Pathophysiology of Gallstone Formation and Pancreatitis

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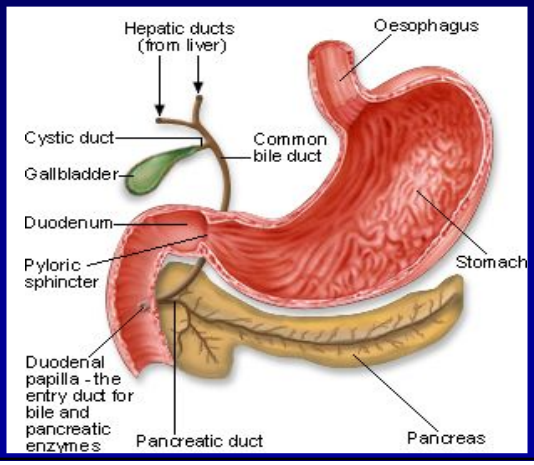
Pancreatic secretions and bile are required for digestion

- Bile: Emulsification of fat
- Pancreatic secretions: -Digestion of proteins, carbohydrates and fat
  -Neutralization of the acidic chyme



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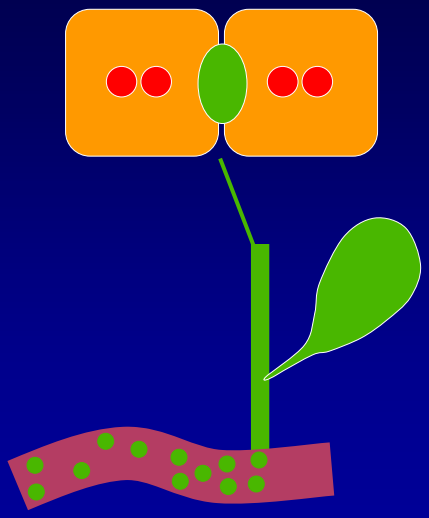
Bile



- 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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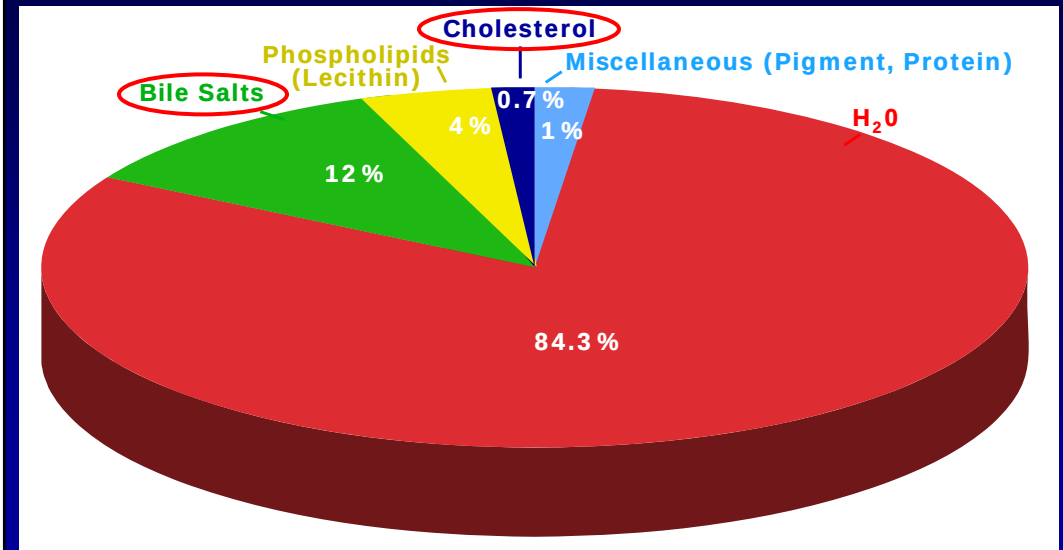
Bile composition



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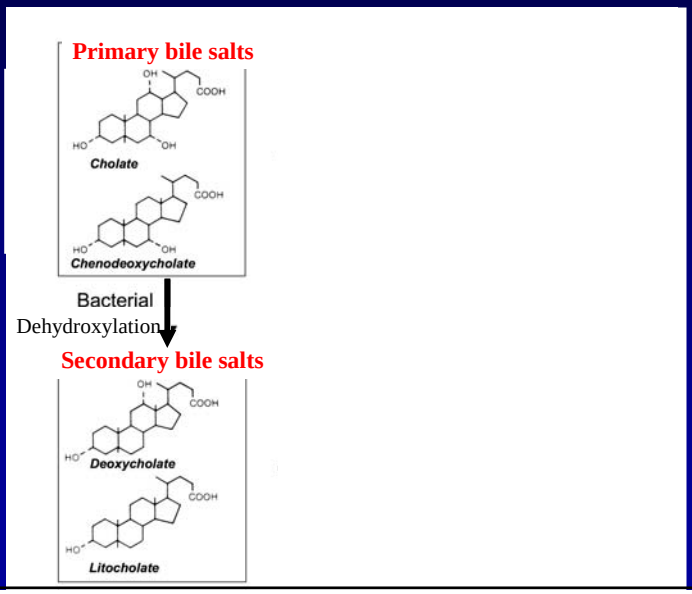
Bile salts are conjugated with glycine or taurine to increase their solubility at lower pH



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Important functions of bile

1. Emulsification of fats in the intestine

2. Cholesterol excretion

a. Bile salts are generated from cholesterol and their synthesis thus decreases the cholesterol pool

b. Cholesterol is excreted into bile

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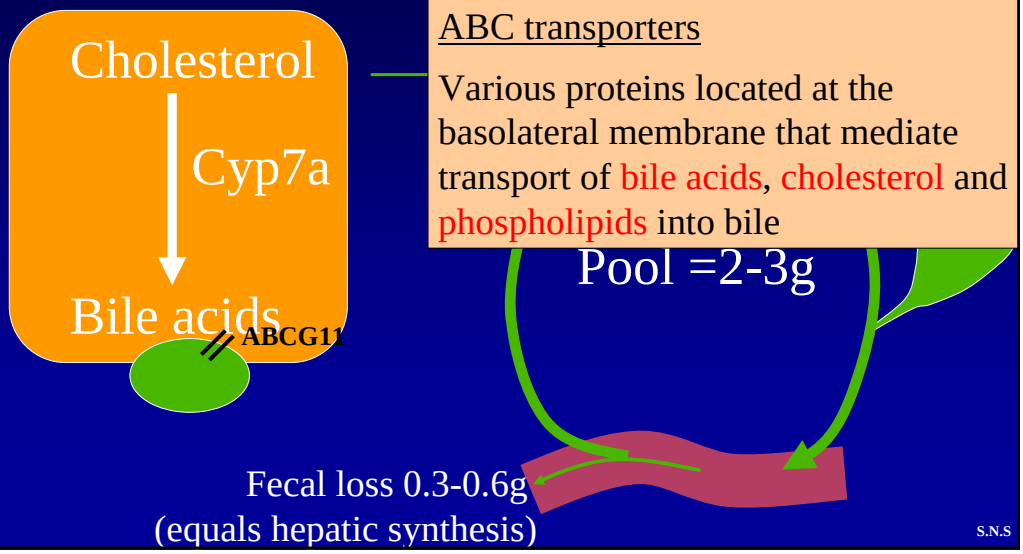
Formation and secretion of bile acids

1. Synthesis (0.3-0.6g)

2. Enterohepatic circulation (5-10x daily)



ABC transporters

Various proteins located at the basolateral membrane that mediate transport of bile acids, cholesterol and phospholipids into bile

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Why do we have a mechanism for enterohepatic circulation of bile acids?

Reabsorption and redelivery of bile acids allows to very quickly replenish the pool of bile acids in the liver/gallbladder

→ The digestive tract is prepared for the next meal within a relatively short time.

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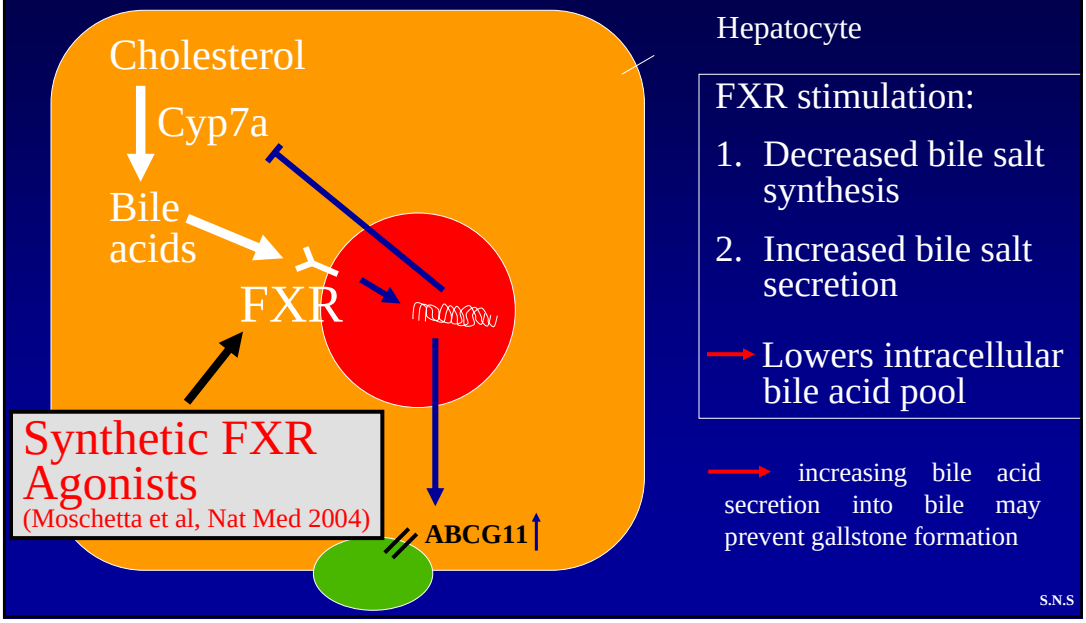
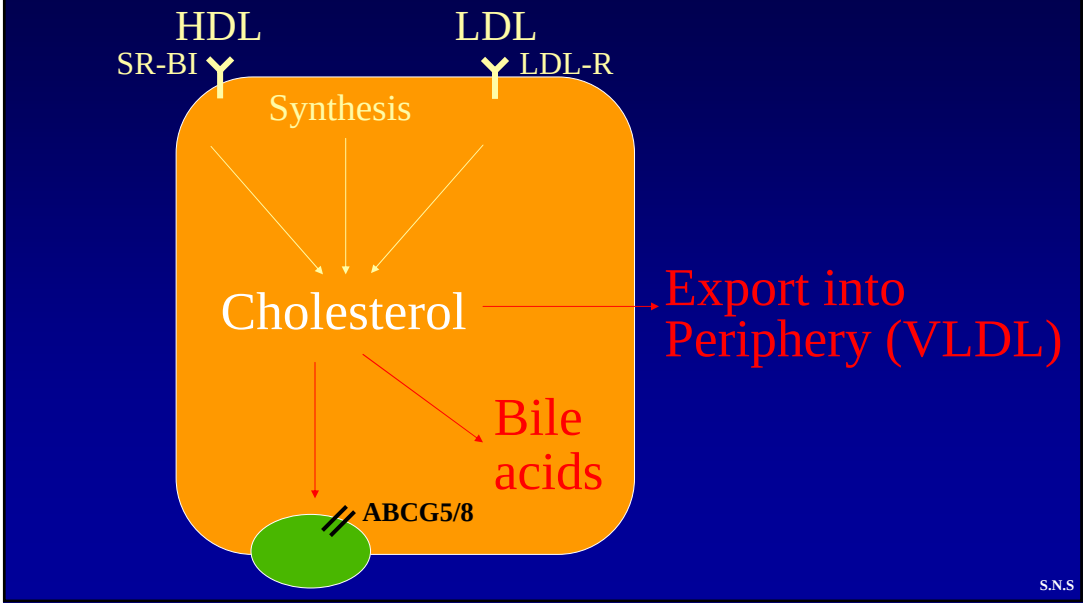
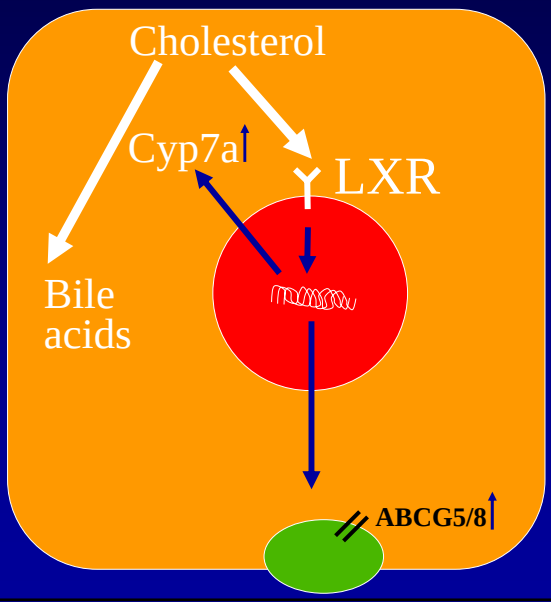
Bile salts are hepatoxic at high concentrations



Secretion of cholesterol



The nuclear receptor LXR is a cholesterol sensor and lowers intracellular cholesterol levels



LXR stimulation:

1. Increased bile salt synthesis decreases cholesterol
2. Increased cholesterol secretion

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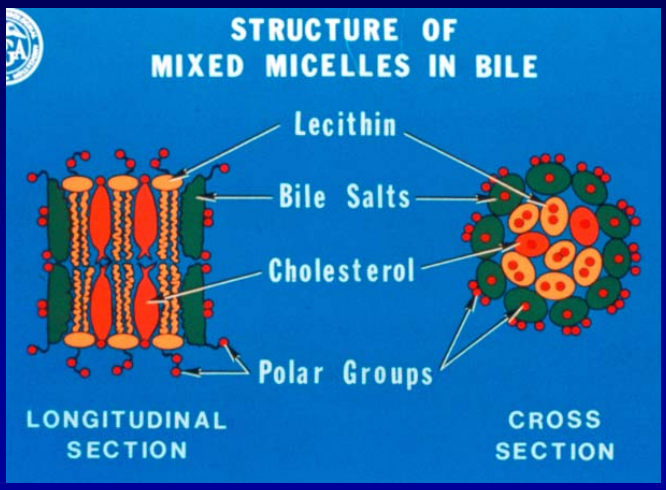
Cholesterol requires bile salts for solubilization



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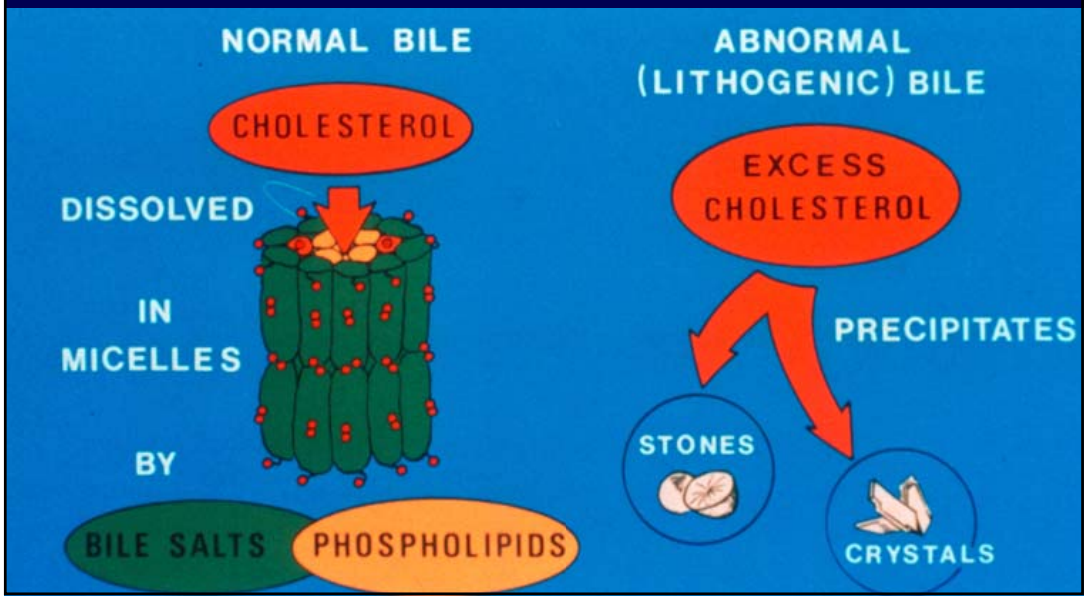
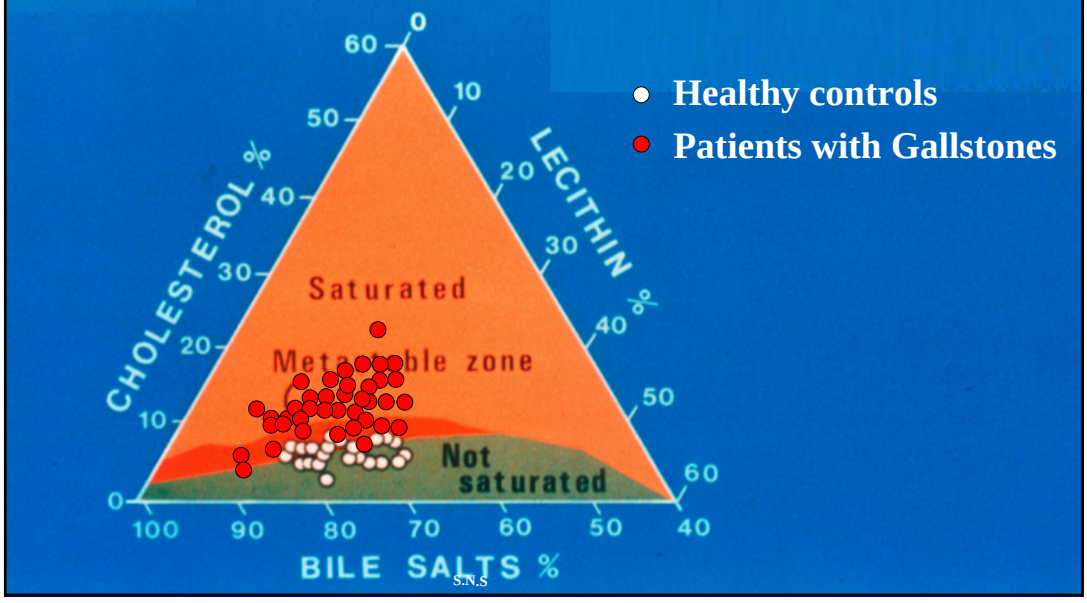
Excess cholesterol precipitates to form cholesterol crystals and stones



Composition of Gallbladder bile

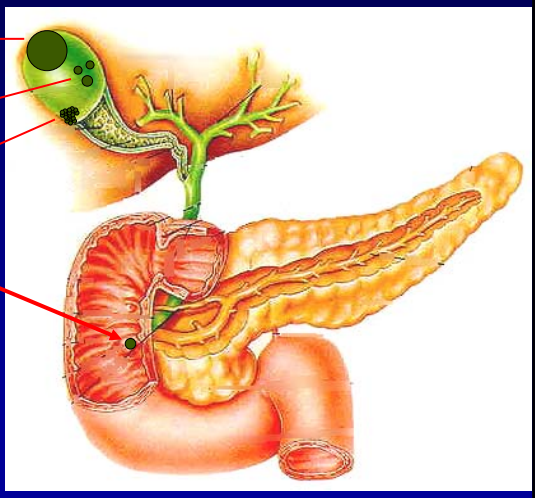


Where do gallstone develop?

Very large stones
Unlikely to pass into the duct but more likely to cause local problems

Smaller stones
Can pass into the duct and cause biliary colic/cholestasis/ pancreatitis

Sludge (viscous aggregate of crystals and mucus)
Can pass into the duct but is much less likely to cause problems as it can easier pass the papilla



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Factors influencing the prevalence of gallstones

Age

under 30y	1-6%
50-60y	9-30%

Female gender/ sex hormones

		PREGNANCY		
Men under 30	1-3%			
Women under 30	2-6%	2. Trim	3. Trim	4-6w pp
Men 50-60y	9-22%	5.1%	7.9%	10.2%
Women 50-60y	16-30%			

Environmental and genetic factors

Female Pima Indians >25y	73%

Low prevalence in Asia and Africa

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Cholesterol stones:

- Great majority of all stones in the US (>80%)
- either pure cholesterol stones or mixed stones (more than 50% cholesterol content)

Main contributing factors:

-Decreased bile acids
-Increased biliary cholesterol
-Gallbladder factors allowing for stasis/nucleation

> Supersaturation

Pigment stones:

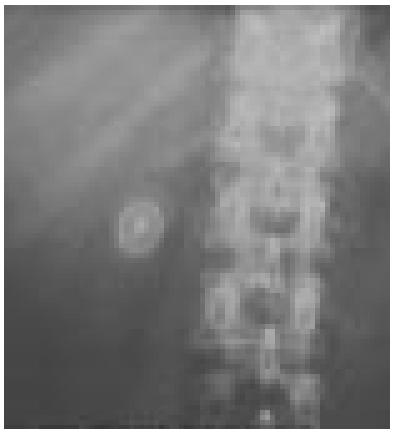
- much less common in US than Cholesterol stones
- contain pigment = bilirubin

Main causes

Chronic Hemolysis → excess bilirubin
Decreased bilirubin conjugation → decreased bilirubin solubility
(cirrhosis, bacterial infections)

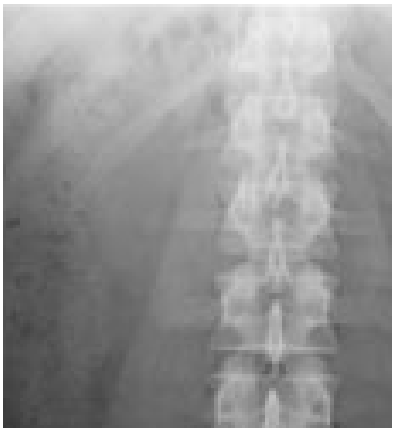
x-Ray Appearance of Gallstones

Radio-opaque



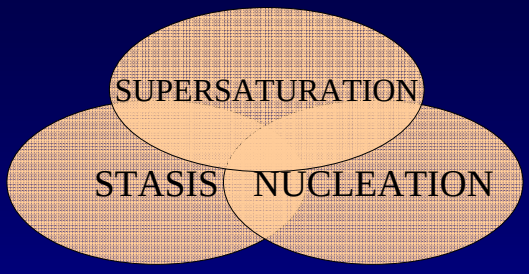
27% = Cholesterol Stones
73% = Pigment Stones

Radioluscent



83% = Cholesterol Stones
17% = Pigment Stones

Factors Favoring Cholesterol Gallstones



- **Hepatic Production of Lithogenic Bile**

A. Excess cholesterol secretion

1. Obesity
2. Estrogens
3. Crash diet
4. Genetic factors/Ethnicity (Pimas) - Point Mutation in ABCA8 accounts probably for 10% of gallstones (Nat. Genetics 2007)

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Factors Favoring Cholesterol Gallstones

- **Hepatic Production of Lithogenic Bile**

  B. Decreased Secretion of Bile Acids

  1. Decreased bile salt synthesis despite diminished pool, e.g. Cyp7a mutations (rare)
  2. Decreased bile acid return to liver (ileal resection)

- **Gallbladder Factors**

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

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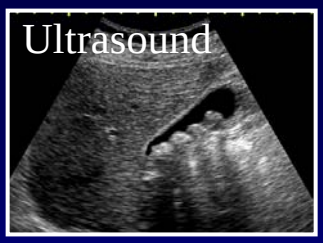
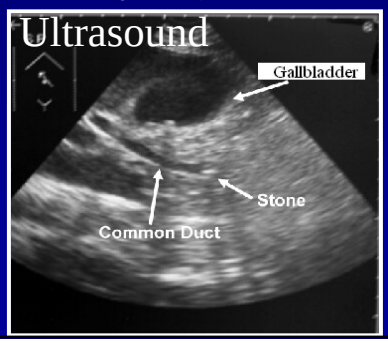
Natural History of Gallstones

- 80% of all gallbladder stones will never cause symptoms

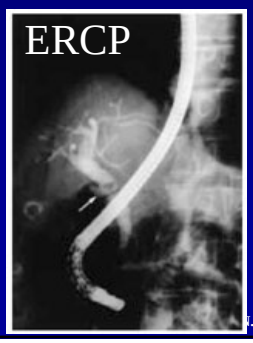


- 1-4% of gallbladder stones/year cause symptoms (e.g. colic, pancreatitis, cholecystitis)



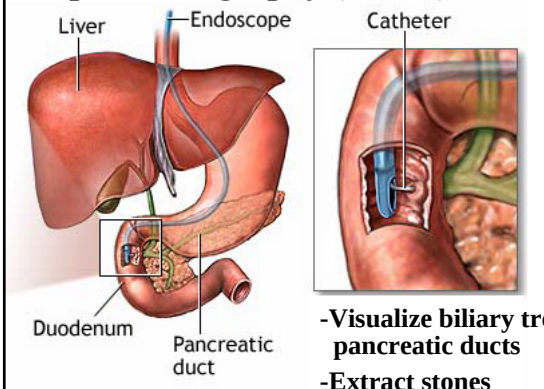
Dilated Duct

Intraductal stone
(not always visible)



Schematic diagram for the management of gallstone disease

Endoscopic retrograde cholangio-pancreatography (ERCP)



-Visualize biliary tree and pancreatic ducts

-Extract stones

l stones

SUMMARY GALLSTONES

1. Over 80% of gallstones are CHOLESTEROL stones caused by a dysbalance between cholesterol and bile acids in bile

2. FASTING (Gallbladder stasis), OBESITY (increased cholesterol secretion) and ESTROGEN (increased cholesterol secretion) promote gallstone formation

3. SMALLER GALLSTONE pass easier into the duct

4. 80% of gallstones remain unsymptomatic

5. Therapy of choice for symtopatic gallstone disease is laparoscopic cholecystectomy

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PANCREAS PHYSIOLOGY

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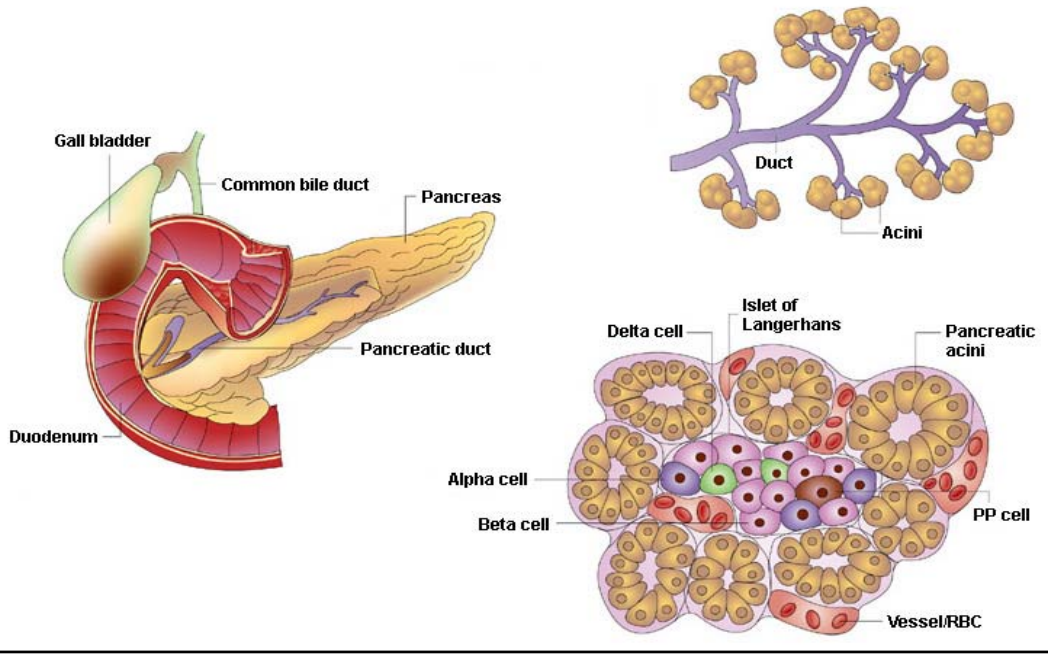
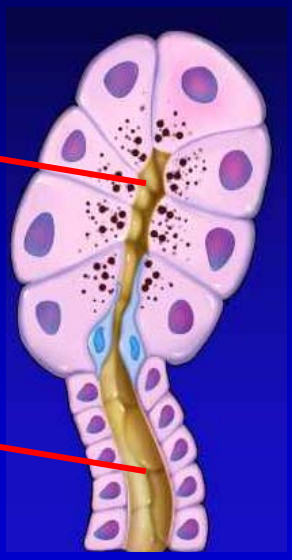
Pancreas macro- and microanatomy



Major functional units

ACINUS
Digestive enzyme secretion
(Trypsin, Elastase, Amylase, Lipase)

DUCTULE
Water, bicarbonate secretion



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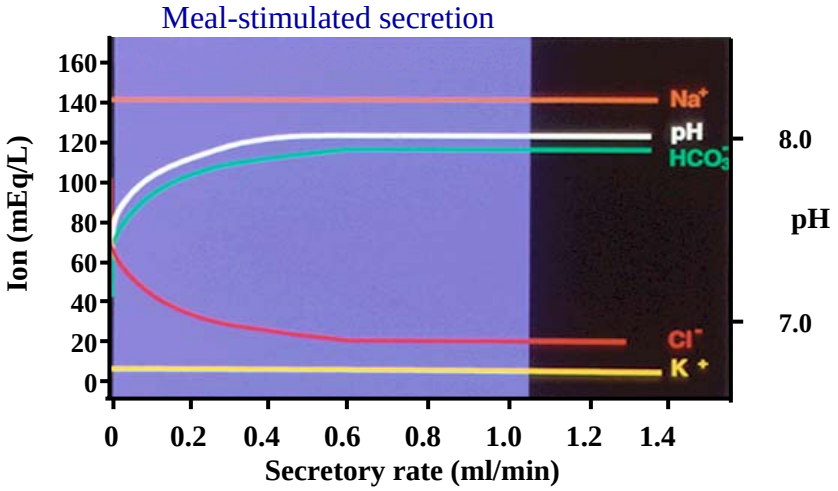
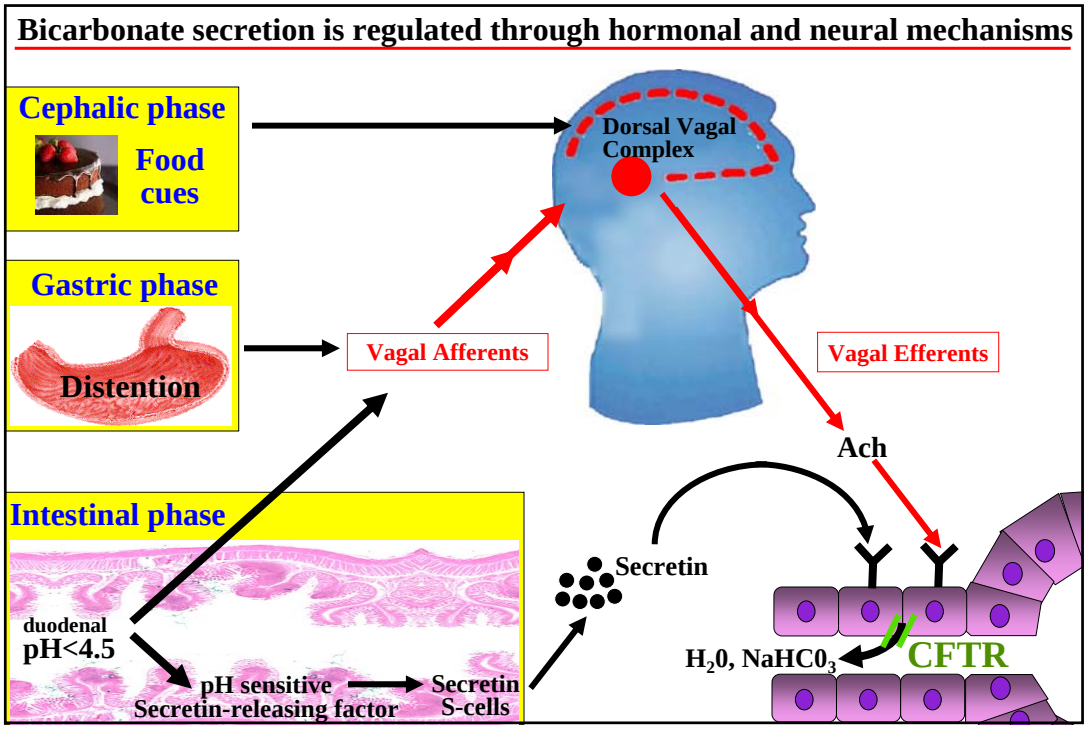
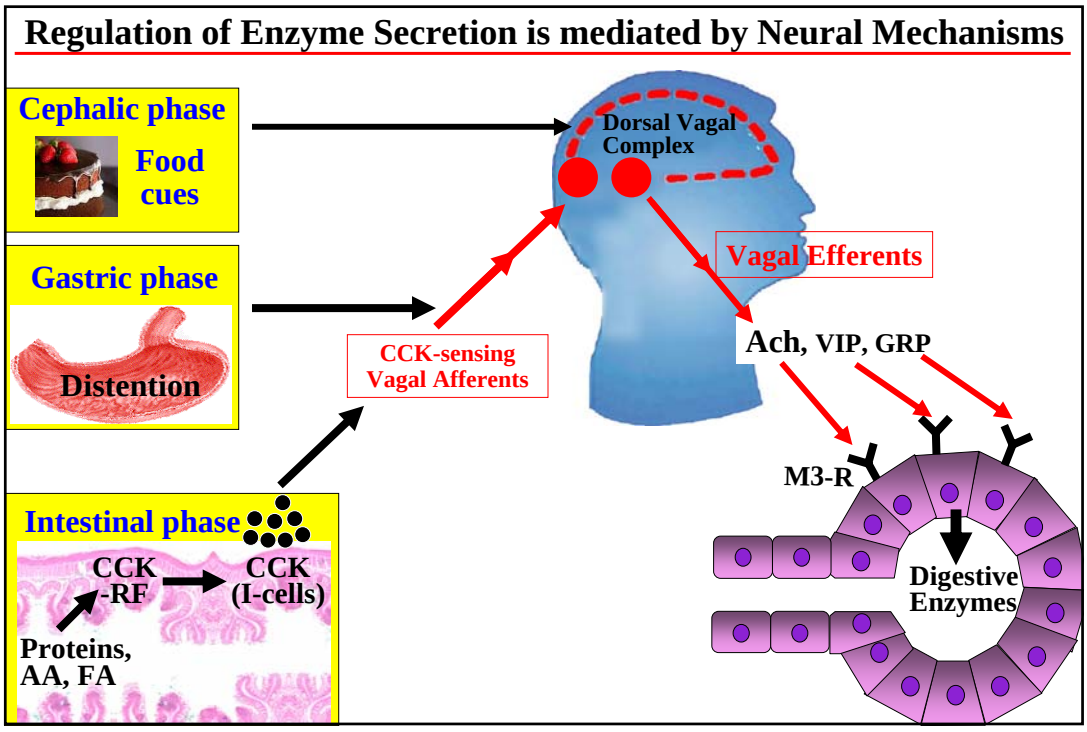
$HC0_3$ concentration and pH increase with increased pancreatic secretion

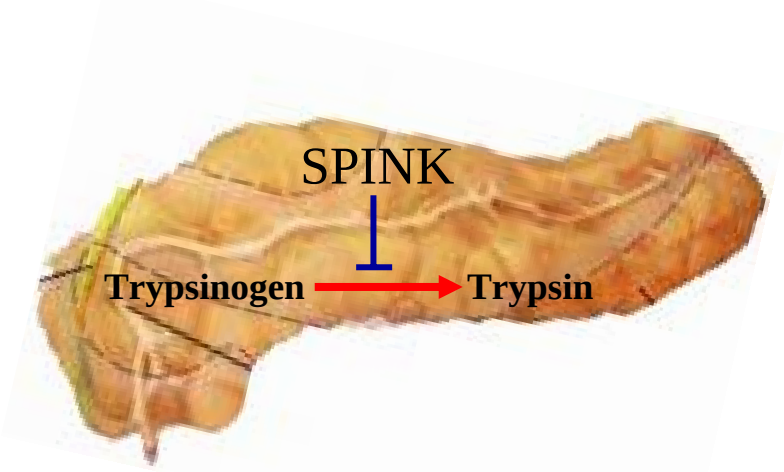
→ **The increase in $HC0_3$ serves to buffer the acidic pH of food after it passes into the duodenum.**




Bicarbonate secretion is regulated through hormonal and neural mechanisms
Cephalic phase
Food cues
Gastric phase
Distention
Intestinal phase
duodenal pH<4.5
pH sensitive Secretin-releasing factor
Secretin S-cells
Vagal Afferents
Dorsal Vagal Complex
Vagal Efferents
Ach
Secretin
H20, NaHC03
CFTR


Regulation of Enzyme Secretion is mediated by Neural Mechanisms
Cephalic phase
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



2 Mechanisms to prevent autodigestion:
-Trypsinogen activation occurs outside of the pancreas
-Pancreatic inhibitor prevents trypsinogen activation

PATHOGENESIS OF PANCREATITIS

Activation of pancreatic enzymes within the pancreas and the resulting autodigestion is the most important mechanism that triggers pancreatitis

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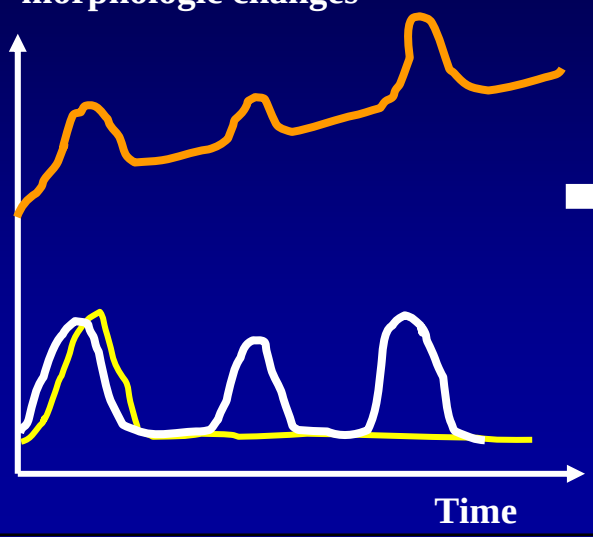
Classification of pancreatitis



CHRONIC
EtOH
Outcome:
Pain
Endocrine insufficiency
Exocrine insufficiency

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

ACUTE
e.g. stone, EtOH
Outcome:
Recovery or death

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Acute Pancreatitis

- Clinically severe

- Typically starts with moderate to severe abdominal pain

- Complications such as pancreatic necrosis, infection, shock and multi-organ failure develop in some patients

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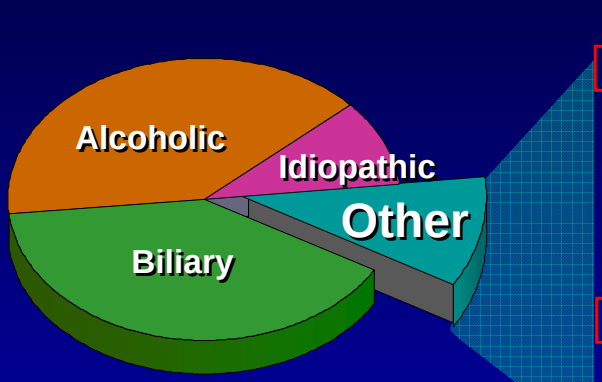
Etiology of Acute Pancreatitis



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

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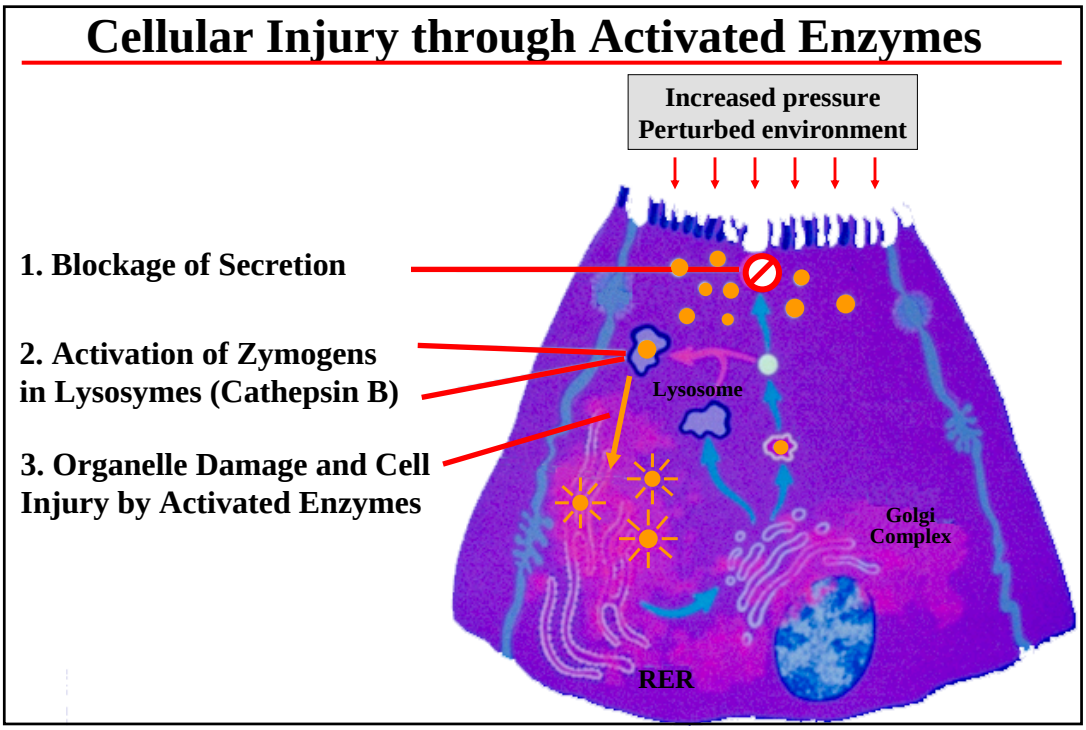
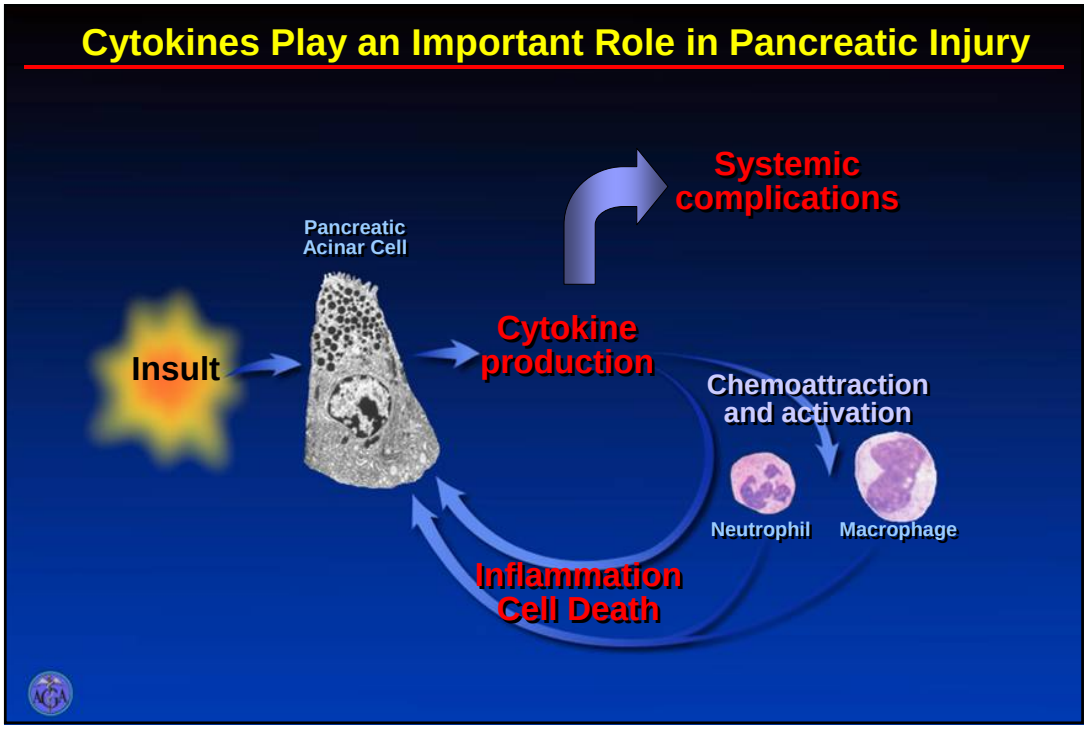
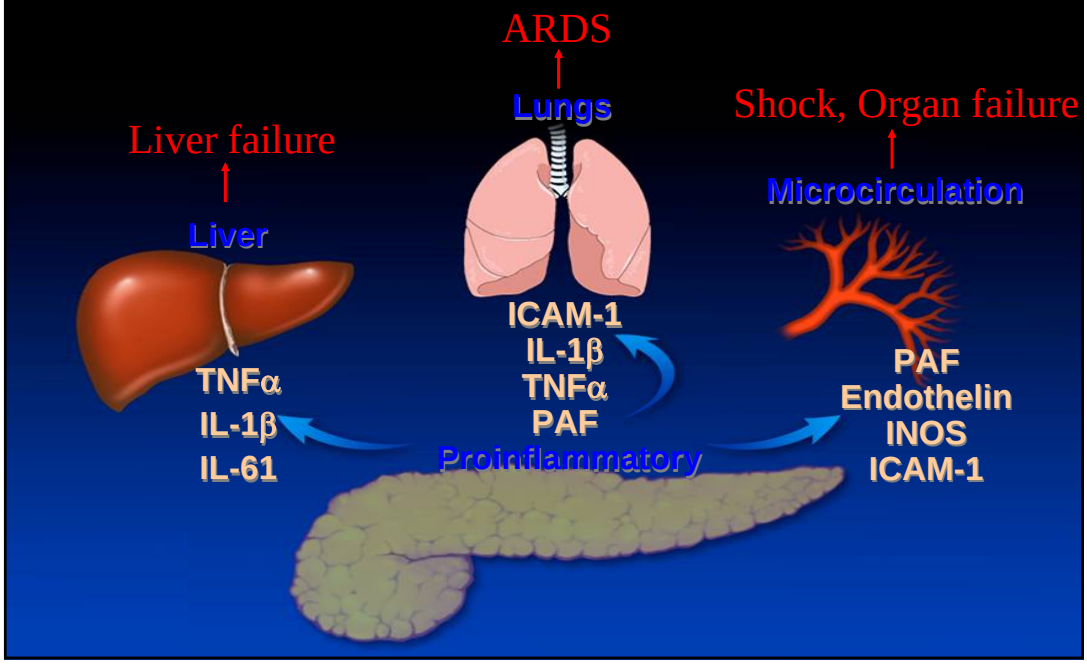
Cellular Injury through Activated Enzymes



Cytokines Play an Important Role in Pancreatic Injury

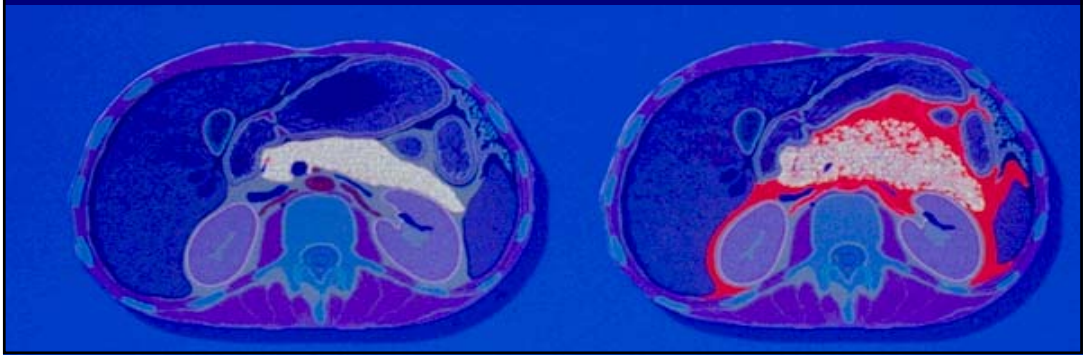


Cytokines Mediate Systemic Complications



Local effects of inflammation and pancreas injury

- Pancreatic and peripancreatic necrosis
- Fat necrosis
- Fluid loss into third space



Chronic Pancreatitis

- Chronic disease

- Pain and malabsorption are the main symptoms

- Weight loss can also be due to food avoidance

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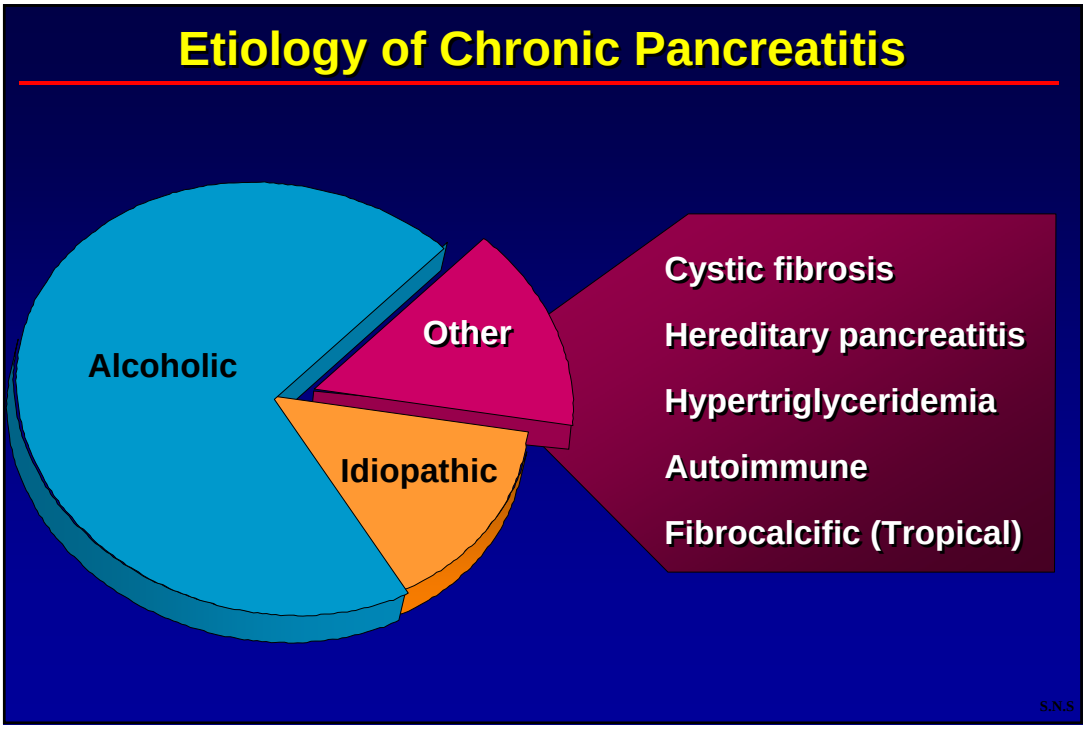
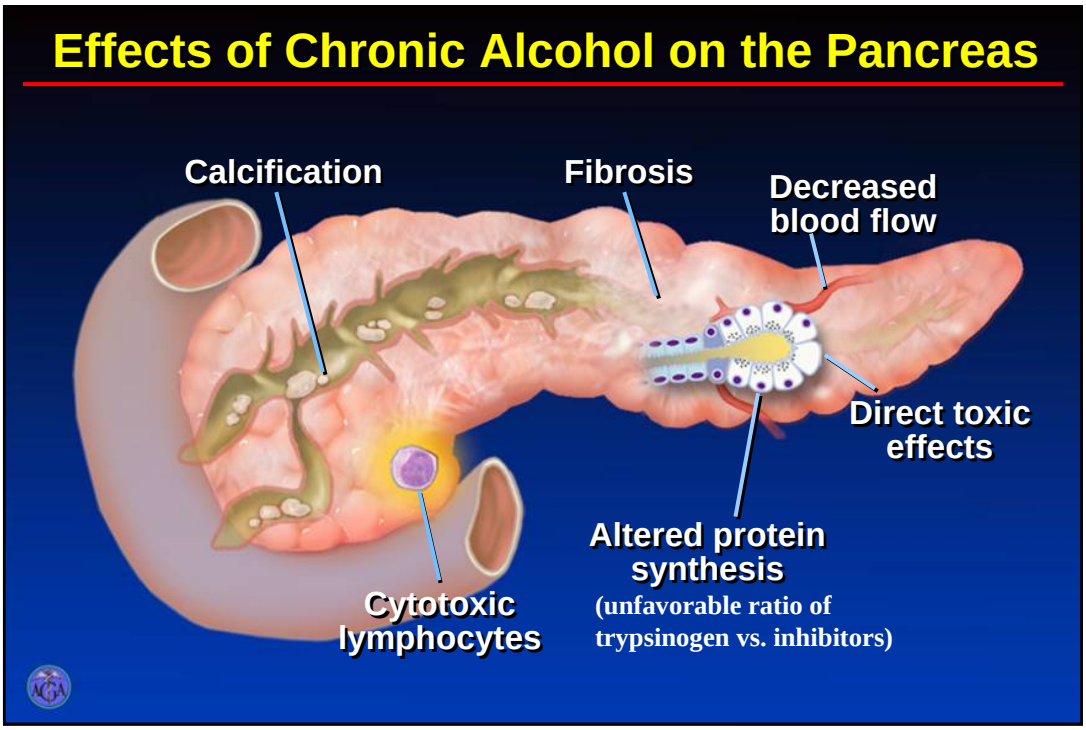
Etiology of Chronic Pancreatitis



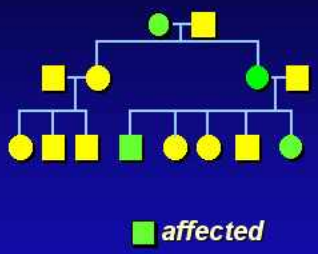
Effects of Chronic Alcohol on the Pancreas



Hereditary Pancreatitis

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

Spink



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PANCREATITIS
CLINICAL CONSIDERATONS

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Laboratory parameters are crucial to establish the diagnosis of acute pancreatitis

Lipase is more specific than Amylase and remains elevated for a longer period

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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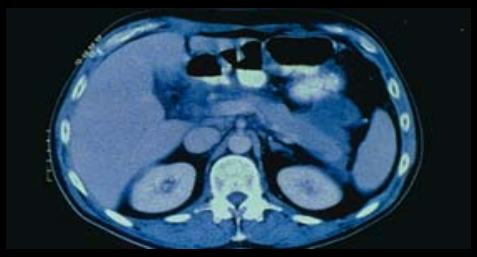
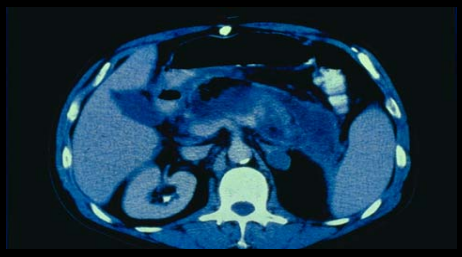
IMAGING DIAGNOSIS is important to judge severity and clinical course of pancreatitis



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, necrosis may not yet be present

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PROGNOSIS OF ACUTE PANCREATITIS

Ranson's severity score & mortality

Admission

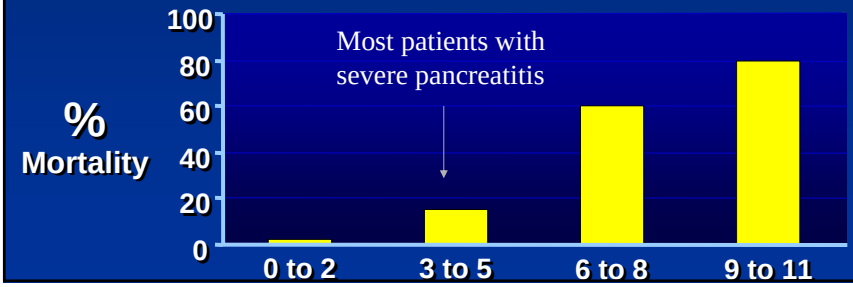
- Age > 55 years
- WBC > 16,000 mm^3
- Glucose > 200 mg/dl
- LDH > 350 IU/L
- AST > 120 IU/L

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

Systemic disease

Fat necrosis



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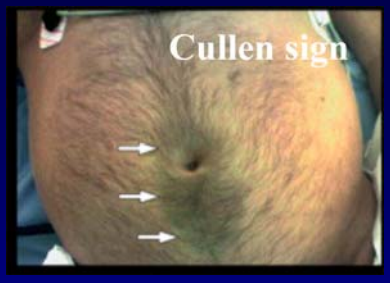
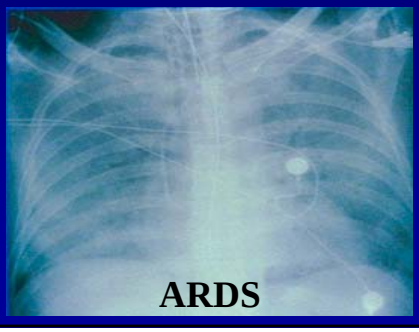
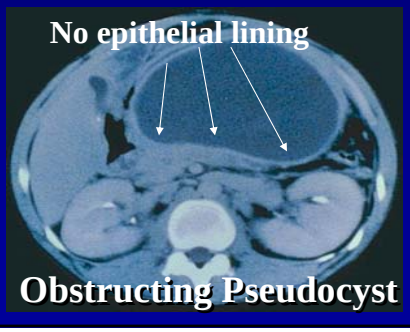
Acute Pancreatitis Complications







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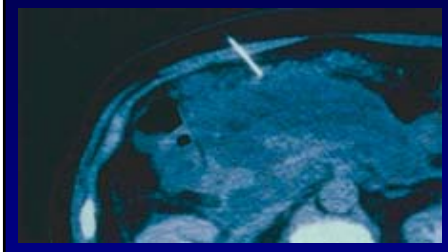
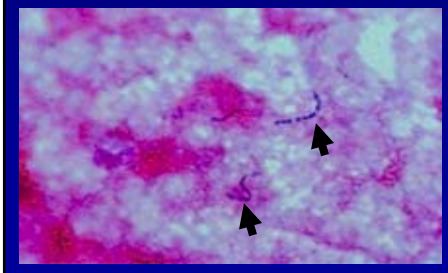
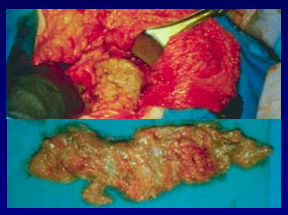
Acute Pancreatitis Complications

Infected Necrosis





Treatment



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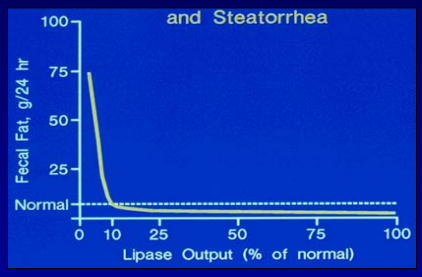
S.N.S

Chronic Pancreatitis: Diagnostic relies on imaging and functional tests

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



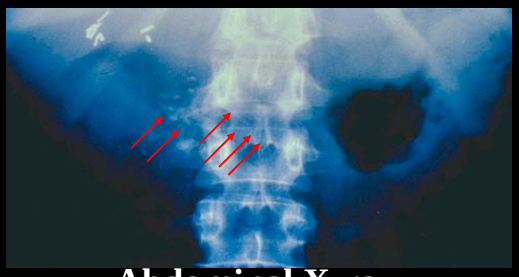
Amylase and Lipase are often within the normal range!!

S.N.S

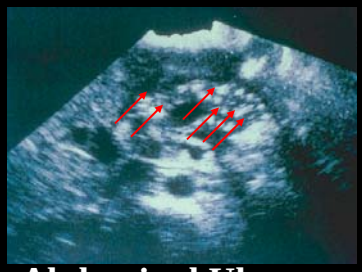
Chronic Pancreatitis: Diagnostic tests

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

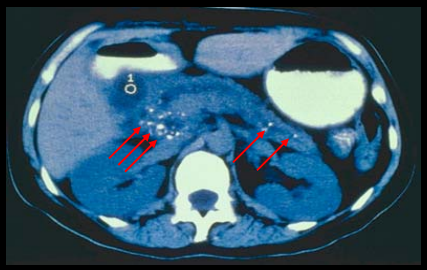
Imaging of Chronic Pancreatitis



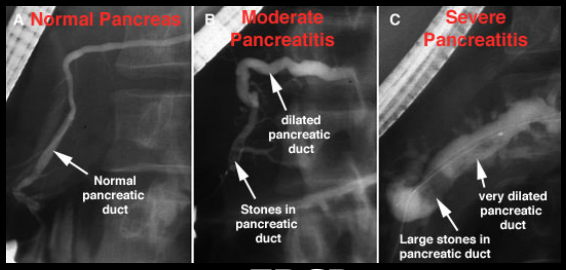
Abdominal X-ray



Abdominal Ultrasound



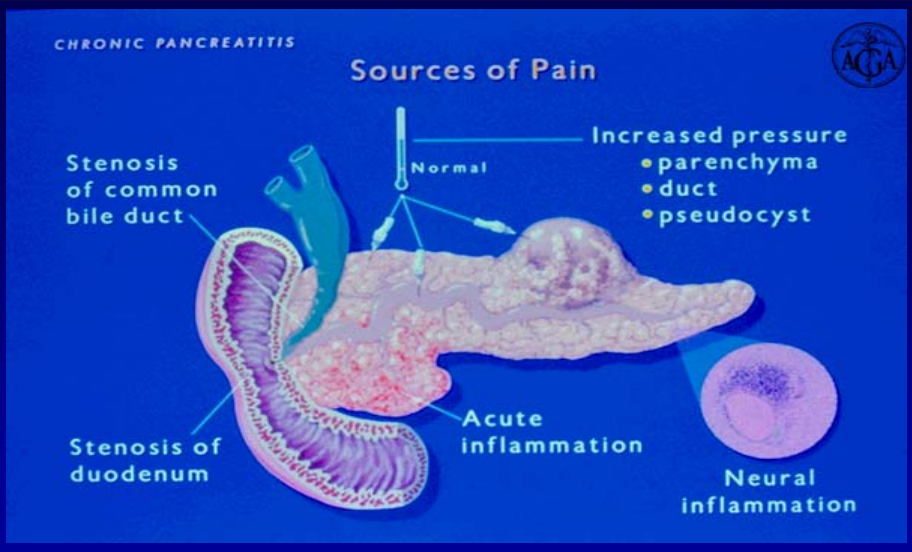
CT scan



ERCP

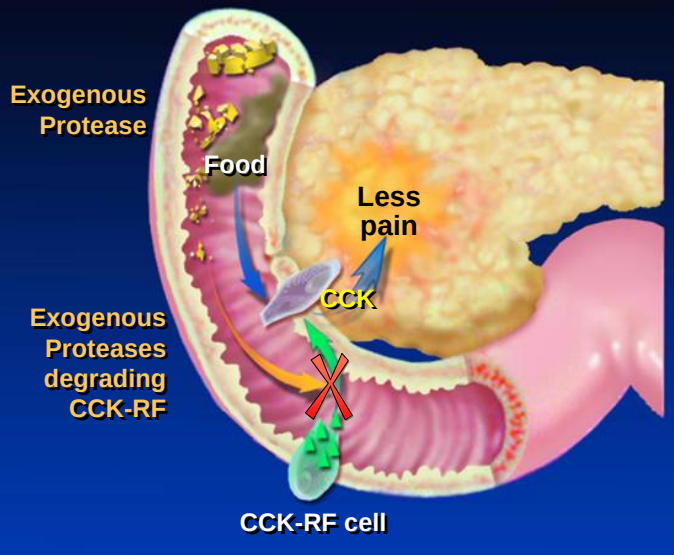
S.N.S

Chronic Pain and Malabsorption/Malnutrition are the most common Symptoms of Chronic Pancreatitis



S.N.S

Exogenous proteases may not only improve maldigestion but also CCK release and pain in chronic pancreatitis



SUMMARY PANCREATITIS

1. ACUTE PANCREATITIS is a clinically severe disease mostly caused by EtOH and GALLSTONES
2. CHRONIC PANCREATITIS causes pain and malabsorption and ist most commonly caused by EtOH
3. The diagnosis of ACUTE PANCREATITIS (but not CHRONIC Pancreatitis) is best made by detection of elevated AMYLASE and LIPASE
4. Imaging (e.g. CT) can reveal severity of acute pancreatitis (interstitial vs. necrotic)
5. CHRONIC PANCREATITIS is diagnosed by imaging (x-Ray, Ultrasound, CT, ERCP) or functional tests (secretin, fecal fat)

S.N.S