GNT block
Nov 2018

Pathology and pathogenesis of acute and chronic pancreatitis

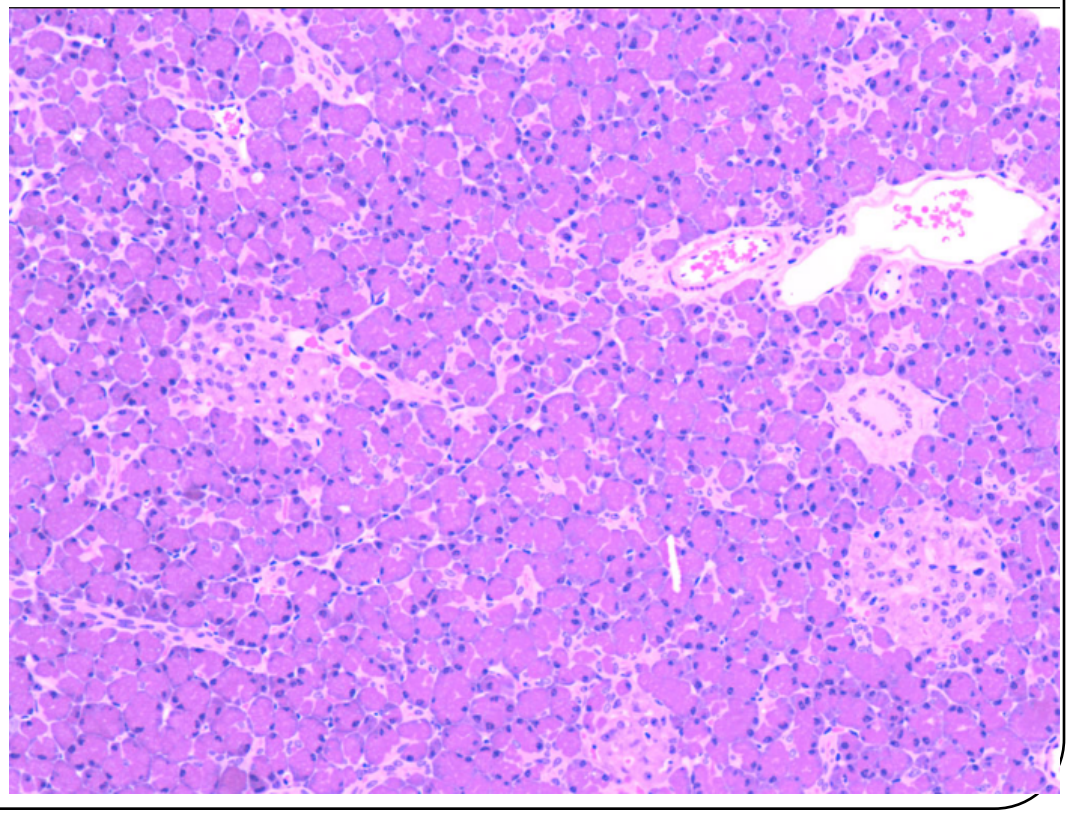
Describe the definition, epidemiology, pathogenesis, morphology, and clinical findings of acute and chronic pancreatitis

Pancreatitis: Definition

- Pancreatitis a group of disorders characterized by inflammation of the pancreas, divided into acute and chronic forms.

- In *acute pancreatitis*, glands can return to normal if underlying cause of the pancreatitis is removed

  - *Chronic pancreatitis:* irreversible destruction of exocrine pancreatic parenchyma.



Acute pancreatitis

Describe its definition, epidemiology, pathogenesis, morphology, and clinical findings

Acute pancreatitis

Definition:

- Is a necro-inflammatory disease that is characterized by infiltration of the pancreas by inflammatory cells and destruction of the pancreatic exocrine cells.
- Reversible condition.

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:

  1. biliary tract disease 2. 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 and 6 : 1 in those with alcoholism

Acute pancreatitis: Etiologic Factors

- **Metabolioc:**

1. Alcoholism
2. Hyperlipoproteinemia
3. Hypercalcemia
4. Drugs (e.g., azathioprine)

- **Genetic:**

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

or proteins that regulate calcium metabolism

- **Mechanical:**

1. Gallstones
2. Trauma
3. Parasites: e.g. *Ascaris lumbricoides* and *Clonorchis sinensis*
4. Iatrogenic injury
   I. Operative injury
   II. Endoscopic procedures with dye injection

- **Vascular:**

1. Shock
2. Atheroembolism
3. Vasculitis (Polyarteritis nodosa)

- **Infectious:**

Mumps, Coxsackievirus, Mycoplasma pneumoniae

10% to 20% of cases of acute pancreatitis are idiopathic pancreatitis

Acute pancreatitis: Pathogenesis

- Autodigestion of the pancreatic substance by inappropriately activated pancreatic enzymes

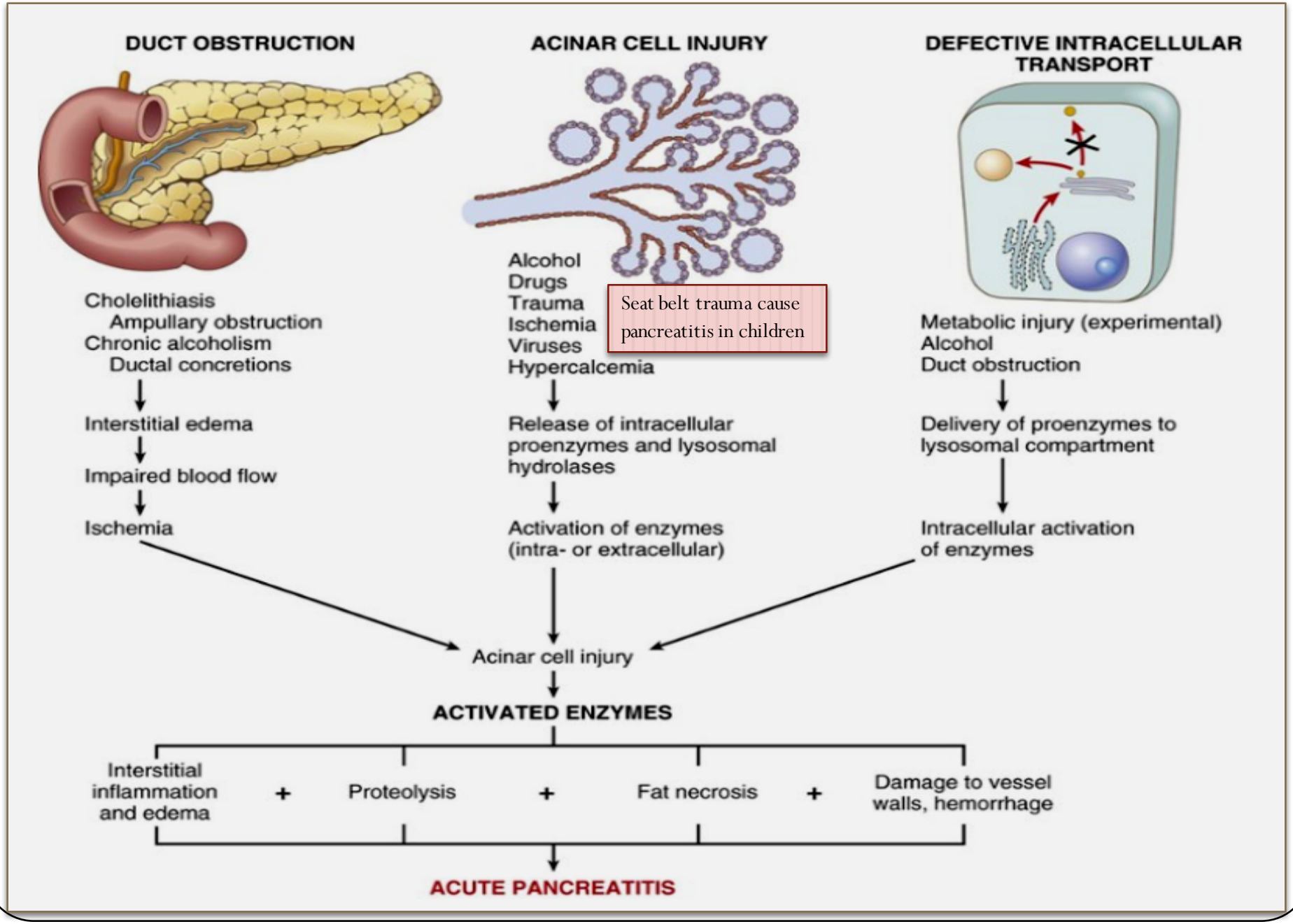
Mechanisms protect the pancreas from enzymatic self-digestion:

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 I (SPINK1), which further limit intrapancreatic trypsin activity.**

Three proposed pathways in the pathogenesis of acute pancreatitis:



Seat belt trauma cause pancreatitis in children

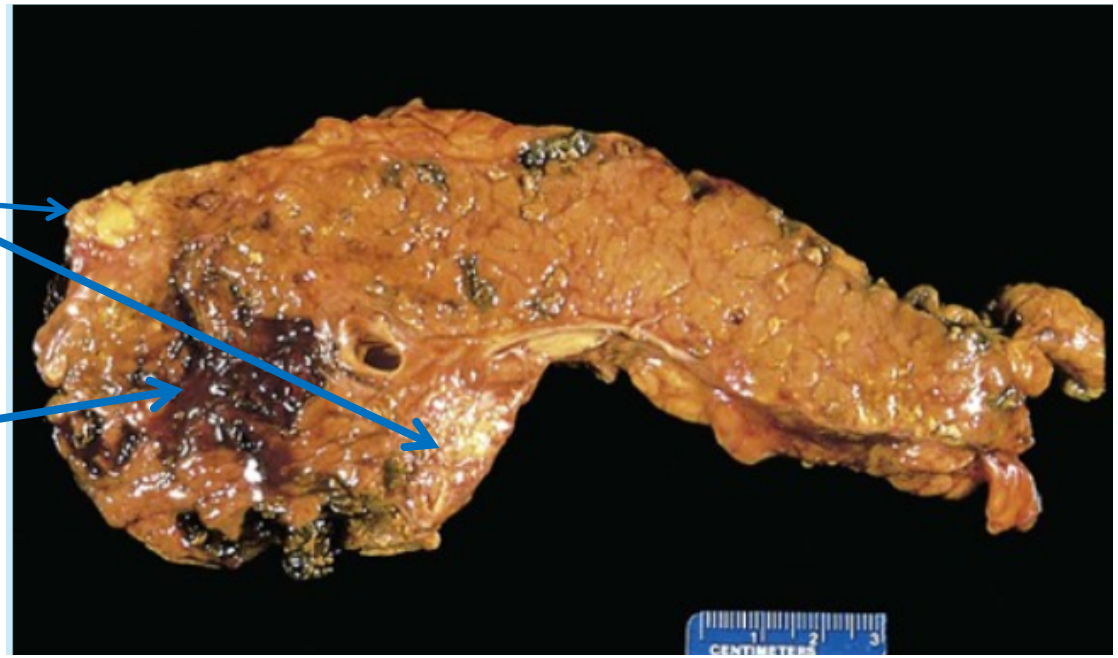
Alcohol consumption and acute pancreatitis

- Alcohol effects:
  - increases pancreatic exocrine secretion and contraction of the sphincter of Oddi
  - direct toxic effects on acinar cells with induction of oxidative stress in acinar cells
  - Stimualte release of cytokines from acinar cells

Acute pancreatitis: Morphology

Fat necrosis in the peripancreatic fat

Hemorrhage in the head of the pancreas



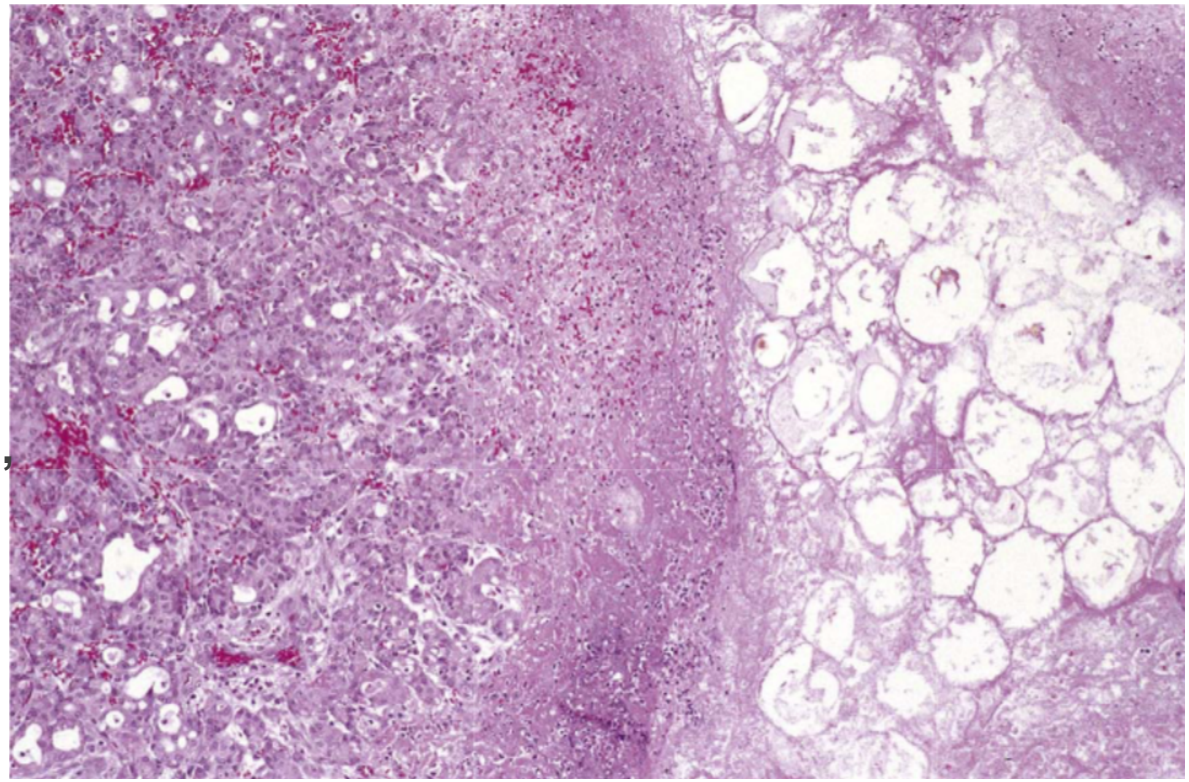
Fat necrosis results from enzymatic destruction of fat cells. The released fatty acids combine with calcium to form insoluble salts that precipitate in situ (appear as foci of yellow-white, chalky material)

Acute pancreatitis: Morphology

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

The basic alterations are:

(1) an acute inflammatory reaction with edema
(2) necrosis of fat by lipolytic enzymes
(3) proteolytic destruction of pancreatic parenchyma,
(4) destruction of blood vessels with subsequent interstitial hemorrhage.



Acute pancreatitis: Clinical Features

- Fever, nausea, and vomiting
- Severe, boring (knife-like) midepigastric pain (the cardinal manifestation of acute pancreatitis) with radiation into the back
- Hypovolemic shock
- Tetany: calcium is used up in binding to fatty acid

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.
- Serum lipase: more specific and lasts longer than amylase in acute pancreatitis; excellent screen for acute pancreatitis
- Release of lipases and phospholipases produce chalky areas of fat necrosis, with precipitation of calcium that lowers serum calcium (the worse the inflammation, the lower serum calcium level which predict a worse prognosis)

Acute pancreatitis: Management

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

Acute pancreatitis: Prognosis

- Most patients recover fully
- About 5% die from:
  1. Shock (during the first week of illness).
  2. Acute respiratory distress syndrome
  3. Acute renal failure

Acute pancreatitis: **Complications**

1. *Pancreatic necrosis* (Systemic signs occur earlier than usual with higher fever than usual; sinus tachycardia and greater degree of neutrophilic leukocytosis and peripancreatic infections)
2. *Pancreatic abscess* (sterile)
3. *Pancreatic pseudocyst* (due to liquefied necrosis area becomes surrounded by granulation tissue, forming a cystic mass with no epithelial lining)
4. Others:
    I. hyperglycaemia (destruction of β-islet cells)
    II. hypocalcaemia
    III. peritonitis

Acute pancreatitis: Summary

- is a form of *reversible* pancreatic parenchymal injury associated with inflammation.
- Acute pancreatitis may be caused by
  1. Excessive alcohol intake
  2. Pancreatic duct obstruction (e.g., gallstones)
  3. Genetic factors (e.g., *PRSS1*, *SPINK1*)
  4. Traumatic injuries
  5. Medications
  6. Infections (e.g., mumps)
  7. Metabolic disorders leading to hypercalcemia
  8. 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

Describe its definition, epidemiology, pathogenesis, morphology, and clinical findings

Chronic pancreatitis

Definition:

- Chronic pancreatitis is defined as prolonged inflammation of the pancreas with *irreversible* destruction of exocrine parenchyma, and, in the late stages, associated with pancreatic insufficiency, steatorrhea, diabetes, pancreatic calcification, and fibrosis.

Epidemiology:

- The prevalence of chronic pancreatitis ranges between 0.04% and 5%
- Occurs in men more often than women
- Most affected patients are middle-aged males

Chronic pancreatitis: Causes

- Majority idiopathic
- Known causes:
  1. Alcohol abuse is the most common known cause

     (protein plugs form in ducts and become calculi)
  2. Cystic fibrosis is the most common cause in children.

     Germline mutations in CFTR gene (cystic fibrosis transmembrane conductance regulator)
  3. Biliary tract disease: calculi or malformation
  4. Malnutrition is the most common cause in developing countries
  5. Autoimmune disorder
  6. Long-standing obstruction of the pancreatic duct by calculi or neoplasm

Chronic pancreatitis: **Pathogenesis**

- Most often follows repeated episodes of acute pancreatitis

- Chronic alcohol ingestion results in the secretion of protein-rich pancreatic fluid, which leads to the deposition of inspissated protein plugs and obstruction of small pancreatic ducts

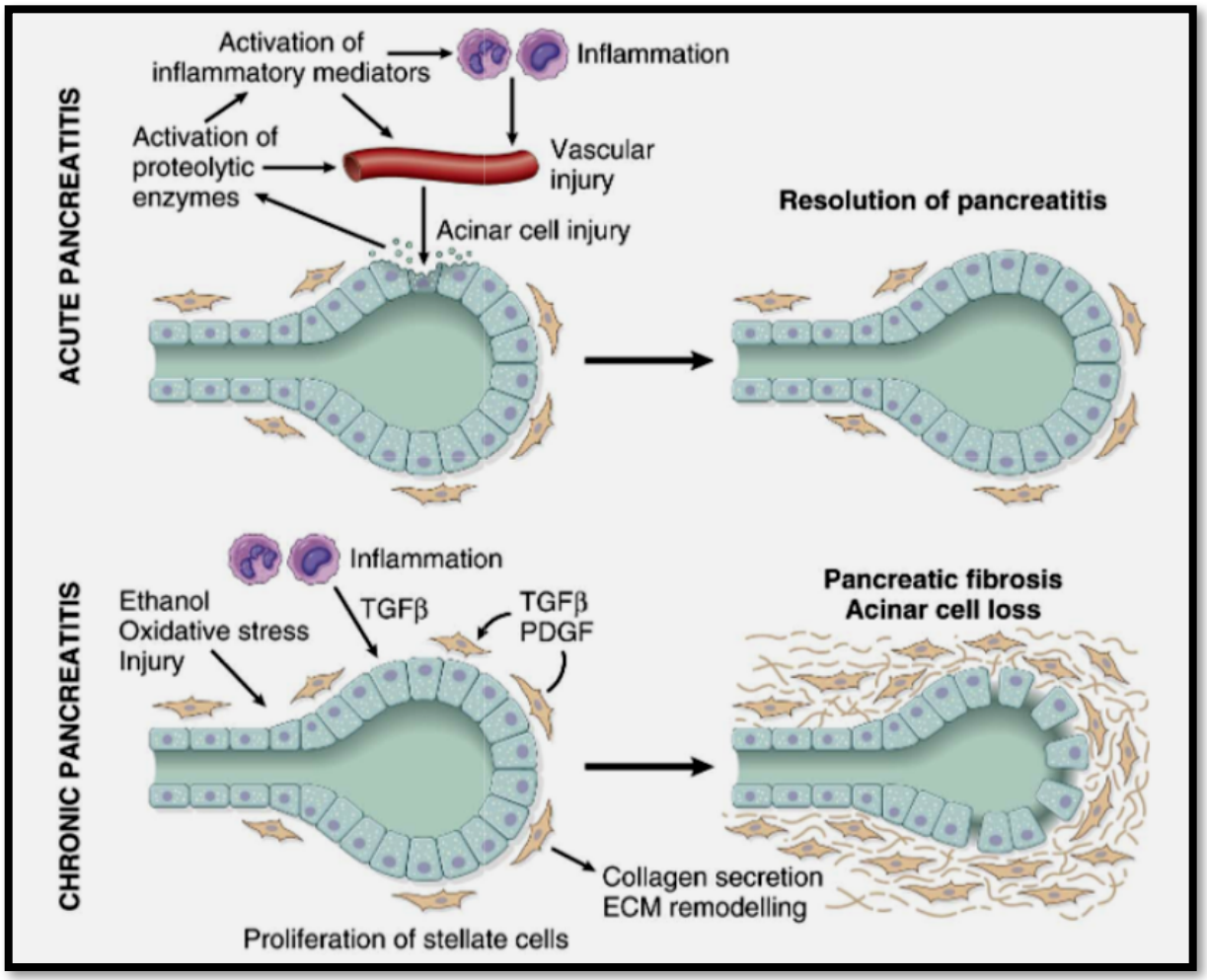
- Chronic pancreatic injury (whatever its cause) leads to local production of inflammatory mediators that promote fibrosis and acinar cell loss
  - e.g. transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF)
    - TGF-β and PDGF result in the proliferation of myofibroblasts, secretion of collagen, and remodeling of the extracellular matrix (ECM).

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 occurs with restoration of acinar cell mass.



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

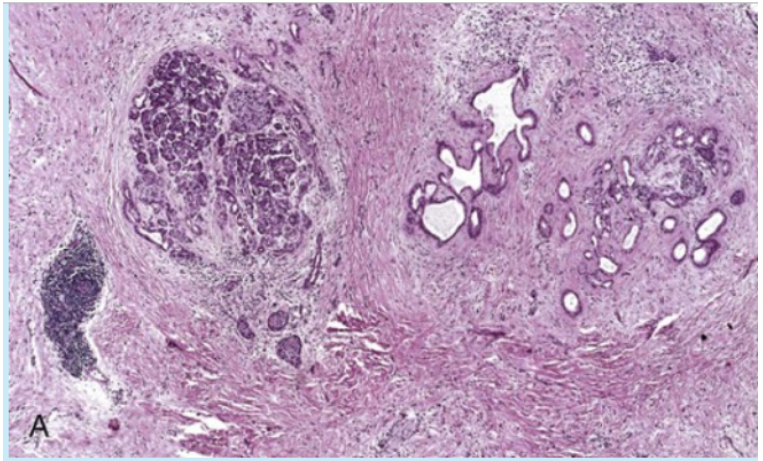
Chronic pancreatitis: Morphology

- **Chronic pancreatitis is characterized by:**
  1. **Parenchymal fibrosis**
  2. **Reduced number and size of acini with relative sparing of the islets of Langerhans**
  3. **Variable dilation of the pancreatic ducts**
  4. **Calcium deposition**

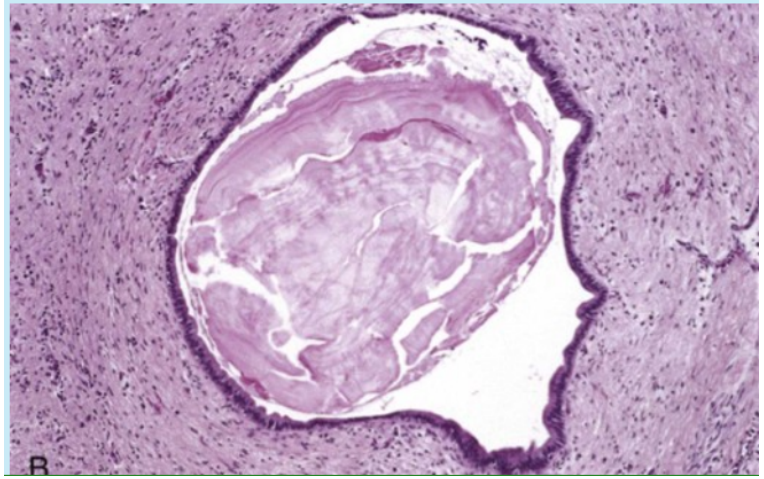
- Grossly: gland is hard, sometimes with extremely dilated ducts and visible calcification

Chronic pancreatitis: Morphology

Extensive fibrosis and atrophy has left only residual islets and ducts, with chronic inflammatory cells



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



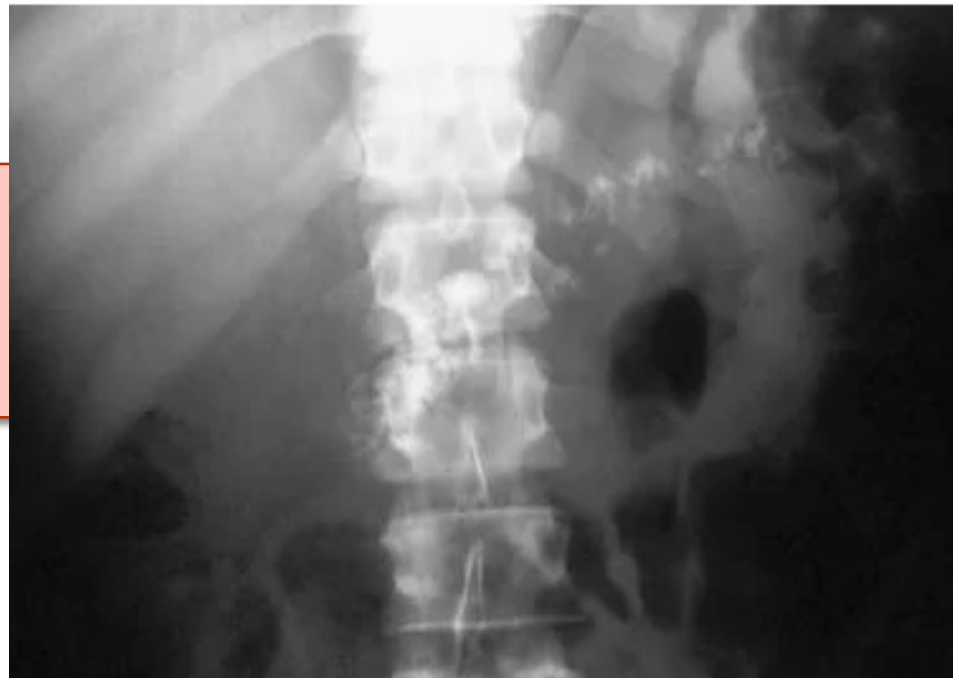
Chronic pancreatitis: Clinical Features

- Silent
- Severe pain radiating into the back (attacks may be precipitated by alcohol abuse, overeating or the use of opiates)
- Malabsorption (indicates >90% exocrine function destroyed)
- Type 1 diabetes mellitus (70% of cases)

Chronic pancreatitis: Diagnosis

- *Requires a high degree of suspicion.*
- Gallstone-induced obstruction may be evident as jaundice or elevations in serum levels of alkaline phosphatase
- Serum amylase is variable and less reliable than in acute disease
- Lipase in chronic pancreatitis is not clinically useful
- Calcifications within the pancreas by computed tomography and ultrasonography

Plain abdominal radiograph shows coarse dystrophic calcification in the distribution of the pancreas



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%.
- Pancreatic exocrine insufficiency, chronic malabsorption, and diabetes mellitus can all lead to significant morbidity and contribute to mortality.
- In other patients severe chronic pain is a dominant problem.
- Pancreatic pseudocysts: in about 10% of patients
- Patients with hereditary pancreatitis, have a 40% lifetime risk of developing pancreatic cancer
  - (whether this increased cancer risk extends to other forms of chronic pancreatitis is unclear)

Chronic pancreatitis: Treatment

- Abstain from alcohol
- Simple analgesics or NSAIDs
- Fat-soluble vitamins

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 may be idiopathic or caused by:
  1. Repeated bouts of acute pancreatitis
  2. Chronic alcohol abuse
  3. Germline mutations in genes such as CFTR
  4. Malnutrition (most common cause in developing countries)
  5. Autoimmune disorder
  6. Long-standing obstruction of the pancreatic duct by calculi or neoplasms
- Clinical features include intermittent or persistent abdominal pain, intestinal malabsorption and diabetes

- https://ar.m.wikipedia.org/wiki/%D9%85%D9%84%D9%81:Chronic_pancreatitis.webm