Lecture 3
Pancreatitis

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by
خولة العماري & هشام الغفيلي

Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

- Describe the pathology of acute and chronic pancreatitis
- Understand the pathogenesis of acute and chronic pancreatitis
- Describe the clinical features and possible complications of acute and chronic pancreatitis.

References: Lecture slides, Robbins.

**** The actual lecture is only 9 pages, the rest are summaries & MCQs ****

The pancreas is in reality two organs in one:

1. 90%: exocrine (digestion of food).
2. 10%: endocrine (hormones).

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, and the duration of the disease can range from a transient attack to an irreversible loss of function.

Acute Pancreatitis	Chronic Pancreatitis
The gland can return to normal if underlying cause of the pancreatitis is removed.	Defined by irreversible destruction of exocrine pancreatic parenchyma.

Onset: in acute it's fast but reversible, in chronic it goes on and on and there is fibrosis and once it's there it's not reversible

Does chronic pancreatitis always come after Acute? NO, but it could be. Sometimes patients experience multiple mild episodes, which patients don't recognize and it becomes chronic!

Mild pancreatitis usually comes with biliary diseases. Gall bladder stone → go to the pancreas → obstruction → little inflammation then it resolves (self limited)

Acute Pancreatitis:

A group of reversible lesions characterized by inflammation of the pancreas ranging in severity from edema and fat necrosis to parenchymal necrosis with severe haemorrhage.

In SA alcoholism is not common but if it's the reason it will be worse because patients will lie about it and it's street wine! The most common cause of acute pancreatitis worldwide is **Biliary Diseases.**
The size of a Gall stone bladder is very important:
Small: WORSE, can get into cystic (biliary) duct and cause obstruction.
Large: some people say if u have a lot of large stones it may ↑ the carcinogenic factor but it's not proven and if it's not doing anything u can leave them.
IT MAY CAUSE ACUTE CHOLECYSTITIS because of the obstruction but not acute pancreatitis.
Acute pancreatitis can kill the patient within few days!

Etiology:

Metabolic

- Alcoholism
- Hyperlipoproteinemia
- Genetic
- Hypercalcemia
- Drugs (e.g., thiazide diuretics)

Vascular

- Shock
- Atheroembolism
- Polyarteritis nodosa

Mechanical

- Trauma
- Perioperative injury
- Gallstones
- Iatrogenic injury
- Endoscopic procedures with dye injection

Infectious

- Mumps
- Coxsackievirus
- Mycoplasma pneumoniae

Causes:

Common Causes	
80% Biliary tract disease or alcoholism.	**35% to 60% Gallstones.**
Less Common Causes	
Obstruction of the pancreatic duct system	Periampullary tumors[1], congenital cystic dilatation of the common bile duct, biliary "**sludge**," and parasites (particularly ***Ascariasis lumbricoides*** and *Clonorchis sinensis* organisms)
Medications	(> 85 drugs cause acute pancreatitis), these include thiazide diuretics, Sulfonamides, azathioprine, estrogens, etc.
Metabolic disorders	Including **hypertriglyceridemia**[2], hyperparathyroidism[3], and other hypercalcemic states.
Acute ischemia	Induced by vascular thrombosis, embolism, vasculitis and shock.
Infections	Mumps virus or coxsackievirus
Trauma	Blunt trauma[4] and iatrogenic injury during surgery or endoscopic retrograde cholangiopancreatography
Inherited mutations	In genes encoding pancreatic enzymes or their inhibitors (e.g., *SPINK1*). For example, ***hereditary pancreatitis*** is an autosomal dominant disease that is characterized by **recurrent attacks of severe pancreatitis**, usually beginning in childhood. It is caused by mutations in the **gene *PRSS1***, which encodes **trypsinogen**, the proenzyme of pancreatic trypsin. **How?** ▪ The pathogenic mutations alter the site through which trypsin cleaves and inactivates itself, abrogating[5] an important negative feedback mechanism. ▪ This defect leads to the hyperactivation of trypsin and many other digestive enzymes that require trypsin cleavage for their activation. ▪ As a result, the pancreas is prone to autodigestion and injury.

[1]From ampulla of Vater.
[2]A condition in which triglyceride levels are elevated.
[3]An excess of parathyroid hormone in the bloodstream due to overactivity of one or more of the body's four parathyroid glands.
[4]Refers to physical **trauma** to a body part, either by impact, injury or physical attack.
[5] Revoke or cancel.

- Ascaris lumbricoides: comes from RAW meat.
- Q: is Biliary Tract Disease always related to stones?
  No, It maybe because of a sludge (not liquid, thick), which can cause obstruction.
- Always keep in mind if young female came to u with abdominal pain to ask her about oral contraceptive and estrogen!
- Hypertriglyceridemia: if we eat a lot of chicken and sweets.
- Iatrogenic injury: caused by doctors
- Mumps especially in boys because it make them infertile, Cox virus some people think it gives DM1, but it gives pancreatitis.

Morphology:

The basic alterations are:

(1) Microvascular leakage causing edema.

(2) Necrosis of fat by lipolytic enzymes (lipase).

(3) An acute inflammatory reaction.

(4) Proteolytic (protease) destruction of pancreatic parenchyma.

(5) Destruction of blood vessels with subsequent interstitial hemorrhage (elastase).

Microscopically	**Mild**	1- Interstitial edema 2- Focal areas of fat necrosis in the pancreatic substance and peripancreatic fat. Fat necrosis results from enzymatic destruction of fat cells; the released fatty acids combine with calcium to form insoluble salts that precipitate in situ.
	Severe	Such as acute necrotizing pancreatitis. 1- Necrosis of pancreatic tissue affects acinar, ductal tissues and islets of Langerhans. 2- Vascular damage causes hemorrhage into the parenchyma of the pancreas
	Most Severe	Which is hemorrhagic pancreatitis. We will find **extensive necrosis** + **diffuse hemorrhage** within the substance of the gland.
Macroscopically		▪ Red-black hemorrhagic areas interspersed with foci of yellow-white, chalky fat necrosis. ▪ Fat necrosis also can occur in extrapancreatic fat. ▪ In most cases the peritoneum contains a serous, slightly turbid, brown-tinged fluid with globules of fat (derived from enzymatically digested adipose tissue).

Pathogenesis:

The pancreas is normally protected from autodigestion by synthesis of pancreatic enzymes in the acinar cell in the proenzyme form.

Autodigestion of the pancreatic substance by inappropriately activated pancreatic enzymes.

Thus, activation of trypsinogen is an important triggering event in acute pancreatitis. Three pathways can incite the initial enzyme activation that may lead to acute pancreatitis:

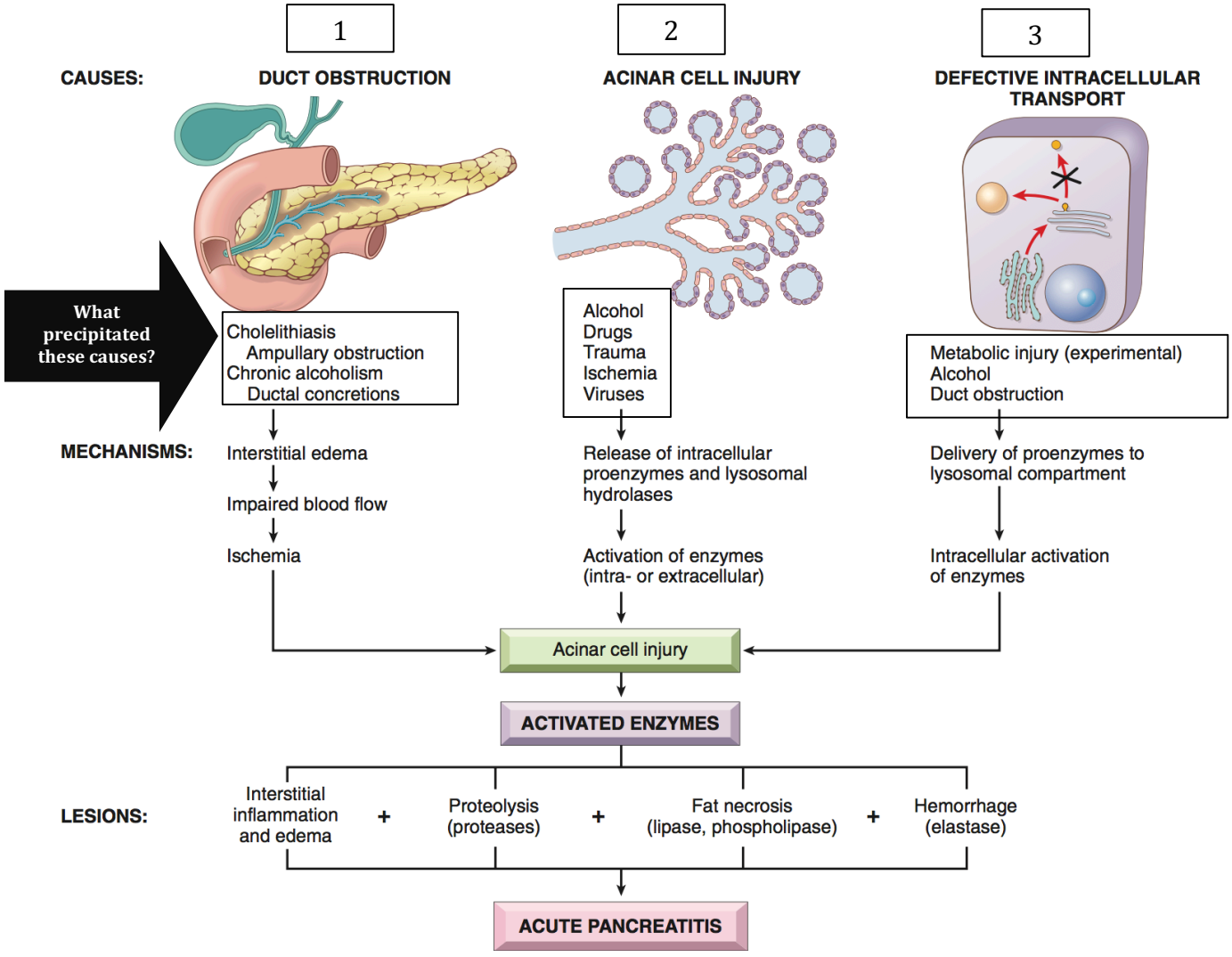


Figure 16–2 Proposed pathogenesis of acute pancreatitis.

Typical Scenario: Female, obese, complaining of very severe abdominal pain and she is on contraceptives.

We MUST differentiate between **type and severity** of abdominal pain if to assist if it needs SURGICAL intervention (appendicitis) or MEDICAL intervention (Acute pancreatitis). IF WE MISS IT WE MIGHT KILL THE PATIENT!

Clinical Features:

- **Abdominal pain** is the cardinal manifestation of acute pancreatitis. It varies from mild to severe.
- *Full-blown acute pancreatitis is a medical emergency of the first magnitude.* These patients usually have the sudden onset of an "acute abdomen" that must be differentiated from other diseases (such as ruptured acute appendicitis, perforated peptic ulcer, acute cholecystitis with rupture, and occlusion of mesenteric vessels with infarction of the bowel).
- Characteristically, the pain is constant and intense and is often referred to the **upper back.** **Very** severe Epigastric pain
- Peripheral vascular collapse and shock with acute renal tubular necrosis may occur.
- Leukocytosis.
- Hemolysis.
- Fluid sequestration.
- Diffuse fat necrosis.
- Disseminated intravascular coagulation.
- Acute respiratory distress syndrome.
- **Laboratory findings:**

  Marked elevation of serum amylase levels during the first24 hours, followed by a rising serum lipase level, which happens within 72 to 96 hours.

Management:

- The key to the management is "**resting**" the pancreas by total restriction of food and fluids and by supportive therapy.
- 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, sequela includes a sterile pancreatic abscess and a pancreatic pseudocyst.

Chronic Pancreatitis:

- Chronic pancreatitis is characterized by inflammation of the pancreas with **destruction of exocrine parenchyma**, **fibrosis**, and, in the late stages, the destruction of **endocrine** parenchyma.

It's **NOT** life threating like acute, but it affects the **life style**. They are always in pain, malabsorption

- Although chronic pancreatitis can result from recurrent bouts of acute pancreatitis, the chief distinction between acute and chronic pancreatitis is the **irreversible impairment** in pancreatic function that is characteristic of chronic pancreatitis.

Causes:

The **most common** cause of chronic pancreatitis is **long-term alcohol abuse and biliary tract disease**, and these patients are usually middle-aged males.

Alcohol abuse is more related to chronic than acute pancreatitis

Less common causes of chronic pancreatitis include the following:

- Hypercalcemia, hyperlipidemia.

Acute → Pseudocysts→ obstruction of duct →inflammation→ Fibrosis (Chronic pancreatitis)

- Long-standing **obstruction** of the pancreatic duct by pseudocysts, calculi, trauma, neoplasms, or pancreas divisum.
- **Tropical pancreatitis**, a poorly characterized disease seen in Africa and Asia. It has been attributed to malnutrition.
- **Hereditary pancreatitis** due to mutations in the pancreatic trypsinogen gene (PRRS1) or the SPINK1 gene encoding a trypsin inhibitor.
- **Idiopathic chronic pancreatitis**, which are associated with inherited mutations in genes important for normal pancreatic exocrine function (CFTR gene for example).
- **Chronic pancreatitis associated with CFTR mutations,** they ↓ **bicarbonate secretion** and ↑ the **viscosity of the secretions**, thereby promoting protein plugging.

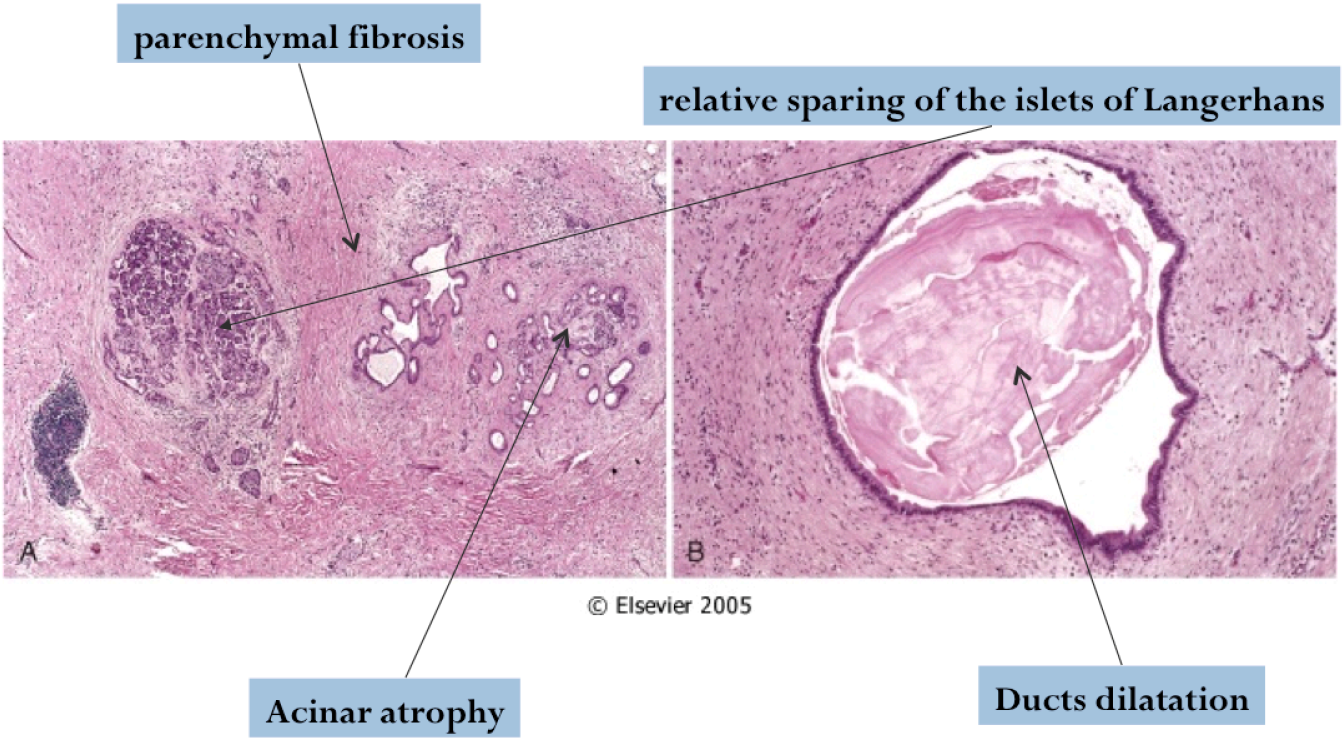
Morphology:

Microscopically

- Characterized by:
  - **Parenchymal fibrosis.**
  - **Reduced number and size of acini with relative sparing of the islets of Langerhans.**
    - → The remaining islets of Langerhans become embedded in the sclerotic tissue and may fuse and appear enlarged; eventually they also disappear.
  - **Variable dilation of the pancreatic ducts.**
    - → The ductal epithelium may be atrophied or hyperplastic or exhibit squamous metaplasia, and ductal concretions may be noted.
- These changes are usually accompanied by a chronic inflammatory infiltrate around lobules and ducts.

Grossly Gland is hard, sometimes with extremely dilated ducts and visible calcification

It's so hard sometimes they get confused and think it's carcinoma because of oxidative fibrosis



Pathogenesis:

Three hypotheses are proposed:

Ductal obstruction	**By concretion,** Inciting agents increase the protein concentration of pancreatic secretions, which can form ductal plugs.
Toxic-metabolic	Toxins can exert a direct toxic effect on acinar cells, leading to lipid accumulation, acinar cell loss, and eventually parenchymal fibrosis.
Oxidative stress	○ Free radicals in acinar cells lead to membrane damage, and subsequent expression of chemokines like interleukin-8 (IL-8), which recruits mononuclear inflammatory cells. ○ Oxidative stress also promotes the fusion of lysosomes and zymogen granules with resulting acinar cell necrosis, inflammation, and fibrosis.

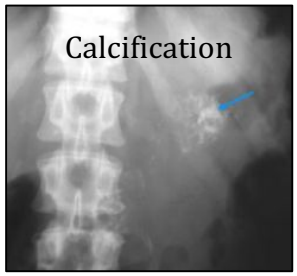
Profibrogenic cytokines:

- A variety of **profibrogenic cytokines** (such as TGF-β, CTGF[6], and PDGF[7]) are secreted in chronic pancreatitis.
- These induce the **activation** and **proliferation** of periacinar myofibroblasts ("pancreatic stellate cells"), which deposit **collagen** eventually leading to **fibrosis**.

[6] Connective Tissue Growth Factor.
[7] Platelet-Derived Growth Factor.

Clinical Features:

- **Silent or repeated attacks of abdominal pain, or persistent abdominal and back pain.**
  - Attacks may be precipitated by **alcohol abuse**, overeating (which ↑ demand on the pancreas), or the use of opiates and other drugs.
  - During an attack of abdominal pain, there may be mild fever and mild-to-moderate **elevations** of **serum amylase**. However, in end-stage disease enzyme elevations are absent (due to advanced acinar destruction).
  - It may be entirely silent until pancreatic insufficiency and diabetes mellitus develop (as a consequence of islet destruction).
- **Repeated bouts of jaundice.**
- **Vague indigestion.**
- **Gallstone-induced obstruction** is manifested by **jaundice or elevated levels of serum alkaline phosphatase.**
- **Calcifications** can be seen within the pancreas by CT scan and ultrasonography. (A very helpful finding)
- **Weight loss** and **hypoalbuminemic edema** (due to malabsorption caused by pancreatic exocrine insufficiency)



Complications:

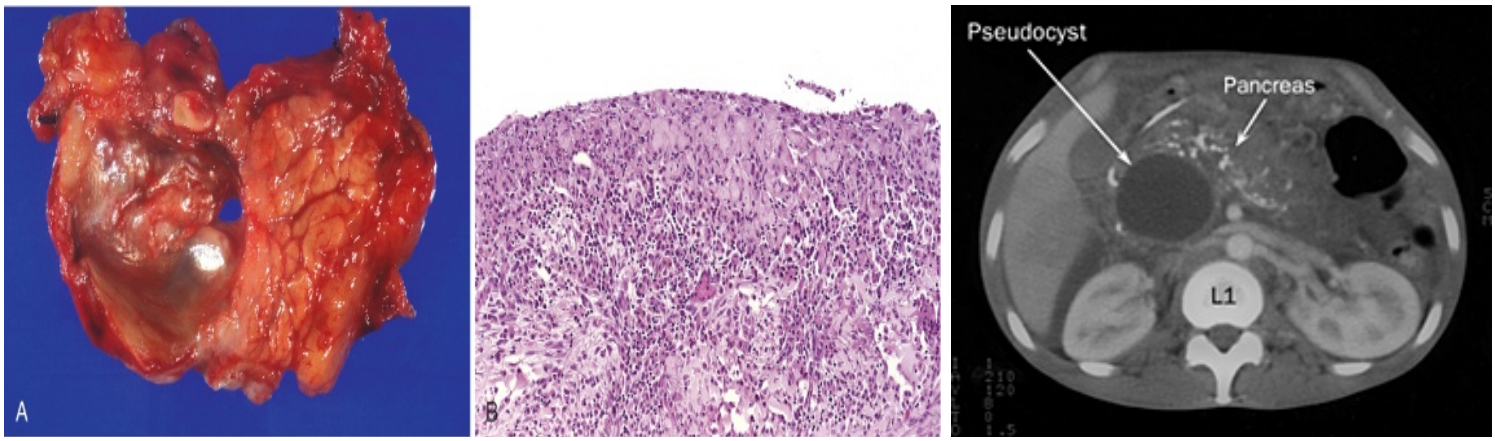
- Severe pancreatic exocrine insufficiency.
- Chronic malabsorption.
- Severe chronic pain.
- Pancreatic pseudocysts.
- Diabetes mellitus (due to destruction of islets of Langerhans).
- Persons with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer.

Pseudocysts of Pancreas:

- Pseudocysts are **localized** collections of **liquefied necrotic-hemorrhagic material rich in pancreatic enzymes.**
- Such cysts **lack** an epithelial lining (hence the prefix "pseudo"), and they account for majority of cysts in the pancreas.
- Usually arise after an episode of acute pancreatitis, or of chronic alcoholic pancreatitis.
- **Traumatic injury** to the abdomen can also give rise to pseudocysts.

Morphology:

- They commonly are **attached** to the surface of the gland and involve peripancreatic tissues such as the lesser omental sac or the retroperitoneum between the stomach and transverse colon or liver.
- Pseudocysts are usually **solitary** and range in size from 2 to 30 cm in diameter.
- While many pseudocysts spontaneously resolve, they may become secondarily infected, and larger pseudocysts may compress or even perforate into adjacent structures.
- They can produce abdominal pain and predispose to **intraperitoneal hemorrhage or peritonitis.**



Pancreatic pseudocyst

A: Cross-section through this previously bisected lesion revealing a poorly defined cyst with a necrotic brown-black wall.

B: Histologically, the cyst lacks a true epithelial lining and instead is lined by fibrin and granulation tissue.

Lecture Summary

	Acute pancreatitis	*Chronic pancreatitis*
Etiology	***Metabolic, mechanical, infectious & vascular*** *Ductal obstruction* and *long-term alcohol abuse* are the most common causes.	Can be precipitated by: Alcohol abuse, overeating & opiates or other drugs that increase the muscle tone of the sphincter of oddi.
Characteristics	Inflammation and reversible parenchymal damage	Irreversible parenchymal damage and scar formation
Clinical presentation	Varies widely, from mild abdominal pain to rapidly fatal vascular collapse.	▪ Chronic malabsorption. ▪ Diabetes mellitus. ▪ During an attack of abdominal pain: mild fever and modest elevations of serum amylase. ▪ In end-stage disease: enzyme elevations are absent. ▪ Gallstone-induced obstruction: jaundice or elevated levels of serum alkaline phosphatase. ▪ Calcifications. ▪ Weight loss and hypoalbuminemic edema.
Pathogenesis	• Inappropriate activation of pancreatic digestive enzymes. • Primary acinar injury. • Recurrent acute pancreatitis can result in chronic pancreatitis	○ **Ductal obstruction by concretions.** ○ **Toxic-metabolic.** ○ **Oxidative stress** ○ **Profibrogenic cytokines.**
Prognosis	Acutely life- threatening	Not acutely life-threatening, but the long-term outlook is poor, with a 50% mortality rate over 20 to 25 years.

Further Reading:

Autoimmune pancreatitis (AIP):

A distinct form of chronic pancreatitis that is characterized by one of two morphologic patterns:

1. Striking infiltration of the pancreas by lymphoplasmacytic cells, many of which are positive for IgG4, accompanied by a "swirling" fibrosis and venulitis (lymphoplasmacytic sclerosing pancreatitis), or
2. A duct-centric mixed infiltrate composed of neutrophils, lymphocytes and plasma cells, often obliterating the ductal epithelium (idiopathic duct centric pancreatitis).

Check Your Understanding

MCQs:

1. Pathogenic factors of pancreatitis include the following EXCEPT:

A. Primary acinar injury
B. Mutations in genes encoding trypsinogen
C. Long-term alcohol abuse
D. Ductal obstruction
E. Diabetes mellitus

2. The most helpful finding to diagnose chronic pancreatitis is:

A. Elevations of serum amylase
B. Calcifications within the pancreas
C. Elevated levels of serum alkaline phosphatase.
D. Persistent or recurrent abdominal and back pain
E. Infiltration of PMN

3. Which of the following is NOT a complication of chronic pancreatitis?

A. Pancreatic exocrine insufficiency
B. Malabsorption
C. Acute ischemia
D. Diabetes mellitus
E. Pancreatic pseudocysts

4. Which of the following medications commonly precipitate chronic pancreatitis?

A. Thiazide diuretics
B. Azathioprine
C. Estrogens
D. Opiates
E. NSAIDs

5. Chronic pancreatitis is characterized by long-standing inflammation of the pancreas with .....:

A. At later stages inflammation of the endocrine parenchyma
B. Fibrosis
C. Inflammation of the exocrine parenchyma
D. Destruction of the ducts

1. E 2. B 3. C 4. D 5. B

6. **The pancreatic ducts become extremely dilated in case of :**
   A. Pseudocysts of Pancreas
   B. Chronic Pancreatitis
   C. Acute Pancreatitis
   D. Autoimmune pancreatitis

7. **A 30-year-old male got into a road accident resulting in abdominal trauma, after examination you notice a 17 cm in diameter isolated collection of necrotic-haemorrhagic material in the pancreas. What do you expect?**
   A. Pseudocysts of Pancreas
   B. Chronic Pancreatitis
   C. Acute Pancreatitis
   D. Autoimmune pancreatitis

8. **A patient is complaining from abdominal pain with mild fever, after lab tests you see moderate elevation of serum amylase. What do you expect:**
   A. Pseudocysts of Pancreas
   B. Chronic Pancreatitis
   C. Acute Pancreatitis
   D. Autoimmune pancreatitis

9. **The most common etiologies of acute pancreatitis (AP) are**
   A. Idiopathic and medications.
   B. Endoscopic retrograde cholangiopancreatography and gallstone
   C. Abdominal trauma and pregnancy.
   D. Ethanol and gallstones

10. **The most likely medication to cause AP in a patient taking the following medications is:**
    A. Potassium chloride
    B. Calcium carbonate
    C. Hydrochlorthiazide
    D. L-thyroxine.

11. **What one of the following is the most common cause of acute pancreatitis?**
    A. Hypertension
    B. Chronic obstructive pulmonary disease
    C. Ethanol abuse
    D. Hereditary predisposition
    E. Obesity

6. B 7. A 8. B 9. D 10. C 11. C

12. In pancreatitis, inflammation is caused when:

A. Pancreatic enzymes escape into the pancreatic tissue and begin to digest the pancreas itself
B. Gallstones obstruct the cystic duct
C. Massive amounts of fluid accumulate in the peritoneal cavity
D. Regenerative nodules are formed

13. Gene mutation associated with acute pancreatitis?

A. PRSS1, SPINK1
B. SFTR
C. HLA- DR
D. p53

14. Most common cause of acute pancreatitis?

A. Gall stone
B. Mumps
C. Alcohol intake
D. Hypercalcemia

15. Microscopic feature in sever form of acute pancreatitis?

A. Inflammation with edema
B. Fat necrosis
C. Destruction of blood vessels
D. Cells proliferation

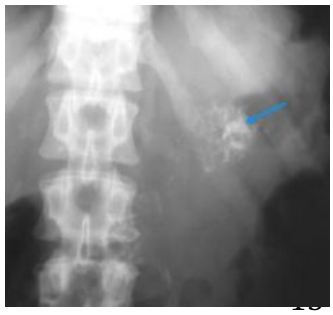
16. Which enzyme causes fat necrosis?

A. Elastase
B. Lipase and phospholipase
C. Proteases
D. DNA polymerase

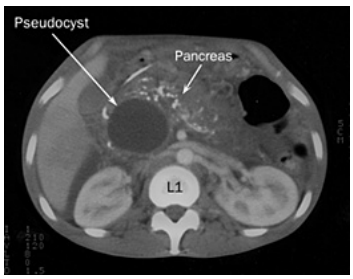
12. A 13. A 14.A 15.C 16. B

17. A 60-year-old alcoholic man presents with a 6-month history of recurrent epigastric pain, progressive weight loss, and foul smelling diarrhea. The abdominal pain is now almost constant and intractable. An X-ray film of the abdomen reveals multiple areas of calcification in the mid-abdomen. Which of the following is the most likely diagnosis?

(A) Carcinoid syndrome
(B) Chronic pancreatitis
(C) Crohn disease
(D) Insulinoma



18. **Which of the following findings is most likely to be encountered in the patient described in previous Question?**
    (A) Achlorhydria
    (B) Hypoglycemia
    (C) Melena
    (D) Steatorrhea
19. **A 50-year-old woman complains of persistent abdominal pain, anorexia, and abdominal distention. Her past medical history is significant for a previous hospitalization for acute pancreatitis. A CT scan of the abdomen shows a fluid-filled cavity in the head of the pancreas. What is the most likely diagnosis?**
    A. Acute hemorrhagic pancreatitis
    B. Pancreatic cystadenoma
    C. Pancreatic islet cell tumor
    D. Pancreatic pseudocyst



Answer Key for last 3 questions:

17. **The answer is B:** Chronic pancreatitis is characterized by the progressive destruction of the pancreas, with accompanying irregular fibrosis and chronic inflammation. Calcification and intraductal calculi often develop. Pancreatic insufficiency results in malabsorption syndrome. Chronic pancreatitis is most commonly seen in patients with a history of alcohol abuse (70% of cases). The other choices are not associated with pancreatic calcifications. Although islets may be affected by chronic pancreatitis, hypoglycemia is an uncommon and late feature of the disease. Diagnosis: Pancreatitis, chronic

18. **The answer is D:** Fat malabsorption in the setting of chronic pancreatitis is most often associated with steatorrhea. In patients with steatorrhea, the fecal matter is foul smelling and floats because of a high fat content. Longstanding malabsorptive disease is accompanied by nutritional deficiency, including weight loss, anemia osteomalacia, and a tendency to bleed. Hypoglycemia (choice B) is incorrect because loss of pancreatic islet cells would be associated with hyperglycemia. Diagnosis: Pancreatitis, chronic; steatorrhea

19. **The answer is D:** Pancreatic pseudocyst is a late complication of acute pancreatitis, in which necrotic pancreatic tissue is liquefied through the action of pancreatic enzymes (e.g., peptidases, lipases, and amylase). The necrotic tissue becomes encapsulated by granulation tissue, which then develops into a fibrous capsule. Pseudocysts may enlarge to compress and even obstruct the duodenum. They may become secondarily infected and form an abscess. Choices B, C, and D are not consequences of acute pancreatitis. Diagnosis: Pancreatic pseudocyst

Contact us: Pathology435@gmail.com

Team Members:

فهد العبداللطيف نوف التويجري

محمد الدغيثر	أثير النشوان	فاطمة الدين
معاذ باعشن	الجوهرة المزروع	فتون الصالح
عبدالناصر الوابل	إلهام الزهراني	كوثر الموسى
عبدالرحمن الزامل	بدور جليدان	لميس آل تميم
محمد الزاحم	خولة العماري	لولوه الصغيّر
عبدالعزيز الزيدان	دانيا الهنداوي	مريم سعيدان
عبدالله الفريح	دانة عمله	منيرة العيوني
ماجد العسبلي	ديما الفارس	مي العقيل
عبدالله العليوي	رزان السبتي	نورة الخراز
عبدالرحمن الناصر	رغد المنصور	نورة الطويل
محمد الفضل	سارة القحطاني	نوف الرشيد
	شما السهيلي	نوف العبدالكريم

قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
