GNT block
Nov 2019

Pathology and pathogenesis of acute and chronic pancreatitis

Definition, epidemiology, pathogenesis, morphology, and clinical findings of acute and chronic pancreatitis

Objectives

- Describe the epidemiology, pathogenesis, morphology, and clinical findings of acute pancreatitis, including the major laboratory tests used in diagnosing the disease.

- Describe the epidemiology, pathogenesis, morphology, and clinical findings of chronic pancreatitis.

Pancreatitis: Definition

- 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	*Chronic pancreatitis*
Glands can return to normal if underlying cause of the pancreatitis is removed	Irreversible destruction of exocrine pancreatic parenchyma

Acute pancreatitis

Definition
Epidemiology
Pathogenesis
Morphology
Clinical findings
Major laboratory tests

Acute pancreatitis
Definition

- Acute pancreatitis is characterized by reversible pancreatic parenchymal injury associated with inflammation (ranging in severity from edema and fat necrosis to parenchymal necrosis with severe hemorrhage)

Acute pancreatitis
Epidemiology:

- The annual incidence in Western countries is 10 to 20 cases per 100,000 people.
- 80% of cases in Western countries are associated with one of two conditions: biliary tract disease or alcoholism.
- Gallstones are present in 35% to 60% of cases of acute pancreatitis
- The male-to-female ratio is
  - 1 : 3 in the group with biliary tract disease
  - 6 : 1 in those with alcoholism

Acute pancreatitis
Etiologic Factors

- **Metabolic:**
  1. Alcoholism
  2. Hyperlipoproteinemia
  3. Hypercalcemia
  4. Drugs (e.g., azathioprine)
- **Genetic:**

Mutations in genes encoding trypsin, trypsin regulators

Mutations in the cationic trypsinogen gene(PRSS1) and trypsin inhibitor (SPINK1) genes

recurrent severe acute pancreatitis often beginning in childhood

- **Infectious:**

Mumps, Coxsackievirus, Mycoplasma pneumoniae

- **Mechanical:**
  1. Gallstones
  2. Trauma (seat belt trauma, posterior penetration of duodenal ulcer)
  3. Iatrogenic injury
     I. Operative injury
     II. Endoscopic procedures with dye injection
- **Vascular:**
  1. Shock
  2. Atheroembolism
  3. Vasculitis

Acute pancreatitis: Pathogenesis

- Autodigestion of the pancreatic substance by inappropriately activated pancreatic enzymes

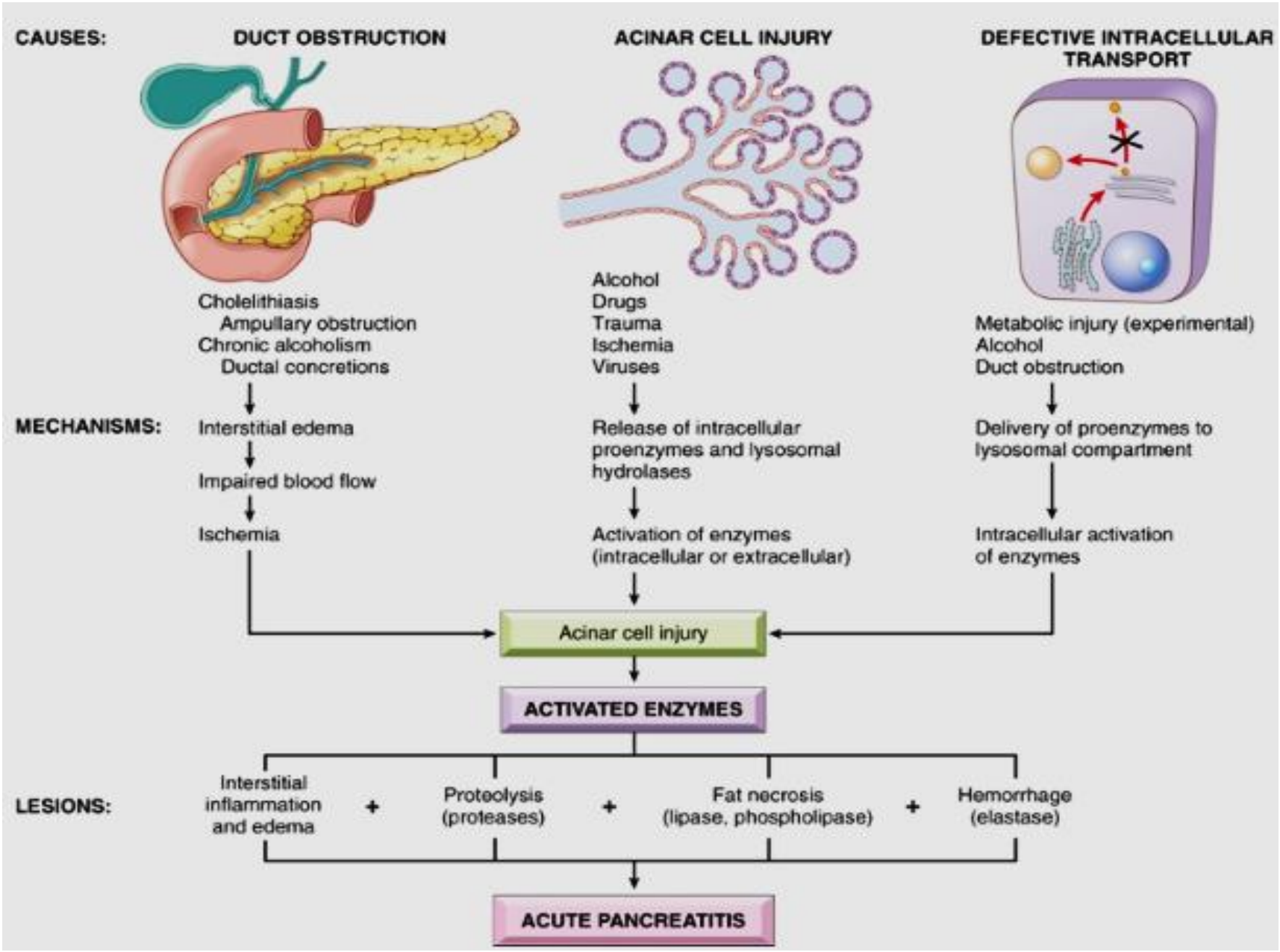
Mechanisms protect the pancreas from enzymatic self-digestion:

1. **Most digestive enzymes are synthesized as inactive proenzymes (zymogens), which are packaged within secretory granules.**
2. **Most proenzymes are activated by trypsin, which itself is activated by duodenal enteropeptidase (enterokinase) in the small bowel.**
3. **Acinar and ductal cells secrete trypsin inhibitors, including serine protease inhibitor Kazal type l (SPINK1), which further limit intrapancreatic trypsin activity.**

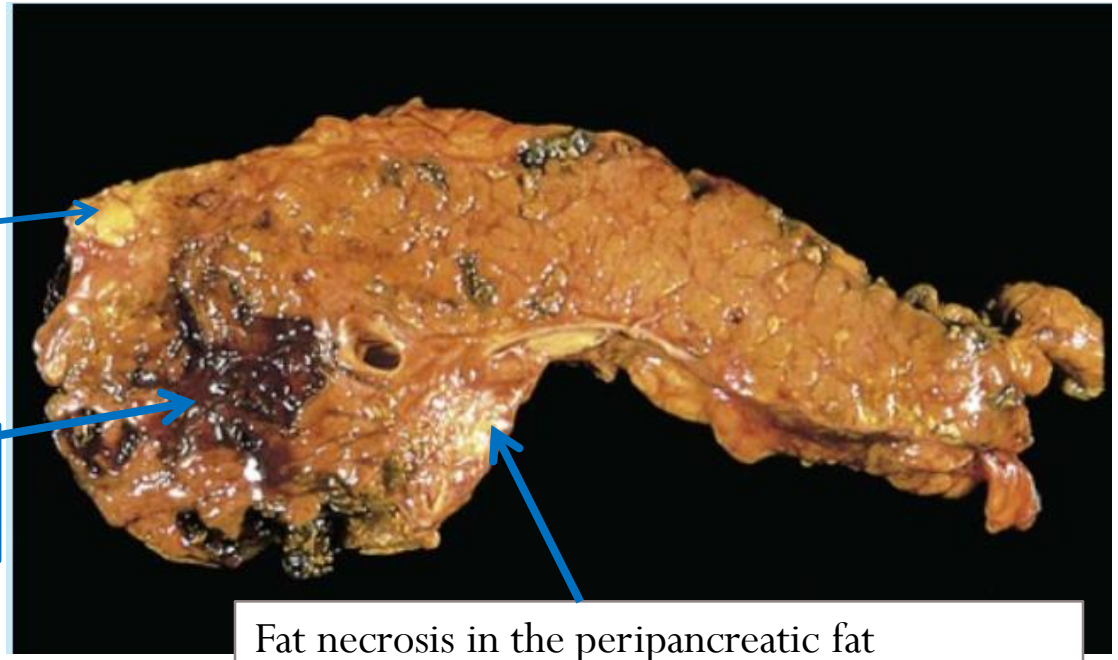
Actions of activated pancreatic enzymes (trypsinogen activation)

1. Proteases damage acinar cell structure.
2. Lipases and phospholipases produce enzymatic fat necrosis.
3. Elastases damage vessel walls and induce hemorrhage
4. Activated enzymes also circulate in the blood.

Three proposed pathways in the pathogenesis of acute pancreatitis:



Acute pancreatitis: Morphology



Fat necrosis results from enzymatic destruction of fat cells.
The released fatty acids combine with calcium to form insoluble salts that precipitate in situ
(appear as foci of yellow-white, chalky material)

Acute pancreatitis
Morphology

The morphology of acute pancreatitis ranges from inflammation and edema to severe extensive necrosis and hemorrhage

The basic alterations are:

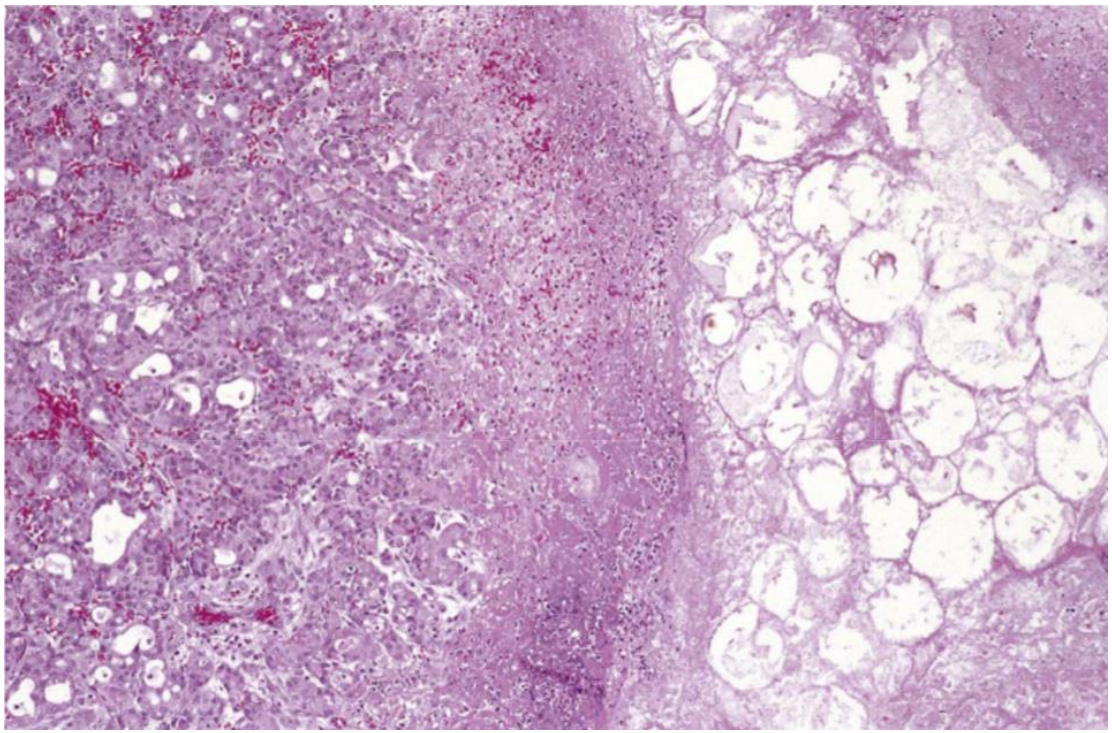
(1) microvascular leakage causing edema

(2) necrosis of fat by lipolytic enzymes

(3) an acute inflammatory reaction

(4) proteolytic destruction of pancreatic parenchyma

(5) destruction of blood vessels with subsequent interstitial hemorrhage.



Acute pancreatitis: Clinical Features

- Fever, nausea, and vomiting
- Abdominal pain
  - is the cardinal manifestation of acute pancreatitis. Its severity varies from mild to severe.
  - Severe, boring (knife-like) midepigastric pain with radiation into the back
- Hypovolemic shock
  - Due to peripancreatic collection of fluid
- Hypoxemia
  - Hypoxemia in acute pancreatitis: circulating phospholipase destroys surfactant
- Hemorrhage
- Disseminated intravascular coagulation
  - (Due to activation of prothrombin by trypsin)
- Tetany
  - (Calcium binds to fatty acids, which decreases ionized calcium leading to hypocalcemia). The worse the inflammation, the lower the calcium level. If persistent, it is a poor prognostic sign.

Full-blown acute pancreatitis is a medical emergency

Acute pancreatitis: Laboratory findings

- Marked elevation of serum amylase levels during the first 24 hours, followed within 72 to 96 hours by a rising serum lipase level

Amylase in acute pancreatitis

Not specific for pancreatitis
Initial increase occurs at 2 to 12 hours; peaks over 12 to 30 hours
Returns to normal in 2 to 4 days
Present in urine for 1 to 14 days

Serum lipase in acute pancreatitis

More specific for pancreatitis
Initial increase occurs in 3 to 6 hours; peaks in 12 to 30 hours; returns to normal over 7 to 14 days
It is *not* excreted in urine.

Serum immunoreactive trypsin in acute pancreatitis

Increases 5 to 10 times normal
Remains increased for 4 to 5 days

Acute pancreatitis: Management

- The key to the management is "resting" the pancreas by total restriction of food and fluids and by supportive therapy.

Acute pancreatitis: Prognosis

- Most patients recover fully
- About 5% die from shock during the first week of illness. Acute respiratory distress syndrome and acute renal failure are fatal complications.
- In surviving patients, complications include:
  - sterile pancreatic abscess
  - pancreatic pseudocyst
- Repeated episodes of pancreatitis, development of chronic pancreatitis.
- Hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer

Acute pancreatitis: Summary

- is a form of *reversible* pancreatic parenchymal injury associated with inflammation.
- Acute pancreatitis may be caused by
  - Excessive alcohol intake
  - Pancreatic duct obstruction (e.g., gallstones)
  - Genetic defects factors (e.g., *PRSS1*, *SPINK1*)
  - Traumatic injuries
  - Medications
  - Infections (e.g., mumps)
  - Metabolic disorders leading to hypercalcemia
  - Ischemia
- The key feature of all of these causes is that they promote the inappropriate activation of digestive enzymes within the substance of the pancreas
- Clinical features include acute abdominal pain, systemic inflammatory response syndrome, and elevated serum lipase and amylase levels

Chronic pancreatitis

Definition

Epidemiology

Pathogenesis

Morphology

Clinical findings

Chronic pancreatitis

Definition

- Prolonged inflammation of the pancreas associated with *irreversible* destruction of exocrine parenchyma, fibrosis
- In the late stages, the destruction of endocrine parenchyma occur.

Chronic pancreatitis
Epidemiology

- The prevalence of chronic pancreatitis ranges between 0.04% and 5%
- Most affected patients are middle-aged males.

Chronic pancreatitis
Causes

- Repeated bouts of acute pancreatitis (Long-standing obstruction of the pancreatic duct by calculi or neoplasms)
- Chronic alcohol abuse (**the most common cause**)
- Hereditary pancreatitis: Germline mutations in genes such as CFTR (the gene encoding the transporter that is defective in cystic fibrosis), particularly when combined with environmental stressors (up to 25% of chronic pancreatitis has a genetic basis)
- Autoimmune injury to the gland (IgG-related disease)

Chronic pancreatitis
Pathogenesis

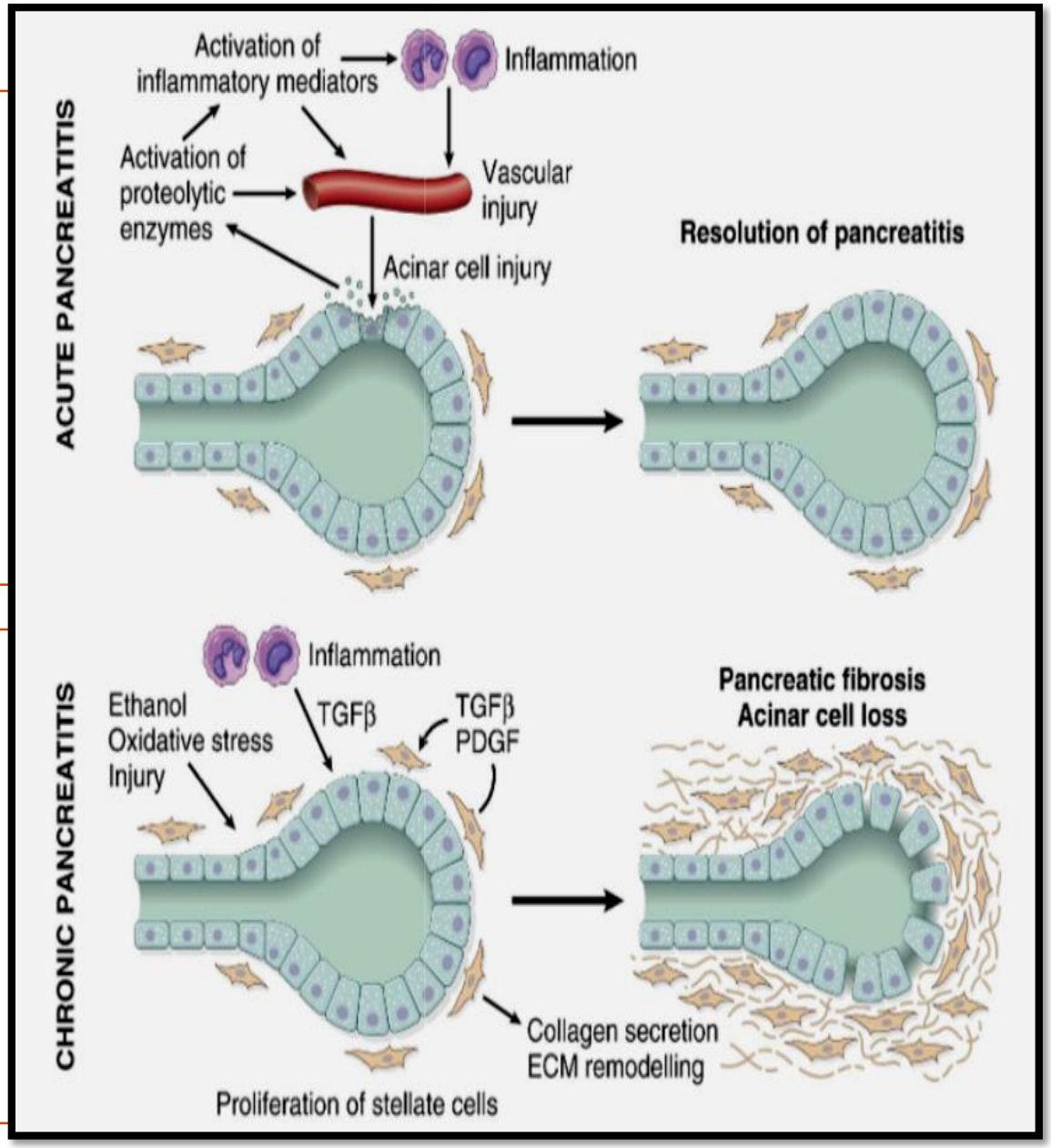
- Most often follows repeated episodes of acute pancreatitis (it initiates a sequence of perilobular fibrosis, duct distortion, and altered pancreatic secretions)
- Chronic pancreatic injury leads to local production of inflammatory mediators that promote fibrosis and acinar cell loss
  - e.g. transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) induce the activation and proliferation of periacinar myofibroblasts (pancreatic stellate cells), resulting in the deposition of collagen and fibrosis

Pathogenesis

Acute pancreatitis Acinar injury results in release of proteolytic enzymes, leading to activation of the clotting cascade, acute inflammation, vascular injury, and edema. In most patients, complete resolution of the acute injury with restoration of acinar cell

Chronic pancreatitis

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



Chronic pancreatitis

Morphology

- Chronic pancreatitis is characterized by parenchymal fibrosis, reduced number and size of acini with relative sparing of the islets of Langerhans, and variable dilation of the pancreatic ducts.

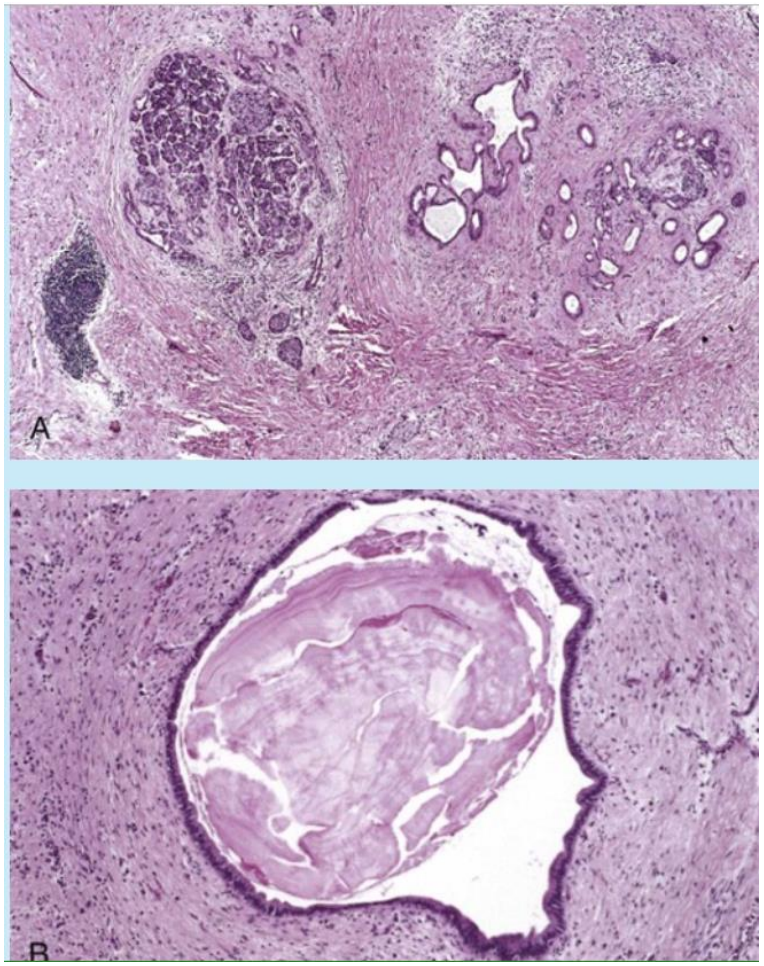
- Grossly: gland is hard, sometimes with extremely dilated ducts and visible calcification

Chronic pancreatitis: Morphology

Extensive fibrosis and atrophy has left only residual islets and ducts, with a sprinkling of chronic inflammatory cells and a few islands of acinar tissue.

Acinar loss is a constant feature

Dilated ducts with inspissated eosinophilic ductal concretions in case of alcoholic chronic pancreatitis.



Chronic pancreatitis: Clinical Features

- Silent or repeated attacks of abdominal pain, or persistent abdominal and back pain. Attacks may be precipitated by alcohol abuse, overeating (which increases demand on the pancreas), or the use of opiates and other drugs.

- may be entirely silent until pancreatic insufficiency and diabetes mellitus develop due to destruction of the exocrine and endocrine pancreas.

Chronic pancreatitis: Diagnosis

- *Requires a high degree of suspicion.*
- Mild-to-moderate elevations of serum amylase
- Gallstone-induced obstruction may be evident as jaundice or elevations in serum levels of alkaline phosphatase
- Calcifications within the pancreas by computed tomography and ultrasonography

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

Chronic pancreatitis
Prognosis

- Not an immediately life-threatening condition
- The long-term outlook for individuals with chronic pancreatitis is poor, with a 20- to 25-year mortality rate of 50%.
  - Problems:
    - Pancreatic exocrine insufficiency
    - Chronic malabsorption
    - Diabetes mellitus
    - In some patients **severe chronic pain** is a dominant problem.
- **Pancreatic pseudocysts** develop in about 10% of patients.
- Patients with hereditary pancreatitis, have a 40% lifetime risk of developing pancreatic cancer

Chronic pancreatitis Summary

- Chronic pancreatitis is characterized by *irreversible injury* of the pancreas leading to fibrosis, loss of pancreatic parenchyma, loss of exocrine and endocrine function, and high risk of developing pseudocysts
- Chronic pancreatitis is most often caused by
  1. Repeated bouts of acute pancreatitis
  2. Chronic alcohol abuse
  3. Germline mutations in genes such as *CFTR* (the gene encoding the transporter that is defective in cystic fibrosis), particularly when combined with environmental stressors

- Clinical features include intermittent or persistent abdominal pain, intestinal malabsorption, and diabetes