GIT Module, Pathology

Pathology and pathogenesis of acute and chronic pancreatitis

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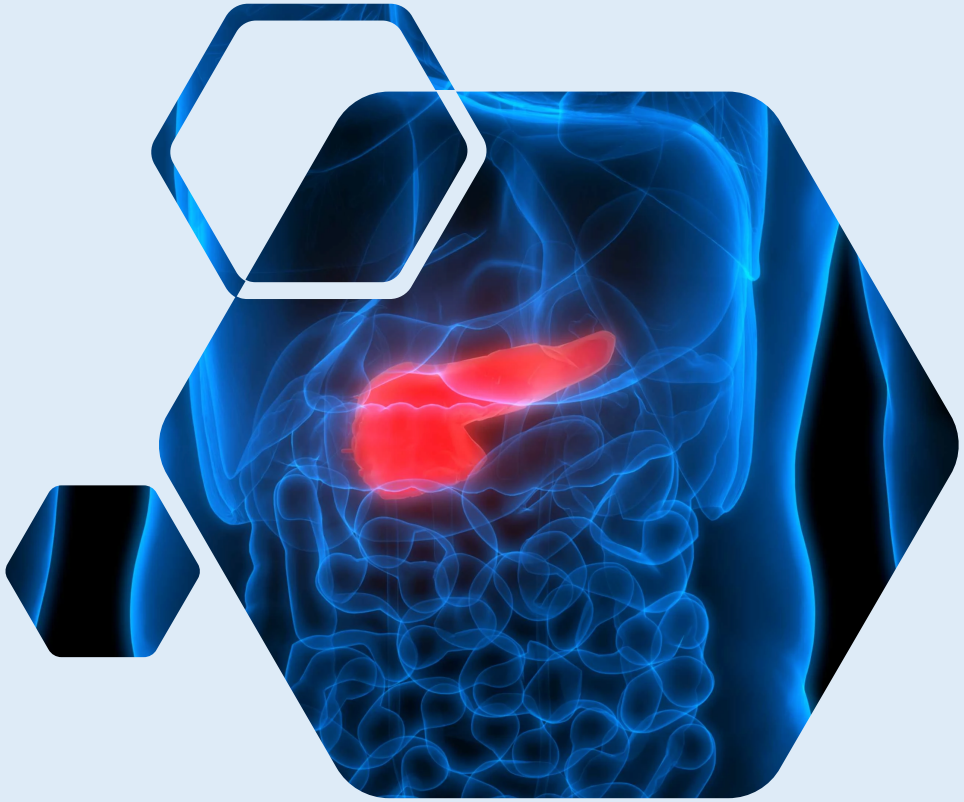
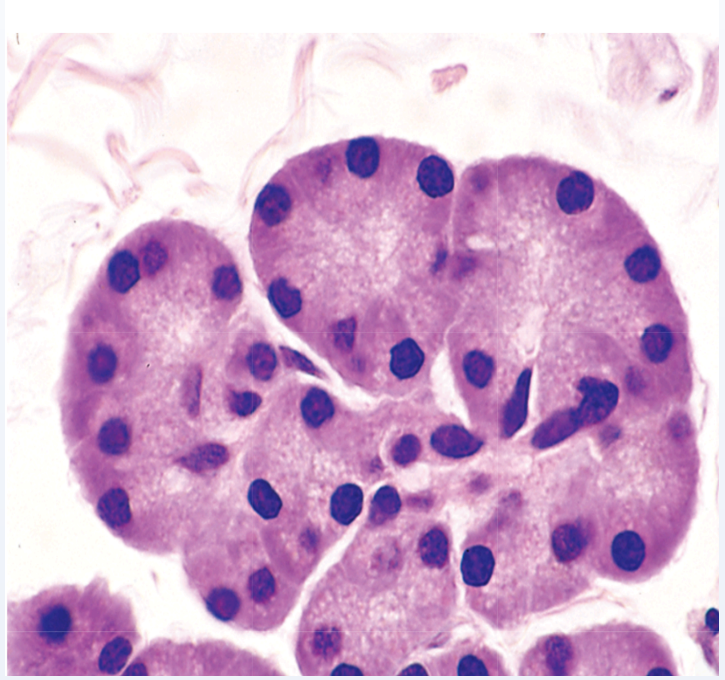


Objectives

- Introduction
- **Acute pancreatitis**
  - Epidemiology
  - Causes & pathogenesis
  - Morphology
  - Clinical findings and prognosis
- **Chronic pancreatitis**
  - Epidemiology
  - Causes & pathogenesis
  - Morphology
  - Clinical findings and prognosis

Introduction

- The pancreas is really two organs packaged into one.
- Endocrine portion
  - ✓ Islets of Langerhans : secrete insulin, glucagon, and somatostatin
  - ✓ The most significant disorders of the endocrine pancreas are diabetes mellitus and neoplasms
- Exocrine portion
  - ✓ Makes up the bulk of this organ is a major source of enzymes that are essential for digestion
  - ✓ Acinar cells and the ductules and ducts that convey their secretions to the duodenum.



Pancreatitis

- Pancreatitis encompasses a group of disorders characterized by inflammation of the pancreas
- The clinical manifestations can range in severity from a mild, self-limited disease to a life-threatening acute inflammatory process
- *Acute pancreatitis* the gland can return to normal if the underlying cause of the pancreatitis is removed
- *Chronic pancreatitis* is defined by the irreversible loss of exocrine pancreatic parenchyma

Acute Pancreatitis

ACUTE PANCREATITIS

- Definition
  - ✓ Reversible pancreatic parenchymal injury associated with inflammation
- Epidemiology:
  - ✓ Acute pancreatitis is relatively common, with an annual incidence rate in Western countries of 10 to 20 cases per 100,000 people.
  - ✓ Biliary tract disease and alcoholism account for approximately 80% of cases in Western countries
  - ✓ Gallstones are present in 35% to 60% of cases of acute pancreatitis, and about 5% of patients with gallstones develop pancreatitis
  - ✓ The male-to-female ratio is
    - 1 : 3 in the group with biliary tract disease
    - 6 : 1 in those with alcoholism

Etiologic Factors in Acute Pancreatitis

Metabolic
Alcoholism*
Hyperlipoproteinemia
Hypercalcemia
Drugs (e.g., azathioprine)
Genetic
Mutations in the cationic trypsinogen *(PRSS1)* and trypsin inhibitor *(SPINK1)* genes
Mechanical
Gallstones*
Trauma
Iatrogenic injury
Perioperative injury
Endoscopic procedures with dye injection
Vascular
Shock
Atheroembolism
Polyarteritis nodosa
Infectious
Mumps
Coxsackievirus

*Most common causes in the United States.

Pathogenesis

Acute pancreatitis appears to be caused by autodigestion of the pancreas by inappropriately activated pancreatic enzymes

1. Pancreatic duct obstruction:

- blocks ductal flow ➡ ↑ intraductal pressure & accumulation of enzyme-rich interstitial fluid ➡ lipase (secreted in an active form) ➡ local fat necrosis
- Injured tissues + periacinar myofibroblasts + leukocytes release pro-inflammatory cytokines ➡ promote local inflammation and interstitial edema
- Edema ➡ compromises local blood flow ➡ vascular insufficiency & ischemic injury to acinar cells

Pathogenesis

2. Primary acinar cell injury:

- This pathogenic pathway comes into play in acute pancreatitis caused by ischemia, viral infections, drugs & direct trauma to the pancreas

Pathogenesis

3. Defective intracellular transport of proenzymes within acinar cells

- In normal acinar cells: After synthesis in the ER, digestive proenzymes goes to zymogen granules & hydrolytic enzymes goes to lysosomes and are transported in discrete pathways
- In animal models: pancreatic proenzymes & lysosomal hydrolases become packaged together ➡ proenzyme activation ➡ lysosomal rupture ➡ local release of activated enzymes
- The role of this mechanism in human acute pancreatitis is not clear

Pathogenesis

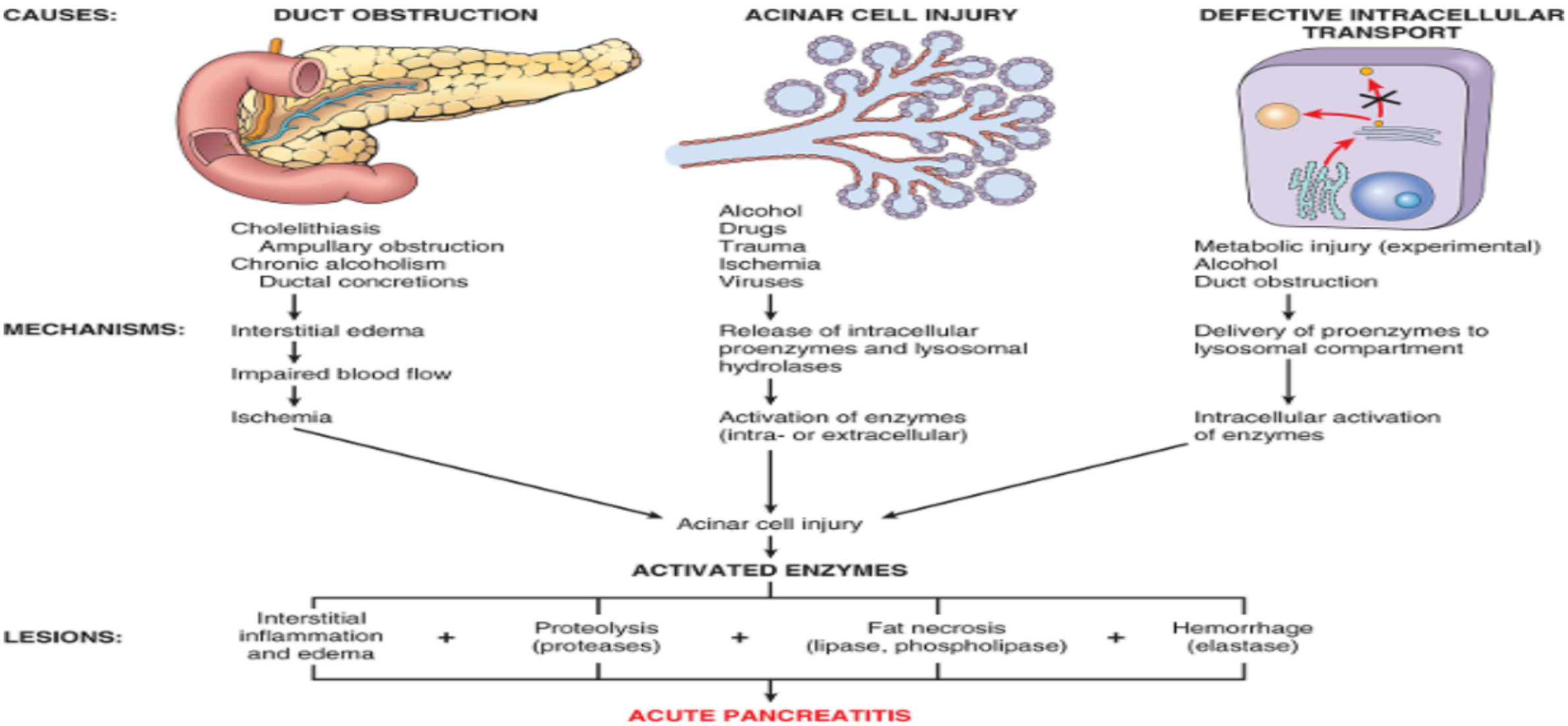
- Activation of trypsin is a critical triggering event in acute pancreatitis
- Inappropriate generation of trypsin from its proenzyme trypsinogen ➡ Trypsin activates itself & other proenzymes (e.g., phospholipases and elastases) ➡ autodigestion of the pancreatic substance

- Trypsin converts prekallikrein to its activated form ➡ activation of kinin system ➡ activation of factor XII (Hageman factor) ➡ activation of clotting & complement systems

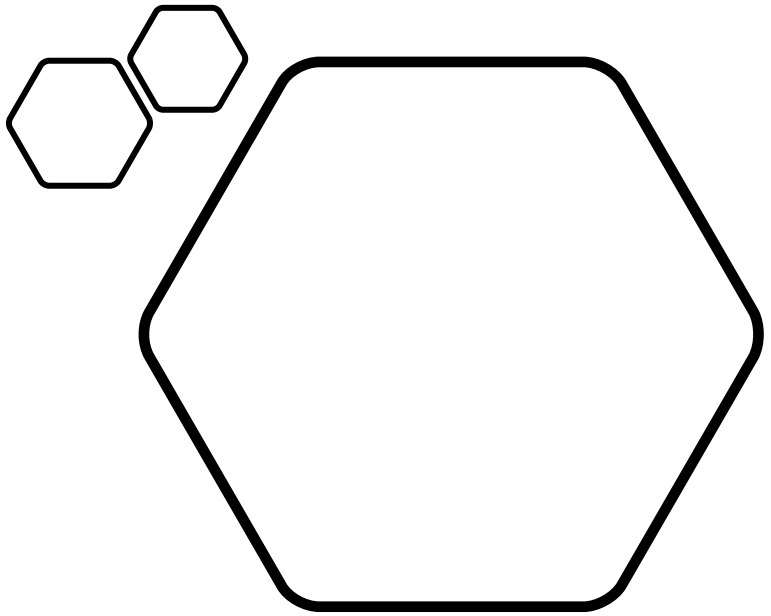
Pathogenesis

Alcohol consumption causes pancreatitis by several mechanisms:

- Alcohol transiently increases pancreatic exocrine secretion & contraction of the sphincter of Oddi
- Alcohol has direct toxic effects on acinar cells
- Chronic alcohol ingestion ➡ secretion of protein-rich pancreatic fluid ➡ deposition of inspissated protein plugs ➡ obstruction of small pancreatic ducts

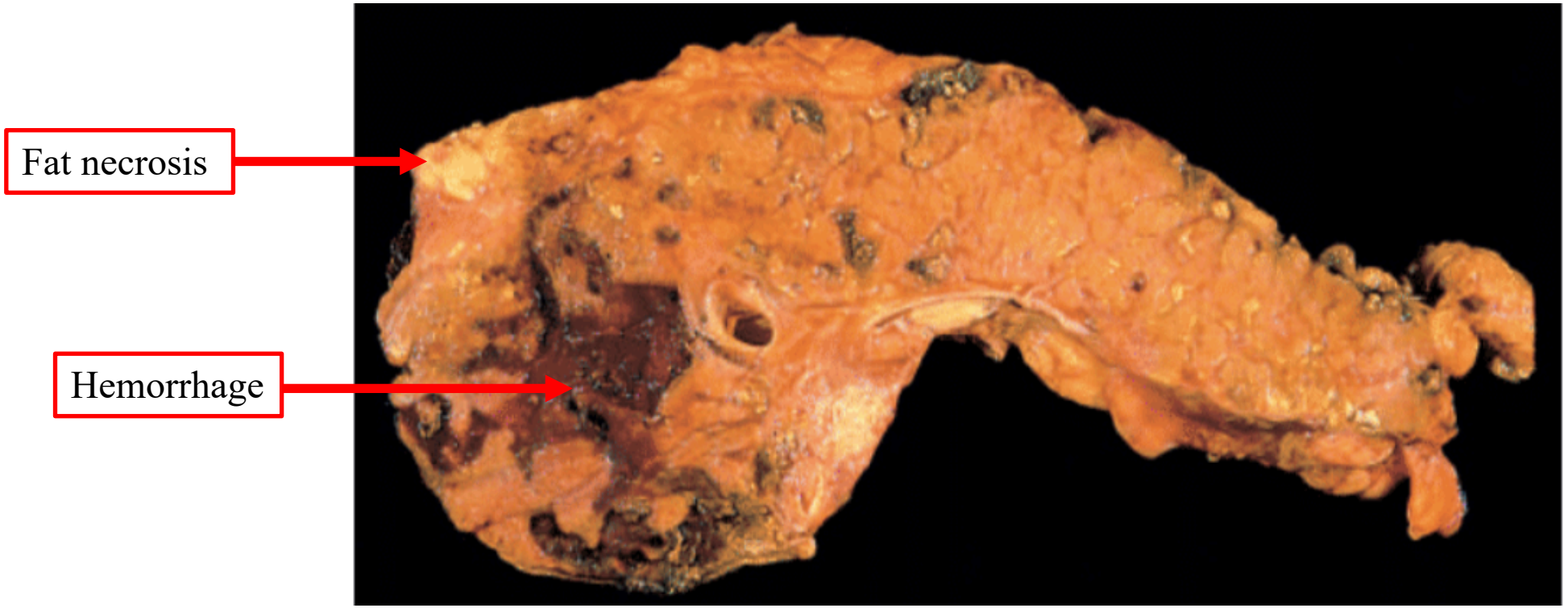

CAUSES:
DUCT OBSTRUCTION
ACINAR CELL INJURY
DEFECTIVE INTRACELLULAR TRANSPORT
Cholelithiasis
Ampullary obstruction
Chronic alcoholism
Ductal concretions
Alcohol
Drugs
Trauma
Ischemia
Viruses
Metabolic injury (experimental)
Alcohol
Duct obstruction
MECHANISMS:
Interstitial edema
Impaired blood flow
Ischemia
Release of intracellular proenzymes and lysosomal hydrolases
Activation of enzymes (intra- or extracellular)
Delivery of proenzymes to lysosomal compartment
Intracellular activation of enzymes
Acinar cell injury
ACTIVATED ENZYMES
LESIONS:
Interstitial inflammation and edema
+
Proteolysis (proteases)
+
Fat necrosis (lipase, phospholipase)
+
Hemorrhage (elastase)
ACUTE PANCREATITIS

Acute pancreatitis Morphology



- **The basic alterations are**
  1. Microvascular leakage causing edema
  2. Necrosis of fat by lipolytic enzymes
  3. Acute inflammation
  4. Proteolytic destruction of pancreatic parenchyma
  5. Destruction of blood vessels and subsequent interstitial hemorrhage

Acute pancreatitis
Morphology



- Red-black hemorrhage interspersed with foci of yellow-white, chalky fat necrosis
- Foci of fat necrosis may also be found in extra-pancreatic collections of fat

Acute pancreatitis
Morphology

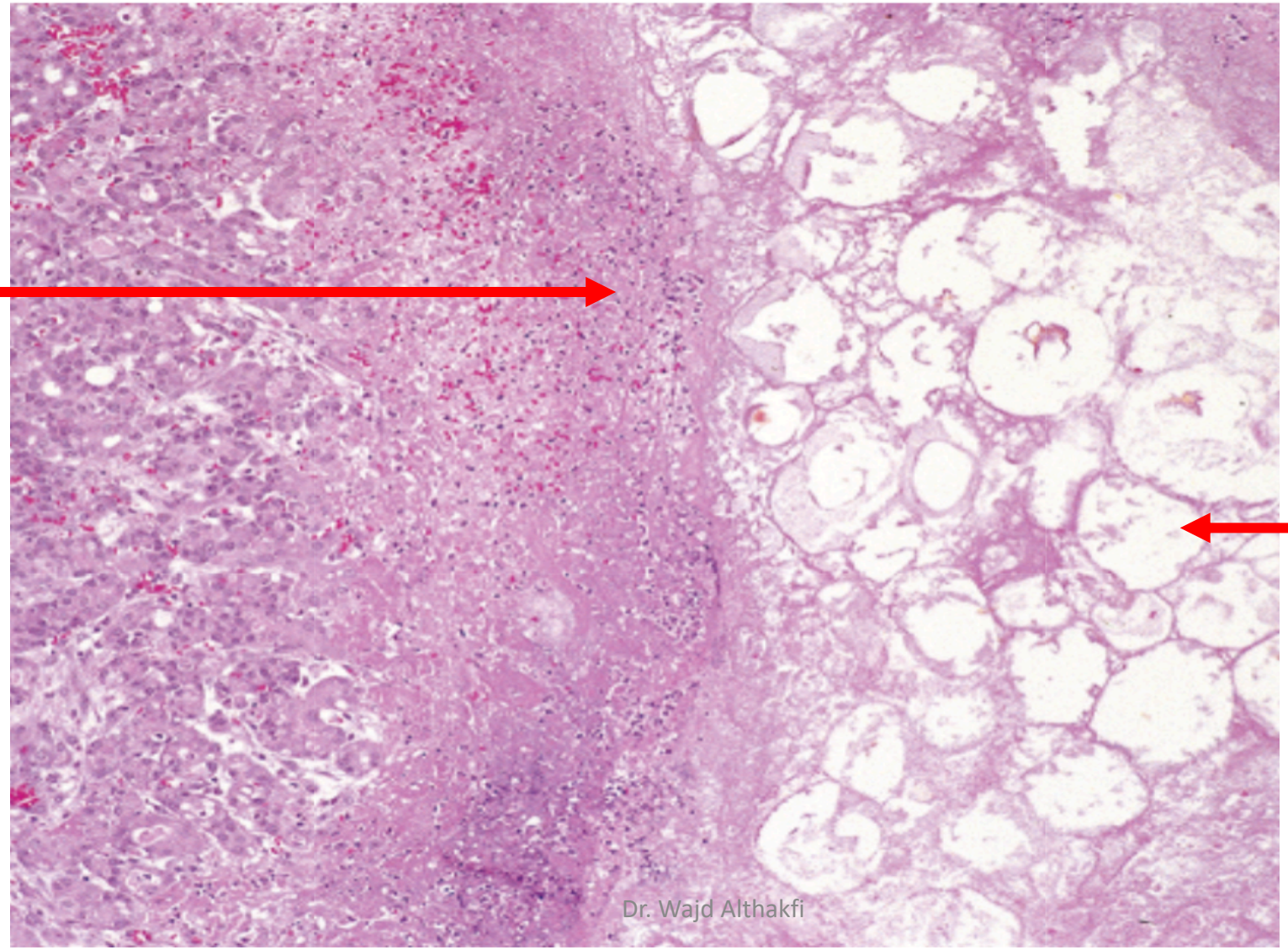
Acute necrotizing pancreatitis (sever form):

- Necrosis of pancreatic acinar & ductal tissues as well as the islets of Langerhans
- Vascular damage ➡ hemorrhage into the parenchyma of the pancreas
- Fat necrosis can occur in extra-pancreatic fat, including the omentum & bowel mesentery, and even outside the abdominal cavity (e.g., in subcutaneous fat)
- Peritoneum usually contains a serous, slightly turbid, brown-tinged fluid with globules of fat (derived from enzymatically digested adipose tissue)

Hemorrhagic pancreatitis (most sever form):

- Extensive parenchymal necrosis and diffuse hemorrhage

Acute pancreatitis
Morphology



Acute pancreatitis - Clinical Features

- Abdominal pain: varies in severity from mild & uncomfortable to severe & incapacitating
- Characteristically, the pain is constant, intense & often is referred to the upper back
- Full-blown acute pancreatitis constitutes a medical emergency “acute abdomen”: sudden onset of abdominal pain, abdominal guarding & absence of bowel sounds
- 80% of cases are mild & self limiting; remaining 20% develop severe disease

Acute pancreatitis - Clinical Features

- Systemic release of digestive enzymes + activation of inflammatory response ➡ leukocytosis, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (due to alveolar capillary injury) & diffuse fat necrosis

- ↑ microvascular permeability ➡ hypovolemia + endotoxemia (from breakdown of the barriers between gastrointestinal flora and the bloodstream) ➡ peripheral vascular collapse (shock) ➡ acute tubular necrosis in kidney ➡ renal failure

Acute pancreatitis – Clinical picture

- Laboratory findings include markedly elevated serum amylase during the first 24 hours, followed (within 72–96hours) by rising serum lipase levels.
- ↑ serum amylase in 1st 24 hr followed by ↑ serum lipase
- Hypocalcemia (due to precipitation of calcium in areas of fat necrosis) If persistent, it is a poor prognostic sign
- CT scan or MRI will show enlarged & inflamed pancreas

Management

- Supportive therapy: such as maintaining blood pressure & alleviating pain "Resting" the pancreas by total restriction of food and fluids

Acute pancreatitis – Prognosis

- Most patients will eventually recover
- 5% can die from shock during the first week of illness
- Some may develop acute respiratory distress syndrome +/- acute renal failure
- Survivors may develop:
  1. Sterile or infected *pancreatic "abscesses"*
  2. Pancreatic pseudocysts

Chronic Pancreatitis

CHRONIC PANCREATITIS

- Definition
  - ✓Characterized by long-standing inflammation & fibrosis then destruction of the exocrine pancreas, followed by loss of the endocrine parenchyma
  - ✓Chief distinction from acute pancreatitis is the irreversible impairment in pancreatic function

- Epidemiology
  - ✓Prevalence ranges between 0.04 - 5% of the U.S. population

Etiologic Factors in chronic Pancreatitis

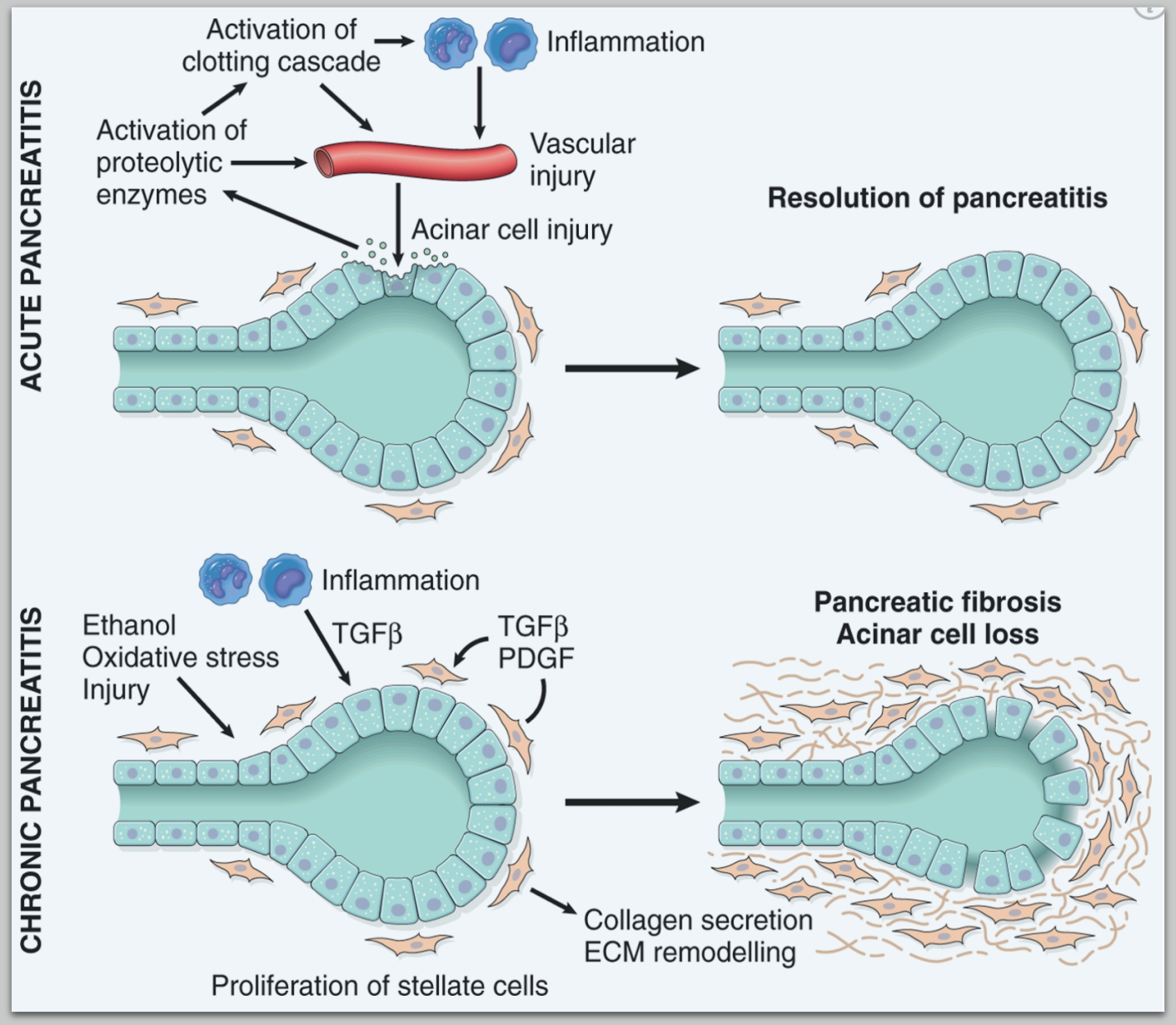
- Repeated bouts of acute pancreatitis (Long-standing obstruction of the pancreatic duct by calculi or neoplasms)
- Chronic alcohol abuse **(the most common cause)**
- Tropical pancreatitis: a poorly understood disorder seen in Africa & Asia, with a subset of cases having genetic basis
- Hereditary pancreatitis
  - ✓ Germline mutations in genes such as CFTR
- Autoimmune injury to the gland (IgG-related disease)
- Idiopathic in 40%

Pathogenesis

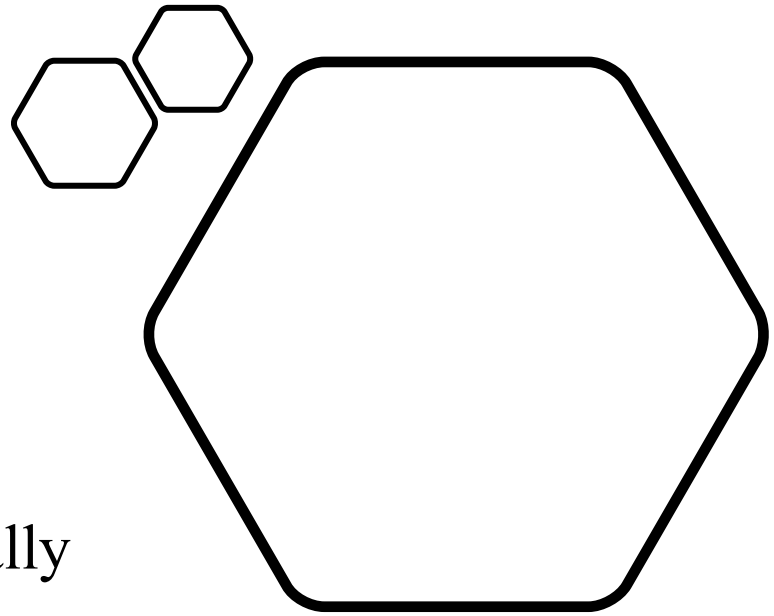
Although the pathogenesis of chronic pancreatitis is not well defined, several hypotheses are proposed:

- Ductal obstruction by concretions
- Toxic-metabolic
- Oxidative stress
- Inappropriate activation of pancreatic enzymes due to mutations affecting genes

Repeated episodes of acinar cell injury lead to the production of TGF-β and PDGF, resulting in proliferation of myofibroblasts, secretion of collagen and irreversible loss of acinar cell mass, fibrosis, and pancreatic insufficiency

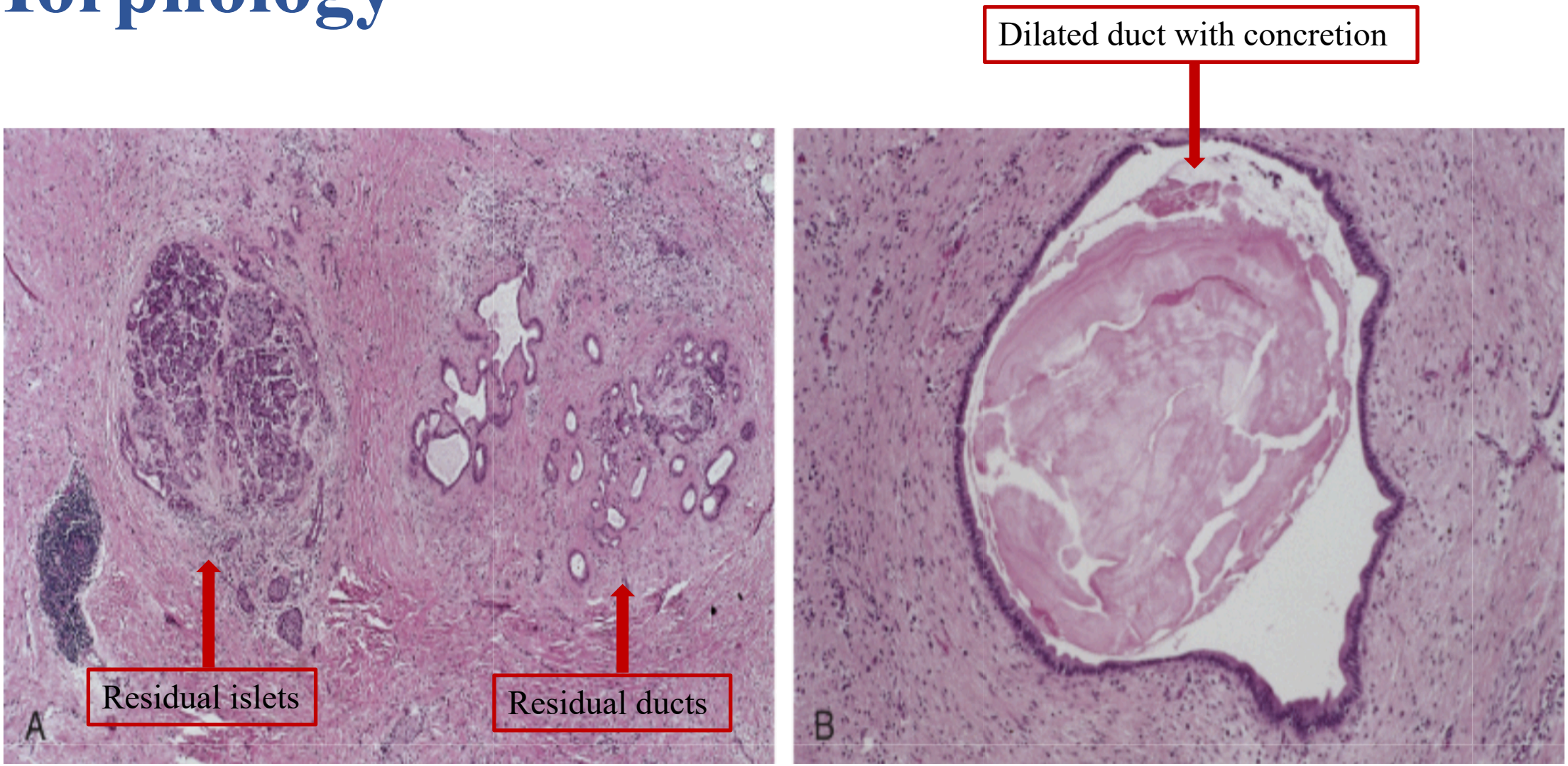


Acute pancreatitis Morphology



1. Parenchymal fibrosis
2. Reduced number & size of acini (acinar loss)
3. Variable dilation of the pancreatic ducts
4. Relative sparing of the islets of Langerhans, eventually will disappear as well
5. Chronic inflammatory infiltrate around remaining lobules and ducts
6. Ductal epithelium may be atrophied, hyperplastic or exhibit squamous metaplasia
7. Ductal concretions may be seen

Chronic pancreatitis Morphology



Chronic pancreatitis - Clinical Features

Present in several different ways:

- Repeated bouts of jaundice
- Vague indigestion
- Persistent or recurrent abdominal and back pain
- Or it may be entirely silent until pancreatic insufficiency (malabsorption led to wt. loss & hypoalbunemic edema) & DM develop
- Attacks can be precipitated by:
  - ✓Alcohol abuse
  - ✓Overeating (increases demand on pancreatic secretions)
  - ✓Drugs as opiates (increases the muscle tone of the sphincter of Oddi)

Chronic pancreatitis – Clinical picture & Prognosis

- Diagnosis requires a high degree of clinical suspicion
- During attack of abdominal pain, there may be mild fever & moderate elevation of serum amylase
- CT or ultrasonography: visualization of calcifications within the pancreas
- ~ 10% develop pancreatic pseudocysts
- Long-term prognosis is poor: 50% mortality rate over 20 to 25 years
- Persons with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer

Chronic pancreatitis - Diagnosis

- Amylase in chronic pancreatitis
  - ✓ Less reliable than in acute disease
  - ✓ Values are variable: either normal, borderline, or slightly increased
- Lipase in chronic pancreatitis
  - ✓ Not clinically useful
- Serum immunoreactive trypsin in chronic pancreatitis
  - ✓ Decreased concentration