

College of medicine
Department of pathology
3rd year

Hepatobiliary system

LEC. 5

Dr. Methaq Mueen

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

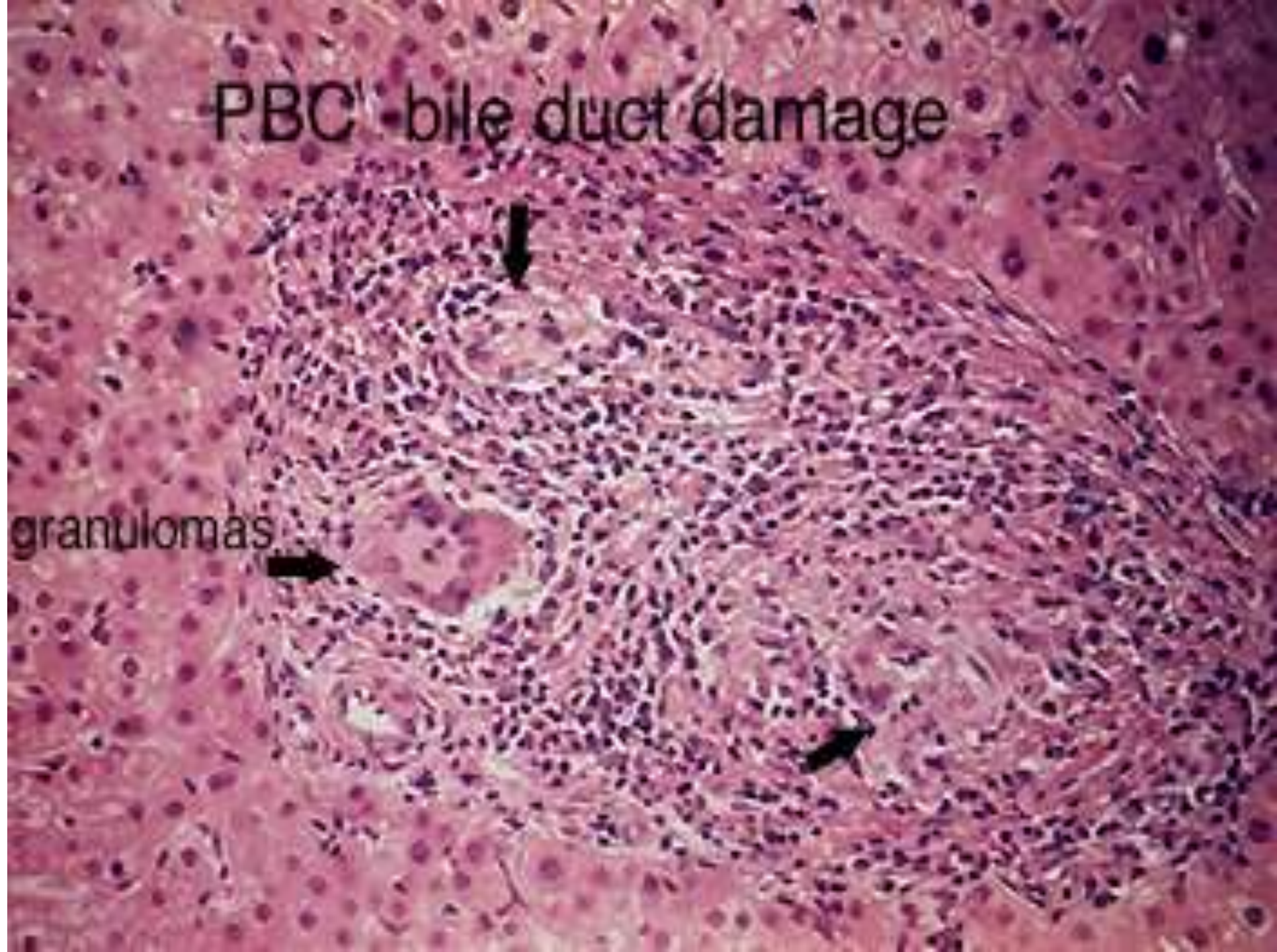
INTRAHEPATIC BILIARY TRACT DISEASE

PRIMARY BILIARY CIRRHOSIS

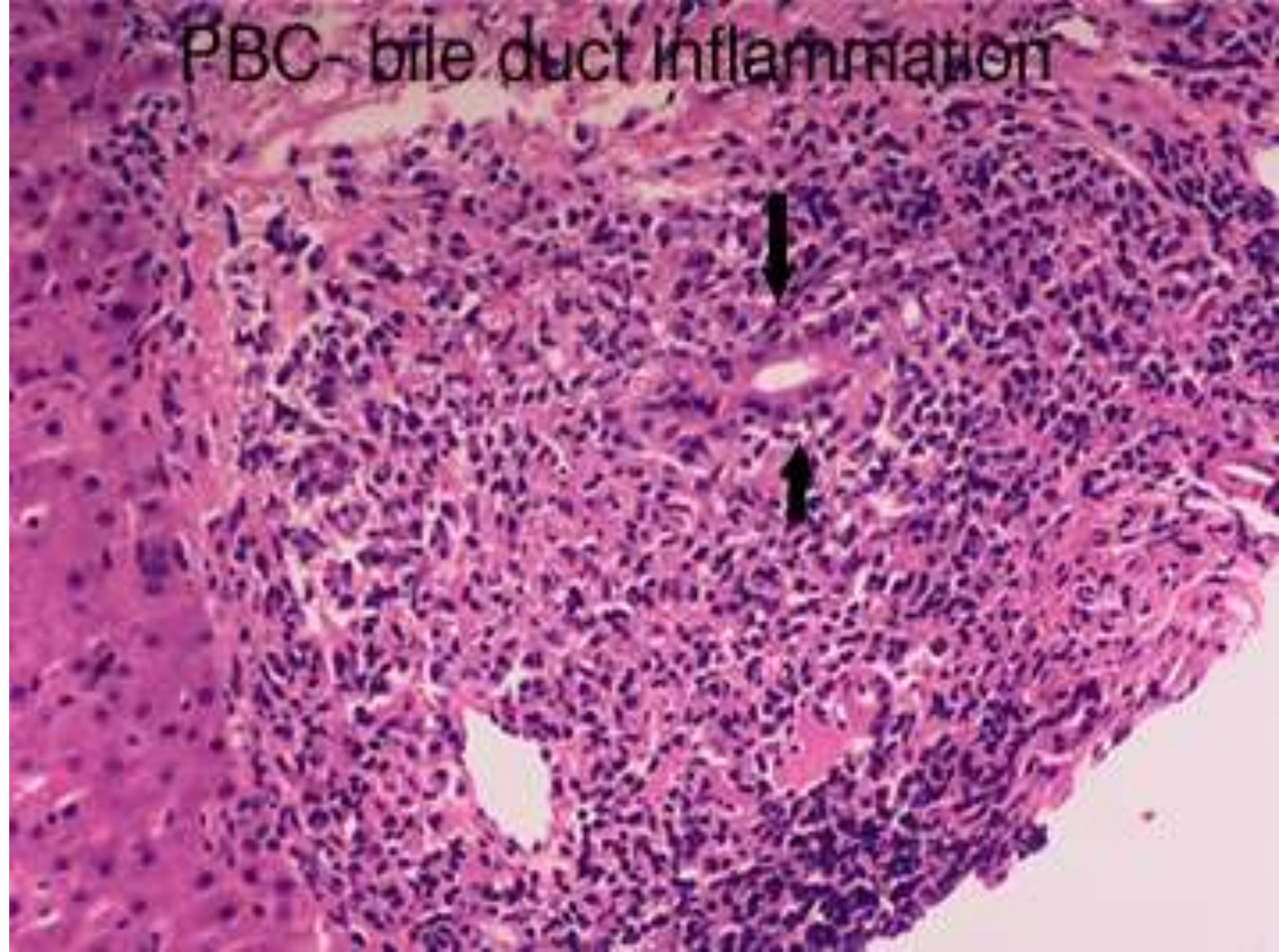
- **Insidious onset:** **pruritis**; **later jaundice** appears
 - **Cirrhosis & hepatic failure** develops over 2 or more decades, with s & s of portal hypertension & hepatic encephalopathy
 - **Lab:** ↑ alk. phosph. & cholesterol; bilirubin is a late development, indicating hepatic decompensation
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

PBC bile duct damage

granulomas



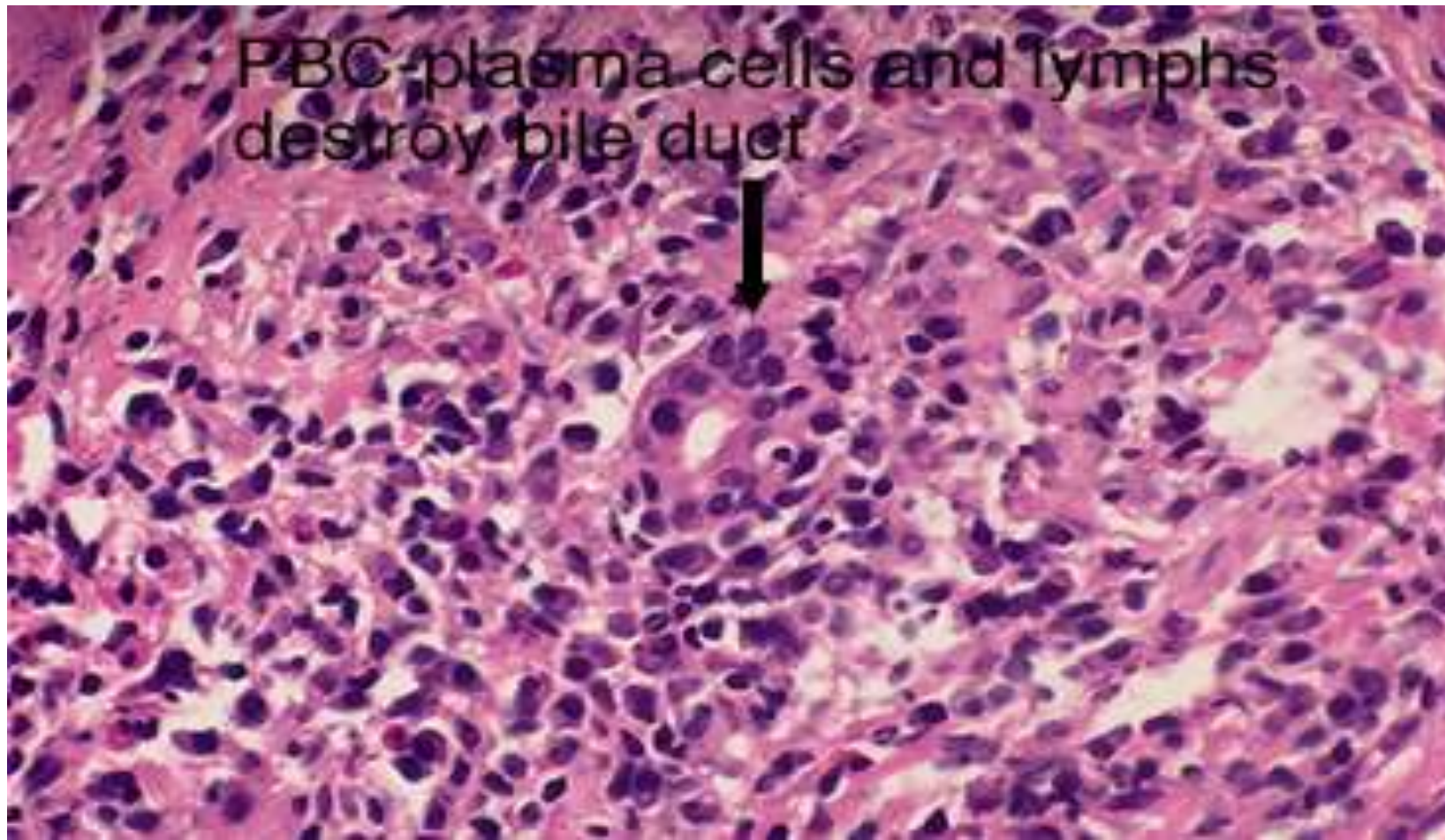
PBC- bile duct inflammation



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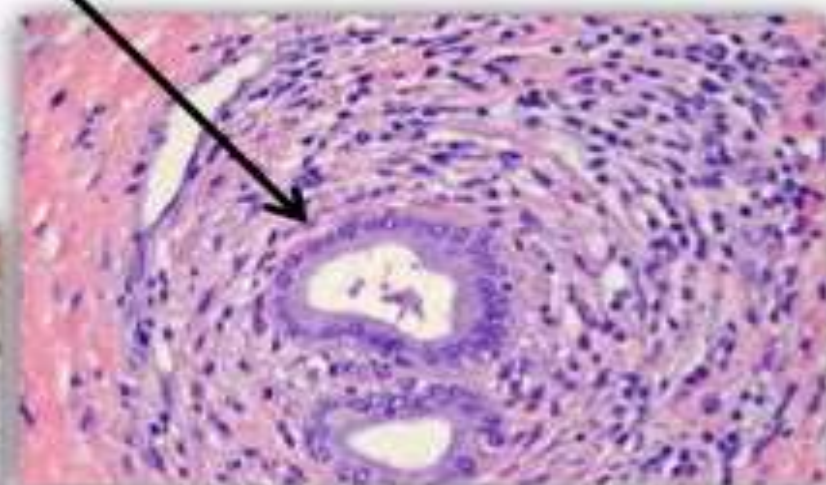
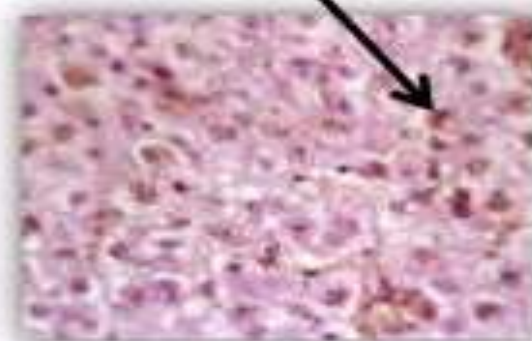
PRIMARY BILIARY CIRRHOSIS

- **Autoimmune disease involving lymphocyte-mediated destruction of bile duct epithelium**



Primary Biliary Cirrhosis

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

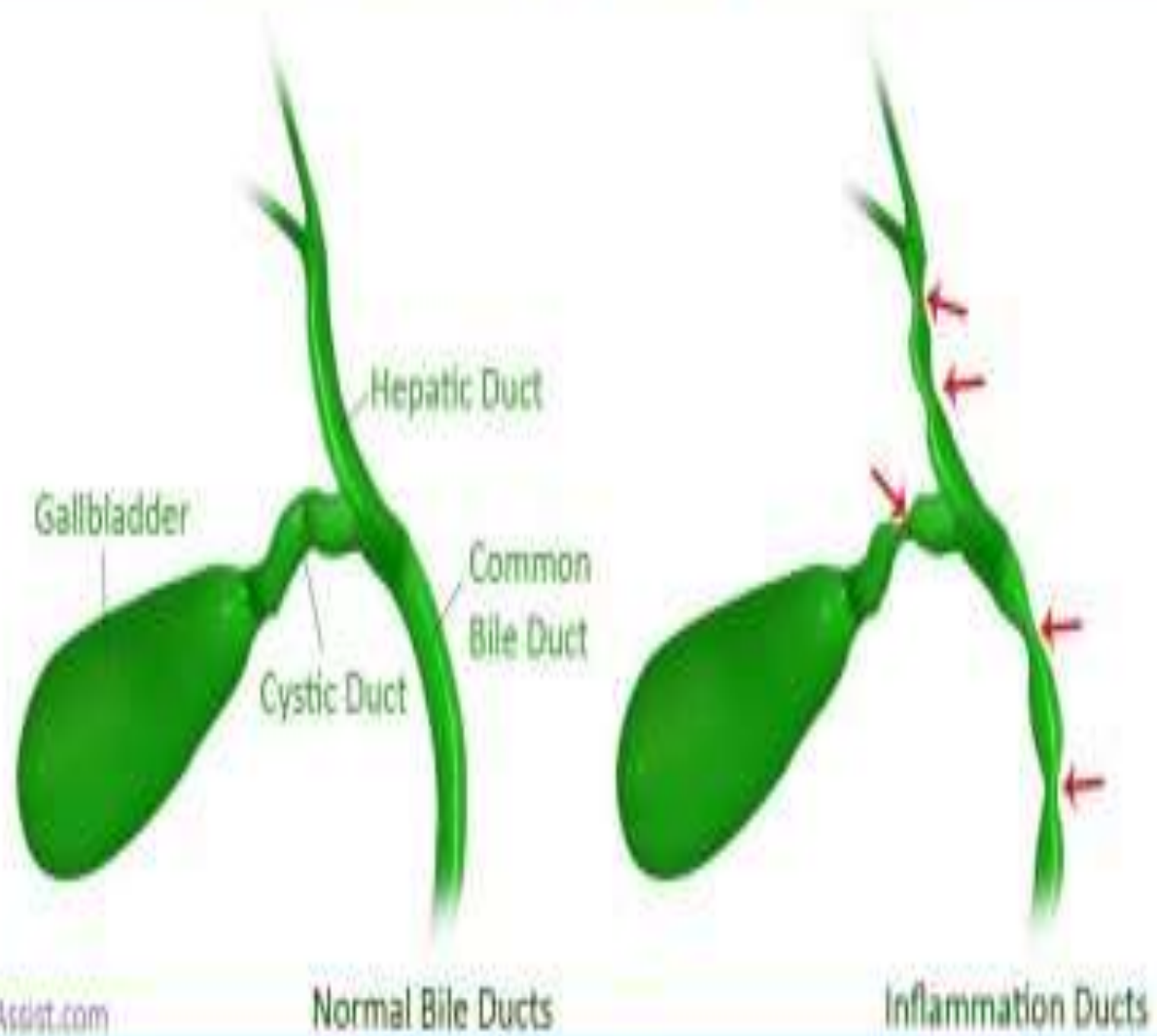


INTRAHEPATIC BILIARY TRACT DISEASE

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

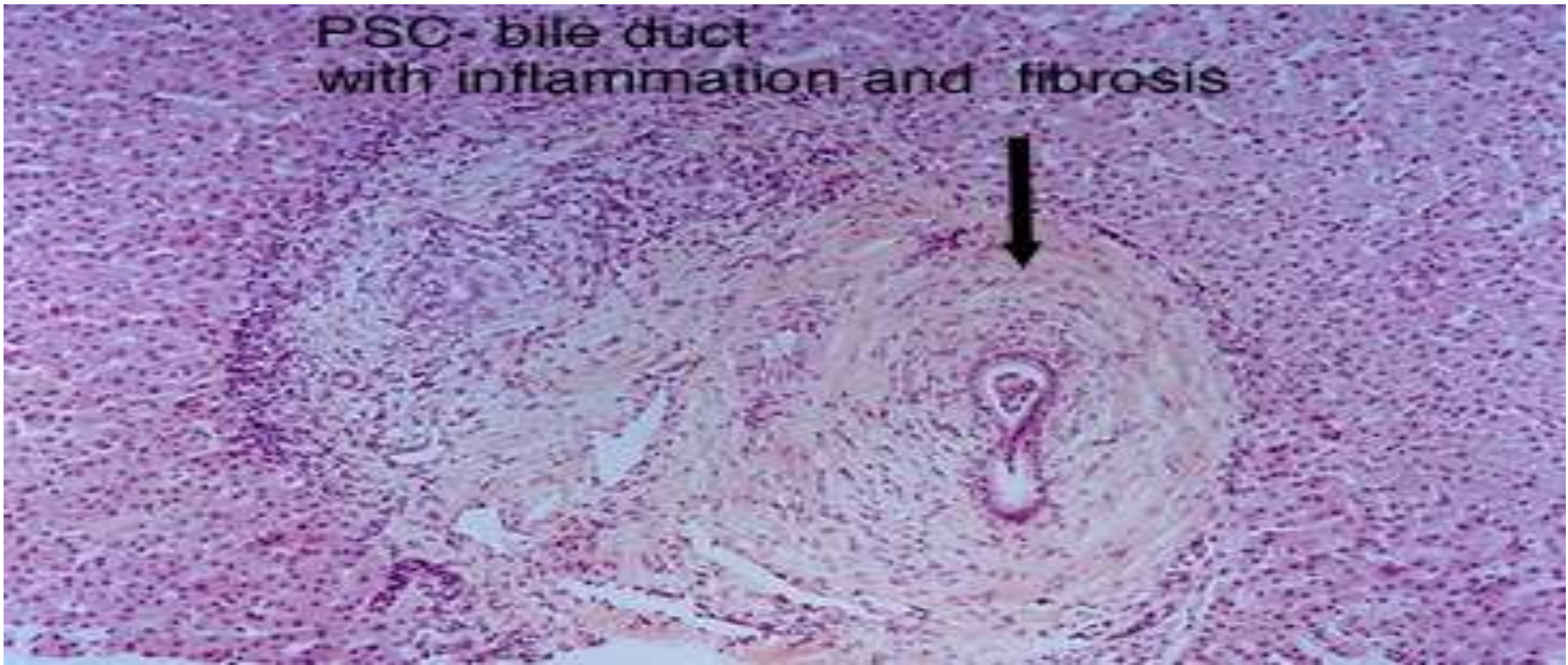
Primary Sclerosing Cholangitis (PSC)

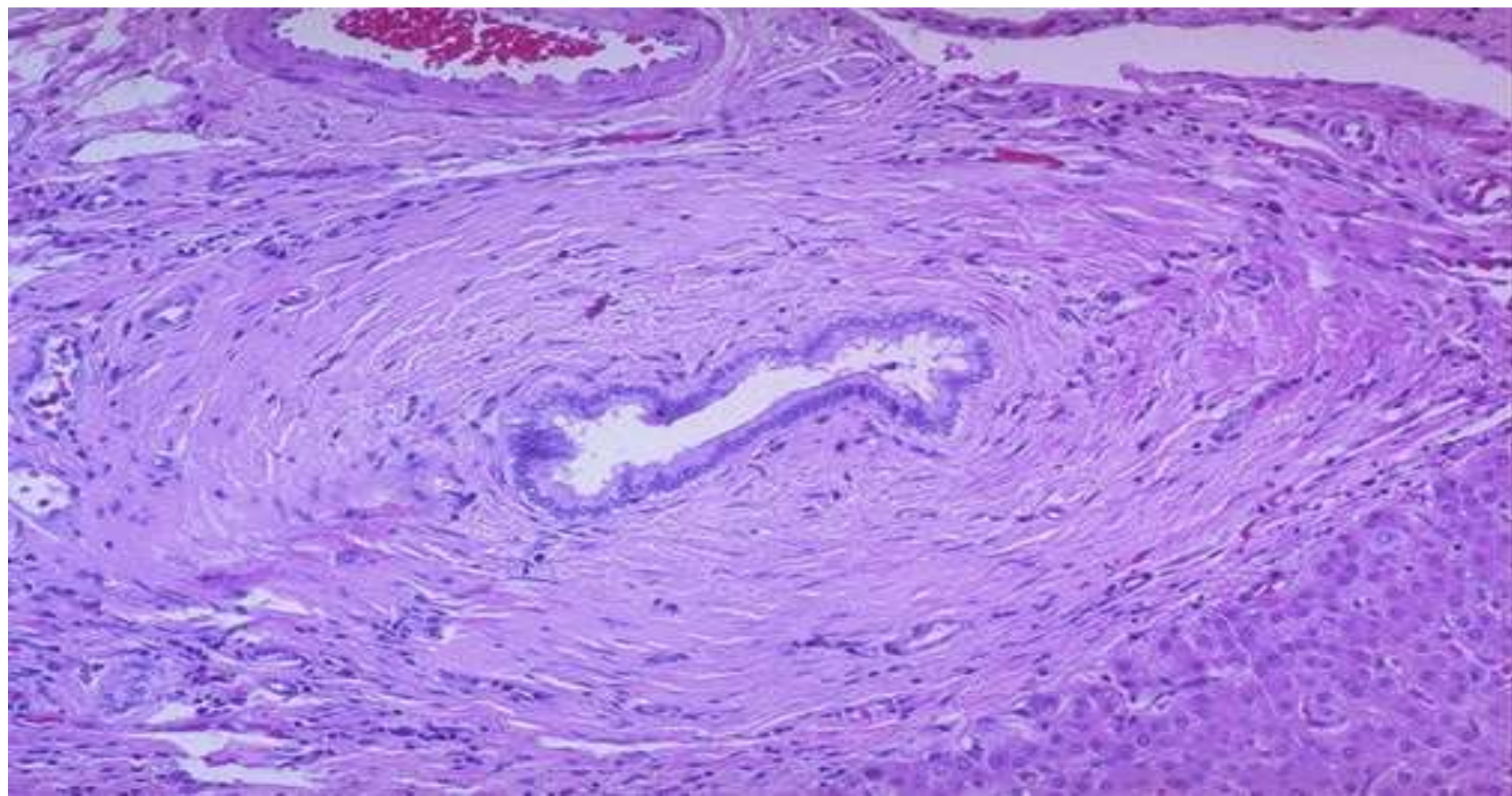


INTRAHEPATIC BILIARY TRACT DISEASE

PRIMARY SCLEROSING CHOLANGITIS

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





Histopathology

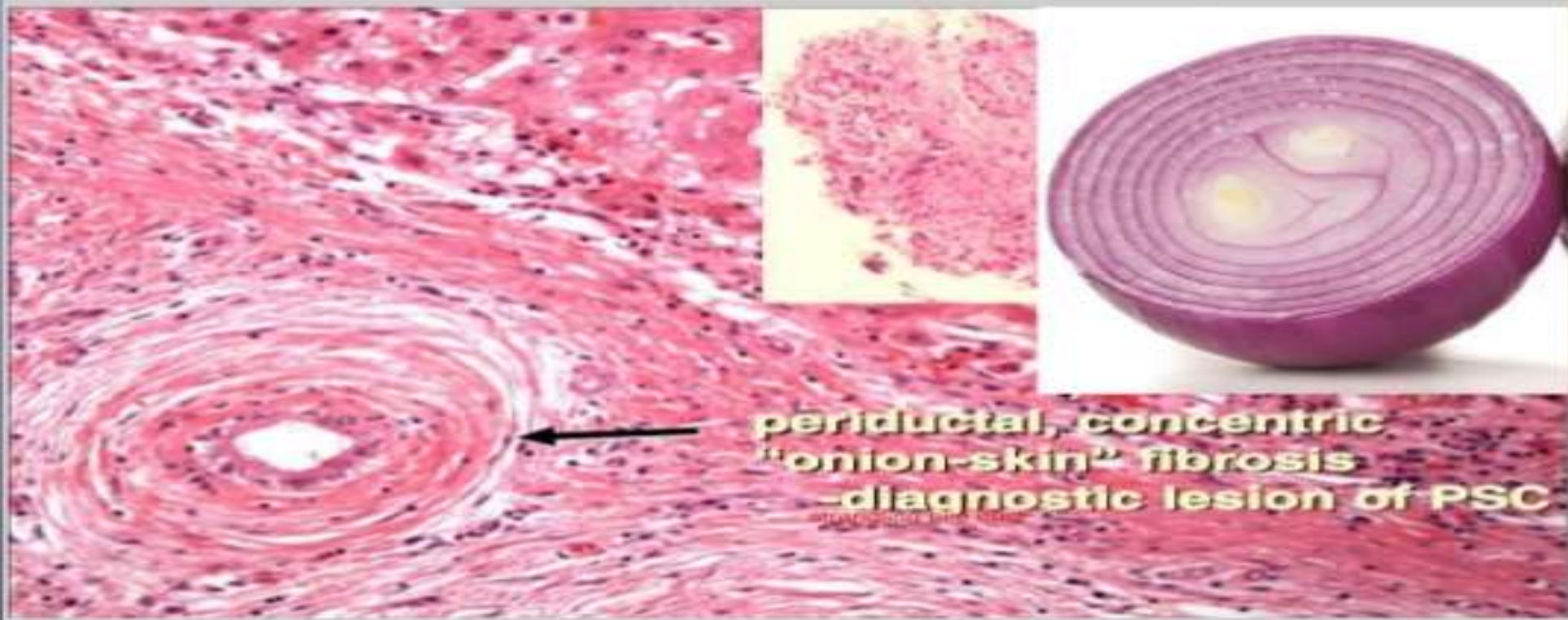


Table 18-11 Main Features of Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

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 ($\leq 25\%$) 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.

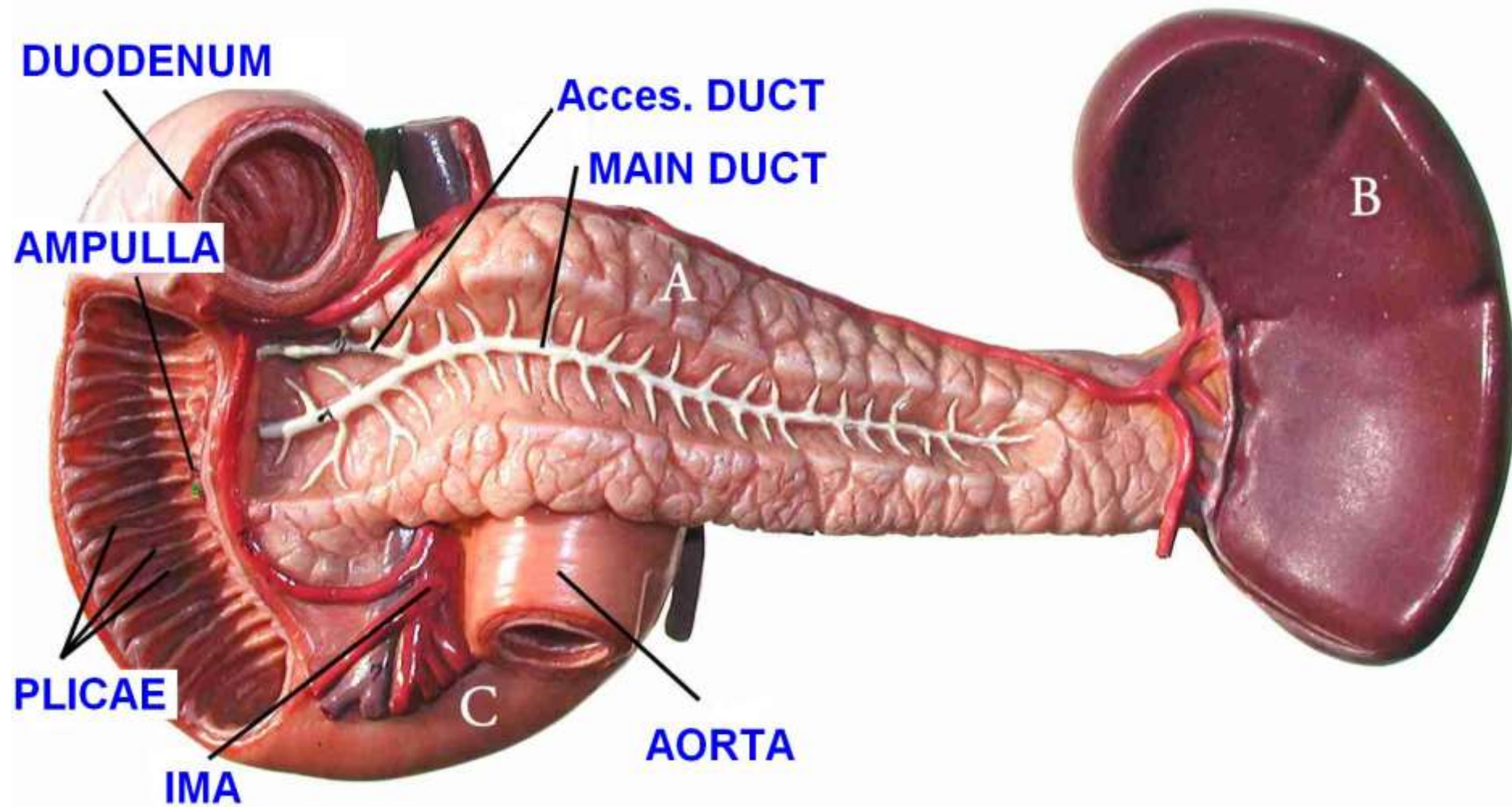
INTRAHEPATIC BILIARY TRACT DISEASE

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



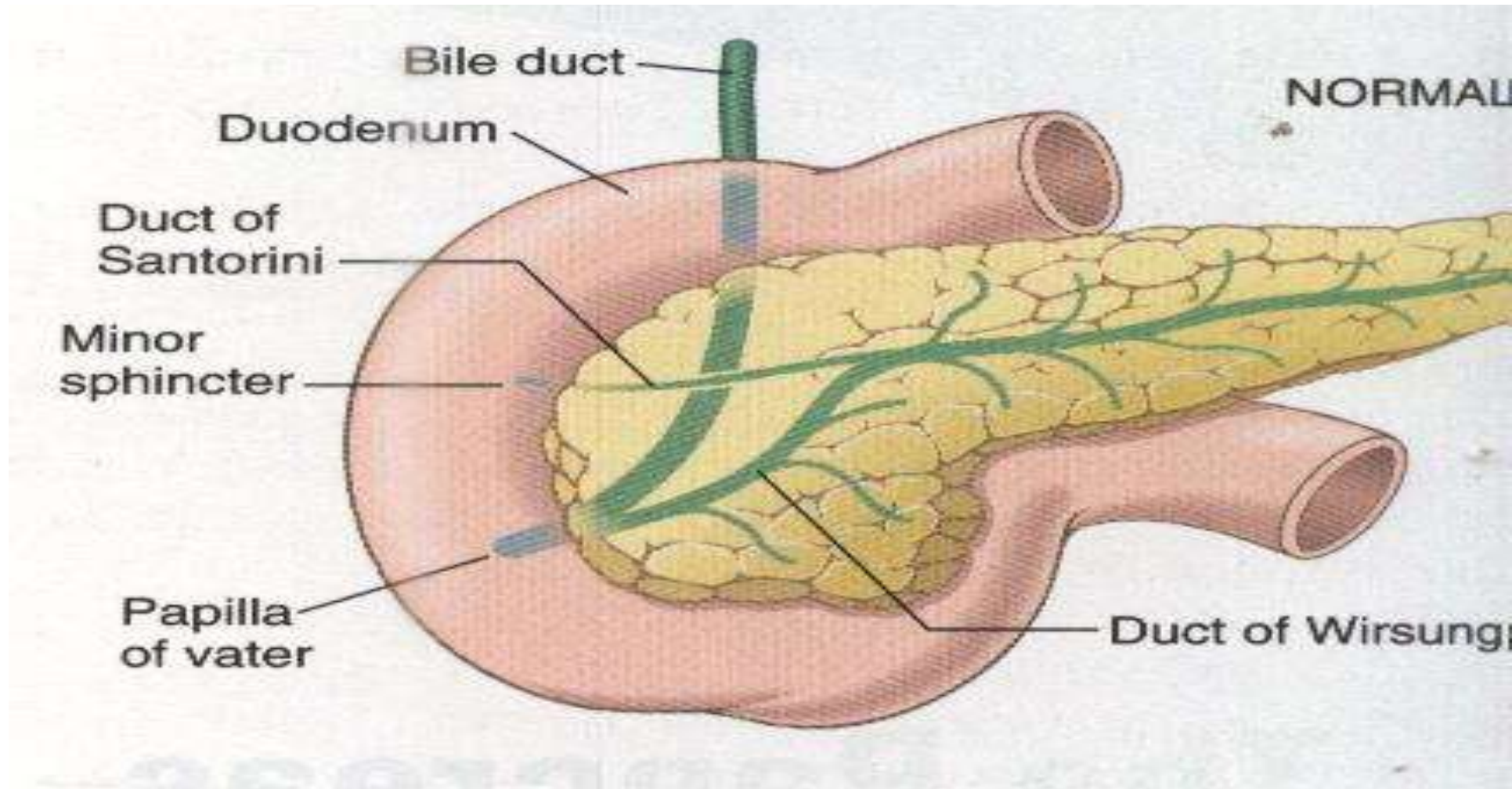
PANCREAS

Pancreas pathology

OBJECTIVES

- Understand the etiology/risk factors,
- pathogenesis,
- clinical features and
- outcome of pancreatic inflammations and neoplasms

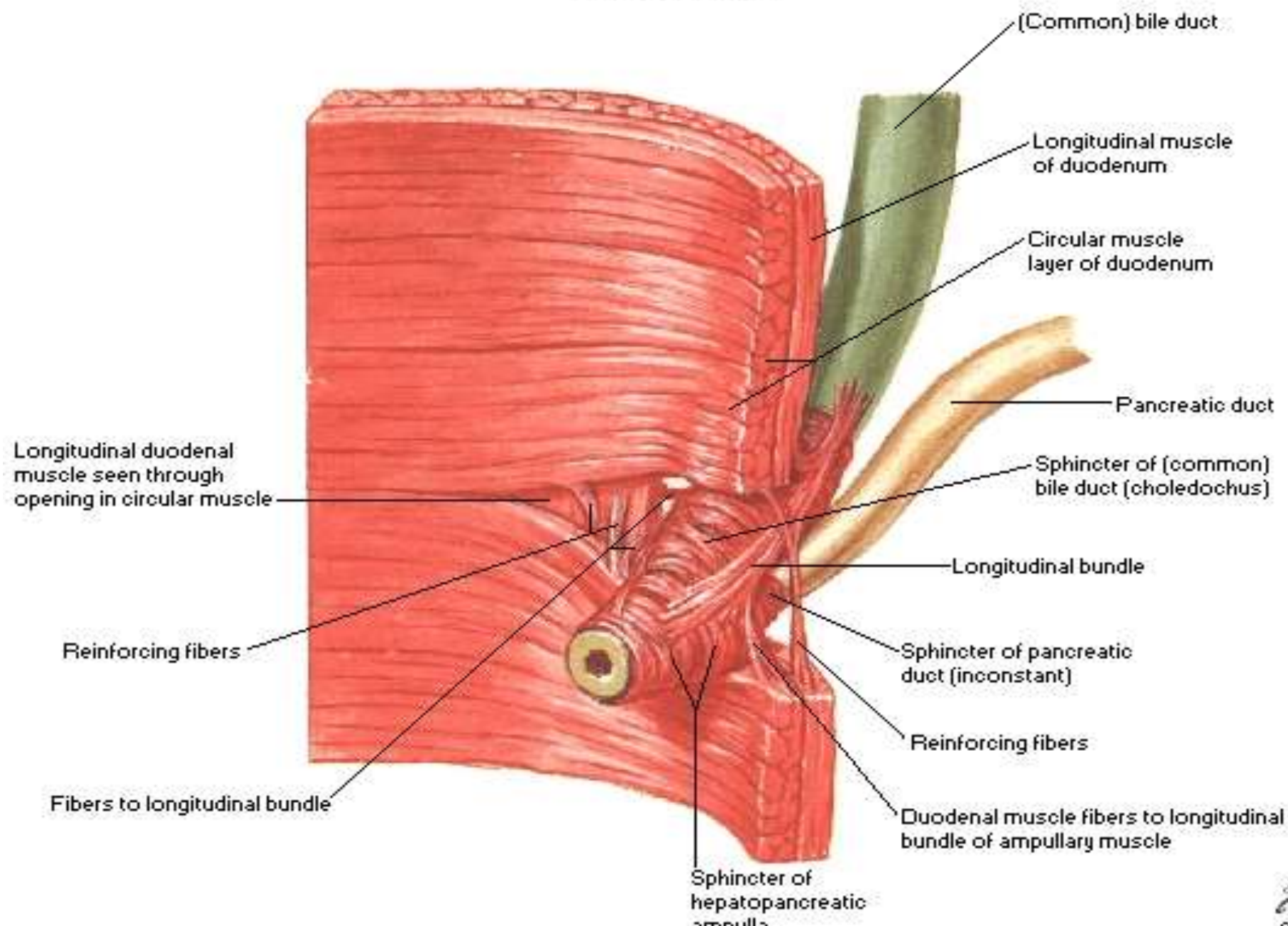
Pathology of pancreas

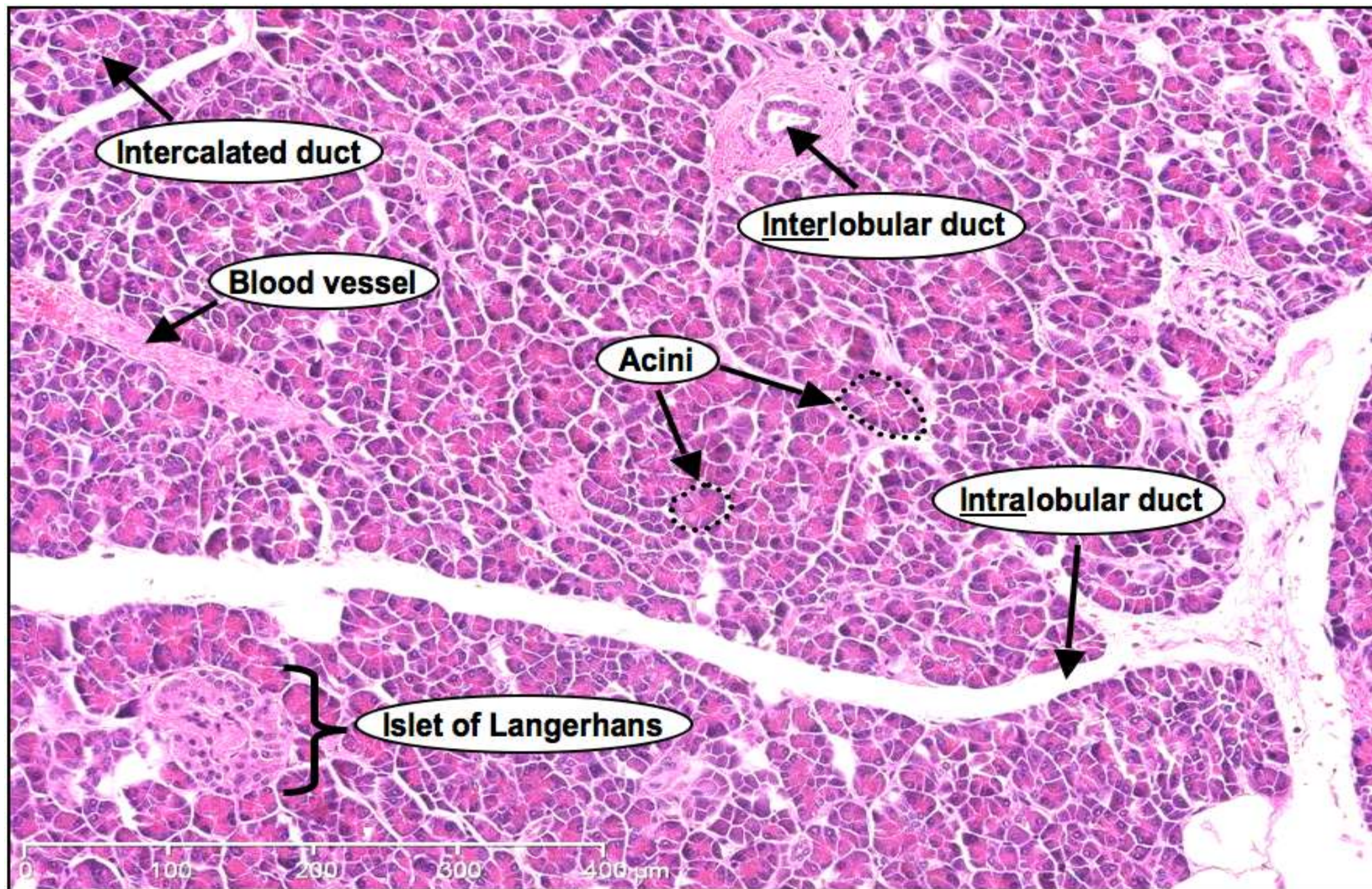


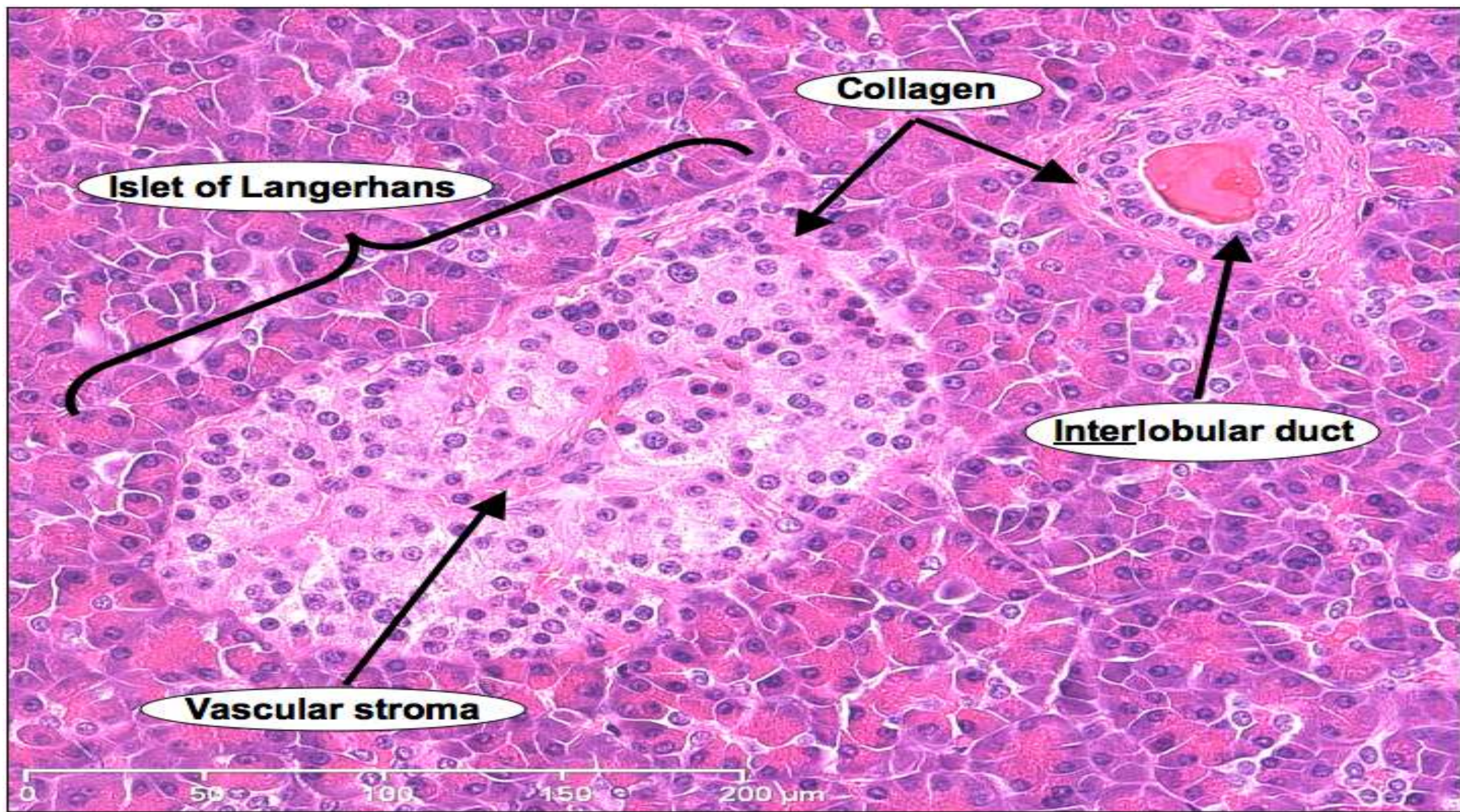
Normal pancreas

Junction of Bile Duct and Duodenum

Dissection







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, **hyper**lipoproteinemia, **Hyper**calcemia, 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.

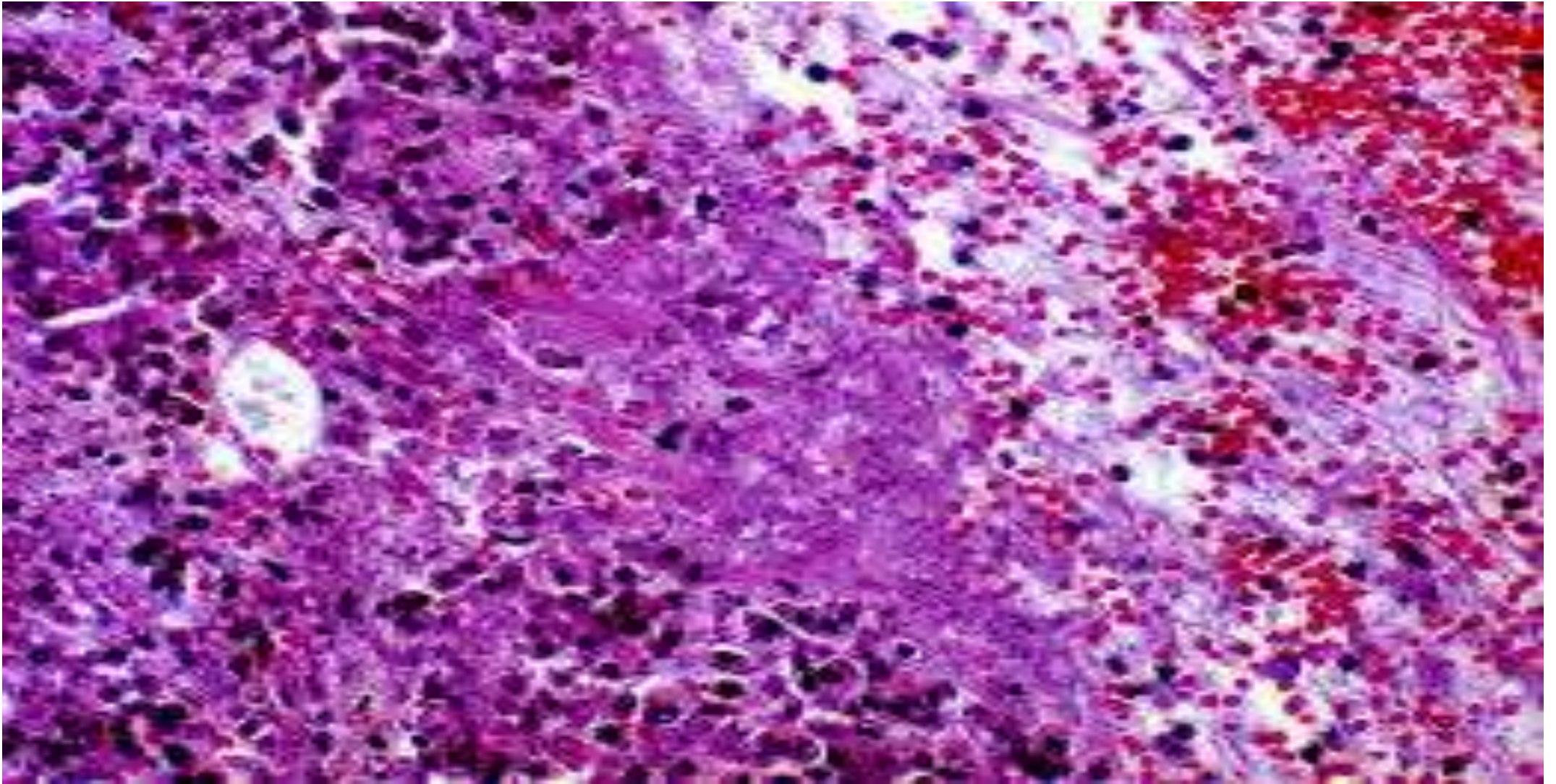
Under normal condition, These enzymes are produced & stored by the acinar cells of exocrine pancreas in forms of Proenzymes. Which convert into enzymes upon the stimuli of secretion, then these enzymes are secreted into the duodenal lumen for digestion of food inside the intestine. (major stimuli is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

Acute hemorrhagic pancreatitis.



Acute hemorrhage with coagulation necrosis
of acinar tissue.



2. Cellular injury response mediated by proinflammatory cytokines.

These cytokines are secreted by injured acinar cellsattract neutrophils, macrophages.....
These inflammatory cells release more cytokines
such as tumor necrosis factor(TNF), interleukin-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).

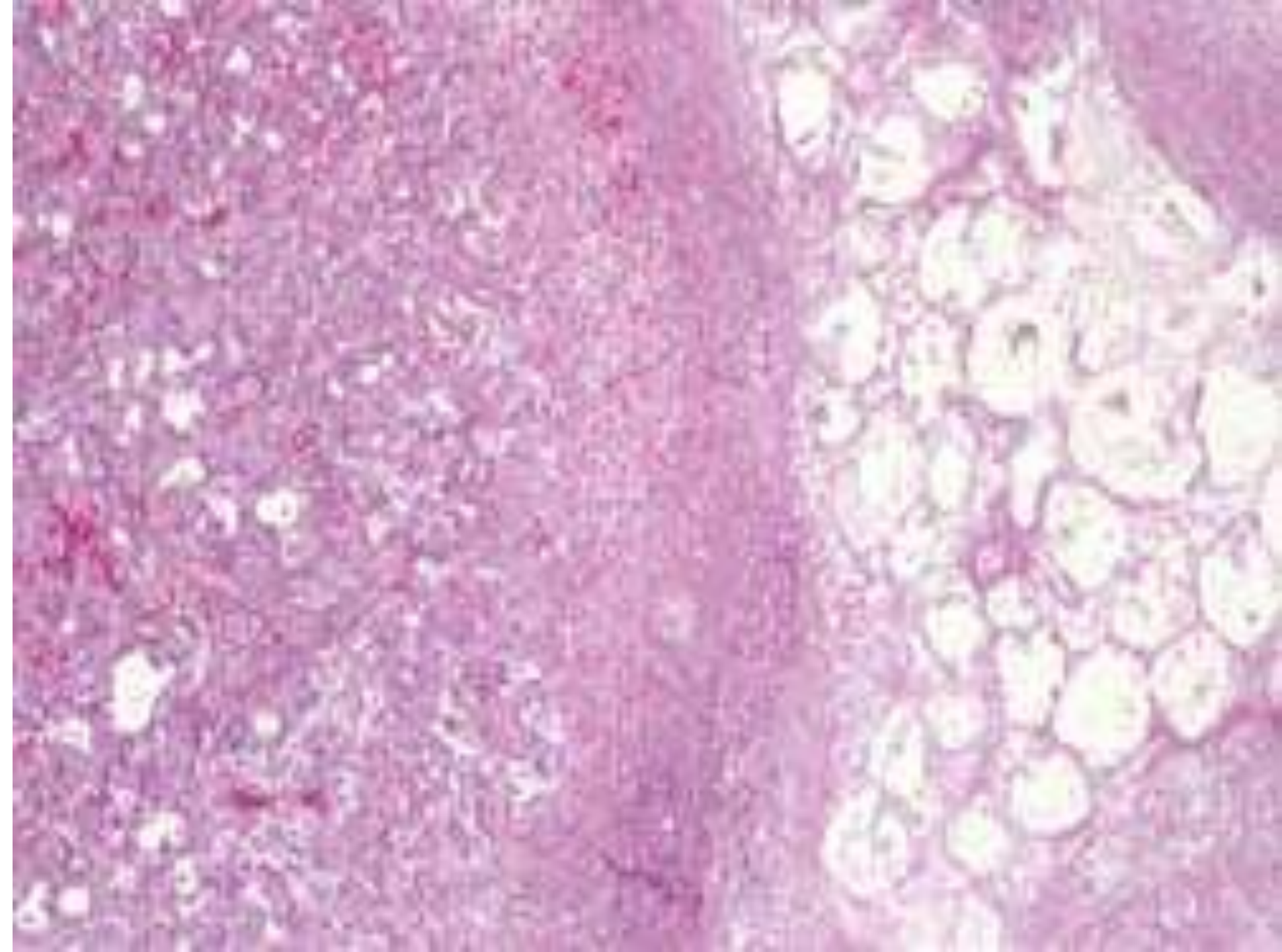
Morphology of acute pancreatitis:

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

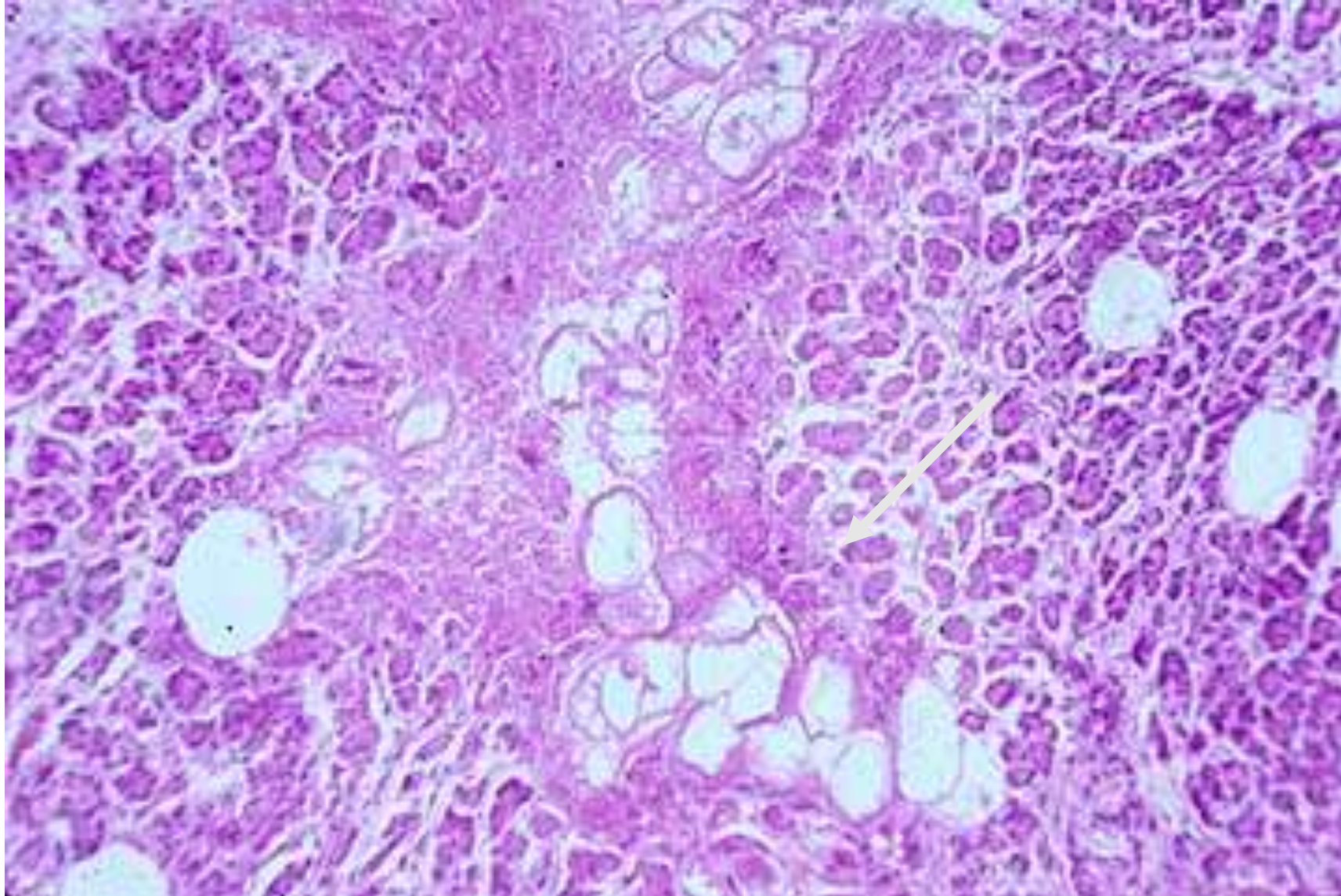
- Areas of blue – black **hemorrhage** interspersed by
- areas of grey – white **necrotic softening &**
- areas of **white – chalky fat necrosis.**

- **Mic.**
- **EDEMA**
- **FAT NECROSIS**
- **ACUTE INFLAMMATORY INFILTRATE**
- **PANCREAS AUTODIGESTION**
- **BLOOD VESSEL DESTRUCTION**
- **“SAPONIFICATION” (stearates, 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).





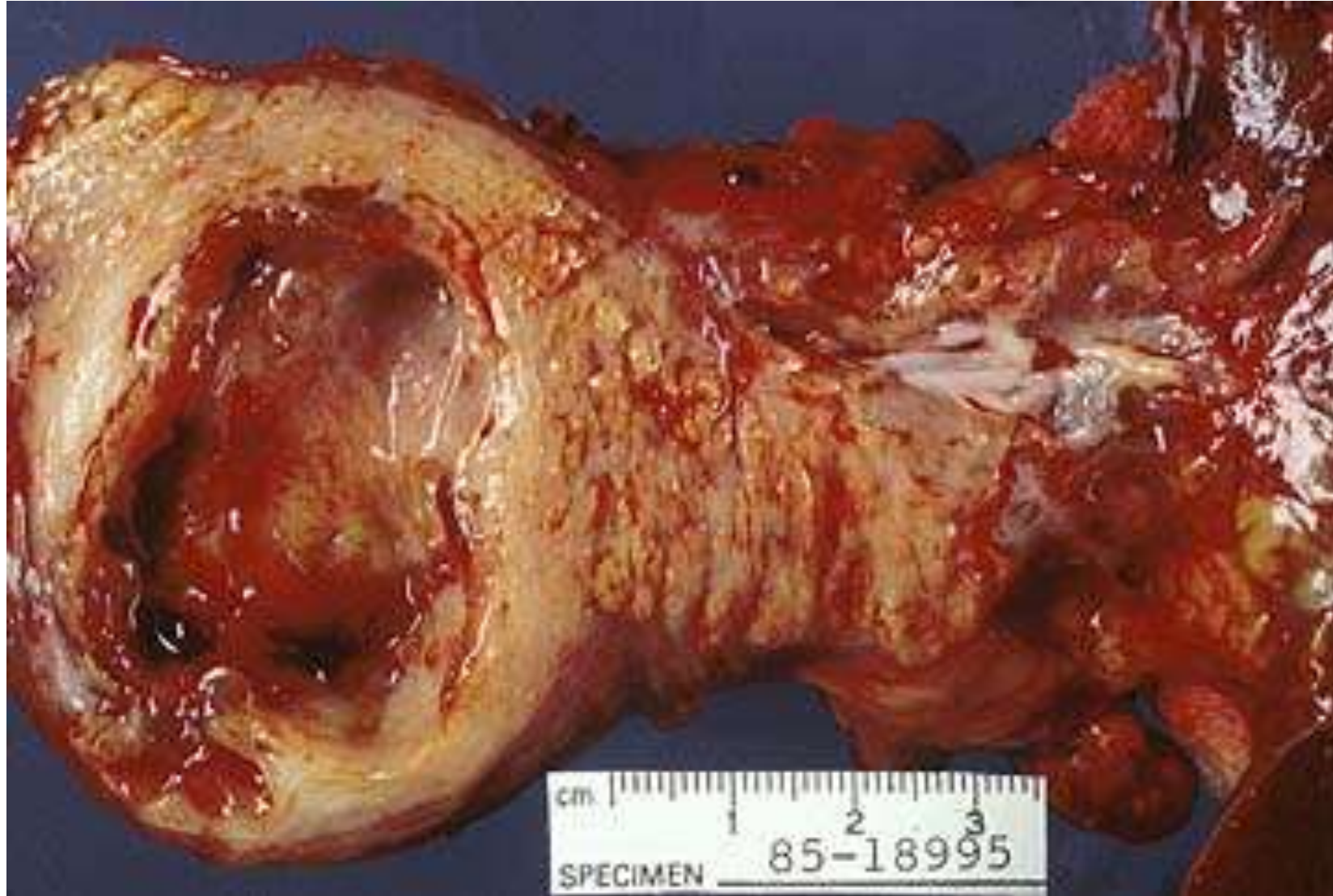
Acute pancreatitis with fat necrosis.



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



Enzymatic fat necrosis



Complications:

- Chemical peritonitis.
- Endotoxic shock & death(mortality rate 50%)
- Local sepsis & pancreatic abscess by E.Coli infection.
- Pseudocyst in the lesser 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. **hyperlipoproteinemia.**
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.

Symptoms:

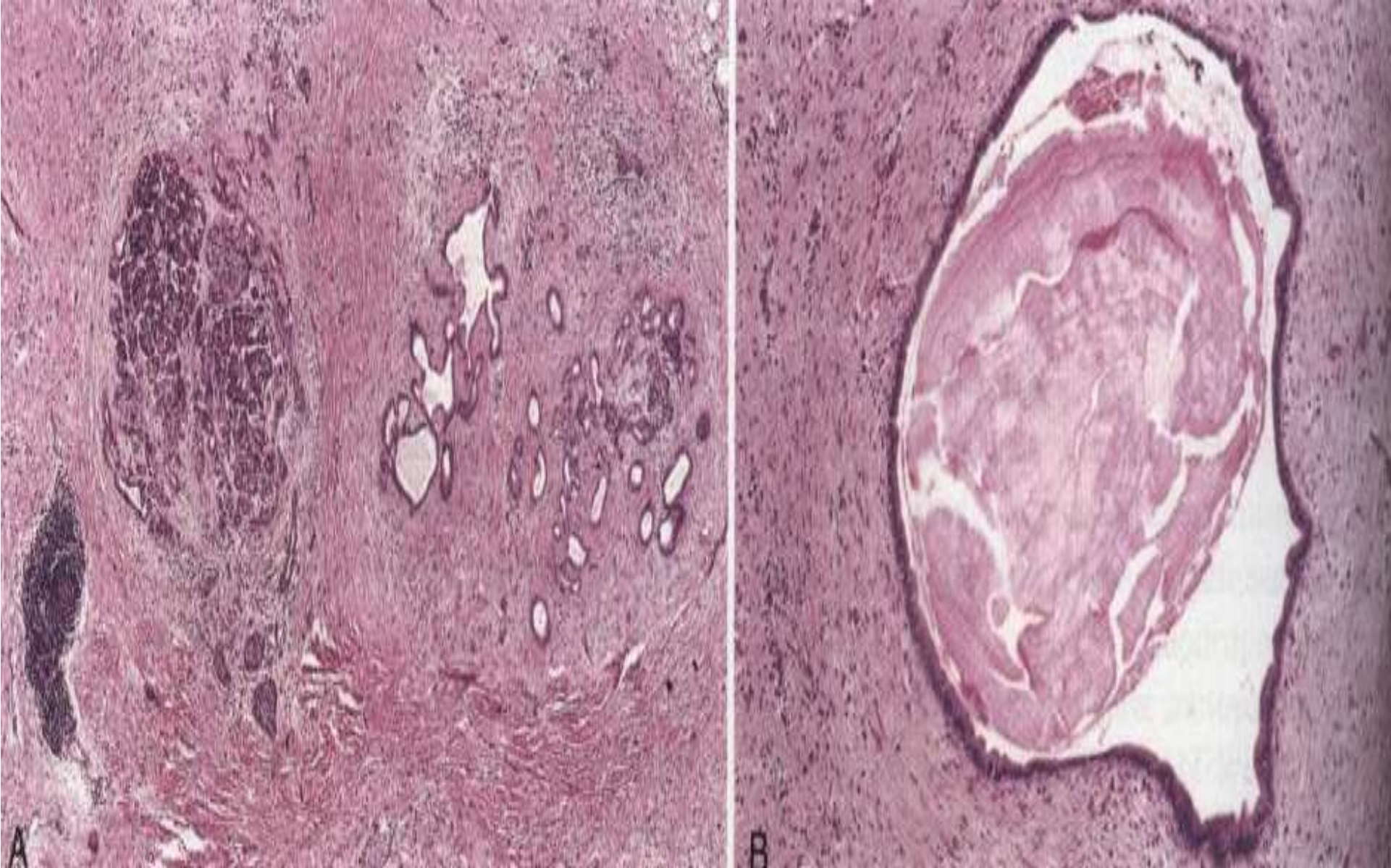
- The disease is either.
- 1. Repeated attacks of moderate to severe abdominal pain
- 2. Persistent abdominal pain & back pain.
- 3. Totally silent till the pancreatic insufficiency & diabetes mellitus develop.
- 4. Repeated attacks of jaundice or vague attacks of indigestion.

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.

Sites:

- 60% to 70% Of cases are arise in the head of pancreas.
- 5% to 10% of cases are in the body of pancreas.
- 10% to 15% of cases are in the tail of pancreas.
- 20% are diffuse cancer involve the entire organ.
- With carcinoma of head of pancreas, the ampullary region is invaded, obstructing the bile flow (obstructive jaundice).

- 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.

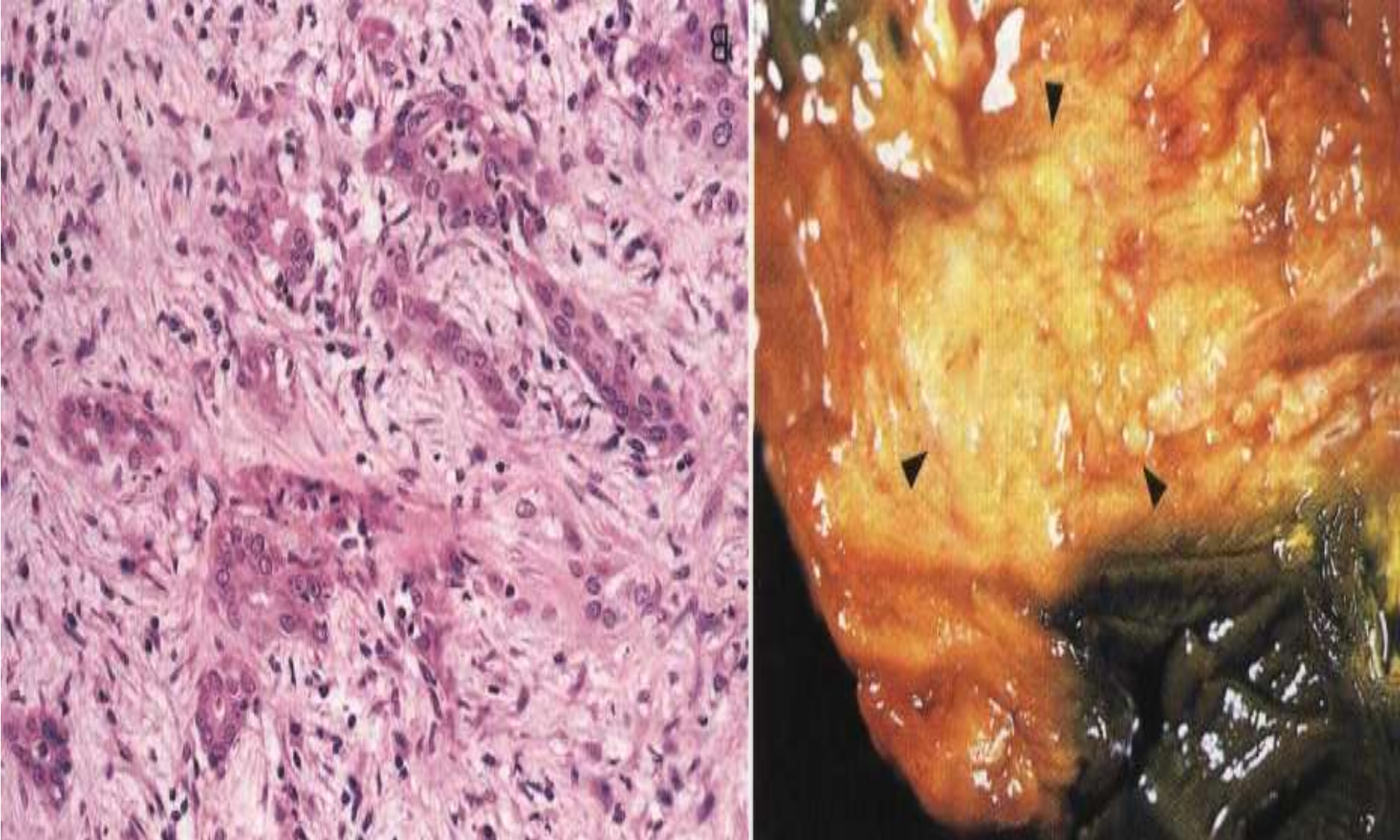
Morphology of pancreatic carcinoma:

- **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 Adenocarcinoma of pancreas

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



Malignant glands in pancreatic adenocarcinoma.

