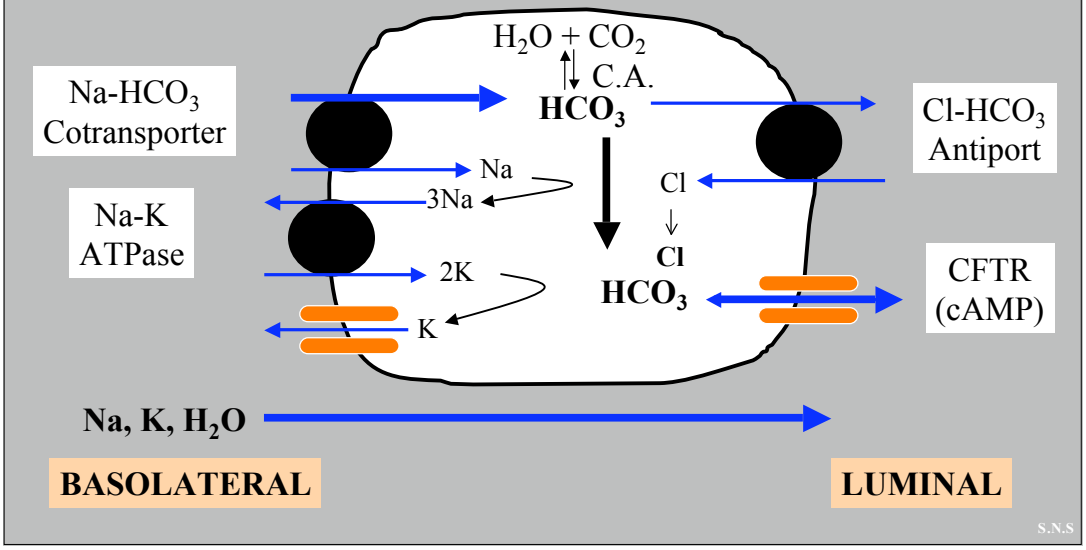
$HC0_3$ concentration and pH increase with increased pancreatic secretion

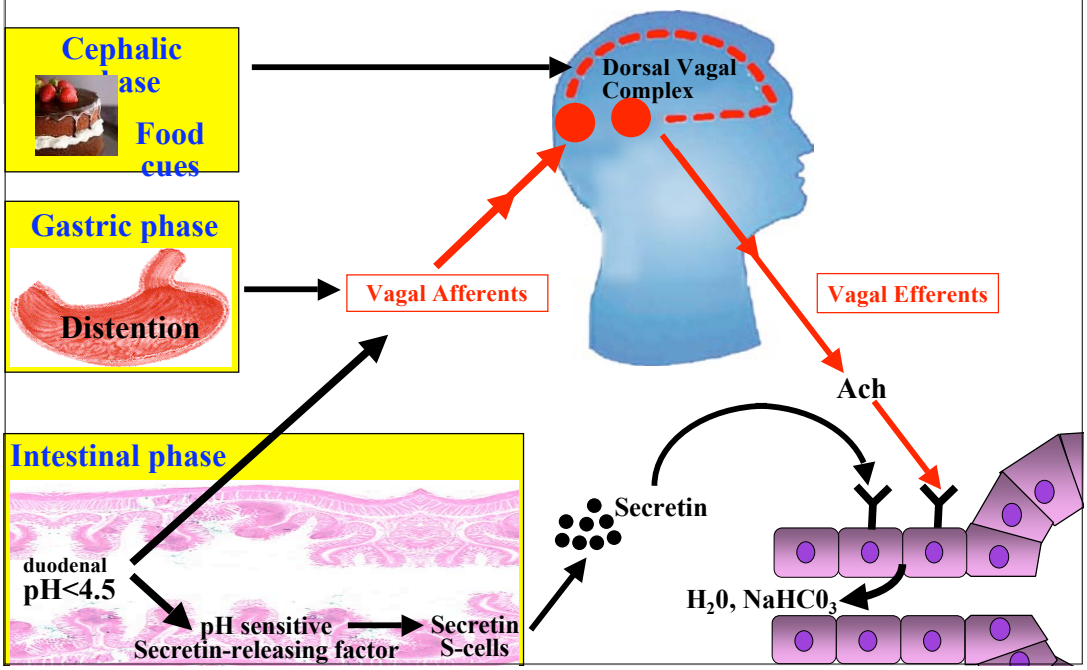


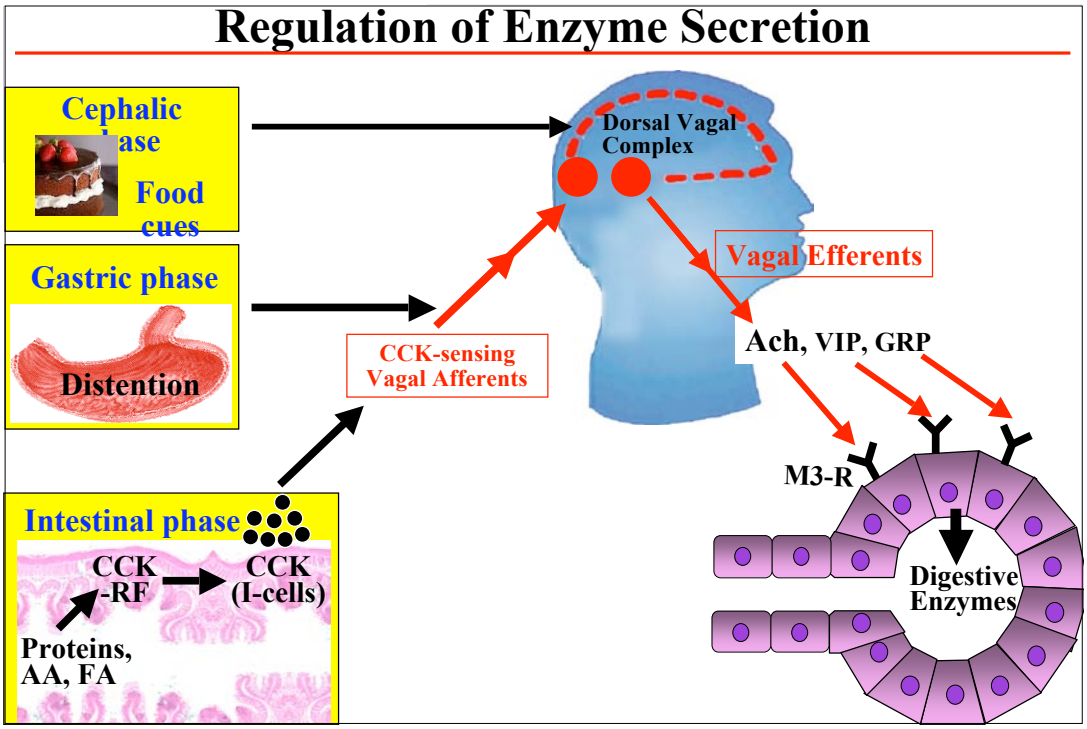
→ **The increase in $HC0_3$ serves to buffer the acidic pH of food after it passes into the duodenum.**

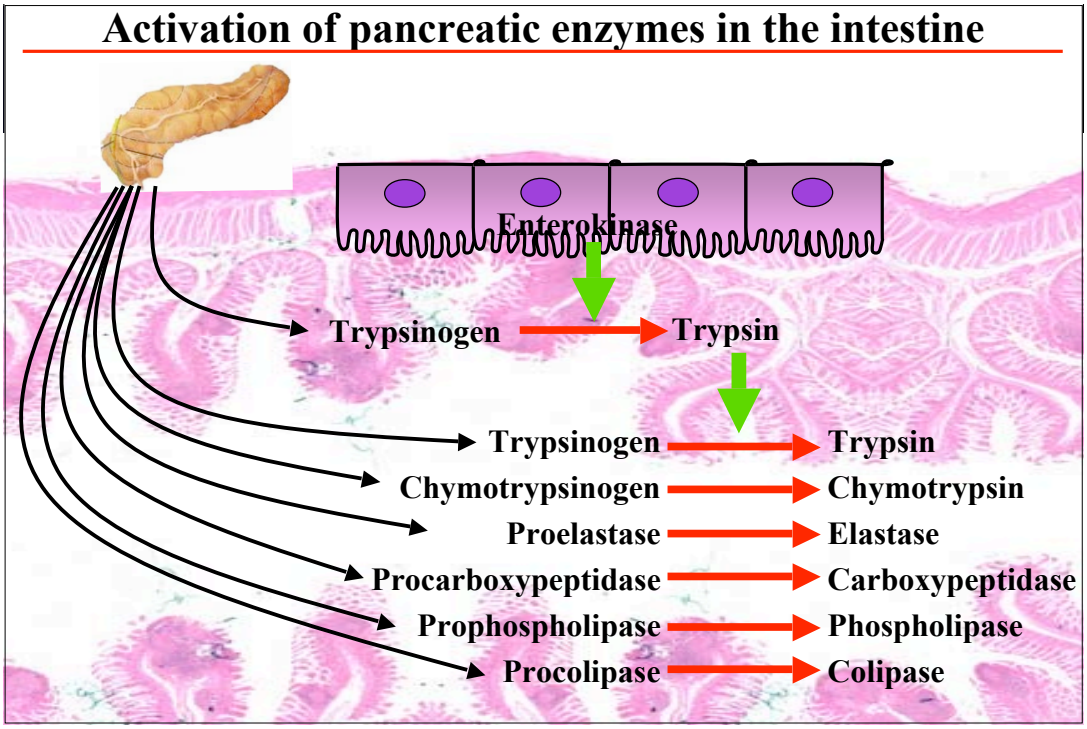
Ion Transport in Duct cells



Bicarbonate secretion is regulated through hormonal and neural mechanisms




Regulation of Enzyme Secretion
Cephalic
ase
Food
cues
Gastric phase
Distention
Intestinal phase
CCK
-RF
CCK
(I-cells)
Proteins,
AA, FA
CCK-sensing
Vagal Afferents
Dorsal Vagal
Complex
Vagal Efferents
Ach, VIP, GRP
M3-R
Digestive
Enzymes


Activation of pancreatic enzymes in the intestine
Enterokinase
Trypsinogen
Trypsin
Trypsinogen
Trypsin
Chymotrypsinogen
Chymotrypsin
Proelastase
Elastase
Procarboxypeptidase
Carboxypeptidase
Prophospholipase
Phospholipase
Procolipase
Colipase

PATHOGENESIS OF PANCREATITIS

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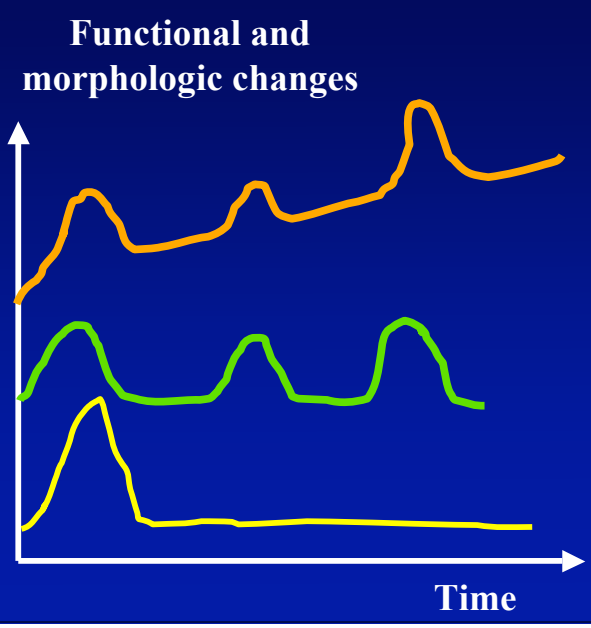
Classification of pancreatitis



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

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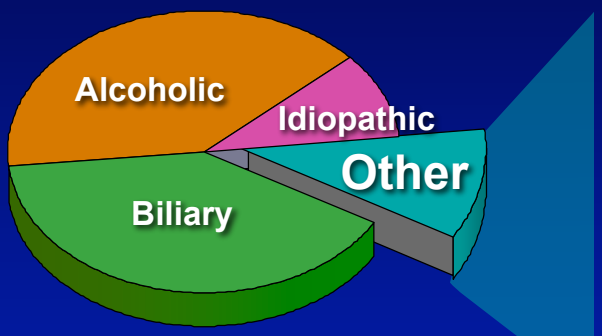
Etiology of Acute Pancreatitis



- Autoimmune
- Drug-induced
- Iatrogenic
- IBD-related
- Infectious
- Inherited
- Metabolic
- Neoplastic
- Structural
- Toxic
- Traumatic
- Vascular

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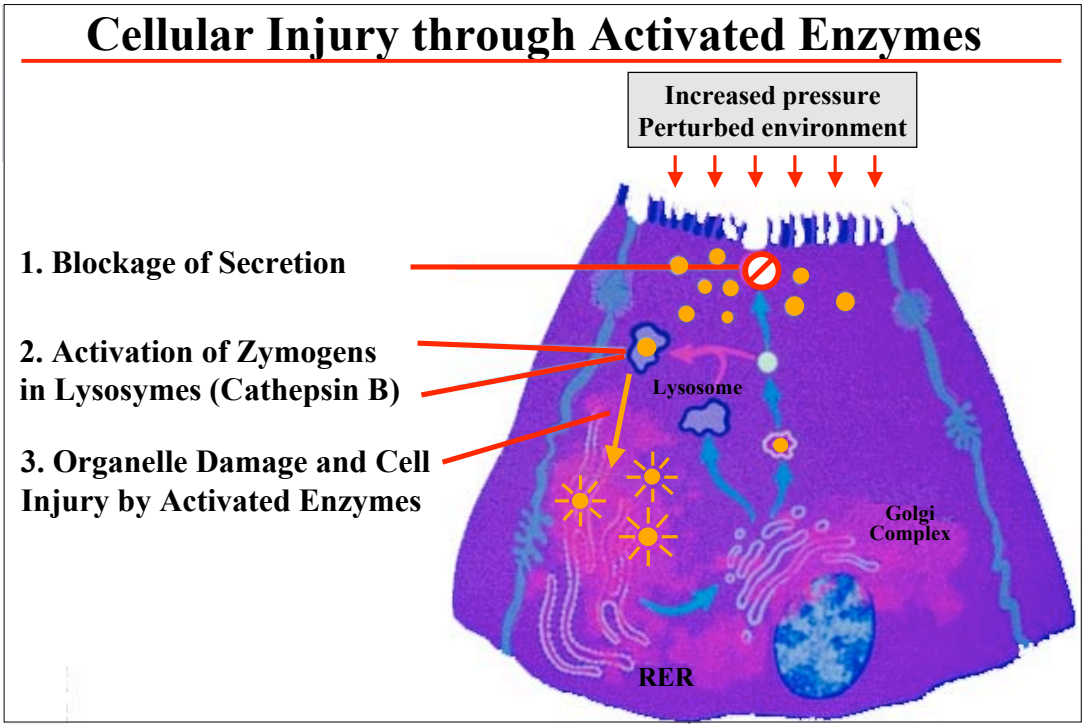
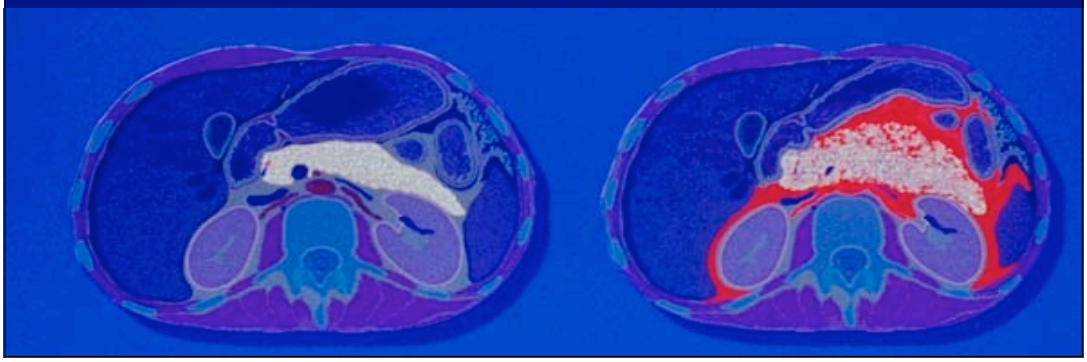
Cellular Injury through Activated Enzymes

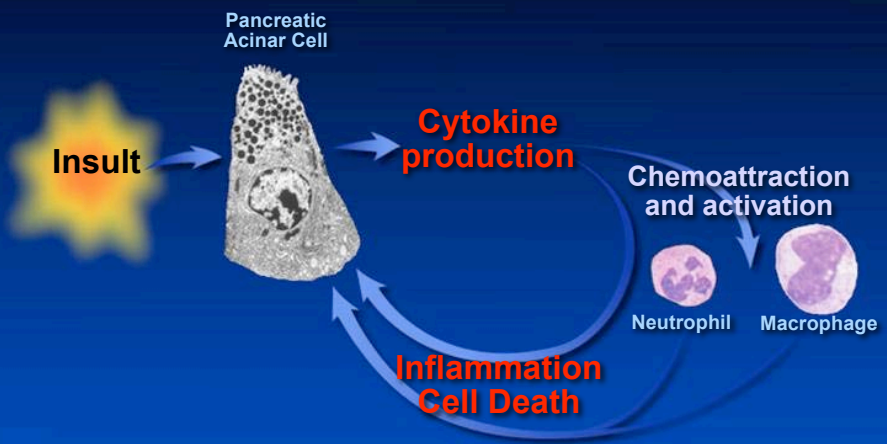


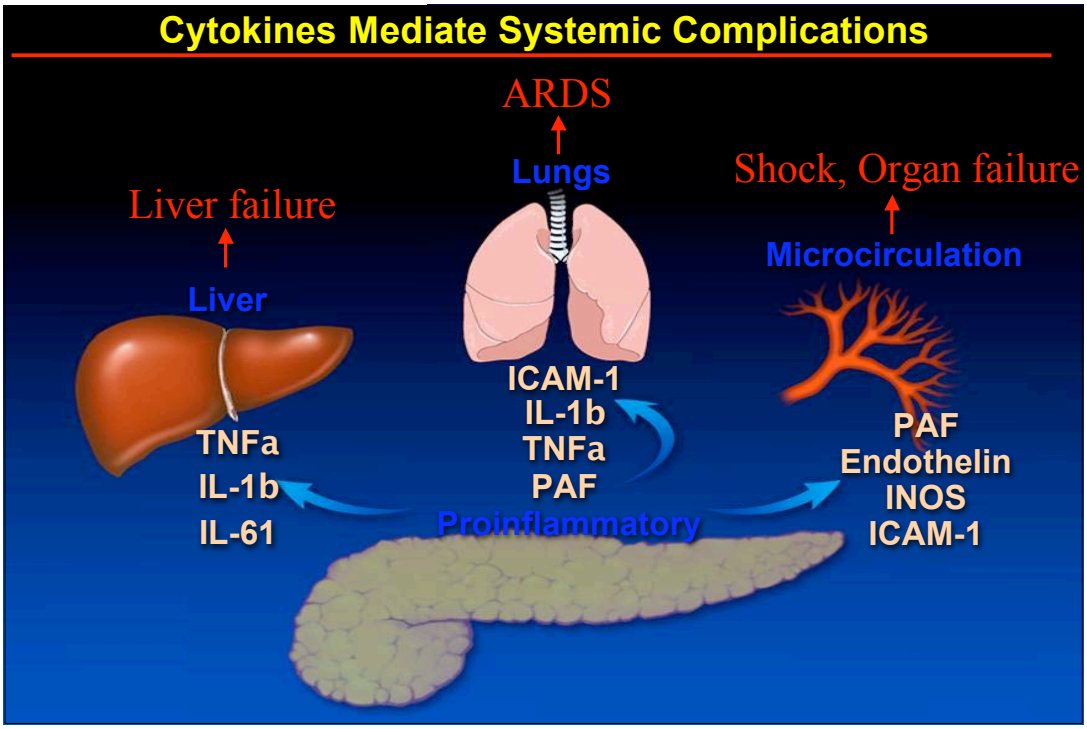
Local effects of inflammation and pancreas injury

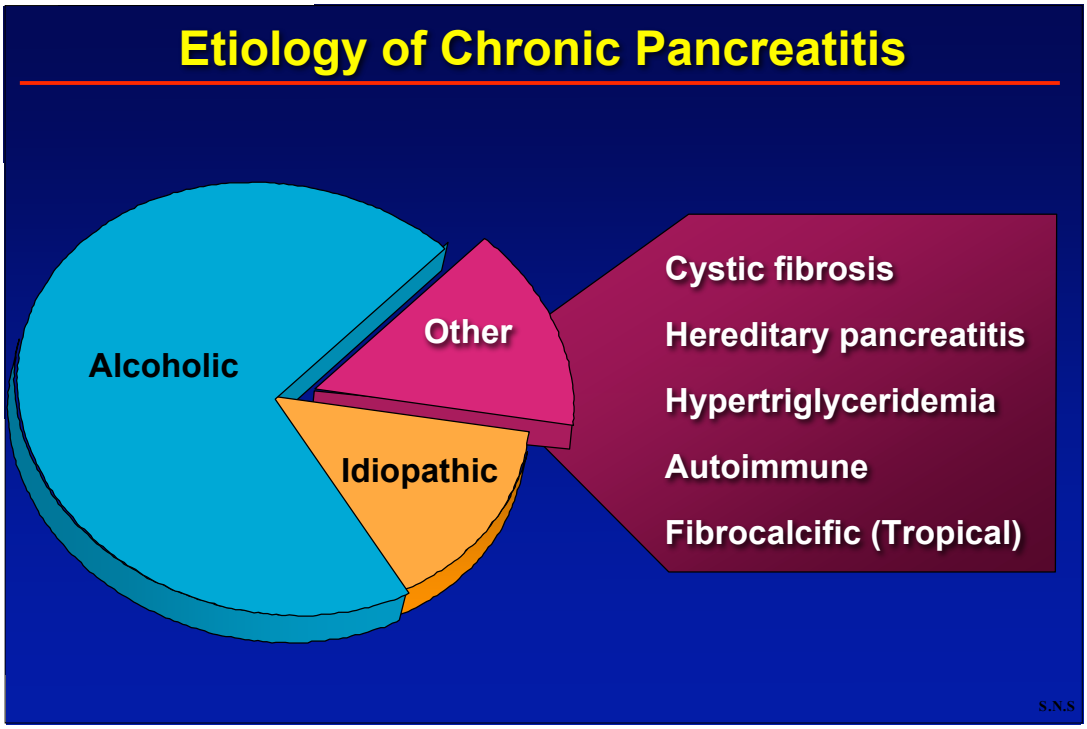
- Third space losses
- Fat necrosis
- Pancreatic and peripancreatic necrosis



Cytokines Play an Important Role in Pancreatic Injury




Cytokines Mediate Systemic Complications
ARDS
Lungs
Liver failure
Liver
Shock, Organ failure
Microcirculation
ICAM-1
IL-1b
TNFa
PAF
Proinflammatory
TNFa
IL-1b
IL-61
PAF
Endothelin
INOS
ICAM-1


Etiology of Chronic Pancreatitis
Alcoholic
Other
Idiopathic
Cystic fibrosis
Hereditary pancreatitis
Hypertriglyceridemia
Autoimmune
Fibrocalcific (Tropical)
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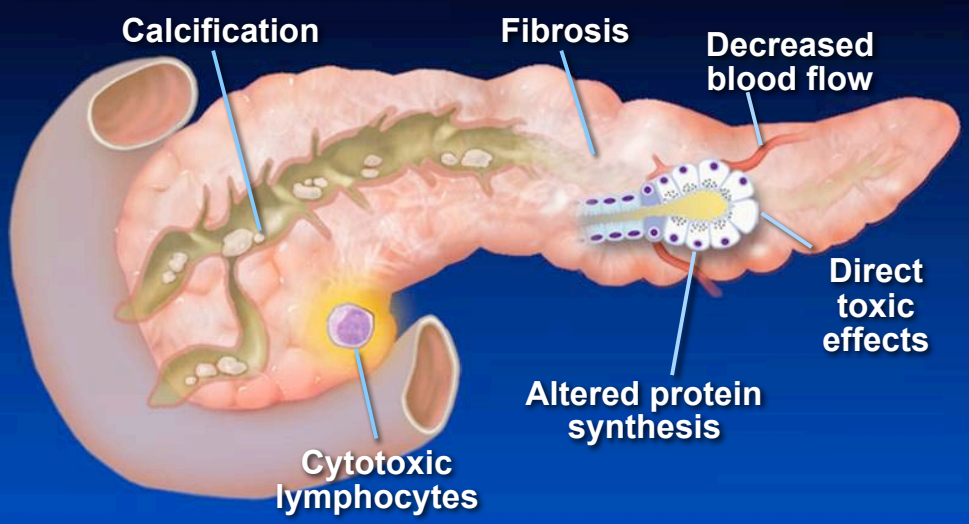
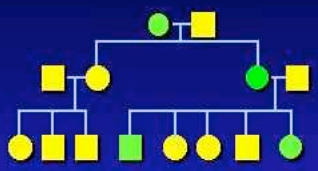
Effects of Chronic Alcohol on the Pancreas



Hereditary Pancreatitis

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



affected

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PANCREATITIS
CLINICAL CONSIDERATONS

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LABORATORY DIAGNOSIS

Amylase and Lipase are typically highly elevated

Other causes of hyperamylasemia and hyperlipasemia:

	Amylase	Lipase
Parotitis	yes	no
Tumors	yes	no
Biliary disease	yes	slight
Pancreatitis	yes	yes
Renal failure	yes	slight
Intestinal obstruction, ulceration, ischemia	yes	yes
Ectopic pregnancy	yes	no
Macroamylasemia	yes	no
Perforated viscus	yes	yes

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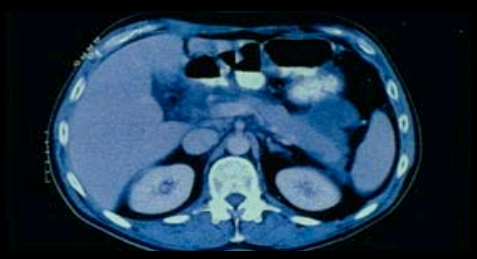
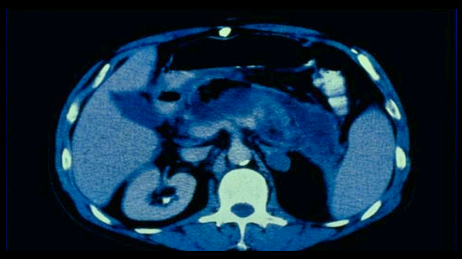
IMAGING DIAGNOSIS



Interstitial pancreatitis



Necrotizing pancreatitis

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

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

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PROGNOSIS OF ACUTE PANCREATITIS

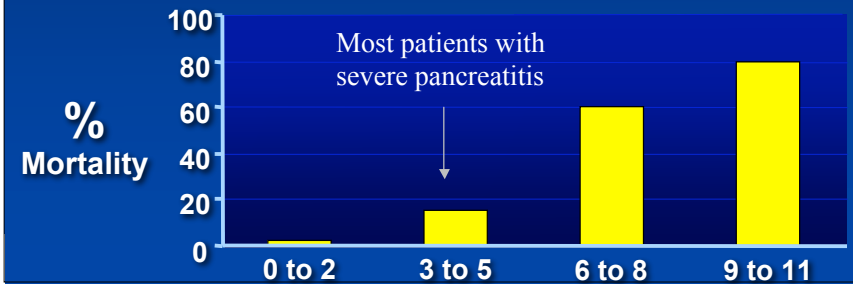
Ranson's severity score & mortality

Admission

- Age > 55 years
- WBC > 16,000 mm^3
- Glucose > 200 mg/dl
- LDH > 350 IU/L
- AST > 120 IU/L

During first 48h

- Hct decrease >10%
- BUN increase > 5 mg/dl
- Ca^{2+} < 8 mg/dl
- PaO_2 < 60 mm Hg
- Base deficit > 4 mEq/L
- Negative fluid balance > 6L



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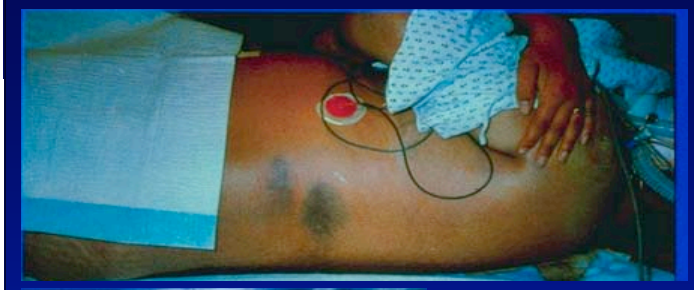
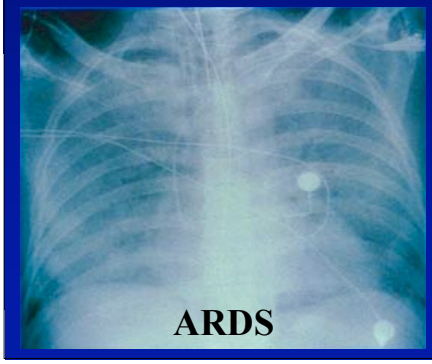
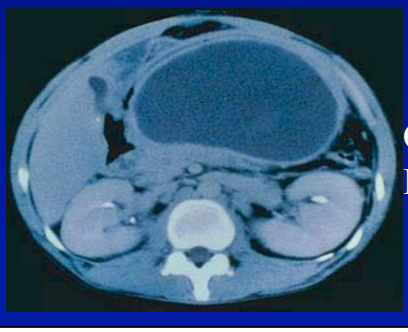
Acute Pancreatitis Complications



Grey-Turner sign



ARDS



Obstructing Pseudocyst

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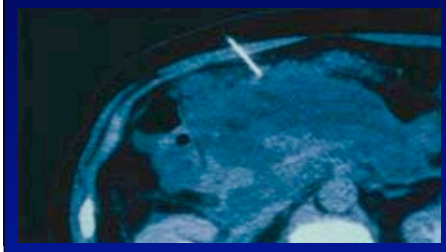
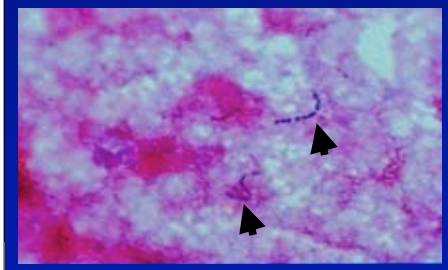
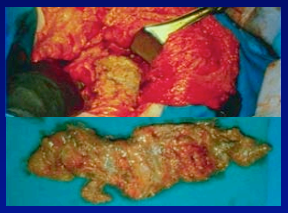
Acute Pancreatitis Complications

Infected Necrosis





Treatment



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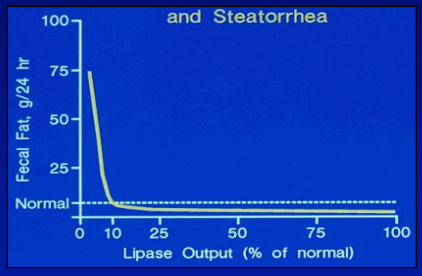
PANCREATIC FLUID COLLECTION NOMENCLATURE

Acute collection	A.P./ trauma, <48 hrs, no wall
Pancr. Necrosis (early)	A.P., 1-2 wks>30 % necr., no wall
Organized necrosis	A.P.,>2-4 wks, partially walled necrotic debris & panc. juice
Acute pseudocyst	A.P.,>4 wks, walled juice
Chronic pseudocyst	C.P., walled juice/"retention"
Pancreatic abscess	A.P./C.P./ trauma, peripanc. collection of pus, no debris

Adapted from *Bradley et al Atlanta Symposium, Arch Surg 1993* & *Baron et al GIE 2002* S.N.S

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!!

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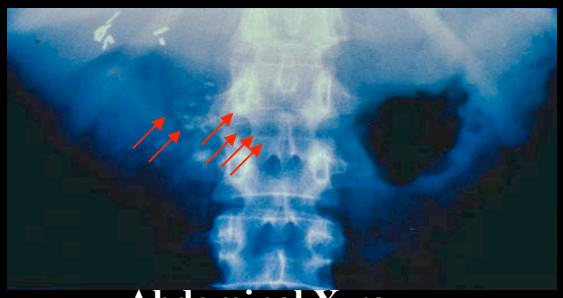
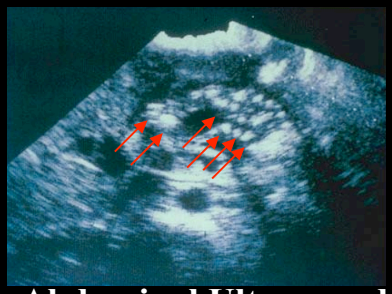
Chronic Pancreatitis: Diagnostic tests

Imaging		Functional
ERCP/EUS	Most sensitive	**Secretin test**
CT Ultrasonogram	Less sensitive	**Fecal chymotrypsin Serum trypsinogen**
Abdominal x-ray	Least	**Fecal fat Blood glucose**

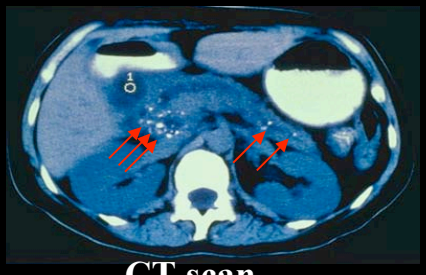
Imaging of Chronic Pancreatitis



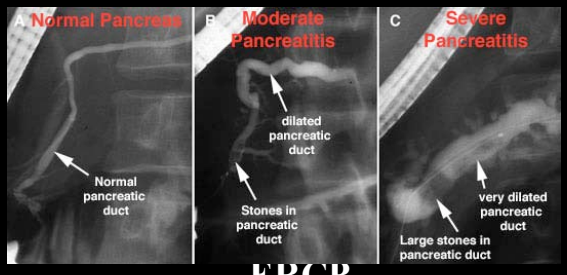
Abdominal X-ray



Abdominal Ultrasound



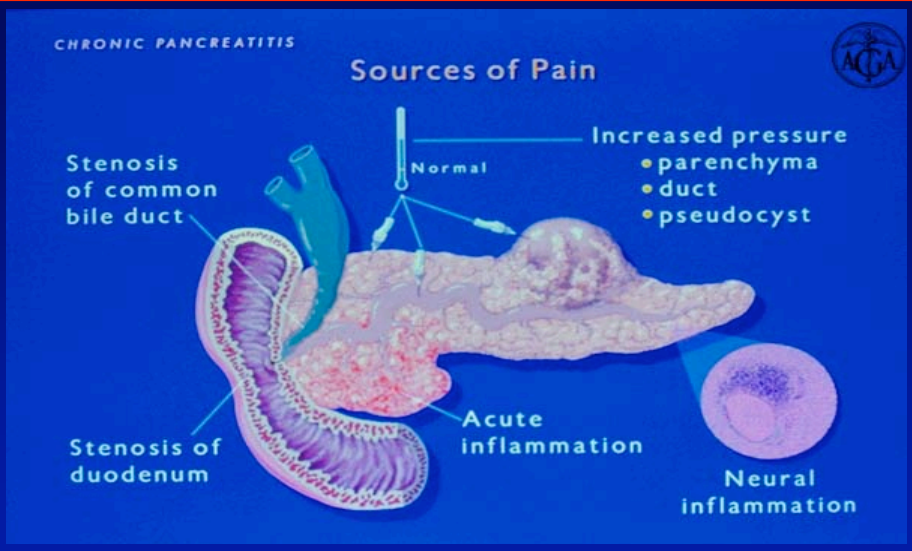
CT scan



ERCP

S.N.S

Chronic Pain is a Common Symptom of Chronic Pancreatitis



S.N.S

Exogenous proteases may decrease CCK release and pain in chronic pancreatitis