DISORDERS OF THE GALLBLADDER & EXTRAHEPATIC

BILIARY TRACT: GALLBLADDER DISEASES

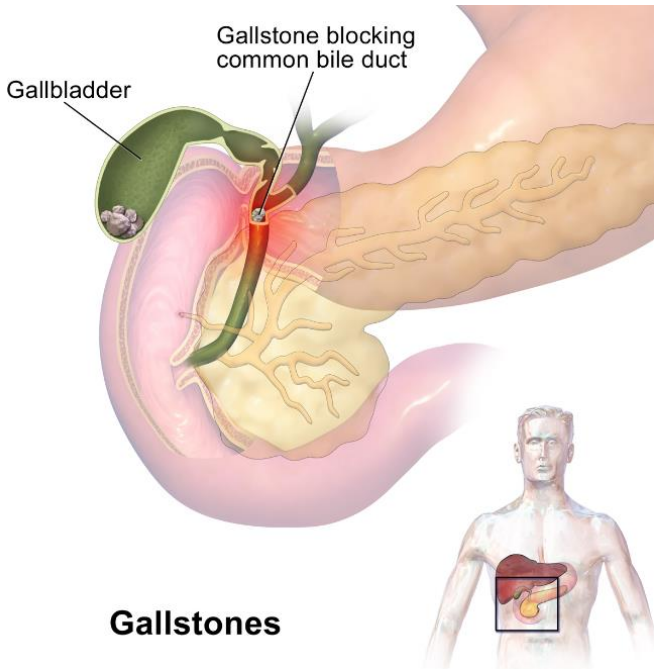
Cholelithiasis (Gallstones, GS)

- GS afflict 10% to 20% of adult populations in northern hemisphere Western countries.

- Adult prevalence rates are higher in Latin American countries (20% to 40%) & are low in Asian countries (3% to 4%).

GS are of 2 main types.

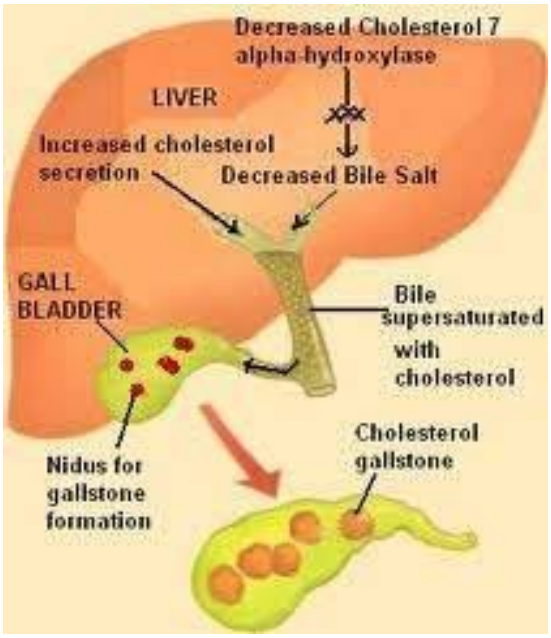
- In the West, about 80% are cholesterol GS, containing crystalline cholesterol monohydrate &
- 20% are pigment GS composed mainly of bilirubin & calcium salts.



Gallstones

Pathogenesis & Risk Factors

- Bile is the only pathway for elimination of excess cholesterol (Ch) from the body, either as free Ch or as bile salts.
- Ch is water insoluble
  & is rendered water soluble by aggregation with + bile salts + lecithins secreted into bile.
- When Ch concentrations exceed the solubilizing capacity of bile (supersaturation),
  Ch can no longer remain dispersed & nucleates into solid Ch monohydrate crystals.



- GS formation involves 4 simultaneously occurring conditions:

  - Supersaturation of the bile with Ch,
  - Nucleation sites establishment by microprecipitates of calcium salts,
  - Stasis = Hypomobility of the GB which promotes nucleation
  - Mucus hypersecretion to trap the crystals, enhancing their aggregation into stones

Risk Factors for GS

Cholesterol GS

- Demography:
  - Northern Europeans,
  -North & South Americans,

- {Advancing age, , Female gender},
  -Female sex hormones,
  -Oral contraceptives,
  -Pregnancy,
  - Obesity,
  -Rapid weight reduction,
  - GB stasis,
  - inborn disorders of bile acid metabolism,
  -Hyperlipidemia syndromes

Pigment GS

- Demography:
  - Asian more than Western,
  - chronic hemolytic syndromes,
  - biliary infection,

- GIT disorders:
  -ileal disease (e.g., Crohn disease),
  - ileal resection or bypass,
  - cystic fibrosis with pancreatic insufficiency.

- However, 80% of individuals with GS have no identifying risk factors other than age & sex.

- Comment on some factors:

- Age & gender.
  -The prevalence of GS increases throughout life.
  - The prevalence in white women is about twice as high as in men.

- Ethnic & geographic.
  -Ch GS prevalence approaches 75% in Native American populations,
  -GS are more prevalent in the West & uncommon in developing societies.

- Heredity,
  -family history alone imparts increased risk associated with impaired bile salt synthesis & secretion.

- Environment.
  -estrogenic influences, like oral contraceptives & pregnancy increase hepatic Ch uptake & synthesis, leading to excess biliary secretion of Ch.
  -Obesity, rapid weight loss, & treatment with the hypocholesterolemic agent clofibrate are also strongly associated with increased biliary Ch secretion.

- Acquired disorders.
  -Any condition in which GB motility is reduced predisposes to GS,
  such as pregnancy, rapid weight loss, & spinal cord injury.
  -However, in most cases, GB hypomotility is present without obvious cause.

Morphology of GS

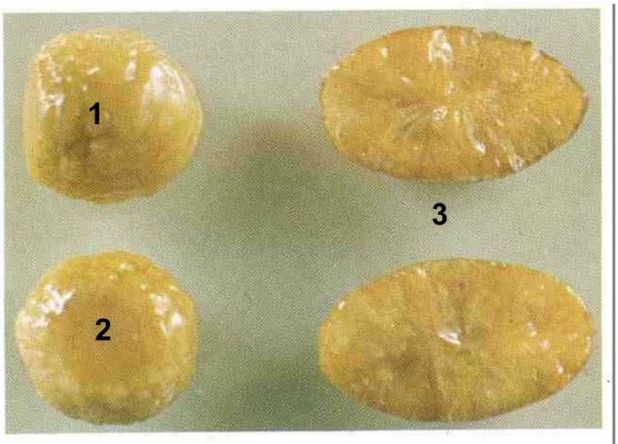
- Cholesterol GS arise only in the GB
  & consist of 50% to 100% cholesterol.

- Pure cholesterol GS are pale yellow ;
- increasing proportions of :
  -calcium carbonate ,
  -phosphates,
  -& bilirubin
  impart gray-white to black discoloration

- They are ovoid & firm;
- they can occur singly or multiple with faceted surfaces resulting from opposition to one another.

- Most cholesterol GS are radiolucent,
  although as many as 20% may have sufficient calcium carbonate to render them radiopaque.

Cholesterol gall stones.
This shows 3 cholesterol gall stones.
The two on the left are spherical &have bosselated surfaces.
The stone on the right has been cut in two to show that it consists throughout of yellow material which is pure cholesterol on chemical analysis



5·33 Cholesterol gall-stones

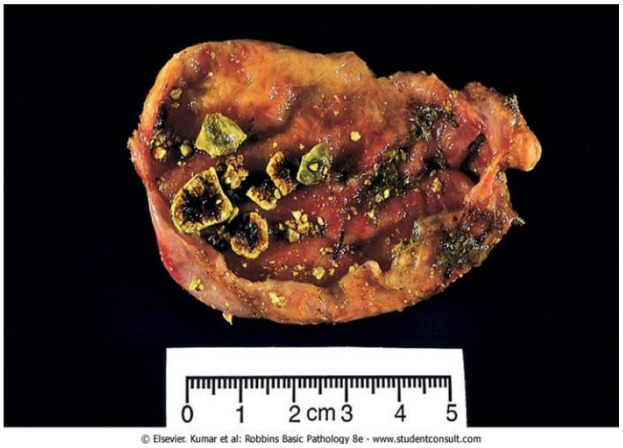
- Pigment GS may arise anywhere in the biliary tree (GB or bile ducts) & are either black or brown.

- Black pigment GS
  - are found in sterile GB bile,
  - small
  - present in large number
  - crumble easily.

- Brown GS
  -are found in infected intrahepatic or extrahepatic ducts,
  - tend to be single or few in number
  - & are soft with a greasy, soaplike consistency
    that results from the presence of retained fatty acid salts released by the action of bacterial phospholipases on biliary lecithins.

- Pigment GS contain calcium salts of:
  unconjugated bilirubin + mucin glycoproteins + cholesterol.
- Because of calcium carbonates & phosphates,
  50% to 75% of black GS are radiopaque.
  Brown GS, which contain calcium soaps, are radiolucent.

Cholesterol gallstones.
Mechanical manipulation during laparoscopic cholecystectomy has caused fragmentation of cholesterol GS, revealing interiors that are pigmented because of entrapped bile pigments. GB mucosa is red & irregular as a result of coexistent acute & chronic cholecystitis



Clinically,

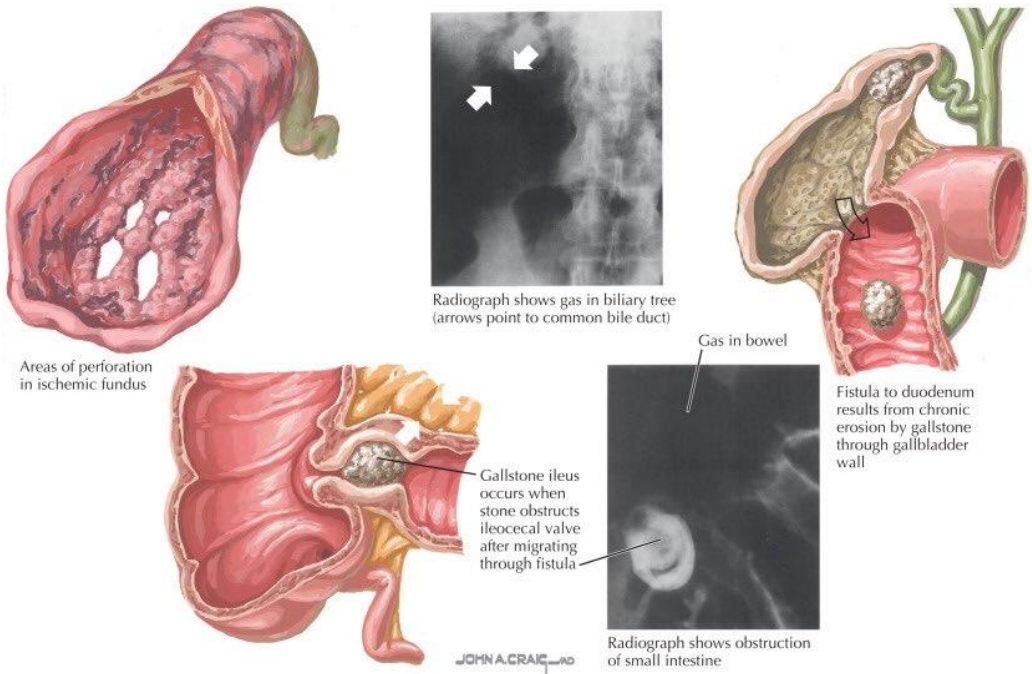
- 70% to 80% of persons with GS remain asymptomatic throughout life,
- the remainder becomes symptomatic at the rate of 1% to 3% per year.

- The symptoms are striking sever pain,
  -either constant or
  -"colicky" (spasmodic) from an obstructed GB or when small GS move down-stream & lodge in the biliary tree.

- Complications, depending on the site of the GS include :

  -GB empyema,
  -perforation,
  -fistulae;
  -inflammation of the biliary tree,
  - obstructive jaundice,
  -or pancreatitis.

- The larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction;
- occasionally a large stone may erode directly into an adjacent small bowel loop, causing intestinal obstruction (“Gallstone ileus").
- It is the very small stones, or "gravel," that are more dangerous!



Pigmented GS, (from a patient with chronic hemolytic anemia).

12 faceted black GS are present in this, otherwise, unremarkable GB.

Q: What are the effects & complications of GS in each of the following?

Intra-hepatic bile ducts? Common hepatic duct? Gall bladder? Cystic duct? Common bile duct? Ampulla of Vator? Small intestine? Large intestine? Peritoneal cavity

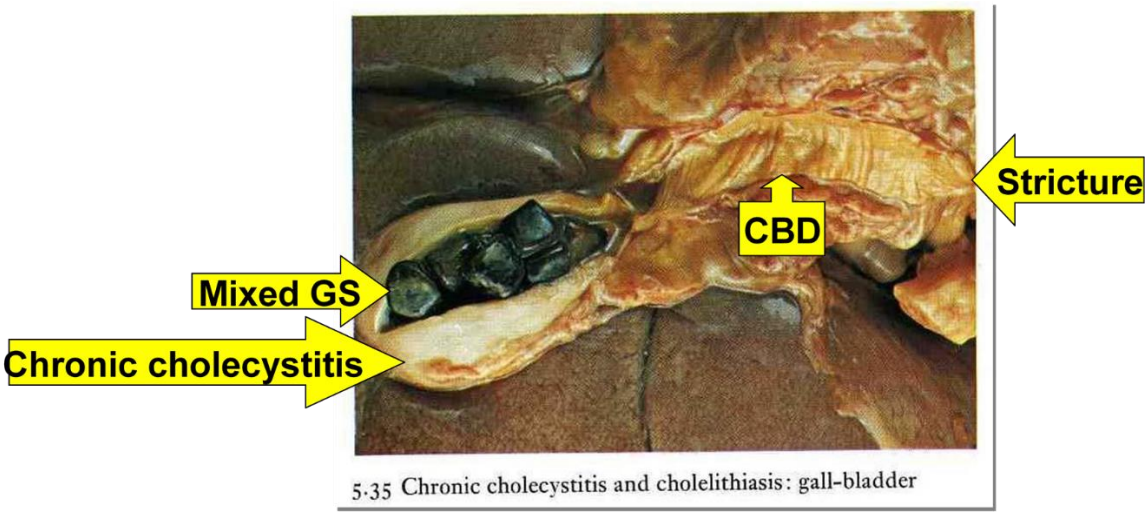
Chronic cholecystitis & cholelithiasis: GB.

This shows the inferior surface of the liver, GB, & CBD.

The GB is contracted, with thickened fibrosed wall & opaque white serosal surface.

GB lumen is full of facetted mixed GS. The CBD is dilated, & it's mucosal surface is bright yellow from bilestaning.

The lumen of the distal 1cm of CBD (right) is narrowed, due to an old inflammatory stricture followed an earlier episode of obstruction at the lower end of CBD by GS



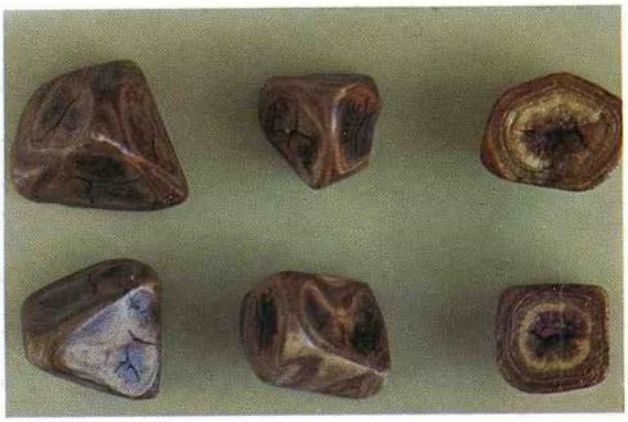
5·35 Chronic cholecystitis and cholelithiasis: gall-bladder

Mixed gall-stones.

These GS were closely packed in a fibrosed GB, the facetted surfaces being in close apposition.

The varied composition of the GS is evident in the two halfsections on the right: a brownish material is present in the center surrounded by multiple laminae, pale & dark in color.

Q: what are the constituents of these stones?



5.36 Mixed gall-stones

Cholecystitis

- GB inflammation may be
  (1) acute,
  (2) chronic, or
  (3) acute superimposed on chronic,

  & almost always occurs in association with GS.

- In US, cholecystitis is one of the most common indications for abdominal surgery.

- Its epidemiologic distribution closely parallels that of GS.

Morphology

- In acute cholecystitis,
  the GB is usually enlarged (X 2 to 3 times) & tense,
  & bright red or blotchy, violaceous to green-black due to subserosal hemorrhages

- The GB serosal covering is frequently covered by fibrinous exudate &,
  in severe cases, by pus.

- In 90% of cases GS are present,
  often obstructing the neck of the GB or the cystic duct.

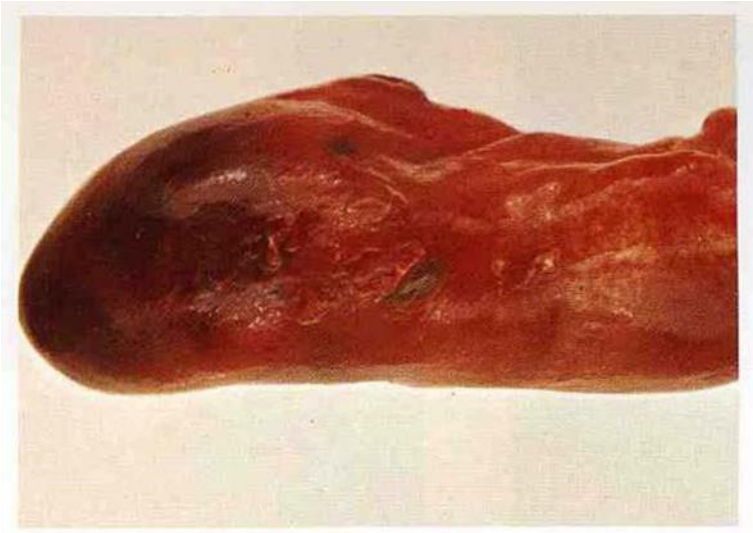
- The GB lumen is filled with cloudy or turbid bile,
  that may contain fibrin, blood, & pus.
- When the contained exudate is virtually pure pus, the condition is called empyema of the GB (F1.7).
- In mild cases the GB wall is thickened, edematous, & hyperemic.

Acute cholecystitis and empyema.

The GB is enlarged, firm & dark reddish-brown.

The lumen was distended with a mixture of bile, pus (empyema), & blood, but GS were not present.

The wall of the GB was thicker than normal from the presence of inflammatory exudate & extravasated blood.



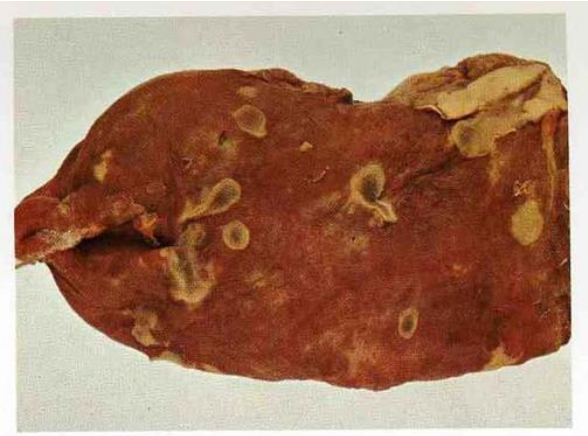
1.7 Acute cholecystitis and empyema

- In more severe cases the GB is transformed into a green-black necrotic organ with multiple abscesses, called gangrenous cholecystitis (F1.8).

Acute gangrenous cholecystitis.

In some acute suppurative cholecystitis, vascular obstruction may occur causing hemorrhagic infarction & gangrene of the GB, as in this case.

The wall is brown, with multiple round yellowish-green abscesses over the serosal surface, which ruptured, causing fatal acute diffuse peritonitis



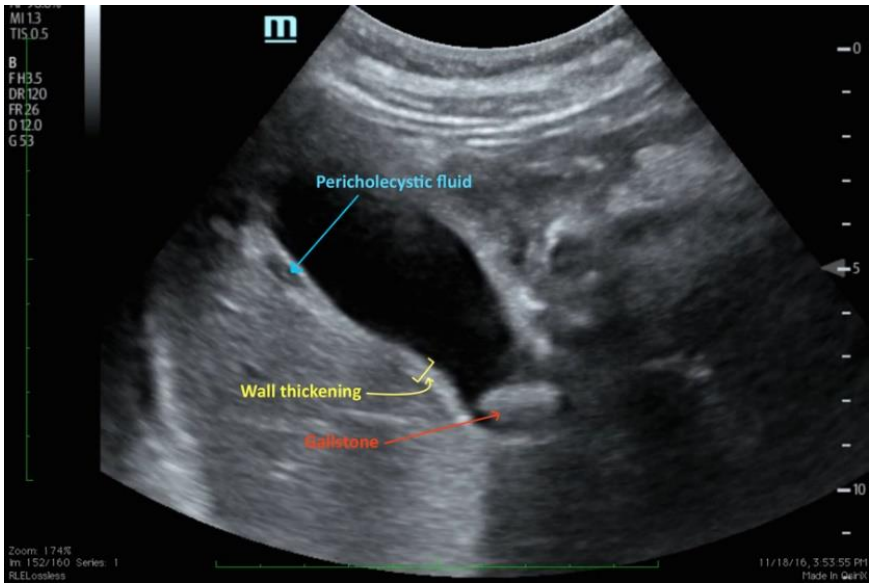
1.8 Acute gangrenous cholecystitis

H

- the inflammatory reactions are non-specific
- & consist of:
  - congestion,
  - edema,
  - WBC infiltration,
  - frank abscess formation, or
  -gangrenous necrosis).

►The **morphologic** changes in chronic cholecystitis are extremely variable & sometimes minimal.

- The mere presence of stones within the GB, even in the absence of acute inflammation, is often taken as sufficient justification for the diagnosis.
- The GB may be contracted, of normal size, or enlarged.
- The submucosa & subserosa are often thickened from fibrosis, with lymphocytic cell infiltration.



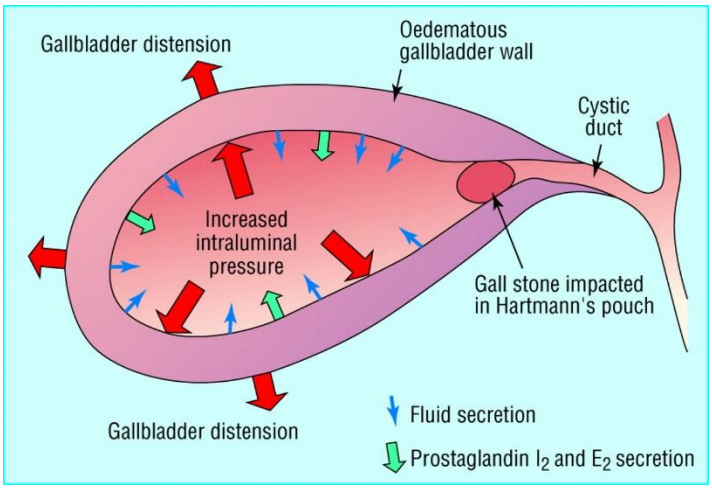
Acute Calculous Cholecystitis

- Acute inflammation of a GB that contains stones is termed acute calculous cholecystitis &
- is caused by obstruction of the GB neck or cystic duct.
- It is the most common major complication of gallstones &
- the most common reason for emergency cholecystectomy.
- Presentation may be sudden as an acute surgical emergency, or may be mild.
- Inflammation of the GB wall in the setting of obstruction to bile outflow with consequent acute calculous cholecystitis results initially from chemical irritation.

  (1) The action of phospholipases derived from the mucosa hydrolyzes biliary lecithin to lysolecithin, which is toxic to the mucosa.
  The normally protective glycoprotein mucous layer is disrupted, exposing the mucosal epithelium to the direct detergent action of bile salts.

  (2) Distention & increased intraluminal pressure may also compromise blood flow to the mucosa.

These events occur in the absence of bacterial infection; only later may bacterial contamination develop.



Acute Non-Calculous (Acalculous) Cholecystitis

- Between 5% & 12% of GB removed for acute cholecystitis contain no GS.

- Most of these cases occur in seriously ill patients:
  (1) the postoperative state after major, nonbiliary surgery;
  (2) severe trauma (eg RTA);
  (3) severe burns; &
  (4) sepsis.

- Events thought to contribute to it include:
  -dehydration,
  -GB stasis &
  - sludging, vascular compromise, &, ultimately,
  - bacterial contamination.

Chronic Cholecystitis

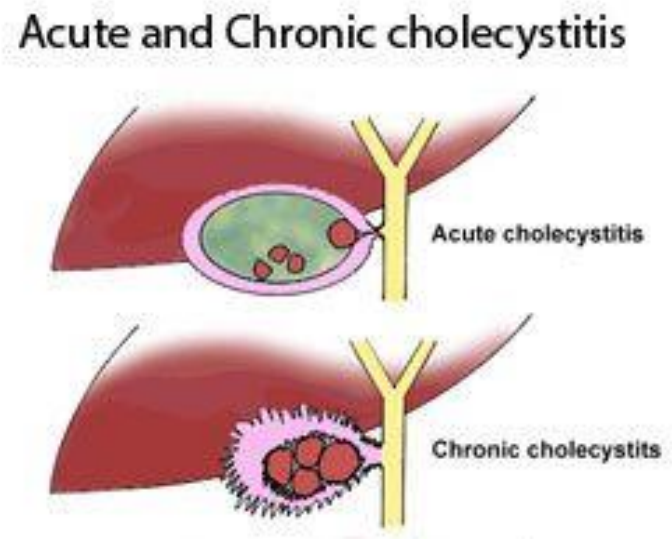
- May be
  (1) the sequel to repeated attacks of acute cholecystitis, but
  (2) in most instances it develops without any history of acute attacks.

- Like acute cholecystitis it is almost always associated with GS; BUT…
- GS do not seem to have a direct role in the initiation of inflammation or the development of pain,
  because chronic acalculous cholecystitis causes symptoms & morphologic changes similar to those seen in the chronic calculous type.

  ►Rather, supersaturation of bile predisposes to both forms (calculous & acalculous) chronic inflammation
  & in most instances, to stone formation.

- Microorganisms, usually Escherichia coli & enterococci, can be cultured from the bile
  in only about 1/3 of cases.

- Symptoms of chronic cholecystitis are similar to that of the acute &
  range from biliary colic to indolent abdominal pain



Clinical Features

- Acute calculous cholecystitis may present with mild pain or with severe, steady upper abdominal pain, often radiating to the right shoulder.

- When GS are present in the GB neck or in ducts, the pain is colicky.

- Spasm of the abdominal muscles result in right subcostal tenderness & rigidity,
  & occasionally a tender, distended GB can be palpated.

- Mild attacks may subside spontaneously over 1 to 10 days;
  but recurrence is common

- Acute acalculous cholecystitis symptoms are usually obscured by the generally severe clinical condition of the patient.

- Diagnosis therefore rests on keeping this possibility in mind.

- Chronic cholecystitis is usually characterized by
  recurrent attacks of either steady or colicky epigastric
  or right upper quadrant pain.

- Nausea, vomiting, & intolerance for fatty foods are frequent accompaniments.

- Diagnosis of acute & chronic cholecystitis usually rests on the detection of GSs or dilatation of the bile ducts by U/S,
  typically accompanied by evidence of a thickened GB wall.

- Complications of cholecystitis:

  -Bacterial superinfection, with cholangitis or sepsis,

  -GB perforation → localized peritonitis +abscess formation

  -GB rupture → diffuse peritonitis,

  -Biliary-enteric fistula,
  with drainage of bile into adjacent organs,
  entry of air & bacteria into the biliary tree,
  & potentially large sized GS-induced intestinal obstruction

- Aggravation of preexisting medical illness, with cardiac, pulmonary, renal, or liver decompensation.

DISORDERS OF EXTRAHEPATIC BILE DUCTS

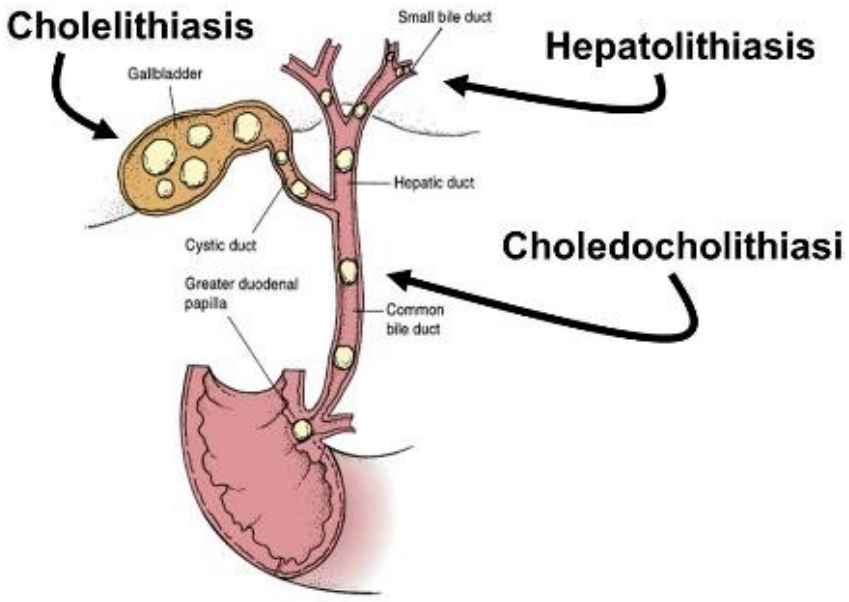
Choledocholithiasis & Cholangitis

- Choledocholithiasis
  is the presence of stones within the biliary tree.

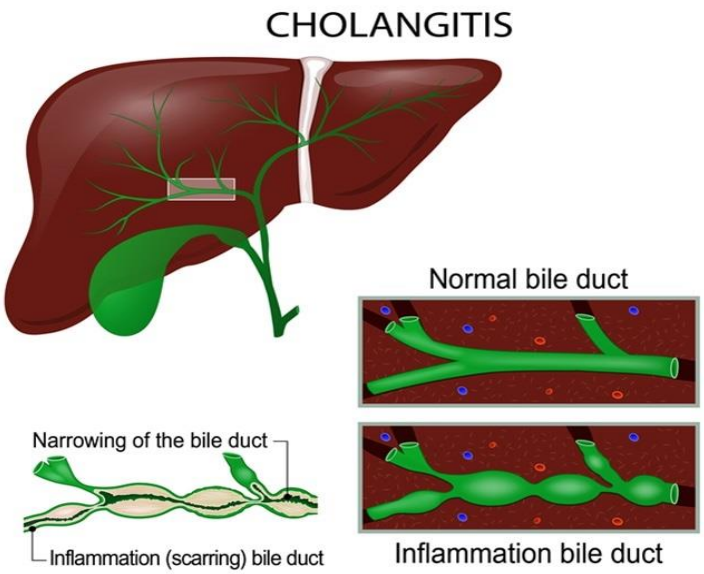
- Almost all stones in the West, are derived from the GB;
- in Asia, there is a much higher incidence of primary ductal & intrahepatic, usually pigmented stone formation.

- Choledocholithiasis may not immediately obstruct major bile ducts;
- asymptomatic stones are found in 10% of patients at the time of surgical cholecystectomy.

- Effects & complications of choledocholithiasis are:
  (1) biliary obstruction,
  (2) pancreatitis,
  (3) cholangitis,
  (4) hepatic abscess,
  (5) chronic liver disease with secondary biliary cirrhosis, or
  (6) acute calculous cholecystitis (by stone obstructing cystic duct).



- Cholangitis is
  acute inflammation of the wall of bile ducts,
  always caused by bacterial infection of the normally sterile lumen,
  the bacteria most likely enter the biliary tract through the sphincter of Oddi (ascending infection).



- **Causes**:
  any lesion obstructing bile flow, most commonly stones & also from surgical reconstruction of the biliary tree.

- **Uncommon causes** include
  - tumors,
  -strictures,
  - indwelling stents or catheters,
  - acute pancreatitis.

- Ascending cholangitis refers to
  the tendency of bacteria, once within the biliary tree, to ascend & infect intrahepatic biliary ducts.

  The usual pathogens are:
  - E. coli,
  - Klebsiella,
  -Clostridium,
  - Bacteroides, or
  - Enterobacter;
  - group D streptococci are also common,
  -& two or more organisms are found in 50% of cases.

- Parasitic cholangitis is a significant in some world populations
  -Fasciola hepatica or schistosomiasis in Latin America & the Near East,
  -Clonorchis sinensis or Opisthorchis viverrini in the Far East, &
  -cryptosporidiosis in individuals with AIDS.

Clinically,

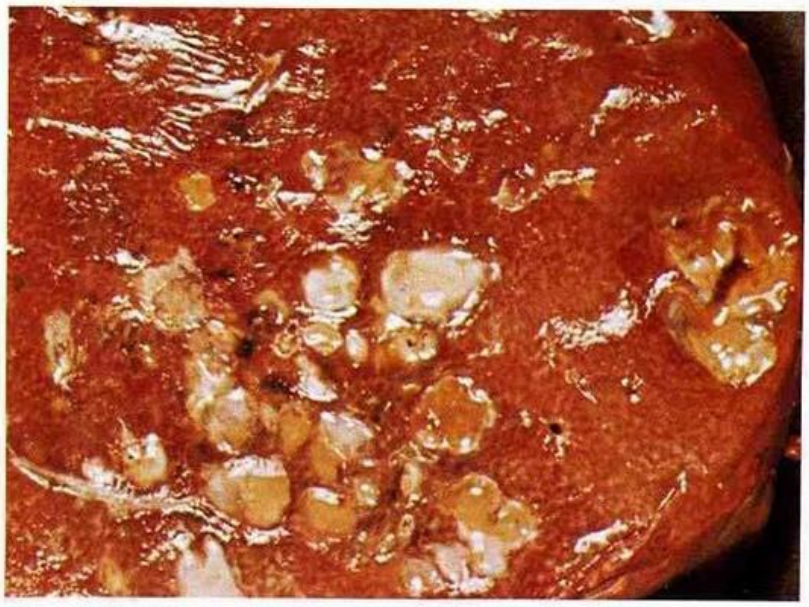
- bacterial cholangitis produces
  - fever,
  -abdominal pain,
  - chills &
  - jaundice.

- In the most severe form
  - suppurative cholangitis,
  - purulent bile fills &
  - distends bile ducts,
  -with risk of liver abscesses formation,

- & because sepsis rather than cholestasis is the main risk in cholangitic patients,
  prompt diagnosis & intervention are imperative.

Suppurative cholangitis: liver.

The patient had ca of the head of pancreas obstructing the CBD,
followed by ascending cholangitis,
which lead to the formation of multiple yellow & white hepatic abscesses,
centered on bile ducts



5.39 Suppurative cholangitis: liver

Secondary Biliary Cirrhosis

- The most common cause of obstruction is extrahepatic cholelithiasis.

- Other causes include:
  - cancers of the head of the pancreas
  -& biliary tree
  -&biliary atresia,
  - & strictures
  resulting from previous surgical procedures.

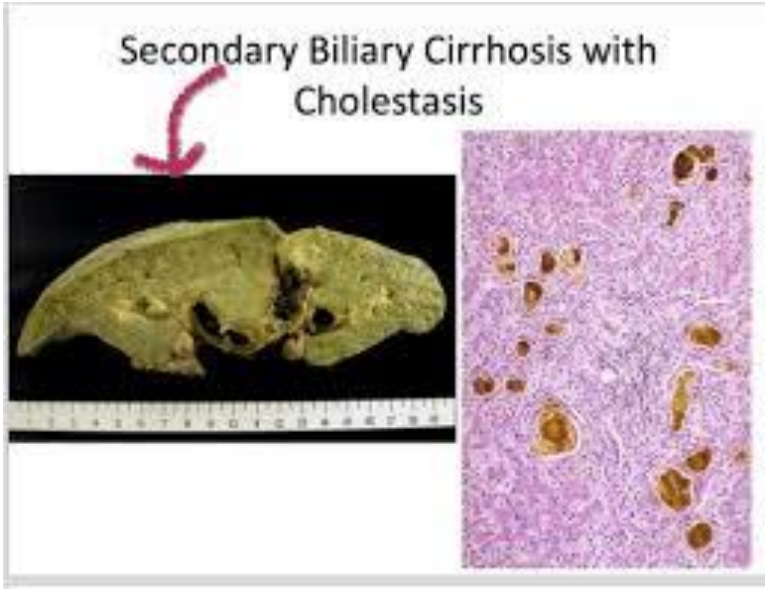
- The initial morphologic features of cholestasis (in the liver) are entirely reversible with correction of the obstruction,

- however Prolonged obstruction of the extrahepatic biliary tree initiates :

  -periportal fibrogenesis,
  -scarring &
  -nodule formation with secondary inflammation,

  generating secondary biliary cirrhosis.

- Subtotal obstruction may promotes ascending cholangitis, which further contributes to the damage.



Biliary atresia

- Is complete obstruction of bile flow caused by destruction or absence of part or all of the extrahepatic bile ducts.

- It is the most frequent fatal liver disease in early childhood &

- accounts for >50% of children referred for liver transplantation.

- Biliary atresia is a major cause neonatal cholestasis {1/3 of cases} & occurring in 1/10,000 live births.

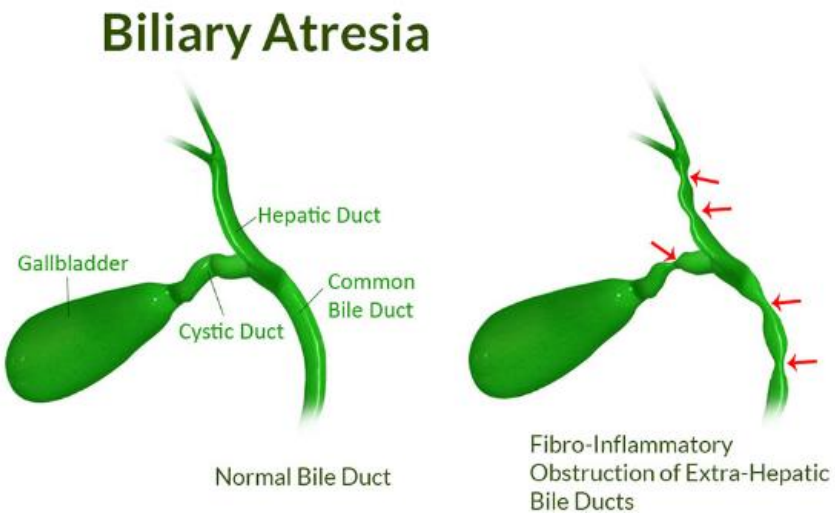
- Salient features:

  (1) Inflammation & fibrosing stricture of hepatic BD or CBD;

  (2) Inflammation of major intrahepatic bile ducts,
  with progressive destruction of the intrahepatic biliary tree;

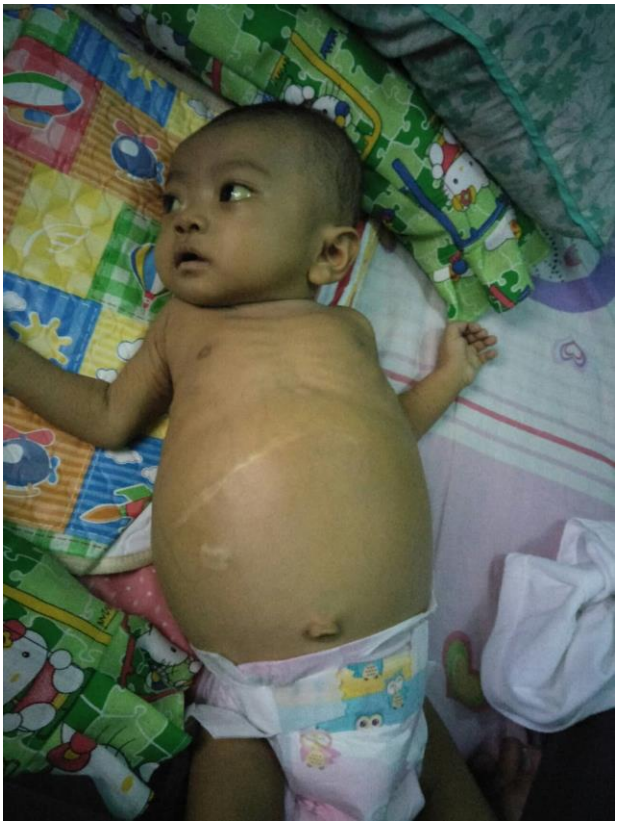
  (3) Florid features of biliary obstruction on liver biopsy
  (i.e.,marked bile ductular proliferation, portal tract edema & fibrosis, & parenchymal cholestasis); &

  (4) Periportal fibrosis & cirrhosis in 3 to 6/12 after birth.



Clinically,

- Infants present with neonatal cholestasis & jaundice.
- Laboratory findings do not distinguish between biliary atresia & intrahepatic cholestasis,
- Liver biopsy provides evidence of bile duct obstruction in 90% of cases
- & Liver transplantation remains the definitive treatment.
- Without surgical intervention, death usually occurs within 2 years of birth.



Carcinoma of the gall bladder (GB Ca)

- GB Ca develops from the GB epithelial lining.
- It is the most frequent cancer of the biliary tract.
- It is slightly more common in women &
  occurs mostly in elderly individuals.
- Preoperative diagnosis is exceptional, occurring in <20% of patients.
- Mean 5-year survival is dismal (sad) 5%, (as in pancreatic carcinoma!)
- GS are present in 60% to 90% of cases.
- Presumably, GB containing stones or infectious agents develop cancer as a result of recurrent trauma & chronic inflammation.

Grossly,
GB Ca grows in one of two patterns:

(I) Infiltrating,
- the more common,
- scirrhous, very firm
- & appears as an ill-defined area of diffuse thickening
- & induration of GB wall that may involves part or the entire GB,

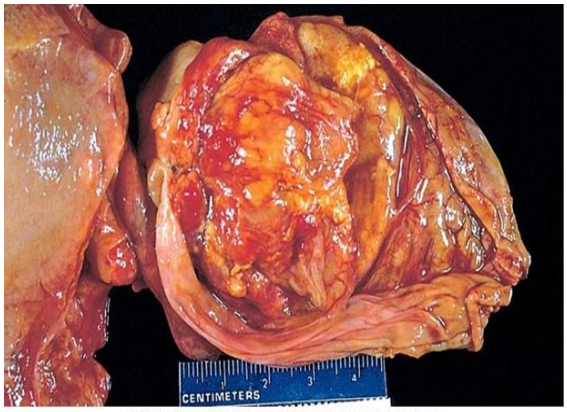
(II) Exophytic,
- less common,
- grows into the lumen as an irregular cauliflower mass,
- but invading the underlying wall concurrently

H,

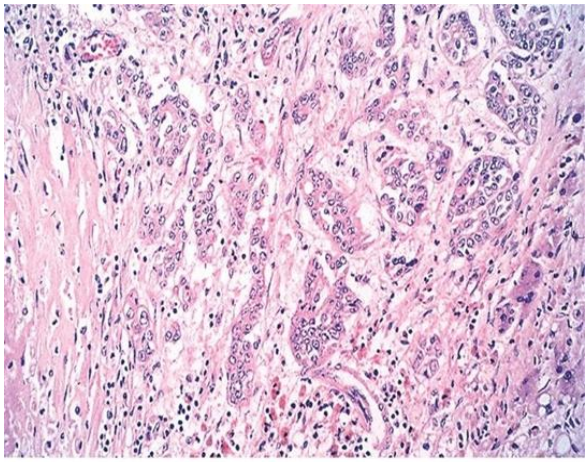
- most GB Ca are adenocarcinomas
  either well , moderate-, poorly-, or un-differentiated infiltrating Ca.

- About 5% are SCC or have adenosquamous differentiation.
- A minority are carcinoid tumors.

Adenocarcinoma of the gall bladder.
The opened GB contains a large, exophytic tumor that virtually fills the lumen.



Adenocarcinoma of the GB.
Malignant glandular structures are present within the GD wall, which is fibrotic.



Spread of GB Ca:

when discovered,

- most Ca have invaded the liver directly
- & many have infiltrate the cystic & other adjacent bile ducts & portal hepatic LNs.

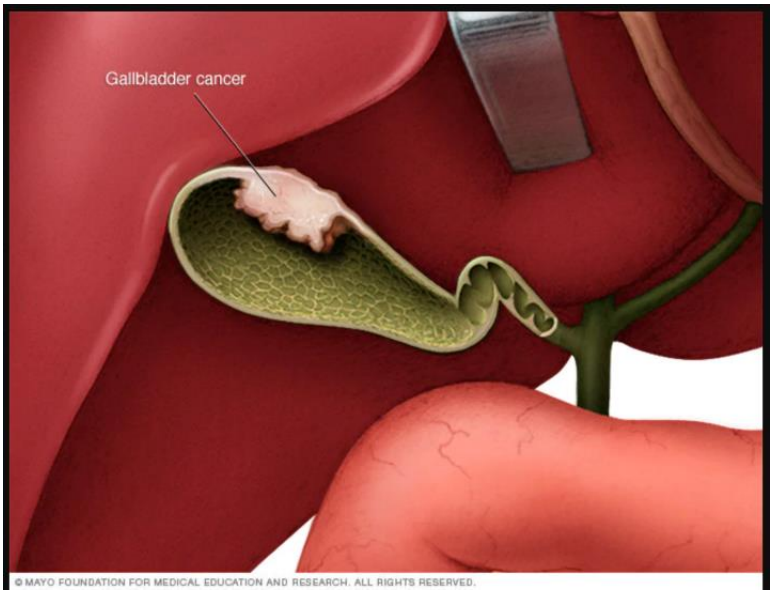
- Distant metastases are less common.

- **Presenting symptoms**
  are insidious & indistinguishable from those associated with cholelithiasis.

- In the event of a very rare discovery of GB Ca at a resectable stage, the fortunate person either
  (I) develops early obstruction & acute cholecystitis before T infiltration into other structures or
  (II) have cholecystectomy for coexistent symptomatic GS!

▼Preoperative **diagnosis** rests on

detection of GS with GB wall abnormalities documented by imaging studies.



Cholangiocarcinomas

- Cholangioca are well-differentiated adenocarcinomas,
  with biliary differentiation,
  arising from cholangiocytes lining intra- or extra-hepatic bile ducts,
  with an abundant fibrous stroma {desmoplasia, F16-40}
  explaining their firm, & gritty consistency.

- Bile pigment & hyaline inclusions are not found within the cells.

- It occur mostly in elderly individuals.

Risk factors

(I) primary sclerosing cholangitis (PSC),

(II) fibrocystic diseases of the biliary tree,

(III) exposure to Thorotrast, previously used in biliary tree radiography.

- 2/3 are extrahepatic T,
  develop at the hilum (known as Klatskin T)
  or more distally in the biliary tree, as far as the peripancreatic portion of the distal CBD.
- 1/3 are intrahepatic,

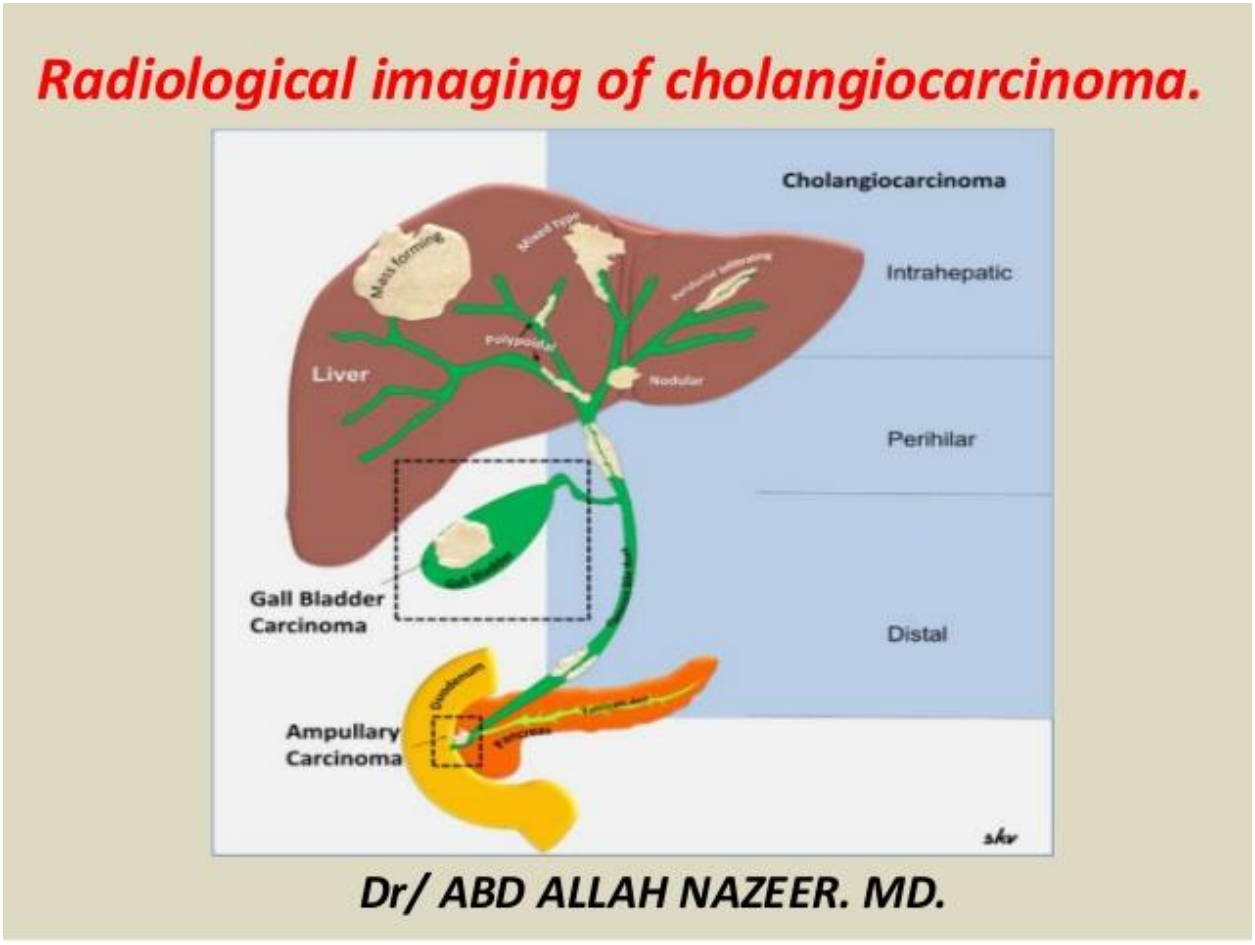
- the incidence of intrahepatic of which increased worldwide,
  while that of extrahepatic T has decreased.

- The causes for these changes are unknown,
  but suggest that intra- & extrahepatic cholangioca may have different pathogenesis

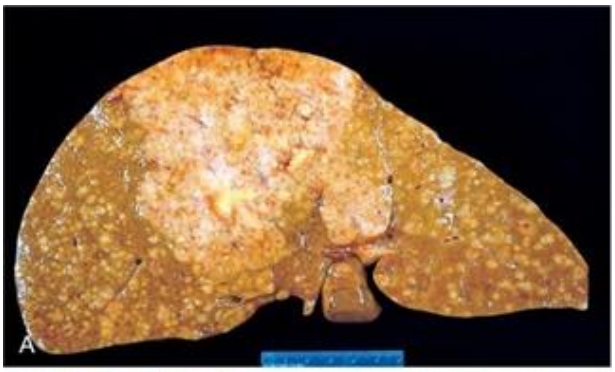
Because

- extrahepatic cholangioca
  -causes obstructive jaundice early,
  -they tend to be relatively small at the time of diagnosis,
  -most appear as firm, gray nodules, some are papillary or polypoid, within the bile duct wall;
  -some may be diffusely infiltrative T, with ill-defined wall thickening.

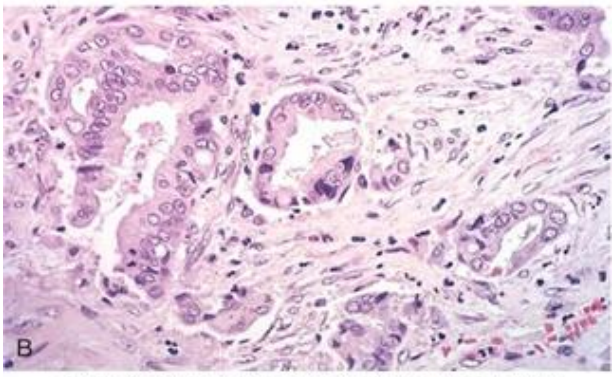
- Intrahepatic cholangioca
  - presented by non-specific symptoms such as weight loss, pain, anorexia, & ascites,
  - & are detected by the presence of liver mass on X-ray or CT.



A, Massive tumor in the right lobe & multiple metastases through out the liver,



B, Tumor cells forming glandular structures surrounded by dense sclerotic stroma.

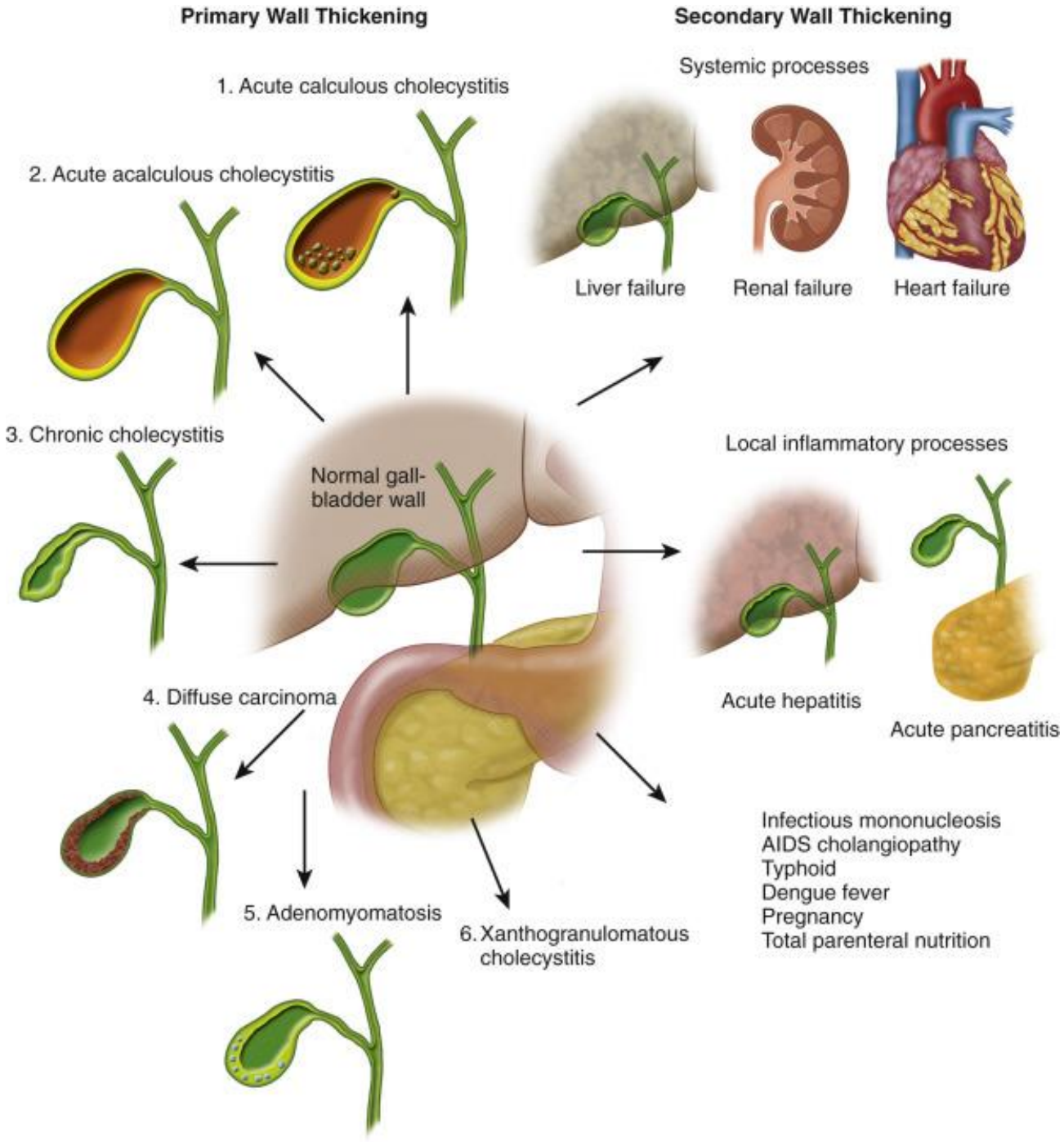


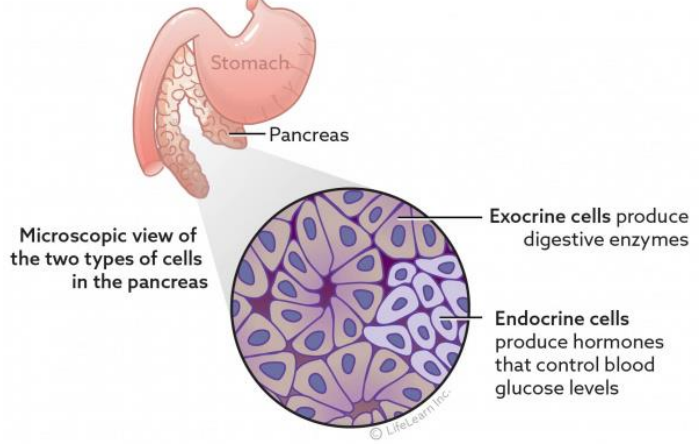
Spread of Cholangioca occur to
- regional LN,
- lungs,
- bones,
- & adrenal glands,

- Indeed, Cholangioca have greater tendency for extrahepatic spread than Hepatocellular ca!

- **Prognosis** is poor,
  because most cholangiocarcinomas are generally asymptomatic
  until they reach an advanced stage
  & most patients have unresectable tumors.

- Surgical resection is the only treatment available,
- & mean survival is 6 to18 months,
  regardless of whether aggressive resection or palliative surgery is performed.


Primary Wall Thickening
Secondary Wall Thickening
1. Acute calculous cholecystitis
2. Acute acalculous cholecystitis
3. Chronic cholecystitis
4. Diffuse carcinoma
5. Adenomyomatosis
6. Xanthogranulomatous cholecystitis
Normal gall-bladder wall
Systemic processes
Liver failure
Renal failure
Heart failure
Local inflammatory processes
Acute hepatitis
Acute pancreatitis
Infectious mononucleosis
AIDS cholangiopathy
Typhoid
Dengue fever
Pregnancy
Total parenteral nutrition



The exocrine Pancreas (P)

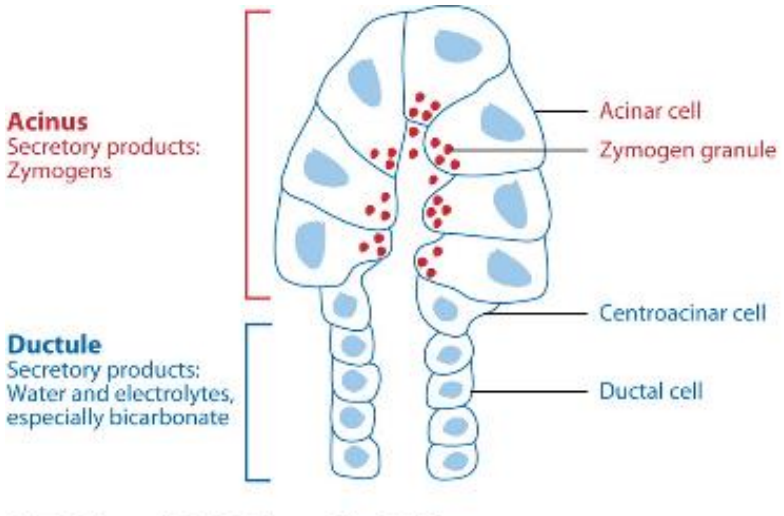
- The exocrine P composed of:

(I) Acinar cells that produce enzymes,
-mostly as an inert proenzymes forms (e.g. trypsinogen);
-{amylase & lipase are exceptions & are secreted in an active form}
-& store proenzymes in membrane-bound zymogen granules.

- When acinar cells are stimulated to secrete,
the zymogen granules fuse with the apical plasma membrane
& release their contents into the central acinar lumen.

(II) Ductules & ducts that transport & convey enzymes to the duodenum.
-The proenzymes remain largely inactive until they reach the duodenum;
there, enteropeptidase (a brushborder enzyme) cleaves trypsinogen into active trypsin.
- Activated trypsin then functions to catalyze the cleavage of the other proenzymes.

- Surgical rule: Don't mess around with the pancreas.

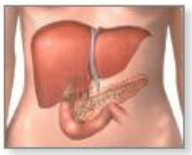


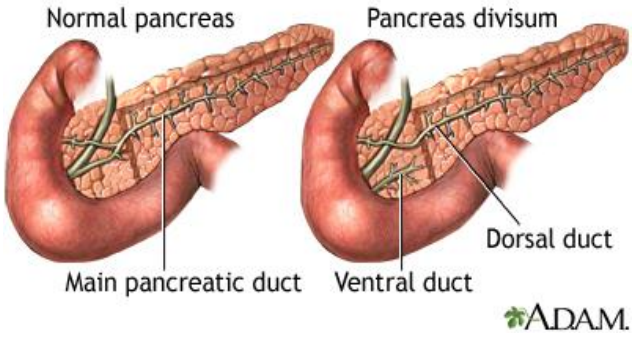
CONGENITAL ANOMALIES

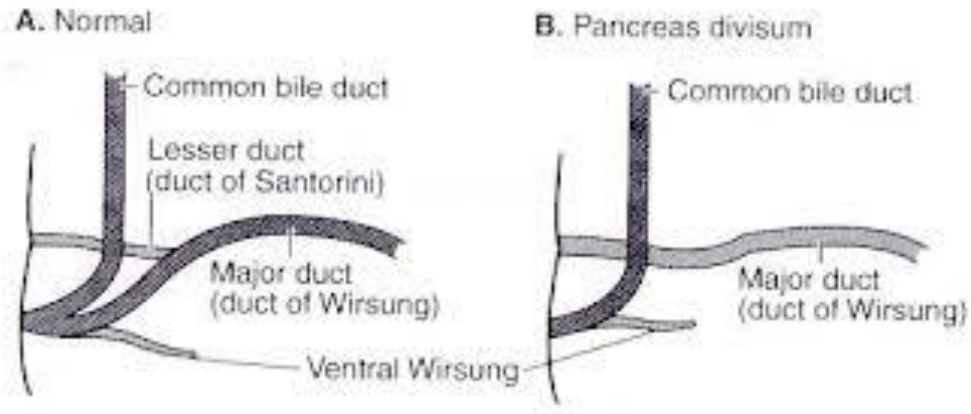
- Agenesis:
  totally absent P, very rare.

- Pancreatic divisum:

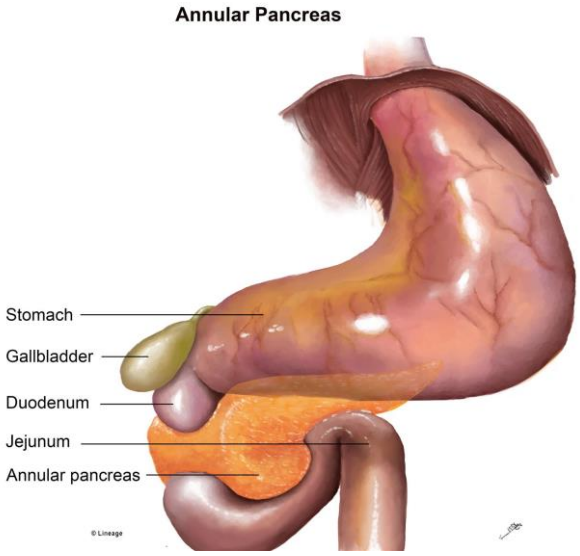
  - is the most common clinically significant congenital P anomaly { incidence of 3%-10%}.
  - It occurs when the fetal duct systems of the P primordia fail to fuse.
  - As a result, the main P duct (Wirsung) is very short & drains only a small portion of the head of the P,
  - while the bulk of the P drains through the minor sphincter.
  - This predisposes such individuals to chronic pancreatitis.





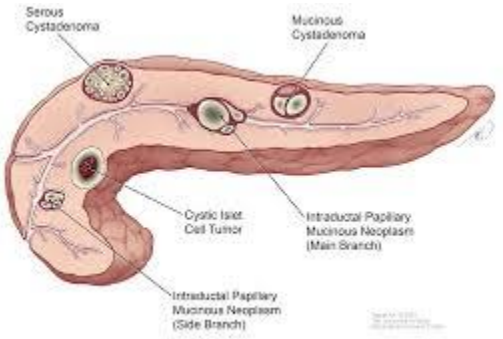


- Annular Pancreas:



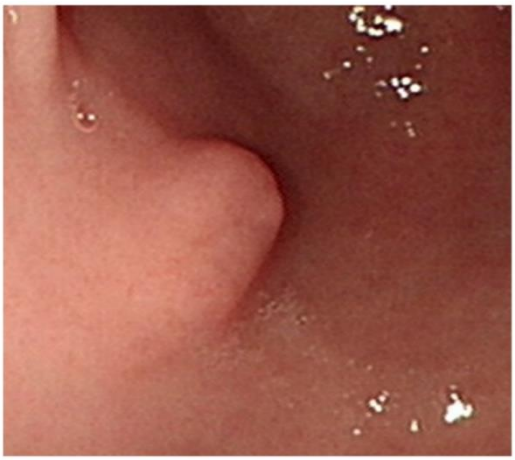
- uncommon variant of P fusion;
- the outcome is a ring of pancreatic tissue that completely encircles the duodenum, cause duodenal obstruction.

- Congenital cysts:



- result from abnormal duct development.
- Cysts range from mm to 5 cm ,
- lack a cell lining or lined by duct cuboidal epithelium
- & enclosed in a thin fibrous capsule.
- in polycystic disease, the kidney, liver, & P can all contain cysts.

❖ Rule:
unilocular P cysts tend to be benign,
while multilocular P cysts are more often neoplastic & possibly malignant.



- Ectopic Pancreas:

  - Abnormally situated, or ectopic, P tissue
  - occurs in 2% of the population;

  - favored sites are:
    -the stomach & duodenum,
    -followed by the jejunum
    -Meckel diverticulum
    -& ileum.

  - Typically small (mms to cms in ?)
  - & are located in the submucosa;

  - they are composed of normal P acini with occasional islets.

  - Although incidental & asymptomatic, ectopic P can cause:
    -pain from localized inflammation,
    -or rarely mucosal bleeding,
    - even more rarely an intussusception (Personal 2 cases),

  - 2% of islet cell T arises in ectopic P tissue.

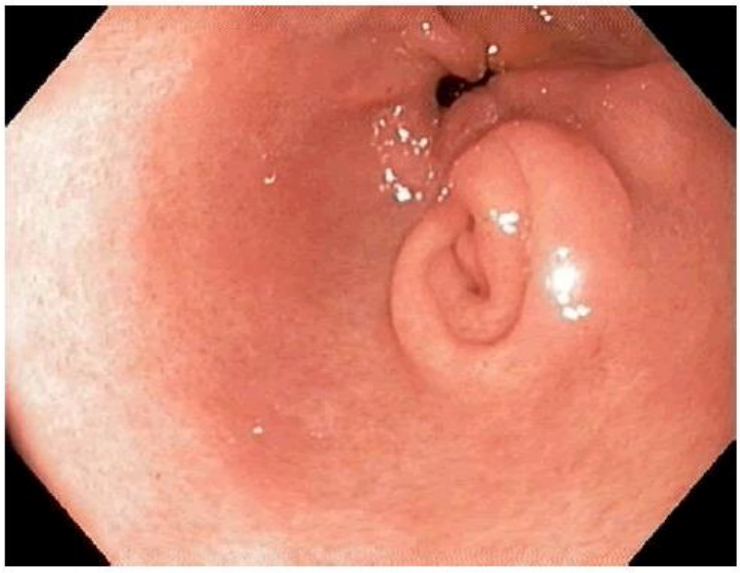


Figure 1. Upper gastrointestinal endoscopy revealed a subepithelial lesion in the gastric antrum with endoscopic appearance consistent with an ectopic pancreas.

Pancreatitis = inflammation of the pancreas

- By definition, in acute pancreatitis the P can return to normal if the underlying cause of inflammation is removed.

- In contrast, chronic pancreatitis is defined by the presence of irreversible destruction of exocrine P parenchyma.

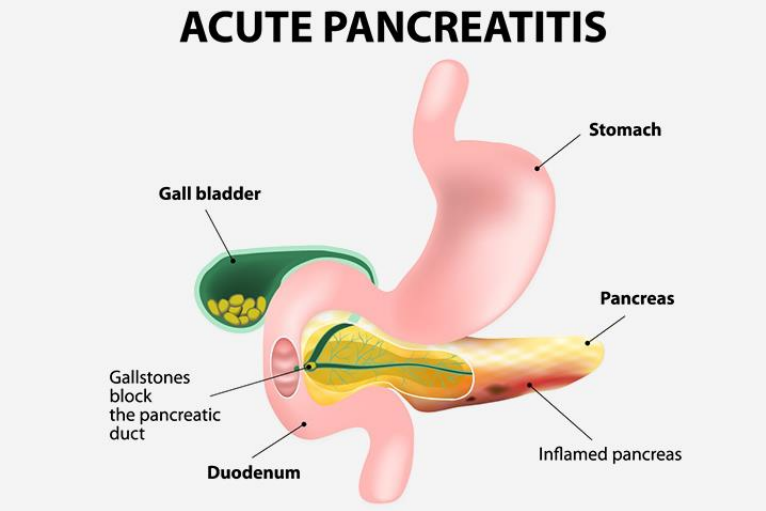
Acute Pancreatitis (Ac P)

- Ac P
  is an acute autodigestion of the P substance by inappropriately activated P enzymes.

- It ranges from mild, self-limited disease to a life-threatening

- Ac P is a group of reversible lesions characterized by inflammation; ranging from focal edema & fat necrosis to widespread parenchymal necrosis with severe hemorrhage.

- Ac P is relatively common, with an annual incidence in industrialized world of 100 to 200 cases/million people.



- 80% of cases are attributable to either

  (I) Biliary tract disease
  (GS are implicated in 35% to 60% of cases,
  & about 5% of patients with GS develop Ac P), &

  (2) Alcoholism;
  excessive alcohol intake as a cause of Ac P varies from 65% of cases in the US,
  to 5% or less in the UK

Etiologic Factors in Ac P:

- Alcoholism & Gallstones (80% of cases)
- 10% to 20% of cases are idiopathic with no identifiable cause.

Other causes of Ac P are:

- Trauma, both blunt force & Iatrogenic injury
  (Perioperative or Endoscopic procedures with dye injection).

- Non-gallstone obstruction of pancreatic ducts =
  -periampullary tumors,
  -P divisum,
  -biliary "sludge,"
  -& Ascaris lumbricoides,

- Medications:

  - thiazide furosemide,
  - procainamide,
  -pentamidine azathioprine,
  -estrogens,
  -methyldopa,
  -sulfonamides,,

- Infections:

  -Mumps,
  -Coxsackie virus,
  -Mycoplasma pneumoniae,

- Metabolic disorders:

  -hypertriglyceridemia,
  -hyperparathyroidism,
  -& other hypercalcemic states,

- Vascular:

  -Shock,
  -Ischemia due to thrombosis,
  - embolism,
  -vasculitis (eg Polyarteritis nodosa).

- Genetic:

  - Hereditary pancreatitis is an autosomal dominant disease with an 80% penetrance
  - characterized by recurrent attacks of severe pancreatitis

  - usually beginning in childhood.

  -It is caused by mutations in the PRSS1 gene that affect a site on the trypsinogen molecule that is essential for the cleavage (inactivation) of trypsin by trypsin itself.
  - When this site is mutated, trypsinogen & trypsin become resistant to inactivation, leading to ongoing activation of other digestive proenzymes, & eventually the development of pancreatitis.

- **Basic pathological changes are**
  (1) edema,
  (2) proteolytic destruction of pancreatic parenchyma,
  (3) fat necrosis by lipases,
  (4) an acute inflammatory reaction, &
  (5) BV destruction with hemorrhage.

- In mild Ac P there are

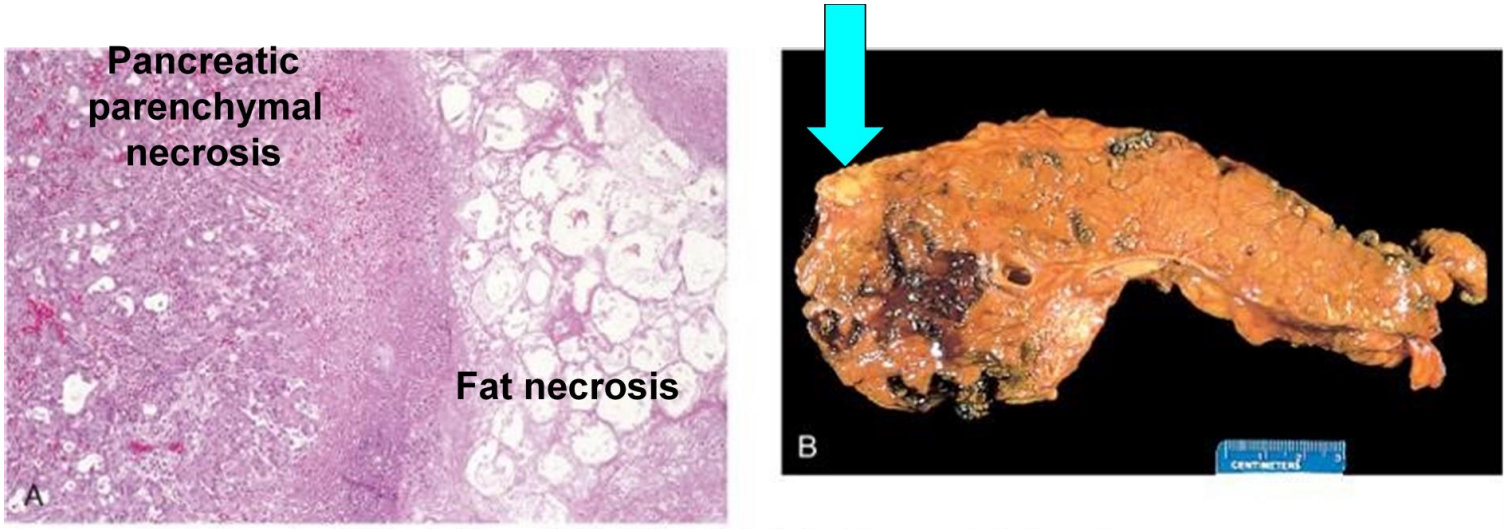
  (I) interstitial edema &
  (2) focal areas of fat necrosis in the pancreatic substance results from enzymatic destruction of peripancreatic fat cells;
  the released fatty acids combine with calcium to form insoluble salts that precipitate in situ.

- In more severe Ac P = acute necrotizing pancreatitis:

  (a) Necrosis of P tissue affects acinar, ductal as well as the islets of Langerhans;
  (b) vascular damage causes hemorrhage into P parenchyma.

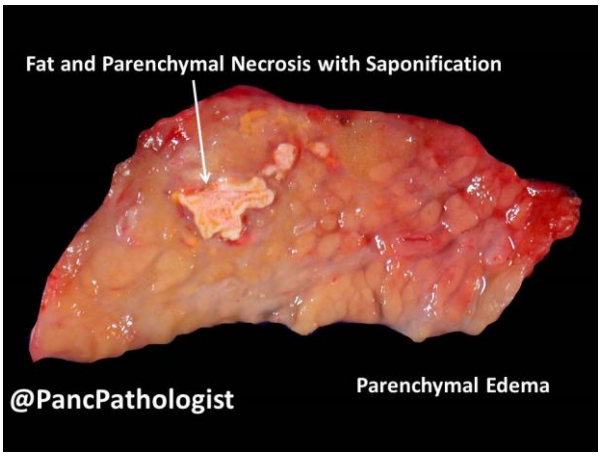
A, Microscopic field shows a region of fat necrosis (right), & focal pancreatic parenchymal necrosis (center).

B, The pancreas has been sectioned longitudinally to reveal dark areas of hemorrhage in the pancreatic substance & a focal area of pale fat necrosis in the peripancreatic fat (upper left)



Grossly,

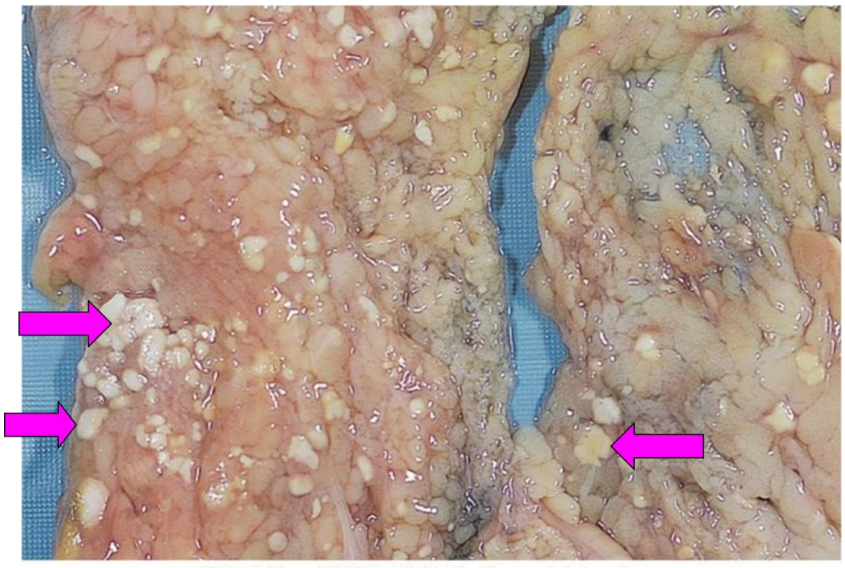
- the P shows red-black hemorrhages interspersed with foci of yellow-white, chalky fat necrosis



- Fat necrosis can also occur in extra-pancreatic fat, including:

  - the omentum
  -bowel mesentery,
  -& even outside the abdominal cavity e.g., in subcutaneous fat,
  -& peritoneum contains a serous, slightly turbid, brown fluid with globules of fat (derived from enzymatically digested adipose tissue).

: Omentum: Fat necrosis in acute pancreatitis



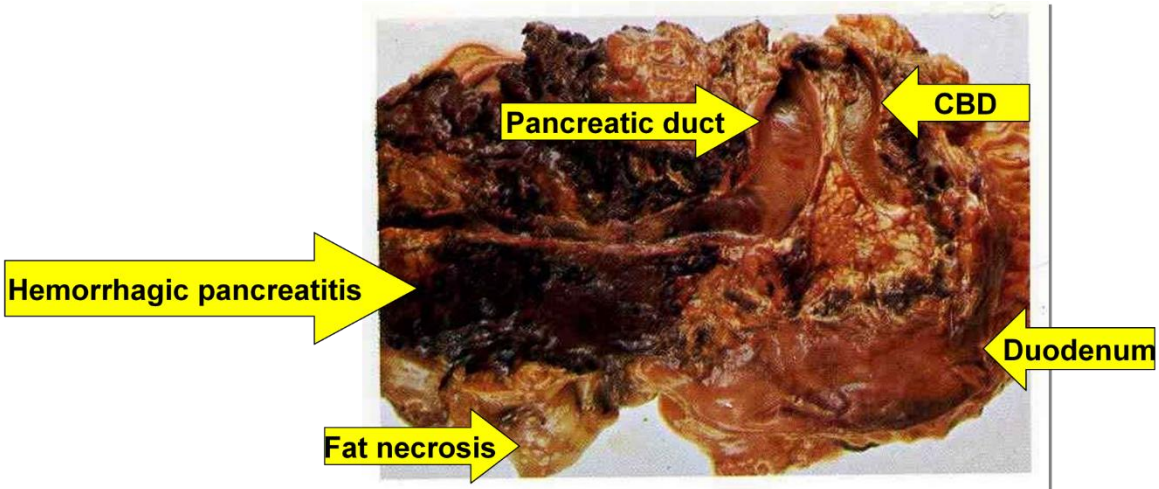
- The severest form, Acute Hemorrhagic pancreatitis shows extensive diffuse hemorrhage & P tissue necrosis.

Acute hemorrhagic pancreatitis.

This is the posterior aspect of the 2nd part of the duodenum (right), the CBD, & the main pancreatic duct.

The pancreas is swollen & edematous & there is extensive hemorrhagic necrosis of the body & tail of the pancreas (left), with the formation of a dark brown hematoma.

Small ovoid yellow-white foci of fat necrosis are visible in the peripancreatic fat (lower border)



5.43 Acute haemorrhagic pancreatitis

Acute hemorrhagic pancreatitis: Omentum.

Omentum studded with small yellow-white foci of fat necrosis

5.44 Acute haemorrhagic pancreatitis: omentum

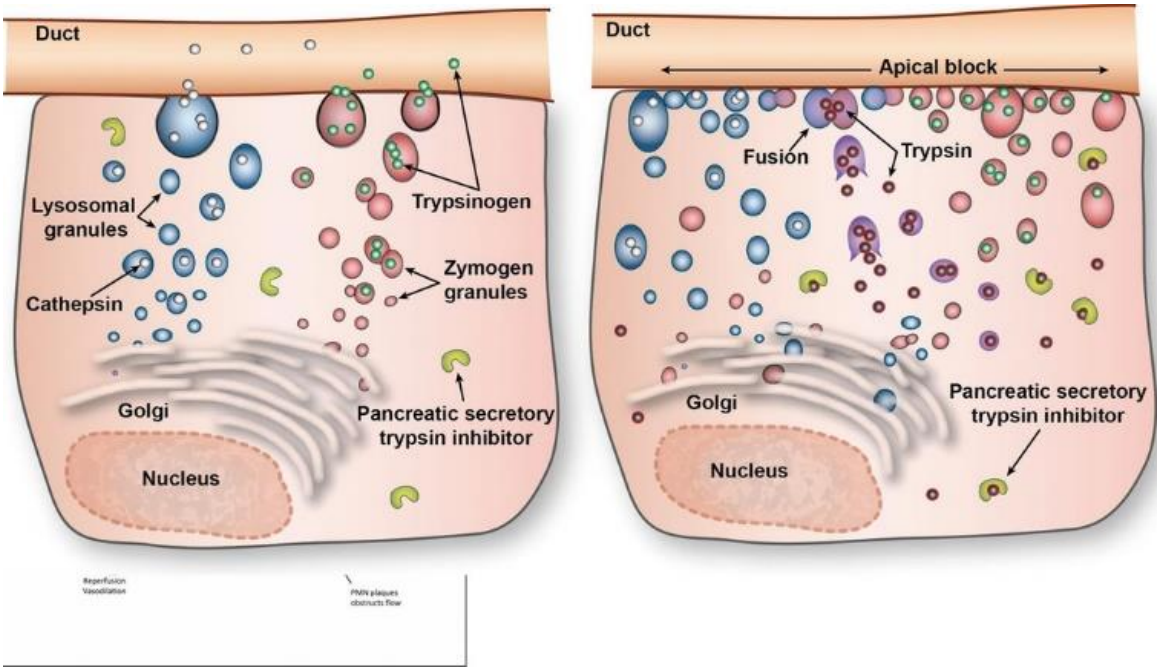
Pathogenesis

- The histologic changes seen in Ac P strongly suggest autodigestion of the P substance by inappropriately activated P enzymes.

- Zymogen forms of P enzymes must be enzymatically cleaved to be activated by trypsin;
- therefore activation of trypsin is a critical triggering event in Ac P.

- If trypsin is inappropriately generated from its proenzyme trypsinogen, it can activate elastases & phospholipases that can cause autodigestion.

- Trypsin also converts prekallikrein to its activated form Kallikrein, activating the kinin system &, by activation of Hageman factor {factor XII} also sets in motion the clotting & complement systems.



☼ Three possible pathways can incite the initial enzyme activation that may lead to Ac P (Fig. 17-2).

(1) Pancreatic duct obstruction:

→ Impaction of a GS or biliary sludge, or extrinsic compression of the ductal system by a mass blocks ductal flow,
increased intraductal pressure,
& allows accumulation of an enzyme-rich interstitial fluid.

→ Since lipase is secreted in an active form, this can cause local fat necrosis, with the result that

→ injured tissues, periacinar myofibroblasts, & WBCs
release pro-inflammatory cytokines that promote local inflammation & interstitial edema.
Edema further compromises local blood flow, causing vascular insufficiency & ischemic injury to acinar cells.

(2)Primary acinar cell injury.

can incite Ac P caused by :

- ischemia,

- viruses (eg mumps),

-drugs,

- & direct trauma to P.

(3)Defective intracellular transport of proenzymes within acinar cells.

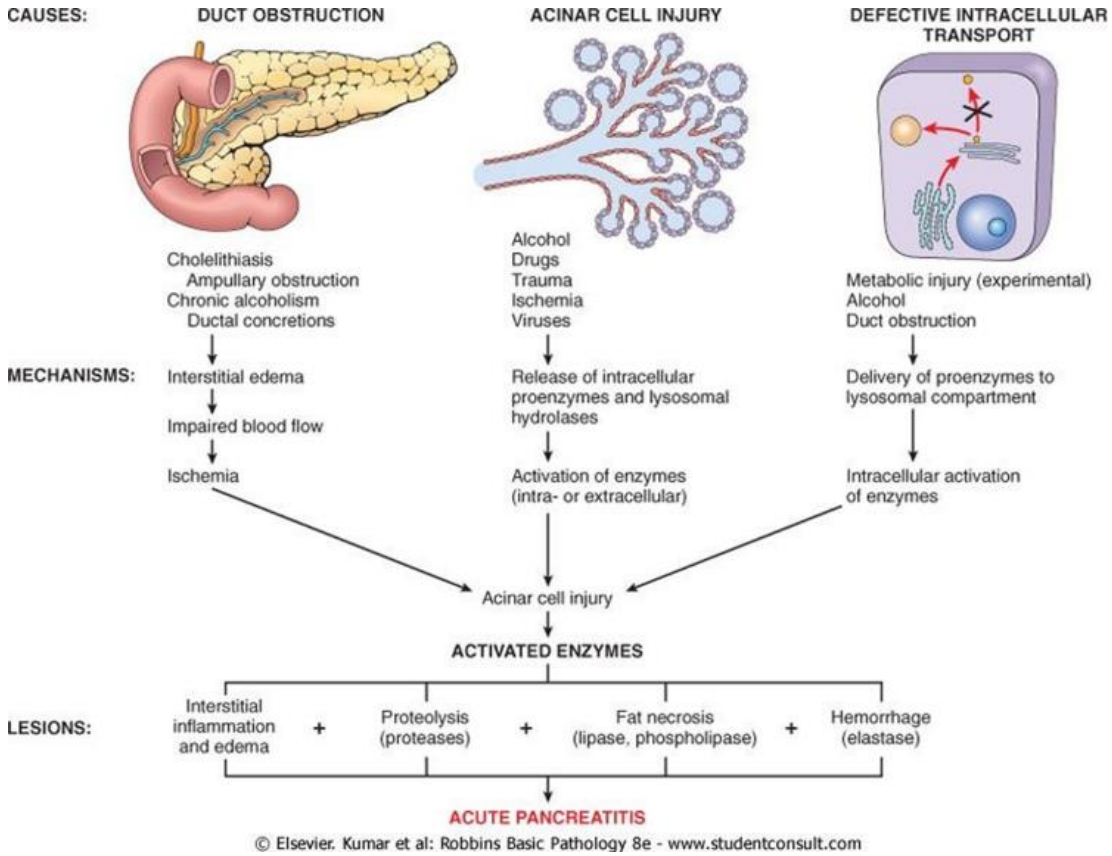
- In normal acinar cells,

digestive enzymes intended for zymogen granules (& eventually extracellular release) & hydrolytic enzymes destined for lysosomes

are transported in discrete (separate) pathways after synthesis in the ER.

-However, at least in some animal models of metabolic injury, pancreatic proenzymes & lysosomal hydrolases become packaged together.

-This results in proenzyme activation, lysosomal rupture (action of phospholipases), & local release of activated enzymes.



Proposed pathogenesis of acute pancreatitis

☻How alcohol causes Ac P?

is unknown,

although:

(1) abnormal proenzyme trafficking has been implicated.
(2) It leads to contraction of the sphincter of Oddi
(3) direct toxic effects on acinar cells, &
(4) Alcohol ingestion causes increased secretion of protein-rich P fluid, leading to deposition of inspissated protein plugs & obstruction of small P ducts.

Clinically,

- Abdominal pain is cardinal symptom;
  vary from mild to sudden severe constant pain,
  often referred to the upper back, with rigid abdomen.

Diagnosis of Ac P depends on

- markedly elevated serum amylase during the first 24 hours
  followed (within 72-96 hours) by rising serum lipase levels.

- Hypocalcemia can result from precipitation of calcium in the extensive areas of fat necrosis.

- The enlarged inflamed pancreas can be visualized by CT or MRI
  & the exclusion of other causes of acute abdominal pain
  - acute appendicitis ,
  -acute cholecystitis,
  - perforated PU ulcer,
  -intestinal obstruction &
  - bowel infarction,
  -ruptured ectopic pregnancy}

- Severe Ac P manifestations are due to
  systemic release of digestive enzymes & explosive activation of the inflammatory response.

  Patients may show:
  - increased vascular permeability,
  - DIVC,
  - ARDS (due to alveolar capillary injury),
  - & diffuse fat necrosis.

- Management of Ac P is by supportive therapy.

- Shock can rapidly follows as a result of loss of blood volume & electrolyte disturbances
- & in 40% - 60% of Ac P the necrotic debris becomes infected, usually by gram- negative bacteria from the GIT & may cause endotoxemia.
- Most Ac P patients eventually recover;
  5% (or more) die from shock.

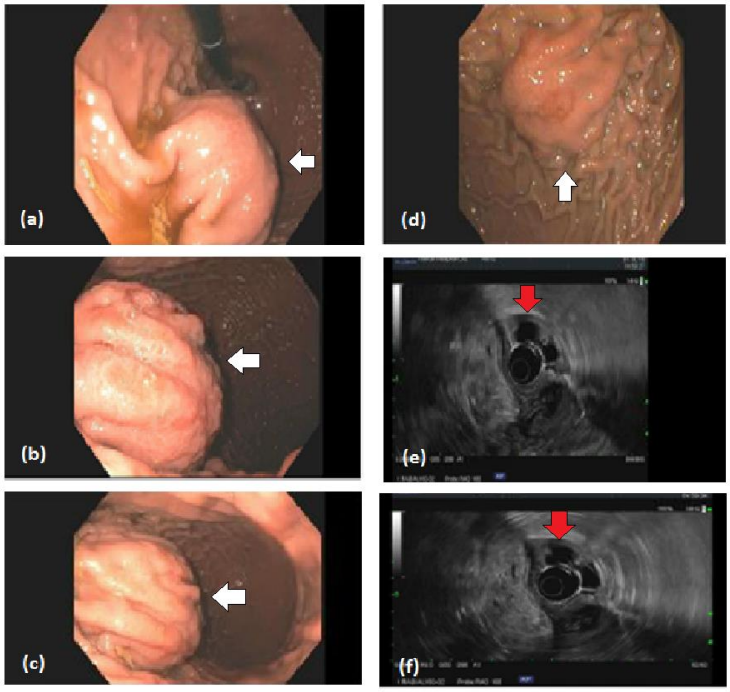
- If the patient survive, a common sequelae is:
  P Pseudocyst (PP)

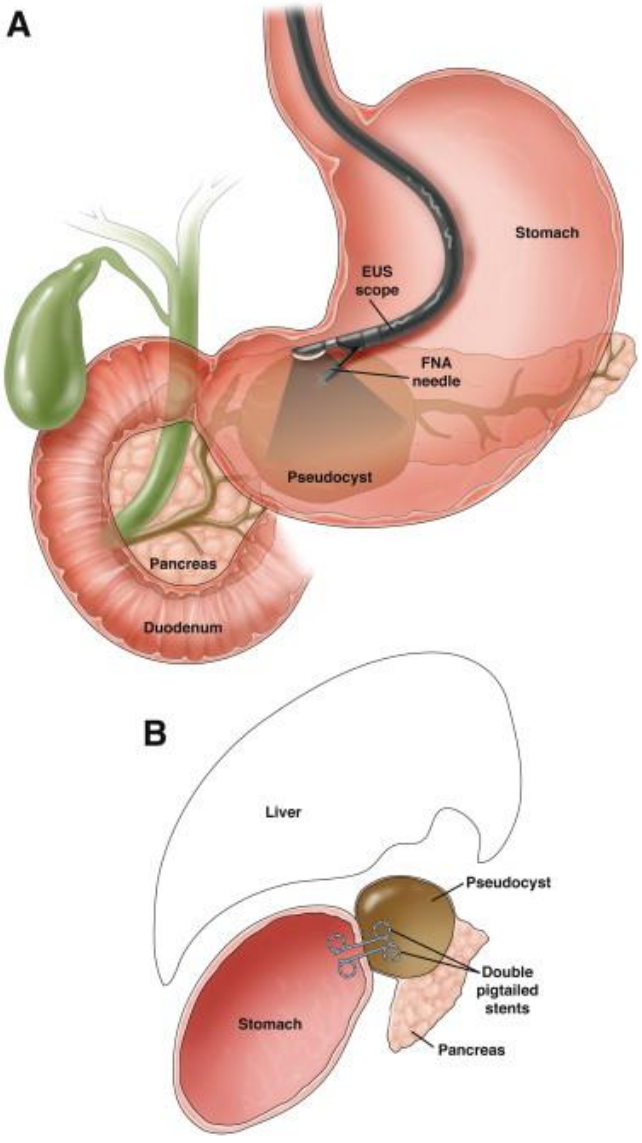
  forms by:

  (1) walling off areas of hemorrhagic fat necrosis, &
  (2) drainage of P secretions (from damaged pancreatic ducts) into cyst over months or years cause massive cyst enlargement (2 to 30 cm in).

- PP account for 75% of all pancreatic cysts

- PP are solitary; attached to the surface of the pancreas
  & involve peripancreatic tissues such as
  - the lesser omental sac or
  -the retroperitoneum between the stomach & transverse colon
  -or liver





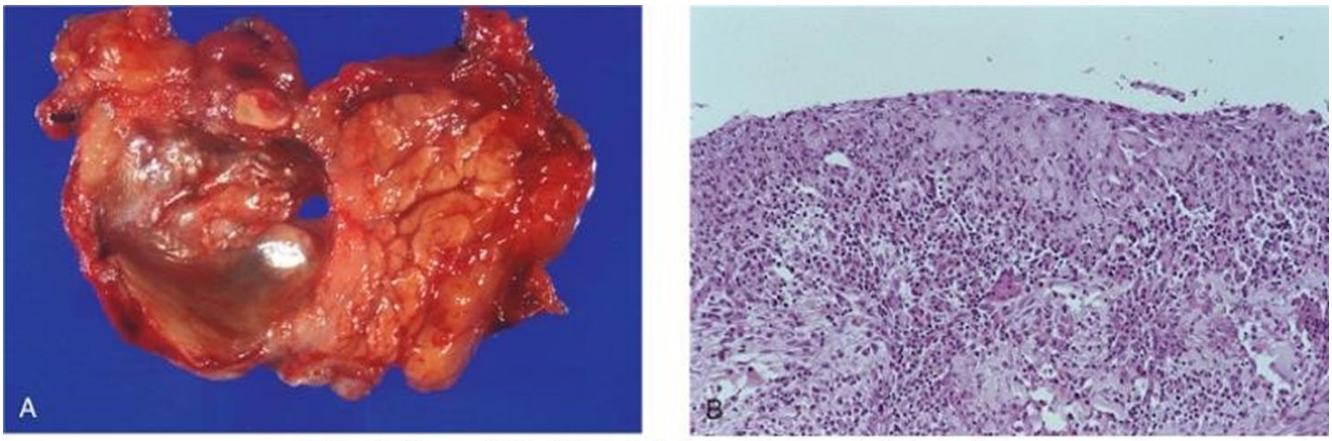
- PP contains necrotic debris encased by fibrous granulation tissue lacking an epithelial lining (pseudo)

- Many PP spontaneously resolve, some can become secondarily infected &
- larger PP can compress or even perforate into adjacent structures

Pancreatic pseudocyst.

A, Cross-section revealing a poorly defined cyst with a necrotic brownish wall.

B, Histologically the cyst lacks a true epithelial lining & instead is lined by fibrin, granulation tissue, &chronic inflammation.



Chronic Pancreatitis (Ch P)

- Is longstanding inflammation & fibrosis of the pancreas,
  with destruction of the exocrine part;
  later, the endocrine part is also lost.

- Prevalence: 0.04% to 5% of populations.

- Although Ch P can result from recurrent attacks of acute pancreatitis
- the chief distinction between acute & Ch P is
  the irreversible impairment of pancreatic function in Ch P.

- The most common **cause** of Ch P is
  long-term alcohol abuse,
  middle aged men constitute the bulk of the group.

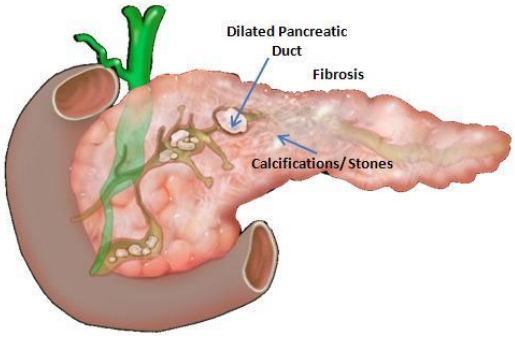
- Less common causes of Ch P include:
  Long-standing pancreatic duct obstruction (pseudocysts, calculi, neoplasms, or pancreas divisum),

- Tropical pancreatitis, attributed to malnutrition,
  is a poorly characterized disorder seen in Africa and Asia,

- Hereditary pancreatitis
  due to PRSS1 mutations, or mutations in the SPINK1 gene encoding trypsin inhibitor.

- Ch P associated with CFTR gene mutations (cystic fibrosis) in which there is decreased bicarbonate secretion, thereby promoting protein plugging.

- 40% of Ch P cases have no predisposing factors.



- **Grossly**, in Ch P,
  the pancreas is hard,
  sometimes with extremely dilated ducts
  & visible calcified concretions.

H,

- Acinar cell loss (reduced number & size) is a constant feature
  (leading to pancreatic insufficiency & malabsorption),

- with a chronic inflammatory cell infiltration around remaining lobules & ducts + severe parenchymal fibrosis

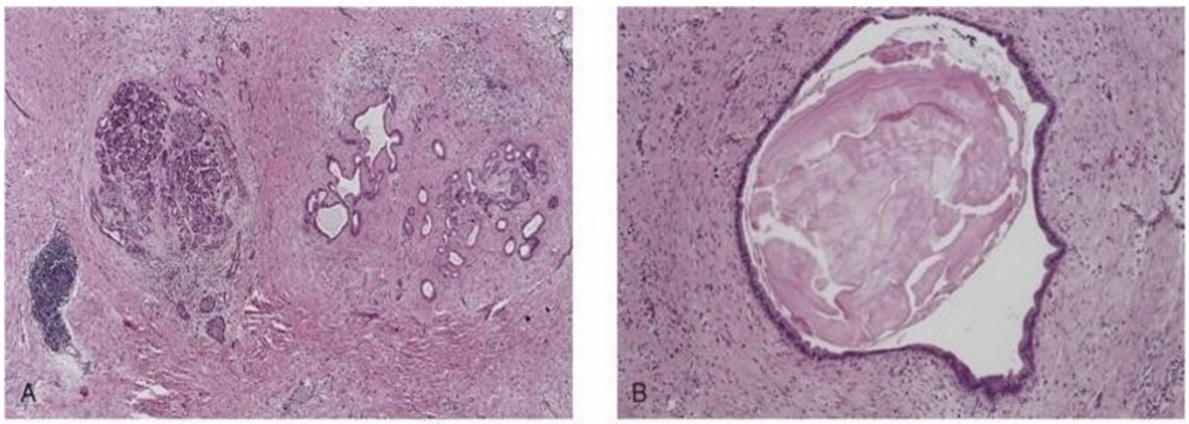
- variable dilation of the pancreatic ducts with atrophic; hyperplastic, or squamous metaplasia of ductal epithelium

- ductal concretions

- Initially, there is sparing of the islets of Langerhans
  ,later, they become embedded in the fibrotic tissue
  & may fuse & appear enlarged; & eventually they disappear →DM.

A, Extensive fibrosis & atrophy has left only residual islets (left) & ducts (right), with a sprinkling of chronic inflammatory cells & acinar tissue.

B, A high power view demonstrating dilated ducts with inspissated eosinophilic concretions in a patient with chronic alcoholic chronic pancreatitis



Pathogenesis:

Several hypotheses are proposed;

- Ductal obstruction by concretions.
  Many of the inciting agents in Ch P (e.g., alcohol) increase the protein concentration of pancreatic secretions, & forming ductal plugs.

- Toxic-metabolic.
  Toxins, including alcohol, can exert a direct toxic effect on acinar cells, leading to:
  - lipid accumulation,
  -acinar cell loss,
  -& eventually parenchymal fibrosis.

- Oxidative stress.
  Alcohol-induced oxidative stress may
  (A) generate FR in acinar cells,
  leading to membrane lipid oxidation & subsequent chemokine expression that recruits mononuclear inflammatory cells,

  (B) promotes abnormal proenzyme trafficking with resulting acinar cell necrosis, inflammation, & fibrosis.

- Necrosis-fibrosis.
  Acute pancreatitis can cause:
  - local perilobular fibrosis,
  - duct distortion,
  -& altered pancreatic secretions.
  Over time & with multiple episodes, this can lead to loss of pancreatic parenchyma & fibrosis.

Clinically,

Ch P can present in several different ways:

► Repeated attacks of jaundice

{with increase in serum levels of alkaline phosphatase},

vague indigestion, persistent or recurrent, severe abdominal & back pain.

The attacks can be precipitated by:

- overeating (increased demand on pancreatic secretions),

-alcohol abuse,

-or opiates or other drugs that increase the muscle tone of the sphincter of Oddi.

► Entirely silent until one or both of the following develop:

(A) Pancreatic insufficiency
resulting in malabsorption with hypoalbuminemic edema & weight loss,

(B) DM (islets loss).

- Pancreatic pseudocysts develop in 10% of Ch P.
- Individuals with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer
- **Diagnosis** of Ch P requires a high degree of suspicion.
- A very helpful finding is visualization of calcifications within the pancreas by CT or U/S.

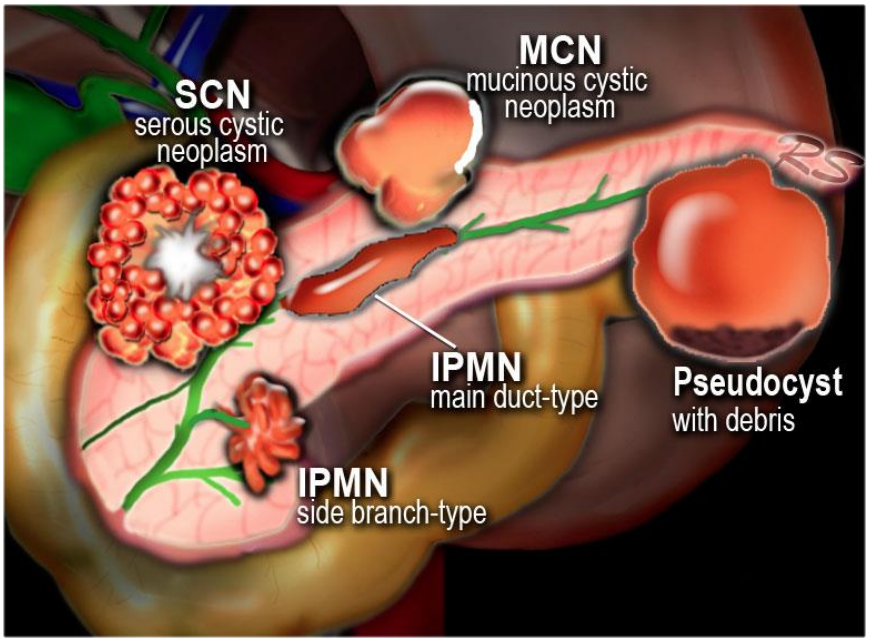
EXOCRINE PANCREATIC TUMORS (T)

Cystic Neoplasms

- Pancreatic Pseudocyst account for 75% of all pancreatic cysts.

- 5% to 15% of all pancreatic cysts are neoplastic;
  these constitute less than 5% of all pancreatic T.

- Some, like Serous cystadenoma are benign,
- while Mucinous cystic T & Intraductal Papillary Mucinous T can be benign, borderline malignant, or malignant T.

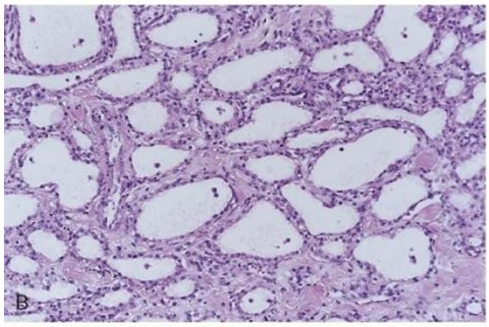


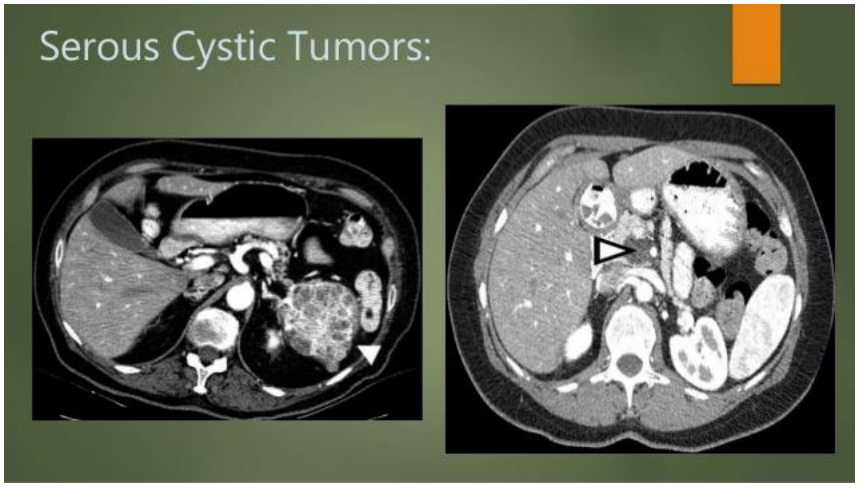
Serous Cystadenomas Neoplasms

- T account for about a 25% of all pancreatic cystic tumors;
- T composed of glycogen-rich cuboidal cells lining cysts containing clear, straw-colored fluid
- T typically presents in the 7th decade of life with abdominal pain;
- M/F ratio is 2: 1.
- T are entirely benign,
- & surgical resection is curative in the vast majority of patients.

A, Cross-section through a serous cystadenoma. Only a thin rim of normal pancreatic parenchyma remains. The cysts are relatively small & contain clear, straw-colored fluid.

B, The cysts are lined by typical cuboidal epithelium.

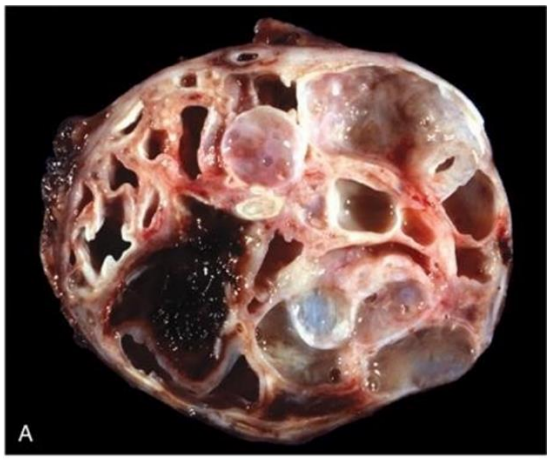




Mucinous Cystic Neoplasms

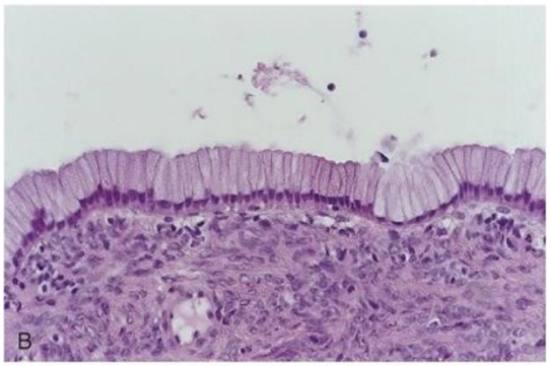
- Always arise in women,
  in the body or tail of the pancreas,

- P/A painless, slow-growing masses.
- The cystic spaces are filled with thick, tenacious mucin,
  & the cysts are lined by a columnar mucinous epithelium with an associated densely cellular stroma



A, Cross-section through a multilocular mucinous cyst in the tail of the pancreas. The cysts are large & filled with tenacious

mucin.



B, the cysts are lined by columnar mucinous epithelium, with a densely cellular stroma.

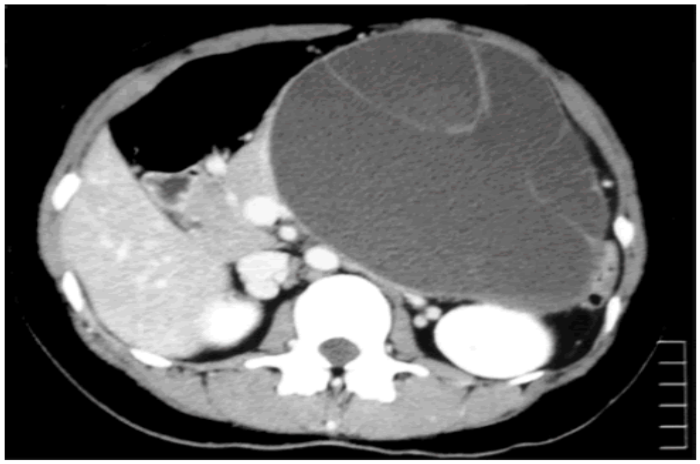


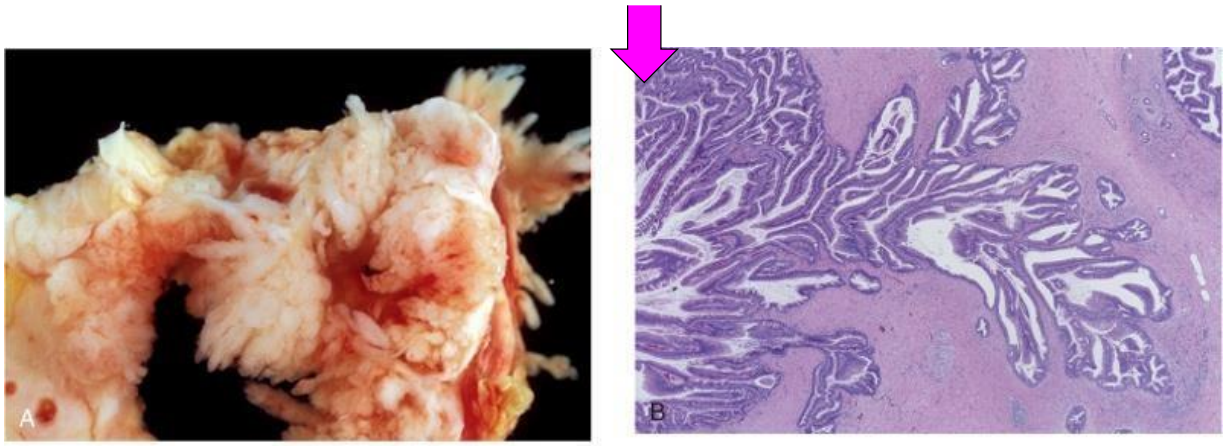
Figure 1. An abdominal CT showing a large (15 cm diameter) cystic tumor of the pancreatic cyst consistent with mucinous cyst adenocarcinoma.

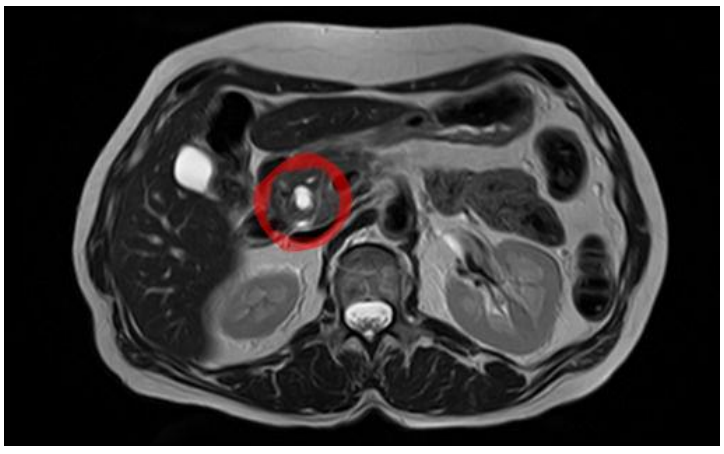
Intraductal Papillary Mucinous Neoplasms

- IPMNs also produce cysts containing mucin;
  BUT In contrast to mucinous cystic neoplasms,
- IPMNs arise more frequently in men than in women &
- more frequently involve the head of the pancreas.
- IPMNs arise in the main pancreatic ducts
  & lack the cellular stroma seen in mucinous cystic T (F17-7).

A, Cross-section through the head of the pancreas showing a prominent papillary tumor distending the main pancreatic duct.

B, The papillary mucinous tumor involved the main pancreatic duct (left) & is extending down into the smaller ducts & ductiles (right)





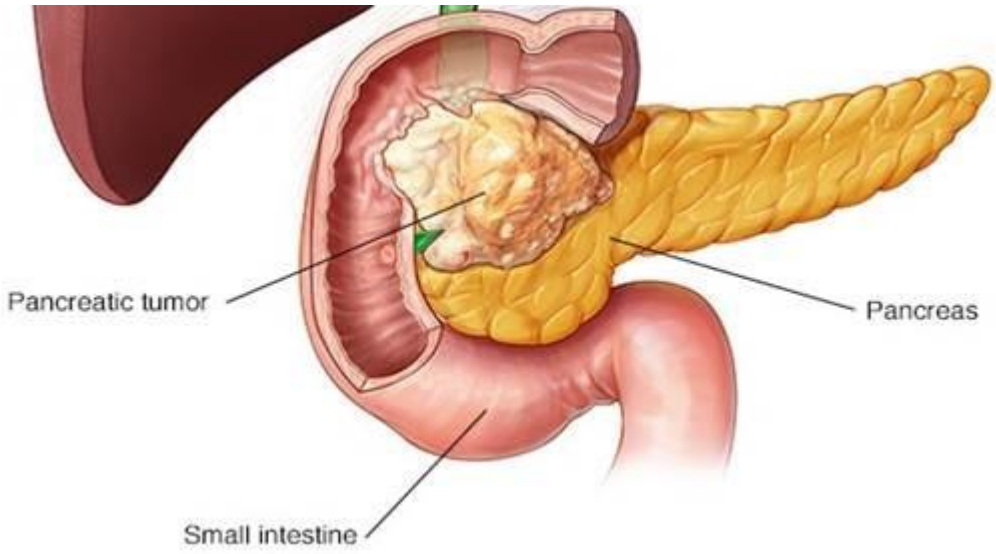
- Both Mucinous Cystic & IPM neoplasms can
  - be benign,
  -lacks significant cytologic or architectural atypia;
  -borderline malignant,
  showing significant cytologic & architectural atypia but no tissue invasion. --
  or malignant, which are invasive.

Pancreatic Carcinoma (P Ca)

- P Ca is the 4th leading cause of cancer death in the US,
  preceded only by lung, colon, & breast cancers.

- 30,000 Americans are diagnosed with P Ca annually
  & all will die of it;

- the 5-year survival rate is dismal <5% (as in GB carcinoma!)



Pathogenesis of P Ca

- There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive lesions in small ducts & ductules, to invasive ca

- Antecedent lesions are "pancreatic intraepithelial neoplasias" (PanINs)

- Evidence in favor of their precursor relationship to frank ca:

  (1) They are often found adjacent to infiltrating P Ca &

  (2) Share a number of the same genetic mutations,

  (3) PanINs epithelial cells show dramatic telomere shortening, potentially predisposing them to accumulating additional chromosomal abnormalities.

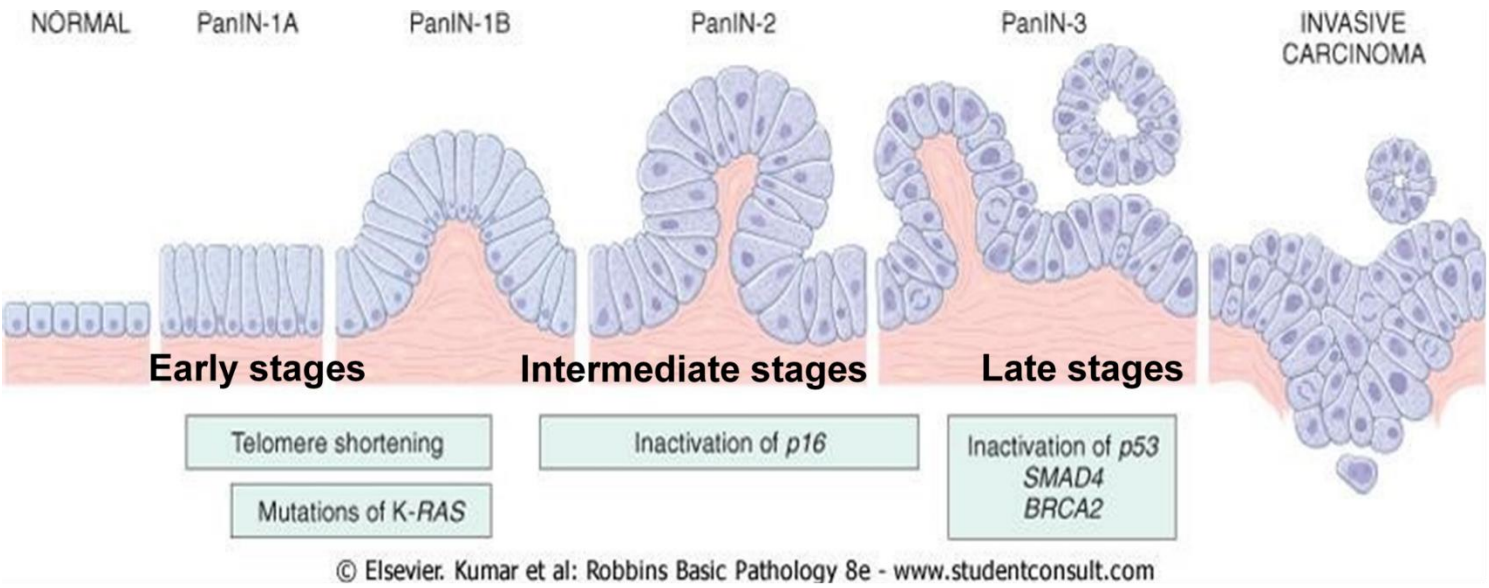
Commonest molecular alterations in pancreatic carcinogenesis:

- K-RAS gene is the most frequently altered oncogene,
  it is activated by point mutation in up to 90% of P Ca cases.

- p16 (CDKN2A) T suppressor gene
  is inactivated in 95%,

- p 53 T suppressor gene
  inactivation occurs in 60%, &

- SMAD4 T suppressor gene
  is inactivated in 55%



- What causes these molecular changes? is unknown.

- P Ca is a disease of elderly,
  80% of patients are 60 to 80y,

- P Ca is more common in blacks than in whites.

- Smoking, strongest environmental influence doubles the risk.

- Chronic pancreatitis & DM are both associated with an increased risk of P Ca.
  BUT it is difficult to sort out whether chronic pancreatitis is the cause of P Ca or an effect of it ?
  since small P Ca can block the pancreatic duct & thereby produce chronic pancreatitis.
  Similarly, DM can occur as a consequence of P Ca.
- Familial clustering of P Ca has been reported.
  In particular, familial pancreatitis (related to mutations in the PRSS1 trypsinogen gene; see above)
  incurs an X 50- to 80-fold increased risk of P Ca.

Morphology

- 60% of P Ca arise in the pancreatic head,
  15% in the body, &
  5% in the tail;

  & in 20%, the P Ca involves the entire organ.

- P Ca is hard, stellate, gray-white, poorly defined T.

- P Ca vast majority are ductal adenoca, forming glands &
  secreting mucin.

- Even early invasive P Ca is highly & extensively invasive T

- P Ca elicits an intense desmoplastic fibrotic response.

- In 50% of cases of P Ca of the head, there is obstruction of the distal CBD as it courses through the head of the pancreas,
  resulting in obstructive jaundice;

  In contrast,
- P Ca of the body & tail do not impinge on the biliary tract & hence remain silent

Spread:

- P Ca invade & infiltrate directly the
  - retroperitoneal space,
  -entrapping nerves,
  & occasionally invading the
  -transverse colon,
  - spleen,
  -adrenals,
  -spine,
  - & stomach.

- Commonly,
  -peripancreatic,
  - gastric,
  - mesenteric,
  -omental, &
  -portahepatic
  LNs are involved,
  as well as the liver.

- Distant metastases occur, mainly to lungs & bones.

H,

- P Ca is usually a moderately to poorly differentiated adenoca forming abortive tubules or cell clusters & with deeply infiltrative growth pattern dense stromal fibrosis & a tendency for lymphatic & perineural invasion.

- P Ca less common variants include:

  -Acinar cell ca showing prominent acinar cell differentiation with zymogen granules & exocrine enzyme production;

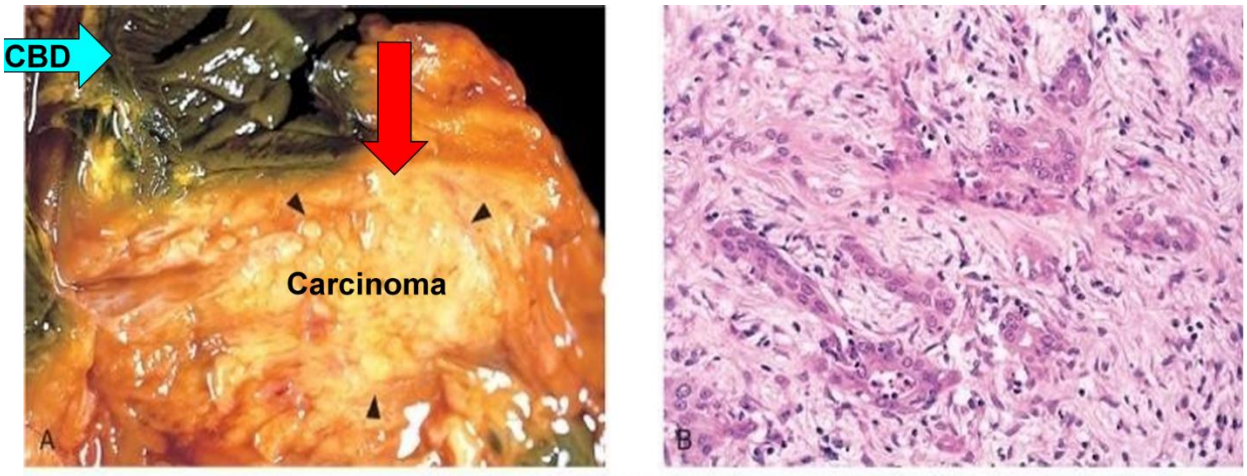
  -Adenosquamous ca with focal squamous differentiation in addition to glandular differentiation;

  -Undifferentiated ca with osteoclast-like giant cells.

A cross-section through the head of the pancreas & adjacent CBD showing both, an ill-defined mass in the pancreatic substance (arrowheads)

& the green discoloration of the CBD resulting from total obstruction of bile flow.

B, poorly formed glands are present in a densely fibrotic (desmoplastic) stroma within the pancreatic substance.

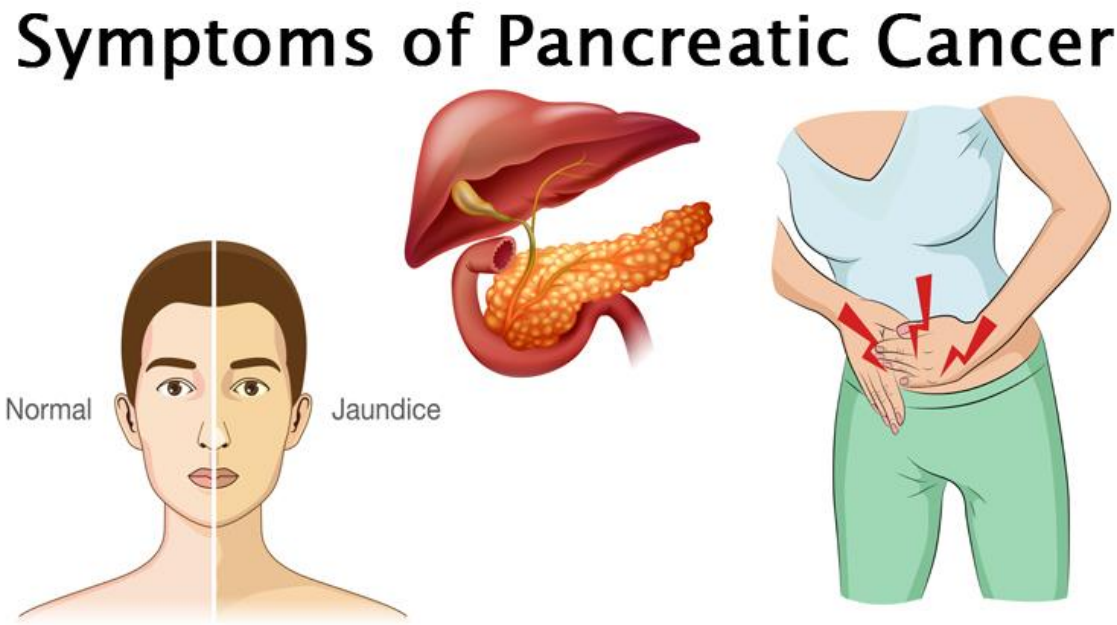


Clinical Features of P Ca

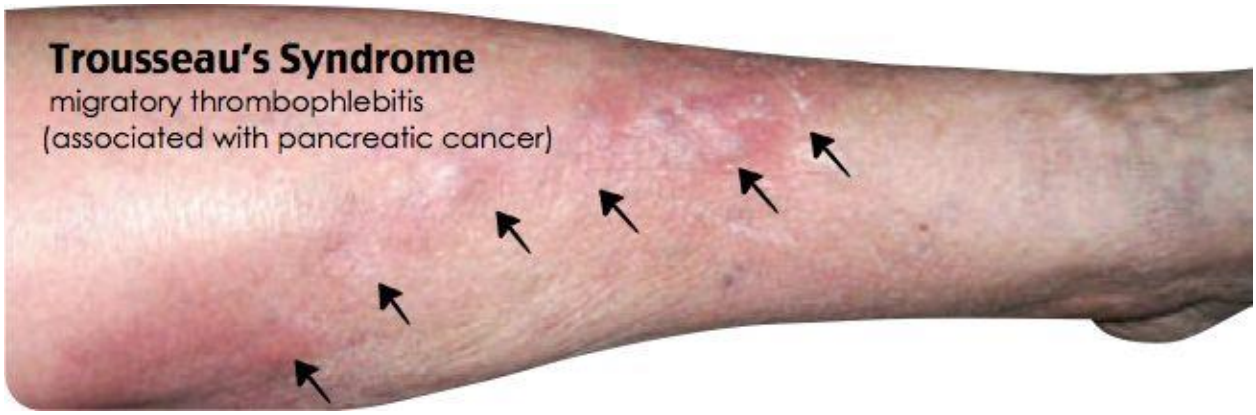
- P Ca typically remains silent until it infiltrates or spreads.

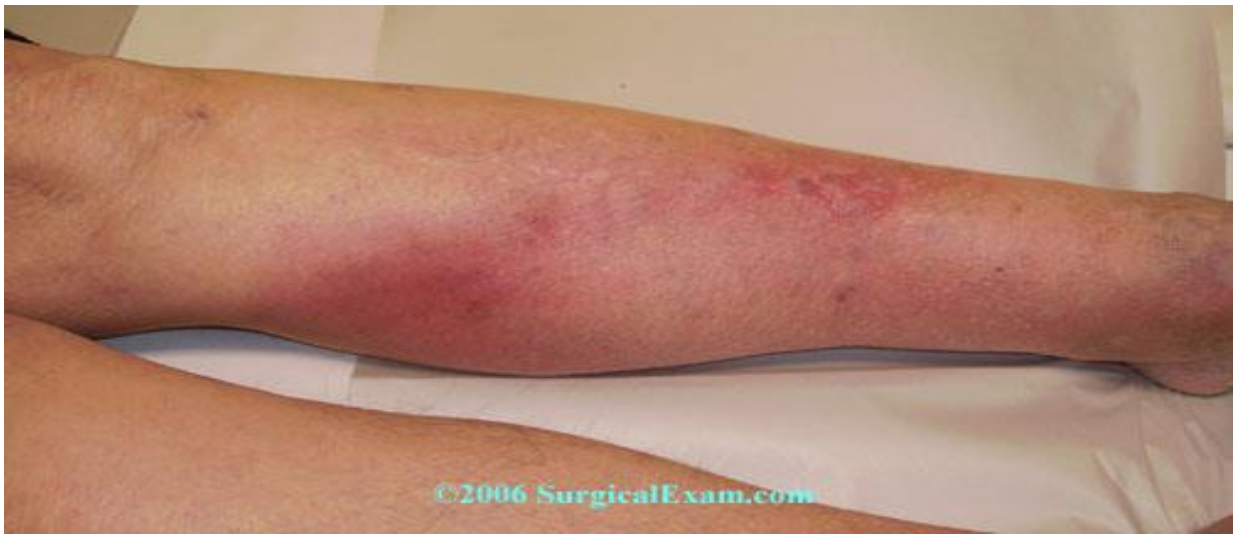
- Pain is usually the first, but unfortunately,
  very late symptom, Obstructive jaundice occurs in 50% of pancreatic head Ca.

- S & S of advanced P Ca include:
  - weight loss,
  - anorexia,
  - malaise &
  -weakness.



- Migratory thrombophlebitis (Trousseau syndrome) occurs in about 10% of patients
  & is due to the elaboration of platelet-aggregating factors & procoagulants from P ca.





- <20% of P Ca are resectable at the time of diagnosis.

- Serum levels of many enzymes & antigens (e.g., CEA & CA19-9 Ag) are elevated,
  but are neither specific nor sensitive to be used as screening tests.

- CT & endoscopic U/S are helpful in the diagnosis & in performing percutaneous needle biopsy,
  but are not useful as screening tests