GIS 16

PATHOLOGY

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The topic of this sheet is the pancreas. There is no recorded lecture this year or a sheet from the previous years. Instead, this sheet will contain information from the slides (bolded) with added explanation (that will not be bolded). A few pictures were added from external sources (mostly Robbins) for the sake of clarification.

Introduction

The pancreas is composed of two parts:

- **An exocrine gland** – This portion makes up the bulk of the organ and is a major source of enzymes that are essential for digestion.
- **An endocrine gland** – Formed by the islets of Langerhans. These cells secrete insulin, glucagon, and somatostatin into the bloodstream.

More on the Exocrine Pancreas:

- The exocrine pancreas is composed of acinar cells and the ductules and ducts that send their secretions to the duodenum.
- The acinar cells synthesize digestive enzymes, **which are mostly made as inactive proenzymes that are stored in zymogen granules**. **The enzymes are confined to membrane-bound compartments before secretion.**
- When acinar cells are stimulated to secrete their contents, **the zymogen granules fuse with the apical plasma membrane and release their contents into the apical lumen for delivery via the pancreatic duct to the duodenal lumen.**

Since the enzymes are made as inactive proenzymes, they need to be cleaved by **trypsin, which is the major activator of other proenzymes. Trypsin is synthesized by acinar cells as the proenzyme trypsinogen.** Once it reaches the duodenum, trypsinogen is converted to trypsin, where it can activate other proenzymes. This serves as a protective function to ensure that the digestive enzymes are not prematurely activated in the pancreas, where they can cause autodigestion, organ injury, and pancreatitis.

- Pancreatitis: exists as both acute and chronic. In acute pancreatitis, function can return to normal if the underlying cause of inflammation is removed. Chronic pancreatitis, however, causes irreversible destruction of the exocrine pancreas.

Acute Pancreatitis

Acute pancreatitis is inflammation of the pancreas that is associated with acinar cell injury.

Clinical Features

- **<u>Abdominal pain</u>**
  - **The cardinal sign of acute pancreatitis.**
  - **Severity varies from mild to severe.**
  - **The pain is epigastric in location with possible radiation to the back.**

A cardinal sign/symptom is a major sign/symptom that the doctor utilizes to make a diagnosis.

- **Shock**
  - **The shock is due to:**
    - **Pancreatic hemorrhage**
    - **Release of vasodilating agents such as bradykinin and prostaglandins.**
  - **It results in:**
    - **Electrolyte imbalance**
    - **Loss of blood volume**
    - **Toxemia** – From breakdown of the barriers between gastrointestinal flora and the bloodstream.

Extra Information regarding the Shock:

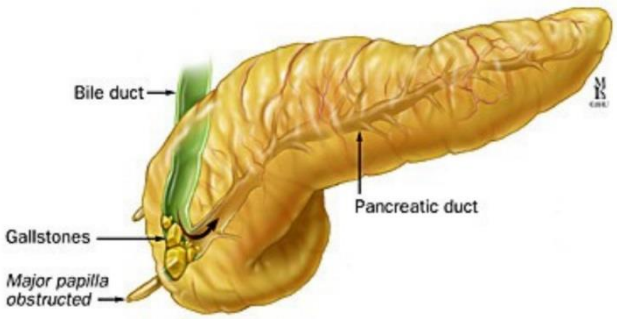
Shock is a life-threatening condition that occurs when the body is not getting enough blood flow. It can be caused by any injury or condition that affects the flow of blood through your body.

In severe cases of acute pancreatitis, necrotizing pancreatitis occurs, causing pancreatic fluid and blood to leak into the abdominal cavity. This leads to a decrease in blood volume and blood pressure, which can lead to hypovolemic shock.

- **Increased Serum Amylase Level**
  - **A pancreatic enzyme whose serum level increases within the first 12 hours and returns back to normal within 48 to 72 hours.**
  - **Other conditions associated with an increase in serum amylase levels:**
    - **Perforated gastric ulcer**
    - **Pancreatic carcinoma**
    - **Intestinal obstruction**
    - **Peritonitis**
    - **Secondary Pancreatic Disease**
- **Increased Serum Lipase Level**
  - **A pancreatic enzyme whose serum level increases within 72-96 hours and lasts for 7-10 days.**
  - **It is highly sensitive and specific for acute pancreatitis**
- **Hypocalcemia**
  - **Calcium binds the fatty acids released from lipolysis of fat in the abdomen.**
  - In other words, hypocalcemia results from the precipitation of calcium in areas of fat necrosis.
- **Jaundice, Hyperglycemia, and Glycosuria**
  - **Occurs in less than 50% of cases.**
  - Glycosuria is a condition characterized by an excess of sugar in the urine.
- **ARDS (Acute Respiratory Distress Syndrome) and Acute Renal Failure**

*Many sources also include nausea and vomiting as common parts of the clinical presentation along with abdominal pain.

Causes of Acute Pancreatitis



- **Pancreatic Duct Obstruction (35%-60%) - Due to:**
  - **Gallbladder Stones**
    - **Increases the risk 25x.**
    - Impaction of gallstones within the common bile duct impedes the flow of pancreatic enzymes through the ampulla of Vater.
  - **Cystic Fibrosis**
  - **Tumors**
  - **Edema**
  - **Parasites – Particularly Ascaris lumbricoides.**

- **Direct Injury of the Acinar Cells of the Pancreas**
  - **Ethanol** (alcohol)
  - **Viruses** – Infection with mumps virus or coxsackievirus can cause direct injury as they directly infect pancreatic exocrine cells.
  - **Drugs – Such as diuretics**
  - **Acute Ischemia – Due to vasculitis, shock**, vascular thrombosis, or embolism.
  - **Trauma** – May be caused by blunt force or iatrogenic during surgery or endoscopy.
  - Metabolic disorders – **Hypercalcemia and hyperlipidemia.**
  - **Obesity**
- **Idiopathic (10%-20% of cases)**
- **Hereditary Pancreatitis**
  - A rare, **autosomal dominant disease**.
  - Characterized by recurrent attacks of severe pancreatitis.
  - **Caused by mutations in the PRSS1 gene,** which encodes trypsinogen. The pathogenic mutations alter the site through which trypsin cleaves and inactivates itself, impairing an important negative feedback mechanism. This leads to hyperactivation of trypsin and other digestive enzymes, which makes the pancreas prone to autodigestion and injury.

Pathogenesis

- **Autodigestion of pancreatic tissue by activated pancreatic enzymes (chymotrypsin, elastase, phospholipase and trypsin).**
- **Cellular injury response mediated by proinflammatory cytokines.**
- **Defective intracellular transport of proenzymes within acinar cells.**

Acute pancreatitis appears to be caused by autodigestion of the pancreas through inappropriately activated pancreatic enzymes (recall how earlier it was mentioned that the enzymes have to remain inactivated until they reach the duodenum to prevent injury to the pancreas).

This premature/inappropriate activation of pancreatic enzymes can be caused by three pathways: pancreatic duct obstruction, primary acinar cell injury, and defective intracellular transport of proenzymes within acinar cells.

→ Further explanation on defective intracellular transport of proenzymes within acinar cells:

In normal acinar cells, digestive enzymes (that will be stored in zymogen granules) and hydrolytic enzymes (for lysosomes) are transported to their destinations in discrete (separate) pathways after synthesis in the endoplasmic reticulum. In some cases of metabolic injury, the pancreatic proenzymes and lysosomal hydrolases become packaged together. This results in proenzyme activation, lysosomal rupture (due to the action of phospholipases), and local release of the activated enzymes. However, the role of this mechanism in human acute pancreatitis is not clear.

Additional Details:

In acute pancreatitis, proenzymes are activated and released from zymogen granules within the acinar cells → Damage of acinar cells and fatty tissue in and around the pancreas → Damage of elastic tissue of blood vessels → Hemorrhage

Premature activation of proenzymes (especially trypsinogen) is the key step and it is favored by:

I. **Low pH**
II. **Increased intracellular Calcium concentration**
III. **Cathepsin B within lysosomes**

Activated trypsin → Converts prekallikrin to its active form → Stimulates the kinin system, and, with activation of the Hageman factor (factor IX) and clotting and complement factors → Small vessels thrombosis → Rupture → Hemorrhage

Damaged acinar cells release potent cytokines → Attraction of neutrophils and macrophages → Release of more cytokines such as IL-1, NO, PAF → Inflammation and pancreatic damage

Morphology

- **Related to duration and severity**
- **Features:**
  - **Proteolytic destruction of pancreatic substance** (=parenchyma).
  - **Necrosis of blood vessels and interstitial hemorrhage.**
  - **Necrosis of fat by lipase.**
    - **This feature is the most distinguishable characteristic.**

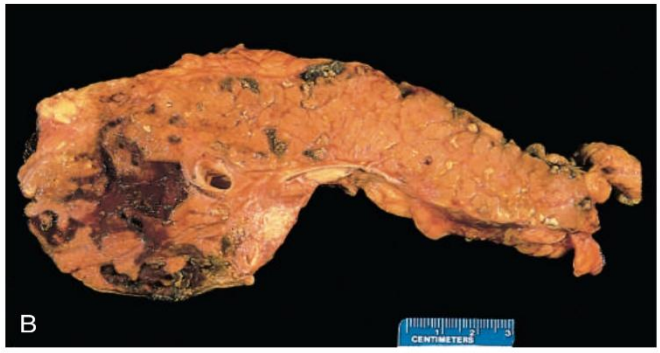
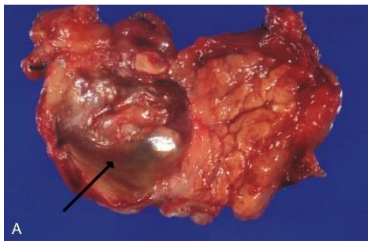


Fig. 17.2 Acute pancreatitis. ~~(A) The microscopic field shows a region of fat necrosis *(right)* and focal pancreatic parenchymal necrosis *(center)*~~. (B) The pancreas has been sectioned longitudinally to reveal dark areas of hemorrhage in the pancreatic substance and a focal area of pale fat necrosis in the peripancreatic fat *(upper left)*.

        - **The hydrolysis of fat** occurs by enzymatic destruction of fat cells**. This provides glycerol and free fatty acids (FFAs) as products. The glycerol is reabsorbed, while the FFAs combine with Ca^{2+}. This leads to saponification and the precipitation of insoluble salts (calcification).**
    - **An acute inflammatory reaction**
    - **Pancreatic pseudocysts**
        - **Formed in 50% of cases.**
        - Liquefied areas of necrotic pancreatic tissue become walled off by fibrous tissue to form a cystic space. It is a *pseudo*cyst because it lacks an epithelial lining.
        - Or more simply, a pancreatic pseudocyst is a fluid-filled sac rich in pancreatic enzymes, blood, and necrotic tissue. The leakage of fluid is due to rupture of the pancreatic duct.



    - **Suppurative Appendicitis**
    - **Obstruction of the duodenum**
    - **Abscess formation**
    - **Hemorrhages** – In the most severe form (hemorrhagic pancreatitis), extensive pancreatic necrosis is accompanied by diffuse hemorrhage within the substance of the gland.

Prognosis

- **Mortality is high (20%-40%)**
- **Death is usually due to:**
    - **Shock**
    - **Abdominal sepsis**
    - **ARDS**

Chronic Pancreatitis

Consists of repeated bouts of mild/moderate pancreatic inflammation with progressive loss of pancreatic parenchyma and fibrosis.

Predisposing Factors

- **Alcoholism** – The most common cause of chronic pancreatitis is long-term alcohol abuse.
- **Hypercalcemia**
- **Hyperlipoproteinemia**
- **Long-standing obstruction of the pancreatic duct** – Could be obstructed by pseudocysts or neoplasms.
- **Biliary tract disease**
- **Hereditary** – Hereditary pancreatitis is due to mutations in the pancreatic trypsinogen gene (PRRS1) or the SPINK1 gene that encodes a trypsin inhibitor.
- **Hemochromatosis**
- **Cystic fibrosis** – Chronic pancreatitis is associated with CFTR mutations (mutations in this gene cause cystic fibrosis).
- **Idiopathic (40% of cases)** – There are no recognizable predisposing factors.

Pathogenesis

- **Increased secretion of proteins from acinar cells in the absence of increased fluid secretion → Precipitation of proteins → Admixture with cellular debris → Ductal plugs → Ductal stones**
  - Many of the inciting agents in chronic pancreatitis (including alcohol) increase the protein concentration in pancreatic secretions, and these proteins can form ductal plugs.
- **Decreased concentration of acinar proteins that inhibit precipitation of Ca^{2+} → Calcification → Obstruction of small ducts → Atrophy**
- **Inflammation →Toxic metabolites → Oxidative stress**
  - Chronic exposure to oxidative stress leads to fibrosis.
  - Ethanol is a well-known inducer of oxidative stress.
  - Alcohol and its metabolites have a direct toxic effect on acinar cells. This can lead to fibrosis.
- **Chronic inflammation → Fibrosis**

*Basically, there are many proposed pathologic mechanisms of chronic pancreatitis, ultimately leading to pancreatic fibrogenesis.

Morphology

- **Atrophy of the exocrine gland** – With reduced number and size of the acini.
- **Fibrosis** – Parenchymal fibrosis
- **Chronic inflammation**
- **Destruction of pancreatic ducts**
- **Calcifications**
- **Pseudocysts**

Clinical Features

- **Asymptomatic** – The disease may be entirely silent until pancreatic insufficiency and diabetes mellitus develop. Or, the disease may manifest with:
  - **Attacks of abdominal pain**
  - **Recurrent attacks of jaundice**
  - **Indigestion**
- **Diabetes Mellitus**
- **Weight loss**
- **Malabsorption** – Due to insufficiency of pancreatic digestive enzymes.

Diagnosis

- **Increased amylase and lipase in the serum.**
- **Visualization of calcifications within the pancreas on X-ray or CT scan.**
- **Presence of pseudocysts.**

Pancreatic Carcinoma

- It is an infiltrating ductal adenocarcinoma of the pancreas.
- It is commonly referred to as pancreatic cancer.
- **Peak Incidence: In individuals between the ages of 60 and 80.**

Predisposing Factors

- **Smoking**
  - Smoking is the strongest environmental influence, and it doubles the risk.
- **Hereditary pancreatitis – Increases risk 40x.**
- **Genetic mutations**
  - **K-ras gene mutation – Most common**
    - Most frequently altered oncogene in pancreatic cancer.
  - **CDKN2A (P16) mutation**
    - Most frequently inactivated tumor suppressor gene in pancreatic cancer.
    - **This mutation, along with the K-ras gene mutation, are both present in 90% of cases.**
  - **TP53 gene mutation**
    - **Present in over 50% of cases.**
  - **HER2/NEU amplification**
    - **Present in over 50% of cases.**
  - **BRCA2 and MLH gene mutations.**

Epidemiology

- **The male to female ratio is 3:1 in younger individuals and 1:1 in older individuals above 60 years of age.**
- **It occurs more often in blacks than whites.**

Risk Factors

- **Smoking increases the risk by 2-3x.**
- **Chemical carcinogens**
- **A diet rich in meat and fat.**
- **Diabetes Mellitus**
- **Chronic pancreatitis**

Location

The carcinoma can be found in different areas of the pancreas. This includes:

- **The head – In 60%-70% of cases.**
- **The body – In 10%-15% of cases.**
- **The tail – In 5% of cases.**
- **Diffuse Infiltration – In 20% of cases.**
  - This means that it diffusely involves the entire organ.

General Features

- **It is an adenocarcinoma** – Microscopically, pancreatic carcinoma usually is a moderately to poorly differentiated adenocarcinoma.
- **Desmoplastic reaction** – It is an intense host reaction in the form of dense fibrosis, elicited by the invasiveness of the cancer.
- **Ulceration of duodenal mucosa**
- **Dilatation of the biliary tree** – A result of when a carcinoma of the head of the pancreas obstructs the distal common bile duct. Patients typically exhibit jaundice. Carcinomas of the body and tail, however, do not impinge on the biliary tree.
- **Involvement of adjacent organs such as the spleen, adrenals, vertebra, colon, and stomach.** This occurs because pancreatic cancers often extend through the retroperitoneal space.
- **Perineural invasion** – This term refers to the invasion of cancer to the space surrounding a nerve.

Metastasis

- **Liver and regional lymph nodes** are frequently involved.
- Distant metastasis to **lungs, bones, adrenals, and peritoneum.**

Clinical Presentation

- **Silent** – Carcinomas of the pancreas typically remain silent until their extension impinges on some other structure.
- **Pain** – Usually is the first symptom.
- **Weight loss**
- **Obstructive jaundice** – Can be associated with carcinoma in the head of the pancreas.
- **Migratory thrombophlebitis (Trousseau sign) in 10% of the cases.**
- **Acute painless dilation of the gallbladder and jaundice (Courvoisier sign).**
- **Increased CEA** (carcinoembryonic antigen) **and CA19-9 antigens in the serum.**

Prognosis

- **50% of cases die within 6 months.**
- **The 5-year survival rate is less than 1%.** (Although Robbins says the 5-year survival rate is 8%, which more closely matches statistics on the internet).