Hepatobiliary PATHOLOGY

LEC 4

DR. Ayser Hameed Latif

INTRAHEPATIC BILIARY TRACT DISEASE

PRIMARY BILIARY CIRRHOSIS

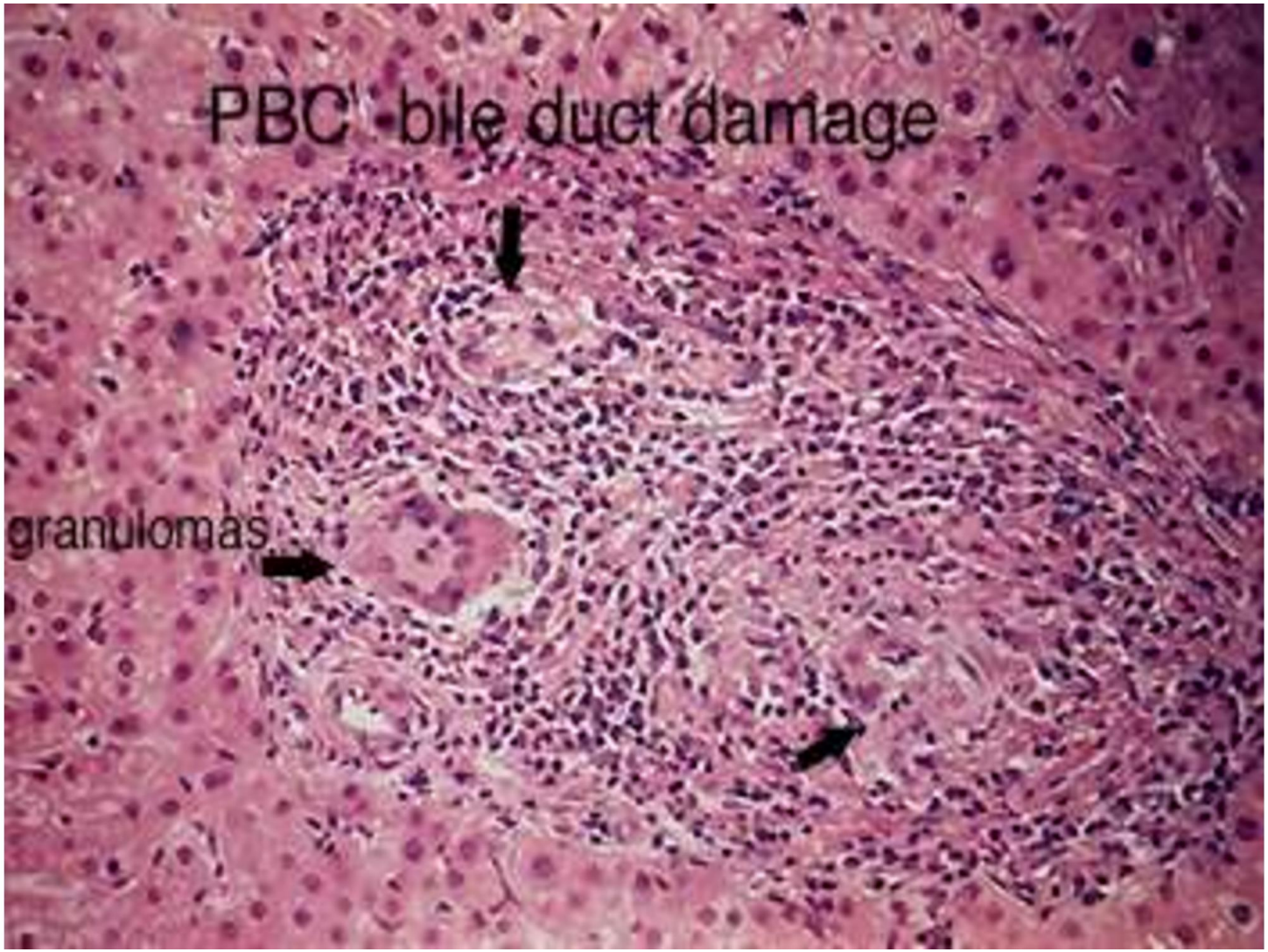
- **Autoimmune disease**
- **Disease of middle-aged women**
- **Associated with other autoimmune disease :Sjogren's, scleroderma, thyroiditis, RA, celiac disease …**
- **Chronic progressive & often fatal cholestatic liver disease, characterized by destruction of small and medium sized intrahepatic bile ducts. Large intrahepatic ducts and the extrahepatic biliary tree are not involved, portal inflammation & scarring**
- **Morphology :** bile ducts are actively destroyed by lymphoplasmacytic inflammation with or without granulomas
- Some biopsy specimens, however, show only absence of bile ducts in portal tracts
- Ductular reactions follow duct injury, and these in turn participate in the development of portal-portal
- septal fibrosis

INTRAHEPATIC BILIARY TRACT DISEASE

PRIMARY BILIARY CIRRHOSIS

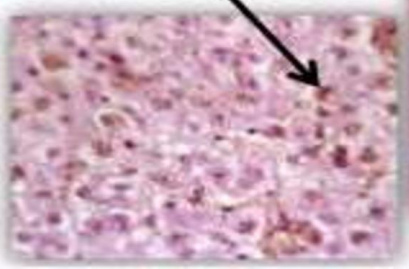
- **Insidious onset: pruritis; later jaundice appears**
- **Cirrhosis & hepatic failure develops over 2 or more decades, with s & s of portal hypertension & hepatic encephalopathy**
- **Lab: ↑ alk. phosph. & cholesterol; bilirubin is a late development, indicating hepatic decompensation**
- **Autoantibodies: anti-mitochondrial Ab in >90% of patients**
- **Rx: Liver transplantation**

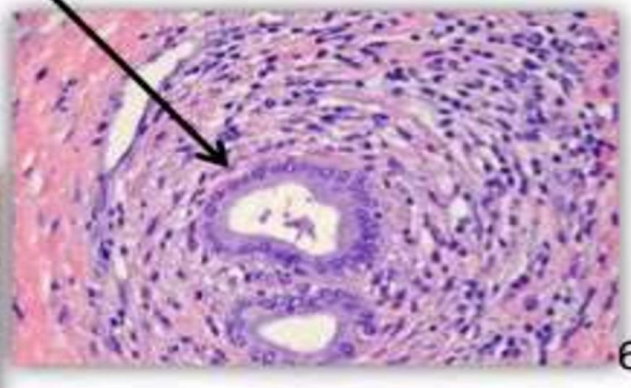
- **Preferred name primary biliary cholangitis as the cirrhosis is a late event**


PBC - bile duct damage
granulomas

Primary Biliary Cirrhosis

- Autoimmune.
- Females 6:1.
- Pruritis, jaundice, hepatosplenomegaly (initial).
- Intrahepatic Bile duct inflammation
- Cholestasis (bile stained liver)





INTRAHEPATIC BILIARY TRACT DISEASE

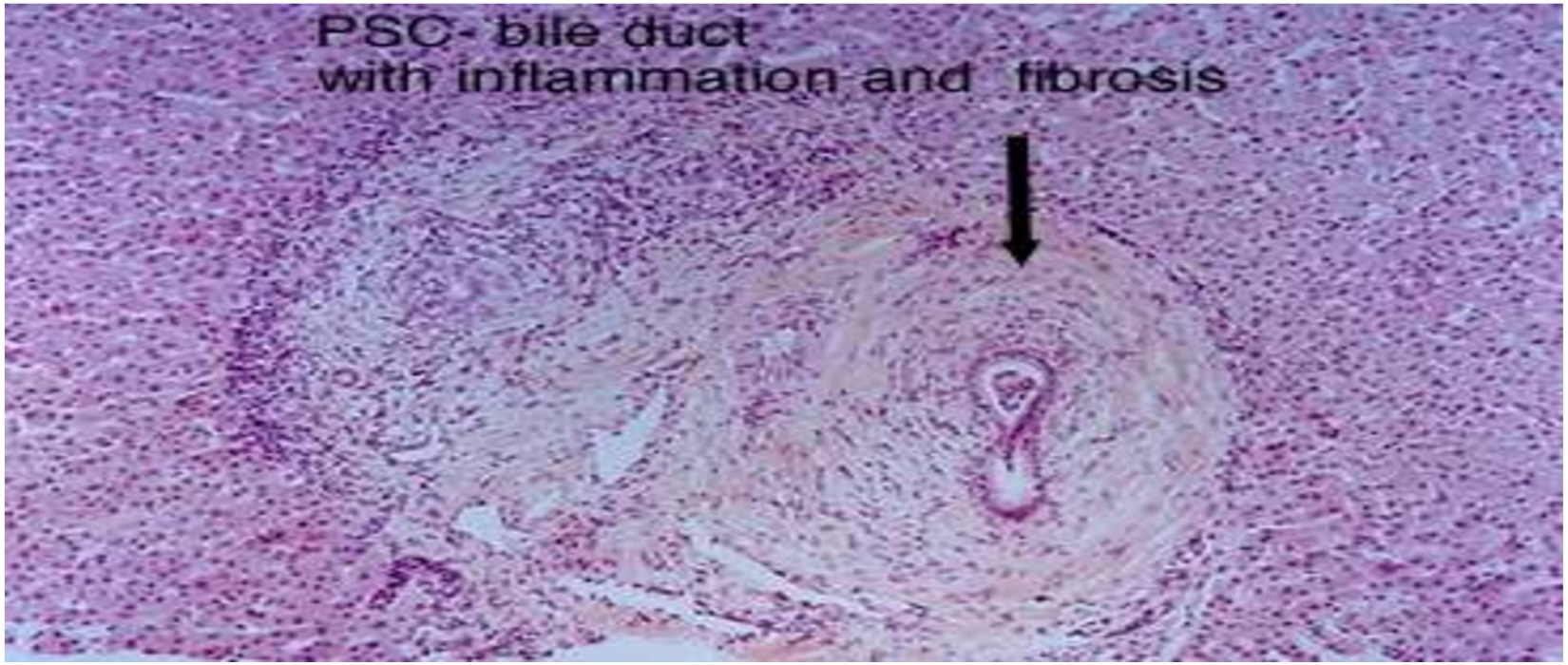
PRIMARY SCLEROSING CHOLANGITIS

- **3rd-5th decades; M:F=2:1**
- **70% of patients have associated ulcerative colitis**
- inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts with dilation of preserved segments ..**Irregular strictures & dilations of affected bile ducts produces characteristic "beading" picture in barium contrast radiography** of the intrahepatic and extrahepatic biliary tree
- **Clinical picture: progressive fatigue, pruritis & jaundice; s & s of chronic liver disease**
- **Lab: ↑alkaline phosphatase**
- **Autoantibodies: <10% of patients**
- **MIC:periductal concentric fibrosis (onion skin)**
- **Px: increased risk of cholangiocarcinoma**
- **Rx: Liver transplantation**

INTRAHEPATIC BILIARY TRACT DISEASE

PRIMARY SCLEROSING CHOLANGITIS

- **Inflammation, obliterative fibrosis & segmental dilation of the obstructed intrahepatic & extrahepatic bile ducts**



Histopathology

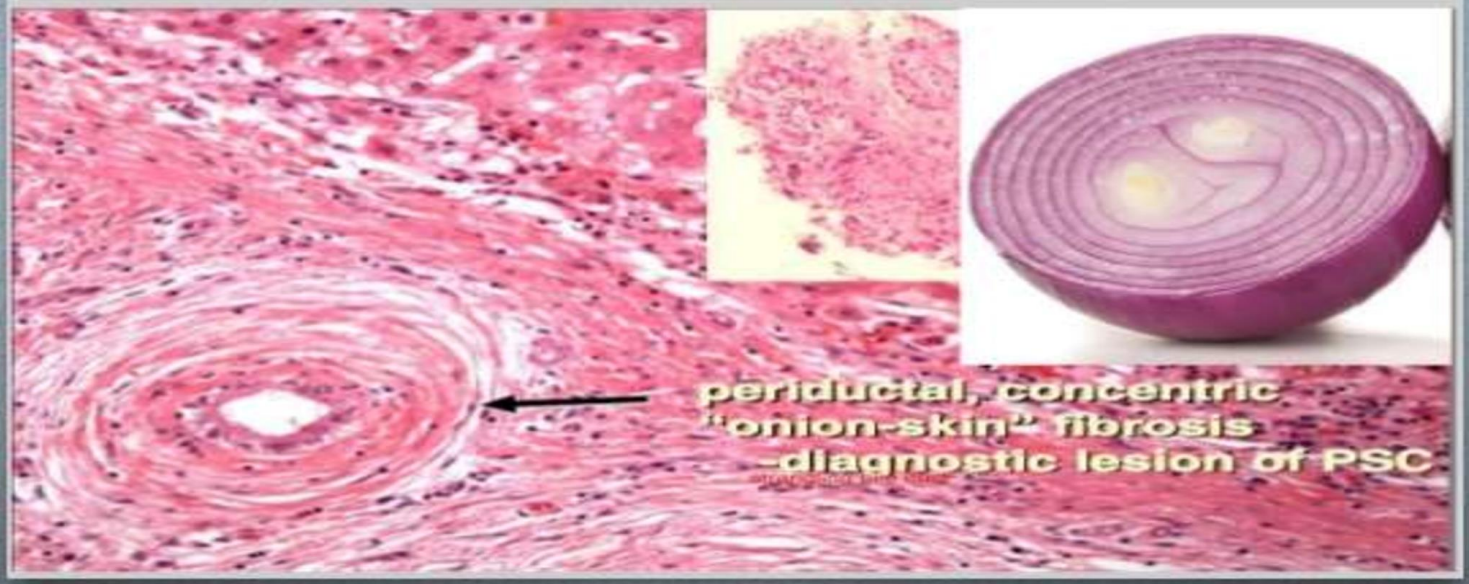


Table 18-11 Main Features of Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

Parameter	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Age	Median age 50 years (30 to 70)	Median age 30 years
Gender	90% female	70% male
Clinical course	Progressive	Unpredictable but progressive
Associated conditions	Sjögren syndrome (70%) Scleroderma (5%) Thyroid disease (20%)	Inflammatory bowel disease (70%) Pancreatitis (≤25%) Idiopathic fibrosing diseases (retroperitoneal fibrosis)
Serology	95% AMA-positive 50% ANA-positive 40% ANCA-positive	0-5% AMA-positive (low titer) 6% ANA-positive 65% ANCA-positive
Radiology	Normal	Strictures and beading of large bile ducts; pruning of smaller ducts
Duct lesion	Florid duct lesions and loss of small ducts only	Inflammatory destruction of extrahepatic and large intrahepatic ducts; fibrotic obliteration of medium and small intrahepatic ducts

AMA, Antimitochondrial antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody.

INTRAHEPATIC BILIARY TRACT DISEASE

SECONDARY BILIARY CIRRHOSIS

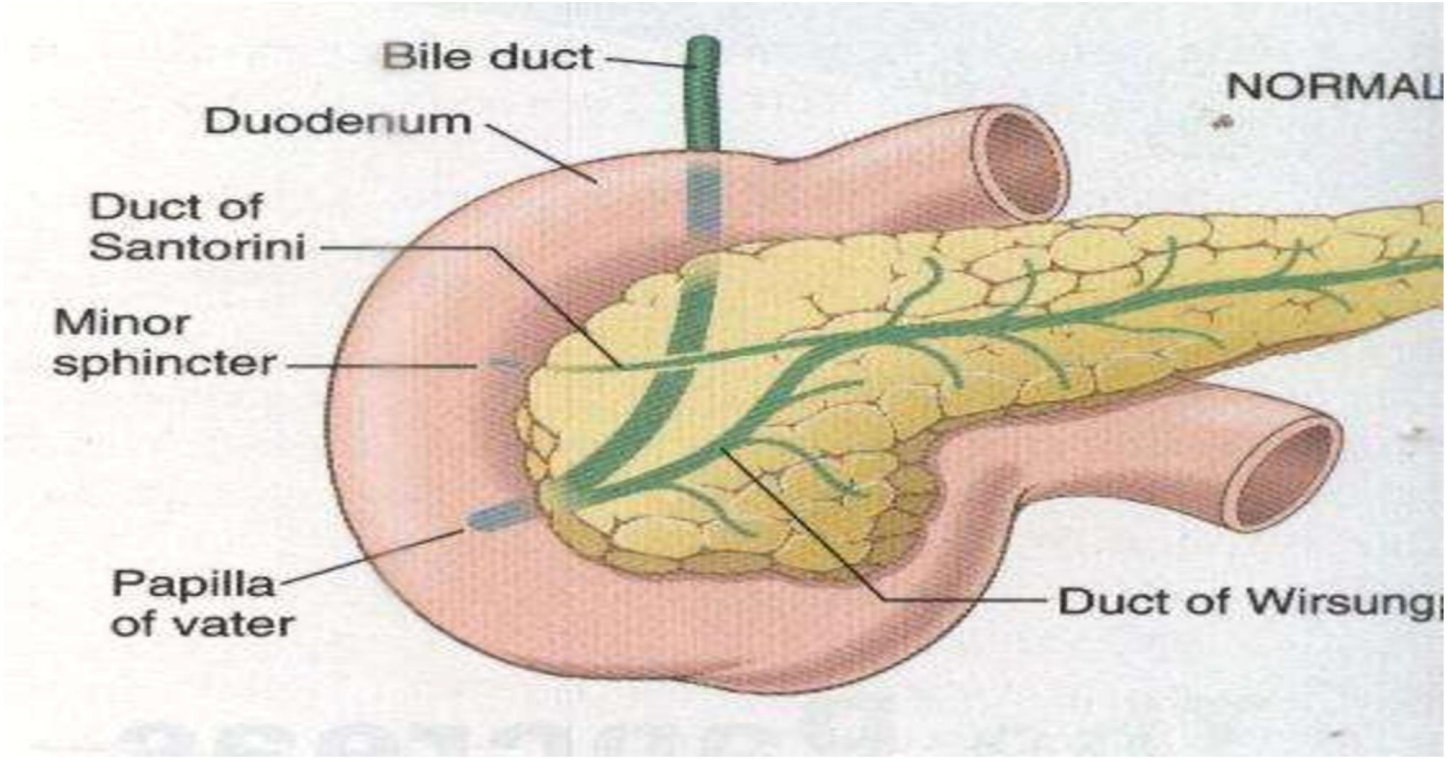
- **Prolonged obstruction to extrahepatic biliary tree results in profound damage to the liver**
- **Causes:**
  - **1) Extrahepatic cholelithiasis**
  - **2) Biliary atresia**
  - **3) Tumors of biliary tree & pancreas head**
  - **4) Strictures secondary to previous surgery**
- **Pathology:**
  - **Initially, reversible features of cholestasis**
  - **Periportal fibrosis, scarring, & nodule formation**
- **Subtotal obstruction causes secondary ascending cholangitis, mostly due to coliforms & enterococci**

TABLE 18-11 -- Distinguishing Features of the Major Intrahepatic Bile Duct Disorders

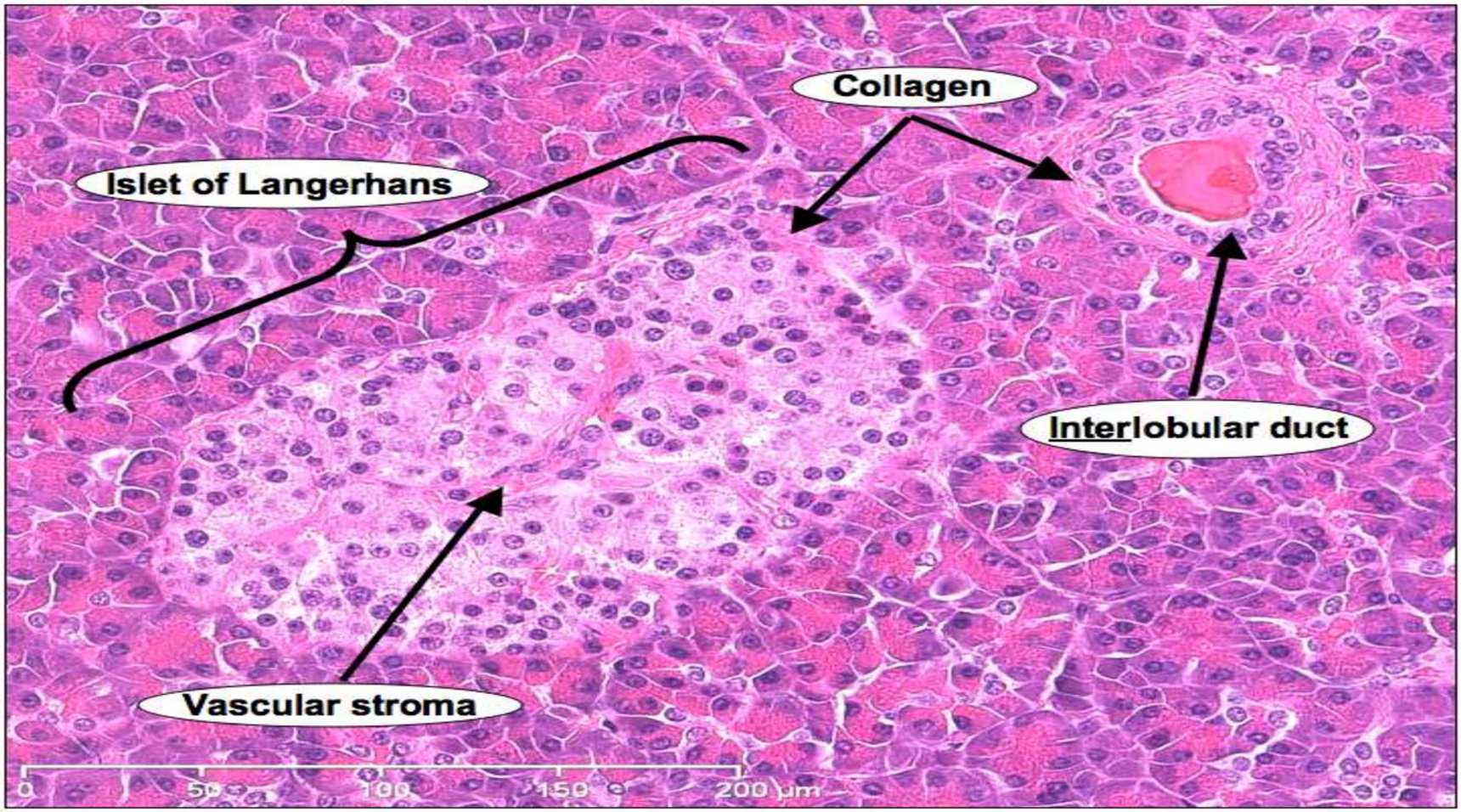
	Secondary Biliary Cirrhosis	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head	Possibly autoimmune	Unknown, possibly autoimmune; 50–70% associated with inflammatory bowel disease
Sex predilection	None	Female to male: 6:1	Female to male: 1:2
Symptoms and signs	Pruritus, jaundice, malaise dark urine, light stools, hepatosplenomegaly	Same as secondary biliary cirrhosis; insidious onset	Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol	Same as secondary biliary cirrhosis, plus elevated serum IgM autoantibodies (especially M2 form of antimitochondrial antibody-AMA)	Same as secondary biliary cirrhosis, plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts	Periductal portal tract fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

Pancreas pathology

Pathology of pancreas



Normal pancreas


Collagen
Islet of Langerhans
Interlobular duct
Vascular stroma
0
50
100
150
200 µm

Pathology of exocrine Pancreas:

The most common 3 pathological conditions that affect the exocrine pancreas are including.

1. **Acute pancreatitis.**
2. **Chronic pancreatitis.**
3. **Carcinoma of pancreas.**

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Acute Pancreatitis :

- Def :inflammation of the pancreas, almost always associated with acinar cells injury.

Causes of acute pancreatitis.

- Metabolic causes. Include (alcohol, hyperlipoproteinemia, Hypercalcemia, drugs like thiazide diuretics & genetics).
- Mechanical causes. Include gallstones, trauma & surgery injury.
- *lead to temporary obstruction of the pancreatic duct at the ampula of vater with reflux of infected bile that preincubated with trypsin lead to ductal inflammation & necrosis*
- Vascular causes. Include shock, atheroembolism, and polyarteritis nodosa.
- Infectious causes. Mumps, coxsackievirus & Mycoplasma.

- Most common causes of acute pancreatitis are :
- gallstones & alcoholism,
- which together are responsible for approximately 80% of cases,

Pathogenesis of acute pancreatitis.

Pathological changes of acute pancreatitis are due to two mechanisms

1.Autodigestion of the pancreatic substances by inappropriately activated pancreatic enzymes.

Under normal condition, These enzymes are produced & stored by the acinar cells of exocrine pancreas in forms of Proenzymes. Which convert into enzymes upon the stimuli of secretion, then these enzymes are secreted into the duodenal lumen for digestion of food inside the intestine. (major stimuli is trypsin).

In acute pancreatitis, proenzymes are activated into enzymes & escape from their granules within the acinar cells. These activated enzymes cause disintegration of acinar cells & fatty tissue in & around the pancreas, damaging the blood vessels & leading to vascular leakage (Acute hemorrhagic pancreatitis).

2.Cellular injury response mediated by proinflammatory cytokines.

These cytokines are secreted by injured acinar cells ……..attract neutrophils, macrophages…… These inflammatory cells release more cytokines such as tumor necrosis factor(TNF), interlukin-1, nitric oxide, platelets activating factor into the pancreatic tissue & circulation which in turn amplifying the local & systemic inflammatory response.

Acute pancreatitis occurs due to 2 important pathogenetic factors:

1. **Pancreatic duct obstruction**: Common causes of obstruction are **gallstones,** which are usually **impacted at ampulla of vater (in 75%-80% of cases)**.

The degrees of pancreatic injury appear to be proportional to the **duration of obstruction**.

2. **Primary acinar cells injury**. (by viruses like Mumps, drugs & after trauma).

Symptoms of acute pancreatitis

1. **Abdominal pain (epigastric pain). Sudden acute abdominal pain , vomiting & Easily confused with perforated peptic ulcer**
2. **Shock.**
3. **Hypocalcemia because calcium bind to fatty acids released by pancreatic enzymes from abdominal fat.**
4. **Biochemical tests.**

Elevated serum level of amylase (one of pancreatic enzymes) which increase within 12hr & decreased within 48hrs - 72hrs.

Also **serum level of lipase** is increased & remains high for 7 – 10 days.

Causes of death in acute pancreatitis:

- 1. Shock
- 2. Secondary abdominal sepsis
- 3. Acute respiratory distress syndrome(ARDS).

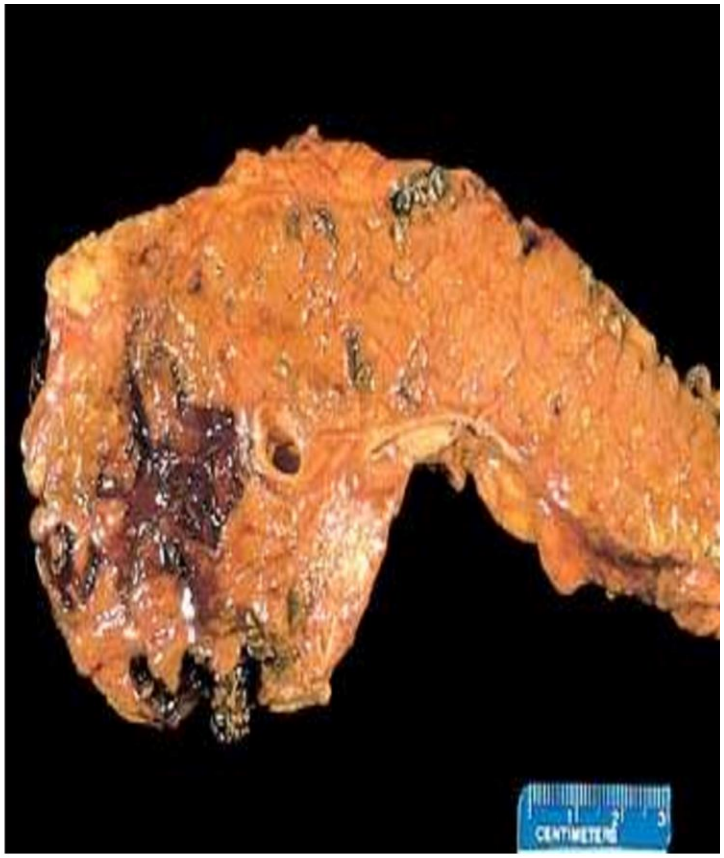
Morphology of acute pancreatitis:

Gross. In acute hemorrhagic pancreatitis (most severe form): characterized by

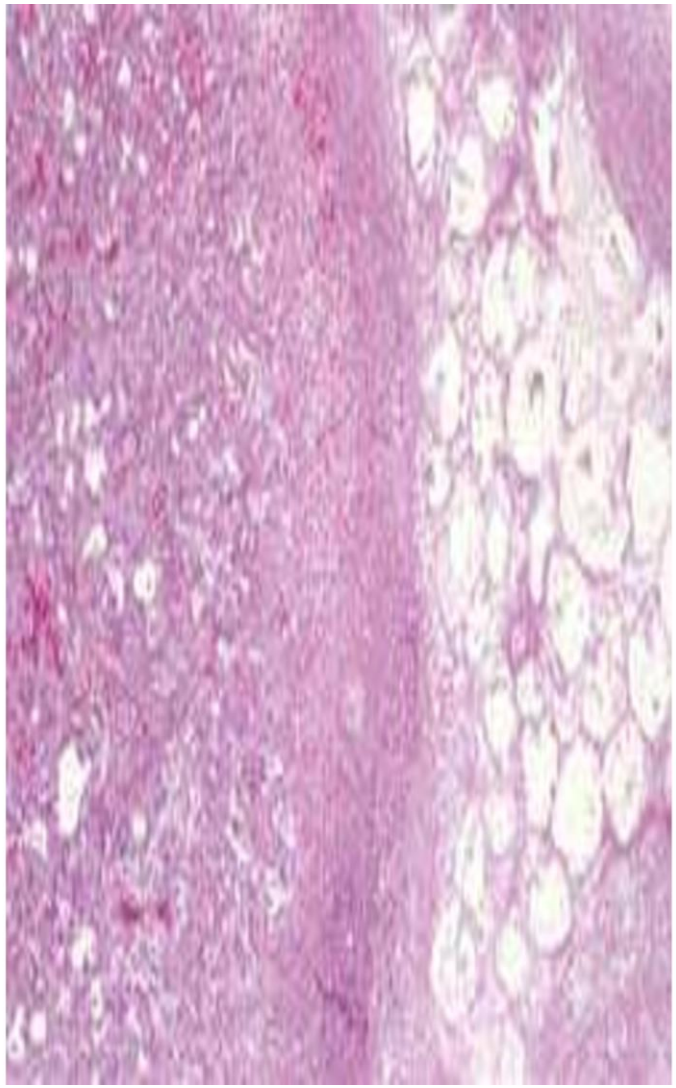
- Areas of blue – black **hemorrhage interspersed by**
- areas of grey – white **necrotic softening &**
- areas of **white – chalky fat necrosis.**

- **Mic.**
- **EDEMA**
- **FAT NECROSIS**
- **ACUTE INFLAMMATORY INFILTRATE**
- **PANCREAS AUTODIGESTION**
- **BLOOD VESSEL DESTRUCTION**
- **"SAPONIFICATION" (Na+, Ca++)**
- the most characteristic histological lesions of acute pancreatitis are the **focal areas of fat necrosis that occur in stromal, peripancreatic fat & in fat deposits throughout the abdominal cavity (by lipase).**

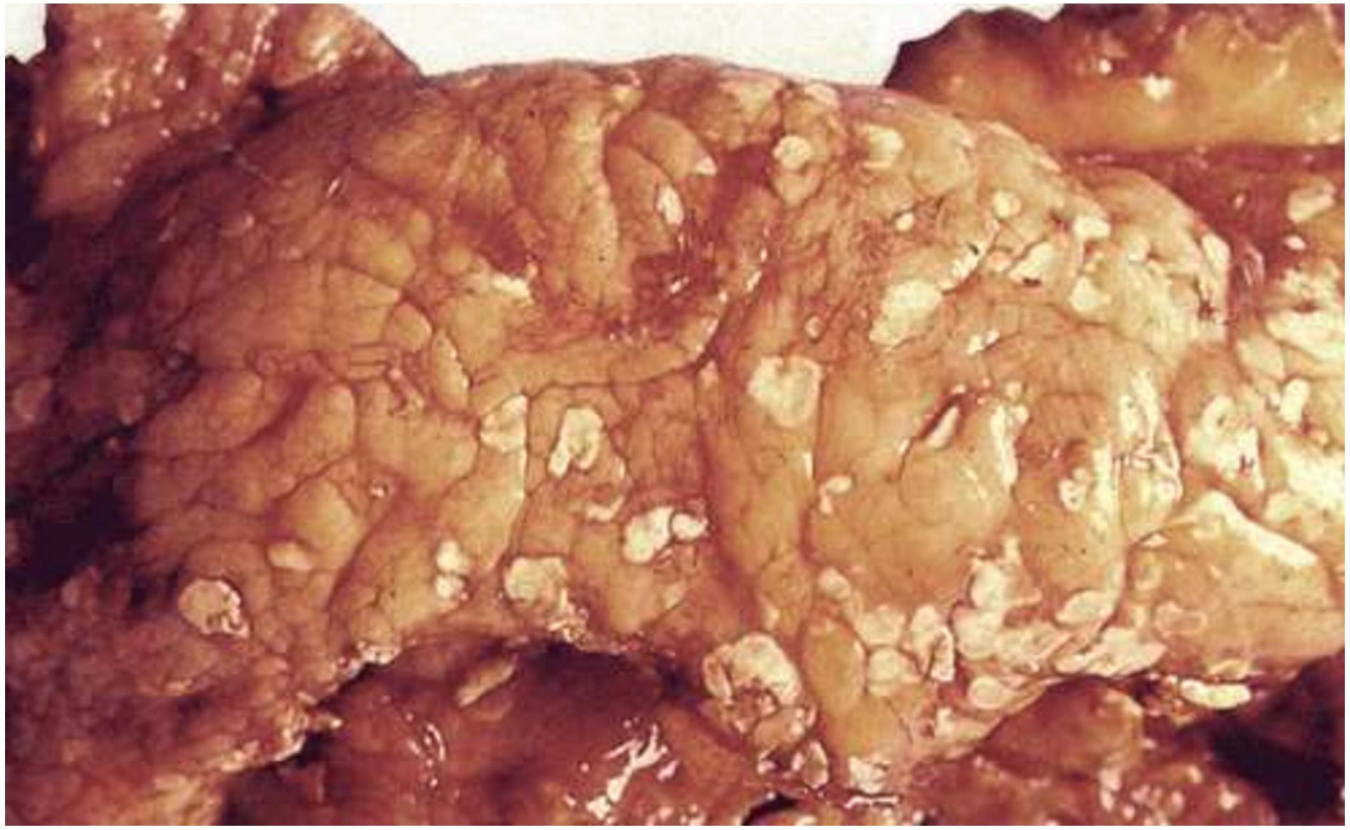
Acute pancreatitis.pancreas has been sectioned longitudinally to reveal dark areas of hemorrhage in the pancreatic substance and a focal area of pale fat necrosis in the peripancreatic fat (upper left).



Acute pancreatitis. The microscopic field shows a region of fat necrosis (right) and focal pancreatic parenchymal necrosis (center).



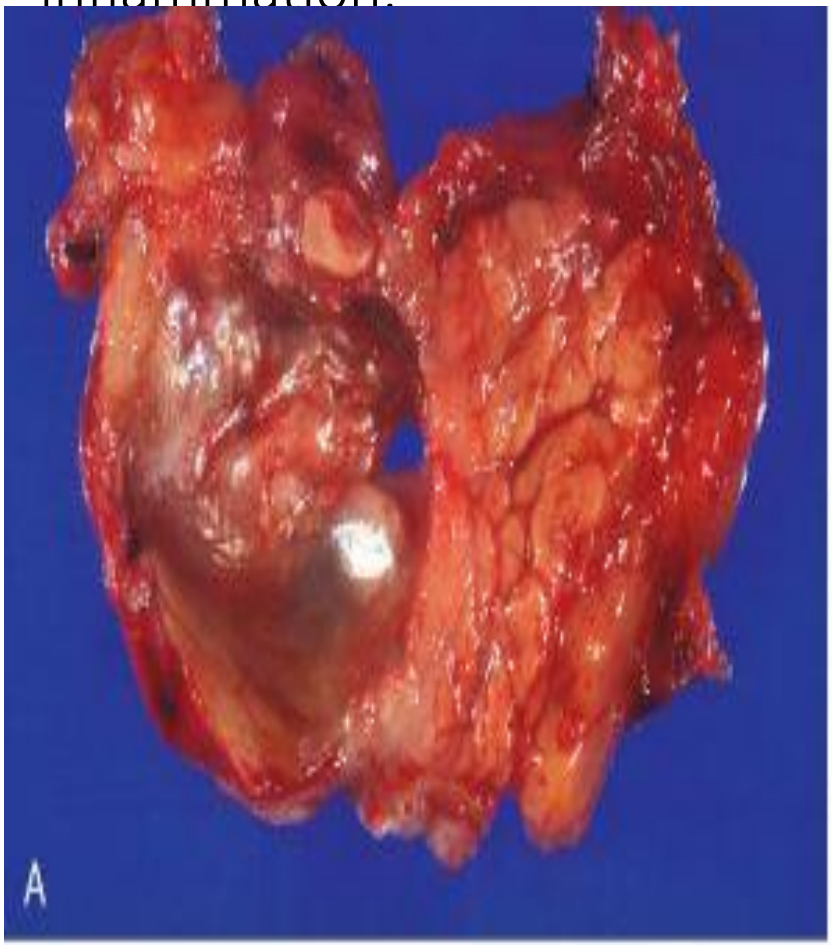
Enzymatic fat necrosis

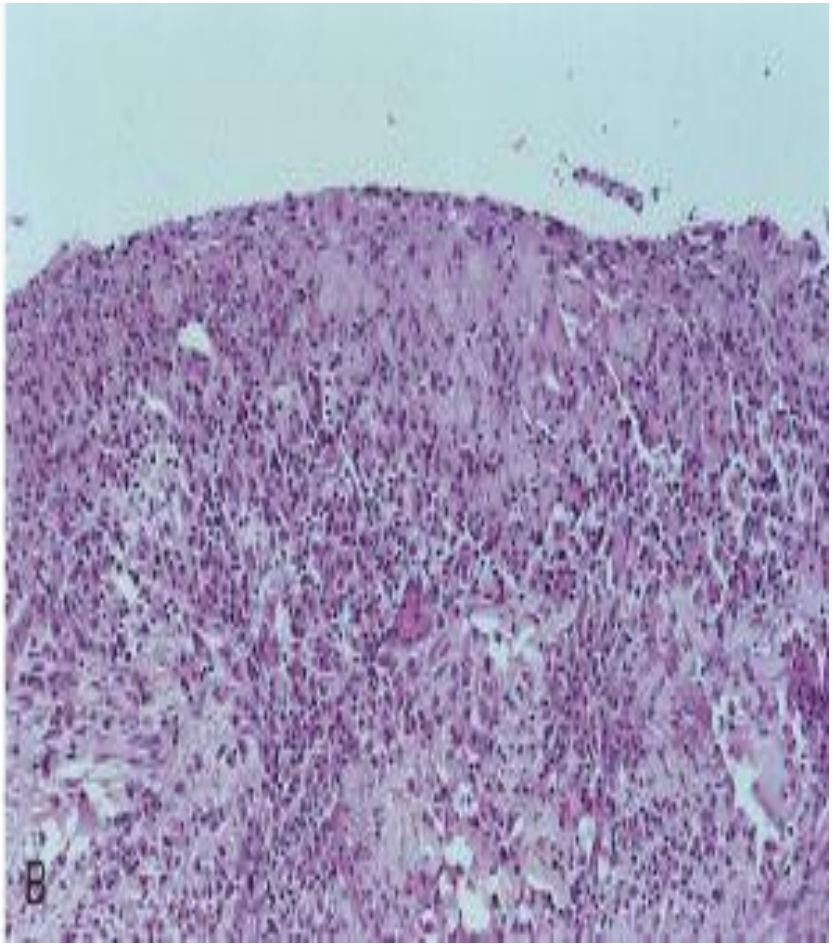


Common sequel of acute pancreatitis

- **is a Pancreatic Pseudocyst.**
- **Which is liquefied areas of necrotic pancreatic tissue are walled off by fibrous tissue to form a cystic spaces which does NOT contain an epithelial lining.**

Pancreatic pseudocyst. (A) Cross-section revealing a poorly defined cyst with a necrotic brownish wall. (B) Histologically, the cyst lacks an epithelial lining and instead is lined by fibrin and granulation tissue, with typical changes of chronic inflammation.





***Complications*:**

- Chemical peritonitis.
- Endotoxic shock & death(mortality rate 50%)

.Local sepsis & pancreatic abscess by E.Coli infection.

- Pseudocyst in the lessor sac due to impaired pancreatic secretion & debris leads to its accumulation.

Chronic pancreatitis:

repeated bouts of mild to moderate pancreatic inflammation, with continued loss of pancreatic parenchyma & replacement by fibrous tissue.

Causes:

1. **Gallstones** (important role than in acute pancreatitis).
2. **hypercalcemia.**
3. **hyperlipoprpteinemia.**
4. **50% of cases are idiopathic.** (1/3 of cases have cystic fibrosis).

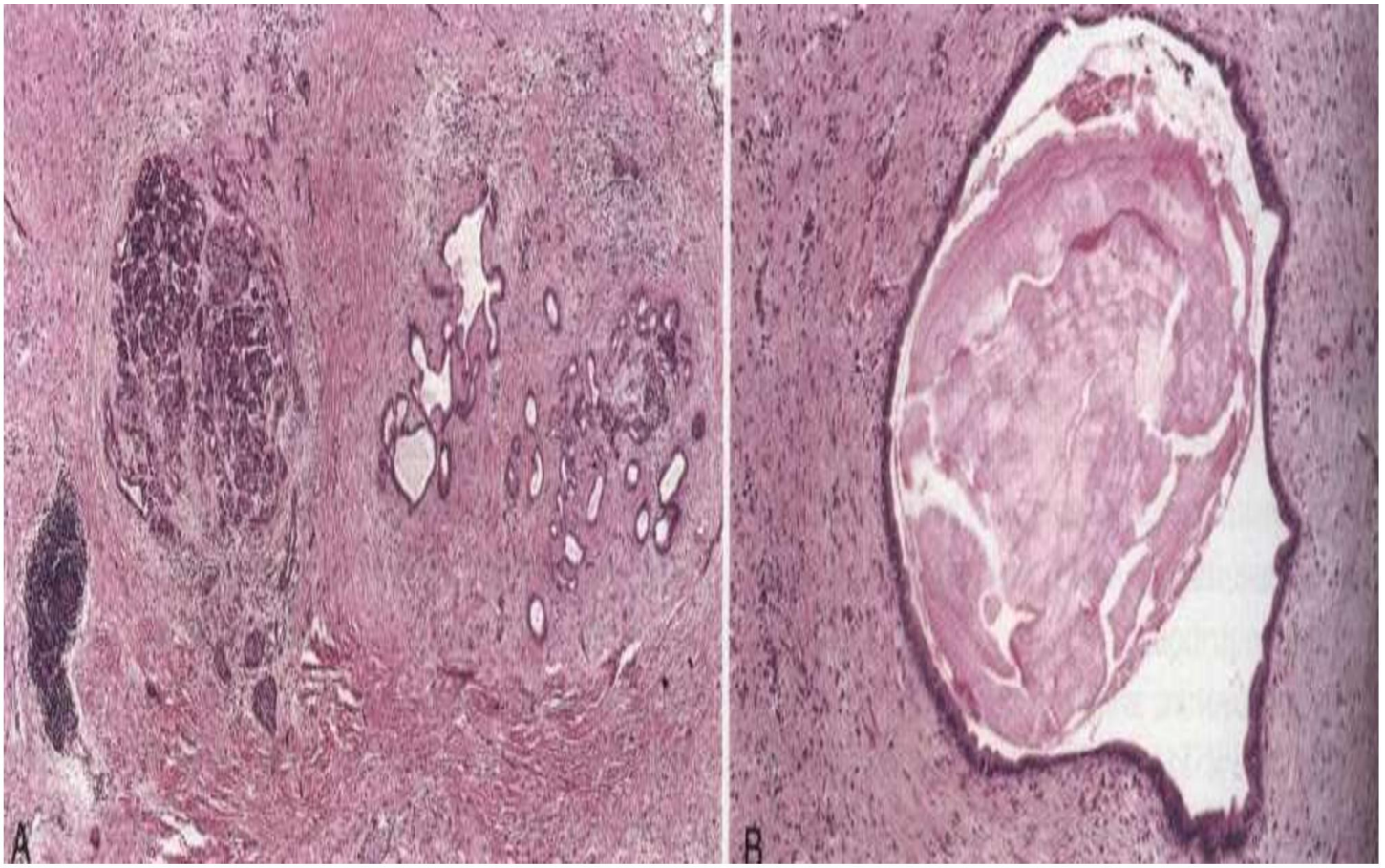
alcohol abuse with high protein diet as alcohol increases the protein concentration in the pancreatic juice with subsequent precipitation of concretions in the ducts. Lead to stones that ulcerate the ductal epithelium lead to periductal inflammation & fibrosis ends with ductal stricture & acinar atrophy behind the stricture.

Grossly

- *Firm pancreas, Cut section shows smooth, grey with loss of normal lobulation due to diffuse fibrosis. Focal dilatation of the main duct, cyst like contains calcified stones.*

Microscopically:

- *Early ductal stricture with the presence of protein precipitate & inflammation in the duct which calcify & enlarge to form stones that cause obstruction leads to atrophy of the ducts.*
- *Late periductal fibrosis leads to destruction of the islets by ischemia result in diabetes mellitus.*



Chronic pancreatitis

Biochemical tests:

May be **there is mild increase in serum level of amylase & lipase**.

Complications of chronic pancreatitis:

1. **Malabsorption syndrome:** (lack of digestive pancreatic enzymes).
2. **Diabetes mellitus**. (destruction of islet cells that secrete insulin).

Morphology of chronic pancreatitis:

Gross: fibrotic organ with extensive **atrophy of exocrine glands, visible calcification, pseudo cysts.**

Mic. chronic inflammatory cells infiltrate around lobules & ducts. & there is variable destruction of pancreatic ducts.

Carcinoma of pancreas:

It is referred to cancer of exocrine part of pancreas. (More in western countries).

Male more than female.

Increase in the incidence after the age of 50 years.

Related to smoking , high fatty & protein diet

Etiology (causes):

1. Smoking.
2. Alcoholic.
3. Hereditary pancreatitis (increase the risk by 40 folds).
4. Mutation in cancer associated genes. Like K-ras mutations are present in 90% of cases. While p53 genes mutations are found in 50% of cases.
5. Obesity.
6. beta-naphthylamine or benzidine exposure.

- Carcinoma of body & tail of pancreas do NOT obstruct the biliary tree & hence remain silent for some time. They may be quite large & widely disseminated by the time they discovered.
- Carcinoma of pancreas is highly invasive cancer. Involve the surrounding organs, & distant metastasis occur principally to lung & bones.

Symptoms:

Usually remain silent until extend into other tissues.

Invade the posterior abdominal wall nerves cause severe backache.

obstructive jaundice (painless jaundice).

Migratory thrombophlebitis. Which is spontaneous occurring phlebothrombosis specially in cases of body & tail cancers.

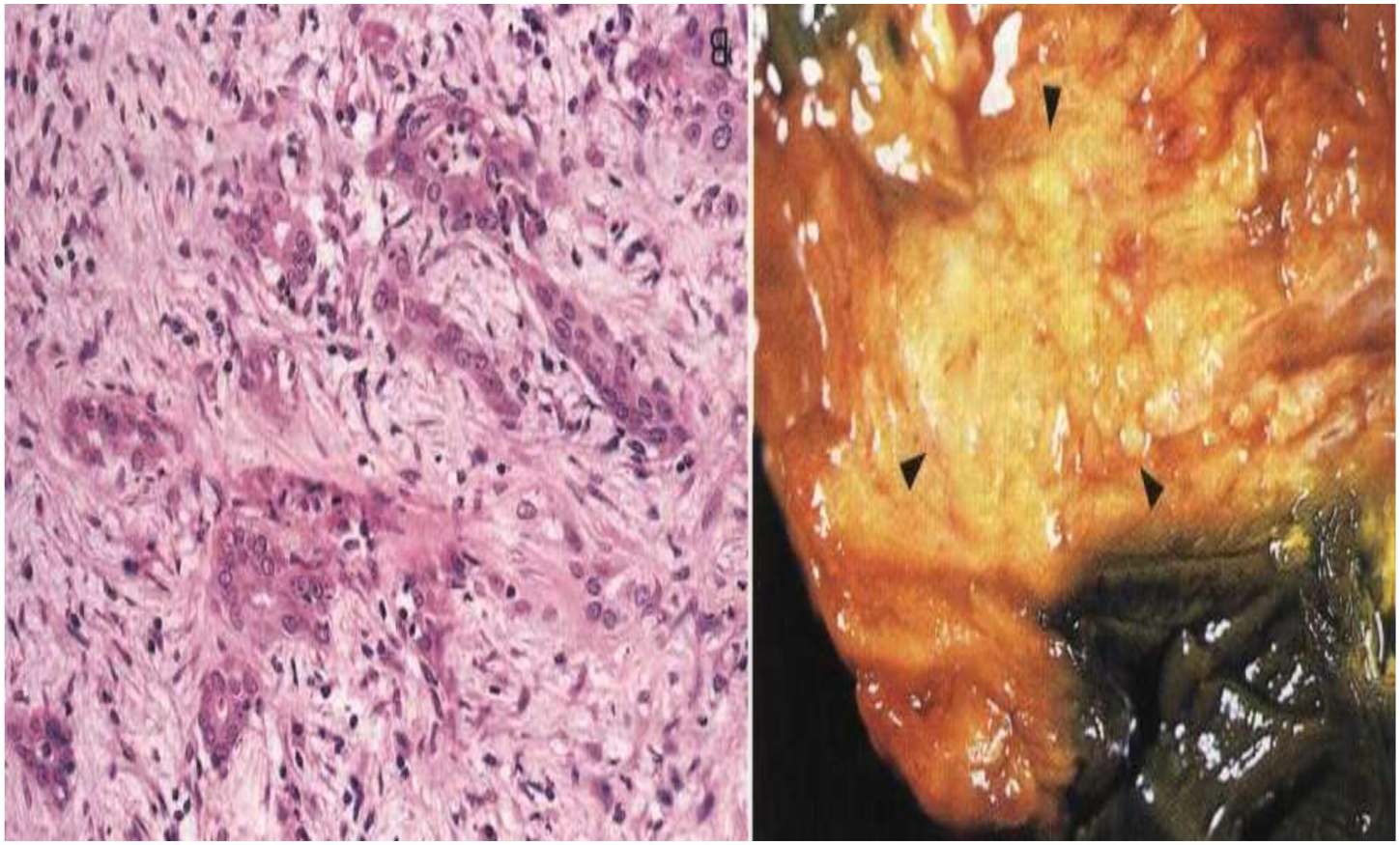
Biochemical tests:

Increase serum level of carcinoembryonic (CEA), CA19-9 antigens.

Morphology of pancreatic carcinoma:

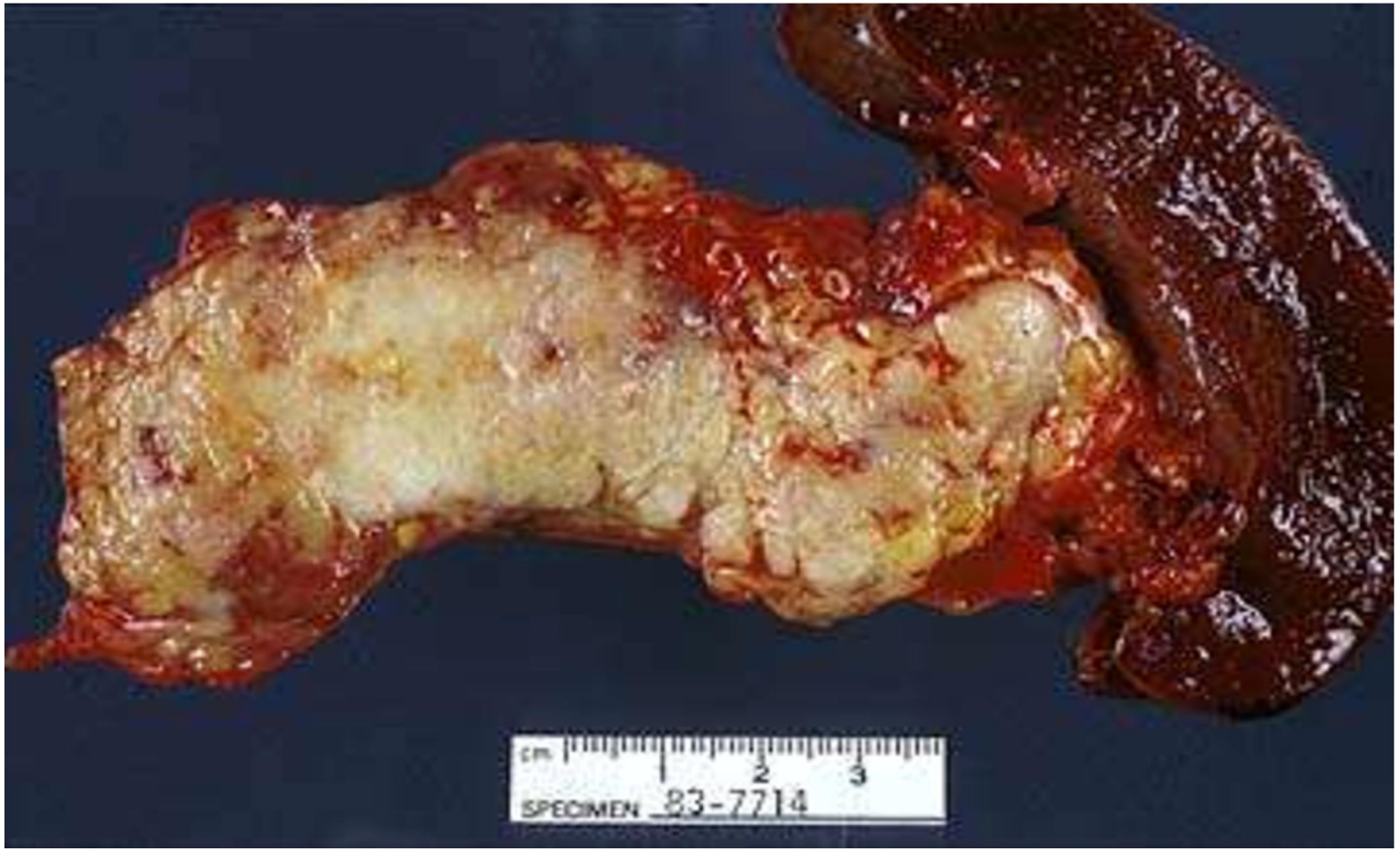
- **Gross:**
  - Poorly defined, gritty, gray-white, hard masses.
  - 20% have multiple tumors.

- **Mic.**
- Most of cases are **adenocarcinoma** arise from ductal epithelium.
- they are mucinous or non- mucinous secreting. Many cases have abundant fibrous stroma (desmoplastic lesion).
- Common **perineural invasion** which is diagnostic for malignancy.
- **Prognosis,** extremely bad, 90% of the patient not surviving for 6 months.
- **Tumors of the endocrine pancreas:** Islet cell tumors either benign (Insulinoma & Gastrinoma) or malignant neuroendocrine tumors.



Poorly differentiated Aenocarcinoma of pancreas

Adenocarcinoma replacing tail and body of pancreas. **Whitish firm mass**



Malignant glands in pancreatic adenocarcinoma.