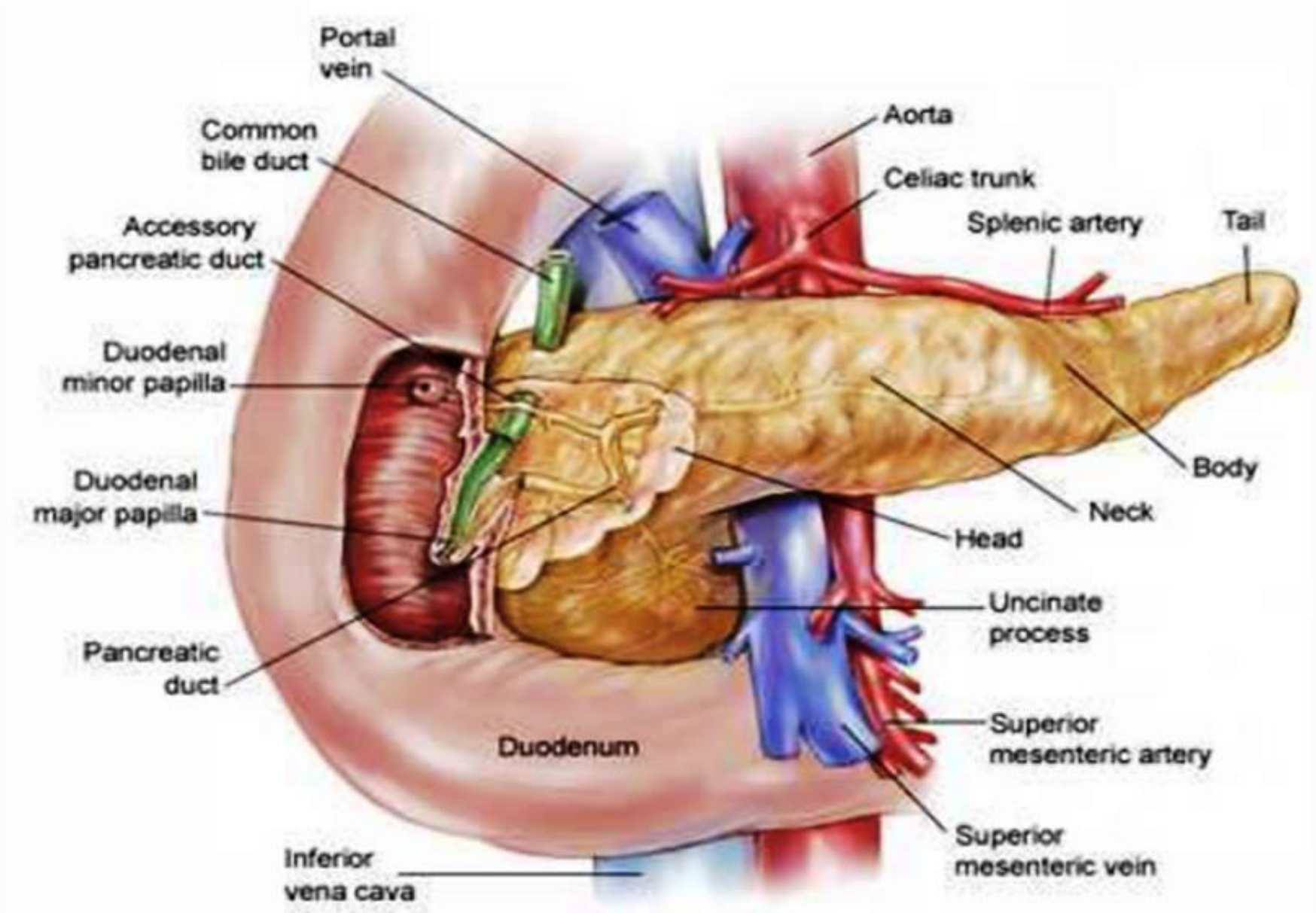
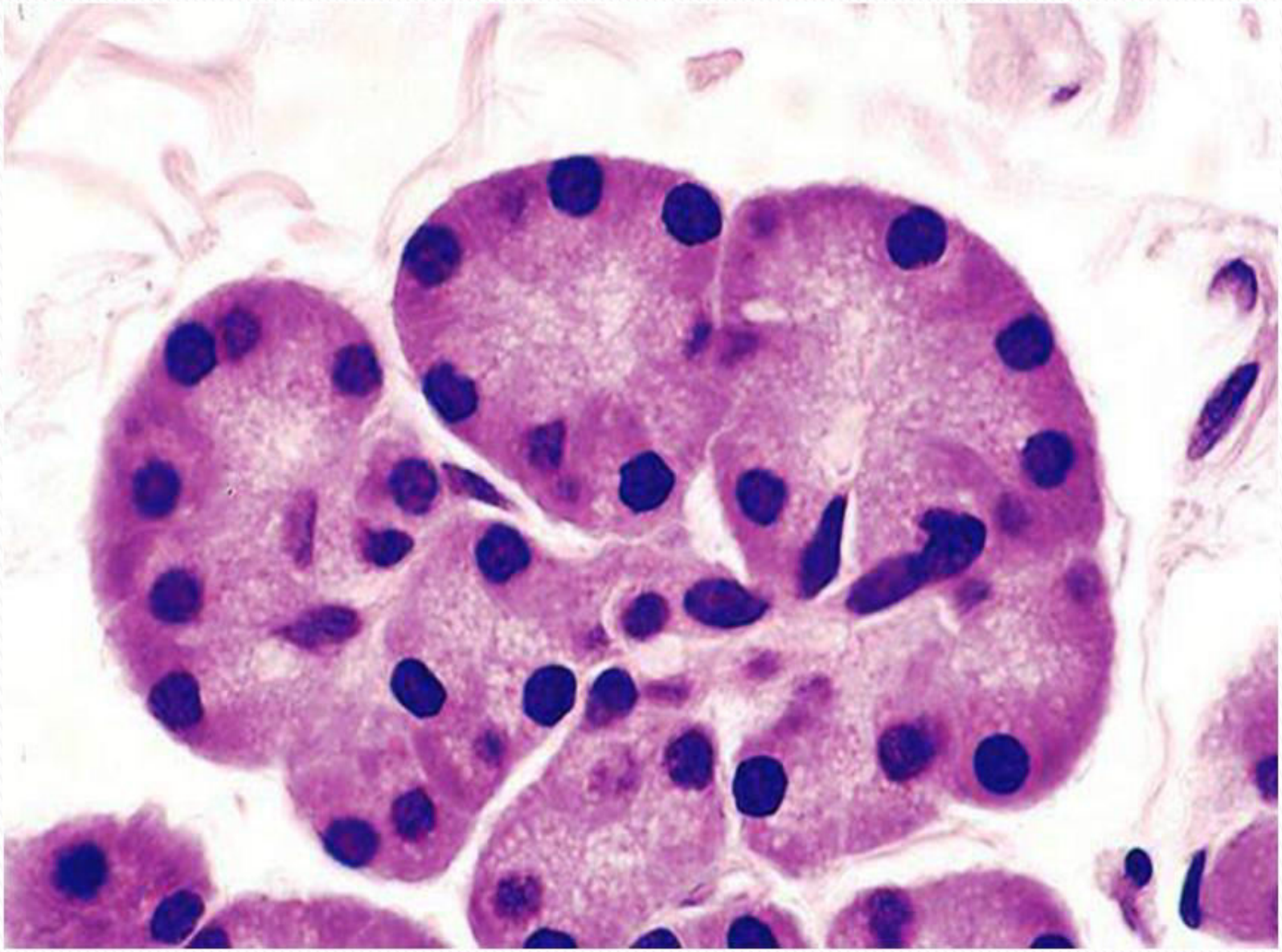
The pancreas



Pancreatic acini



Diseases of the exocrine pancreas

- Cystic fibrosis
- Congenital anomalies
- Acute and chronic pancreatitis
- Pancreatic neoplasms

PANCREATITIS

"Inflammation of the pancreas"

- **By definition**

  - In *acute pancreatitis* the organ can return to normal if the underlying cause is removed.

  - In *chronic pancreatitis* there is an irreversible destruction of exocrine pancreatic parenchyma.

Acute Pancreatitis

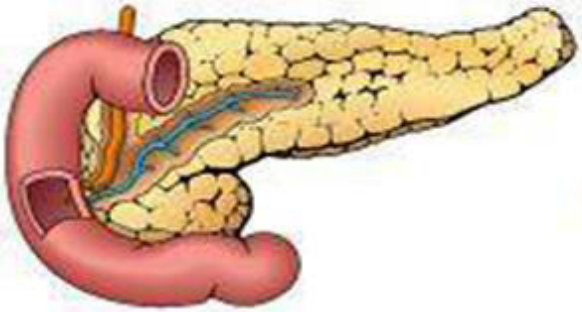
- A group of **reversible lesions** characterized by inflammation of pancreas.
- Range in severity from focal edema and fat necrosis to widespread parenchymal necrosis with severe hemorrhage.
- 80% of cases are due to biliary tract disease* or alcoholism.

Etiologic factors of acute pancreatitis	
Metabolic	Alcoholism 5% Hyperlipoproteinemia, hypertriglyceridemia Hypercalcemia– hyperparathyroidism Drugs (e.g., thiazide diuretics)
Genetics	Hereditary pancreatitis–mutauion in *SPINK1& PRSS1*
Mechanical	Gallstones 75% Trauma Iatrogenic injury, ERCP Periampullary tumors Biliary "sludge," Parasites–*Ascaris lumbricoides*
Vascular	Shock Atheroembolism Vasculitis– Polyarteritis nodosa
Infectious	Mumps, Coxsackievirus *Mycoplasma pneumoniae*
Idiopathic	10% – 20%

Pathogenesis

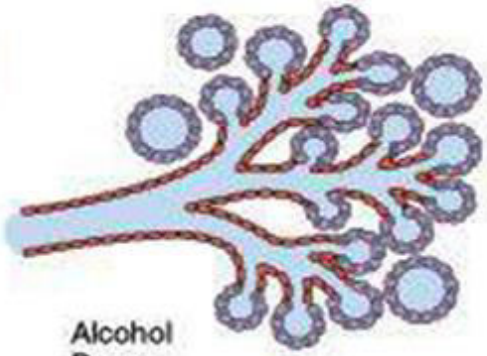
CAUSES:

DUCT OBSTRUCTION



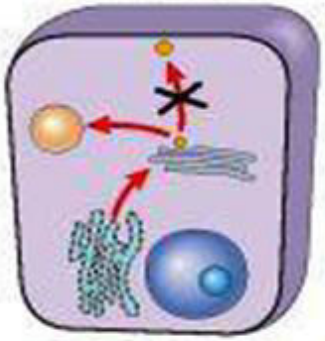
Cholelithiasis
Ampullary obstruction
Chronic alcoholism
Ductal concretions

ACINAR CELL INJURY



Alcohol
Drugs
Trauma
Ischemia
Viruses

DEFECTIVE INTRACELLULAR TRANSPORT



Metabolic injury (experimental)
Alcohol
Duct obstruction

MECHANISMS:

Interstitial edema
↓
Impaired blood flow
↓
Ischemia

Release of intracellular proenzymes and lysosomal hydrolases
↓
Activation of enzymes (intra- or extracellular)

Delivery of proenzymes to lysosomal compartment
↓
Intracellular activation of enzymes

Acinar cell injury
↓
ACTIVATED ENZYMES

LESIONS:

Interstitial inflammation and edema + Proteolysis (proteases) + Fat necrosis (lipase, phospholipase) + Hemorrhage (elastase)

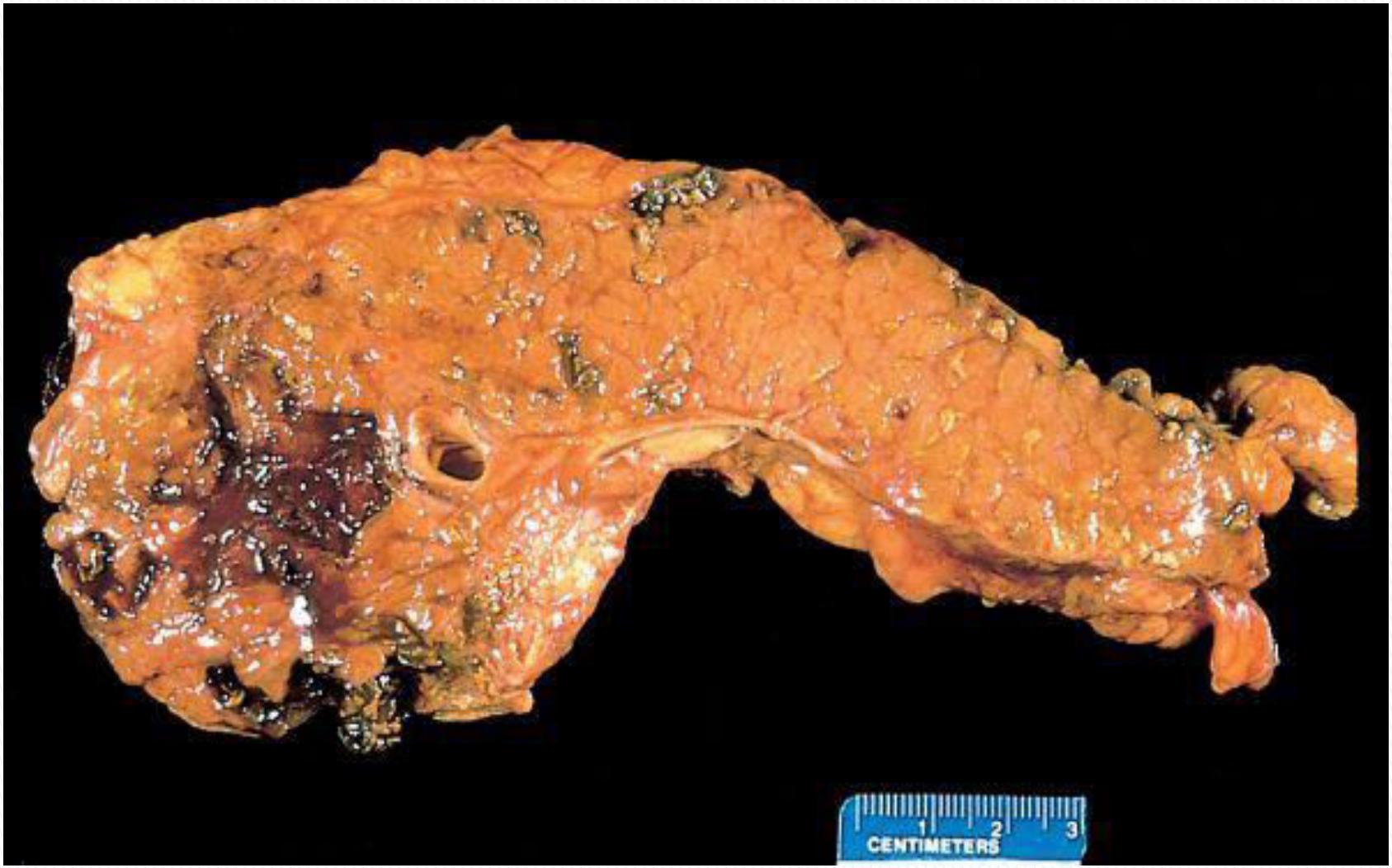
↓

ACUTE PANCREATITIS

Morphology of acute pancreatitis

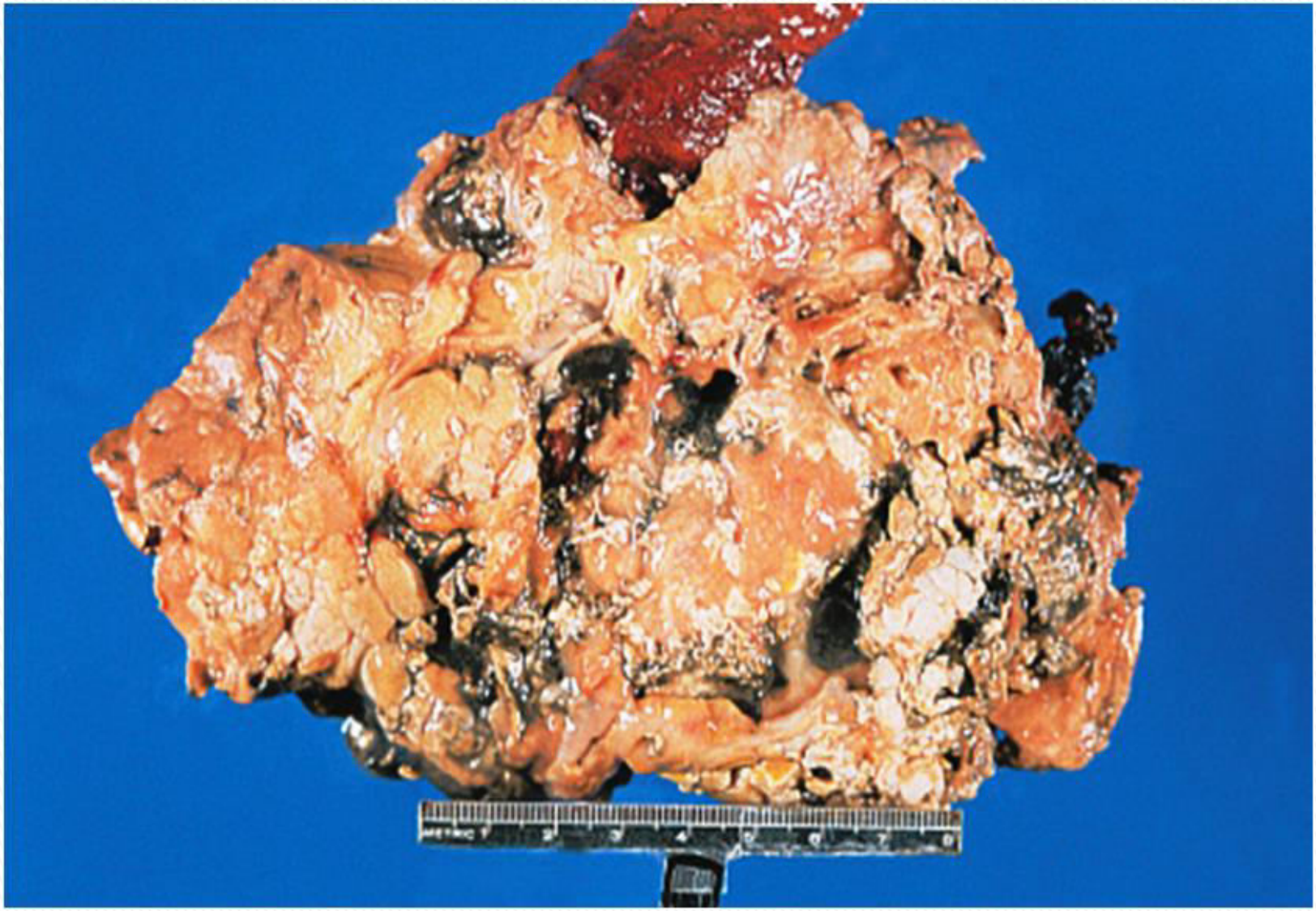
- Microvascular leakage causing edema.
- Necrosis of pancreatic and peripancreatic fat by *lipases* enzyme ± hemorrhage
- Fat necrosis combine with Ca to form salts.
- An acute inflammatory reaction.

Acute pancreatitis



Hemorrhage in the head of the pancreas and a focal area of pale fat necrosis in the peripancreatic fat *(upper left)*

Massive fat necrosis

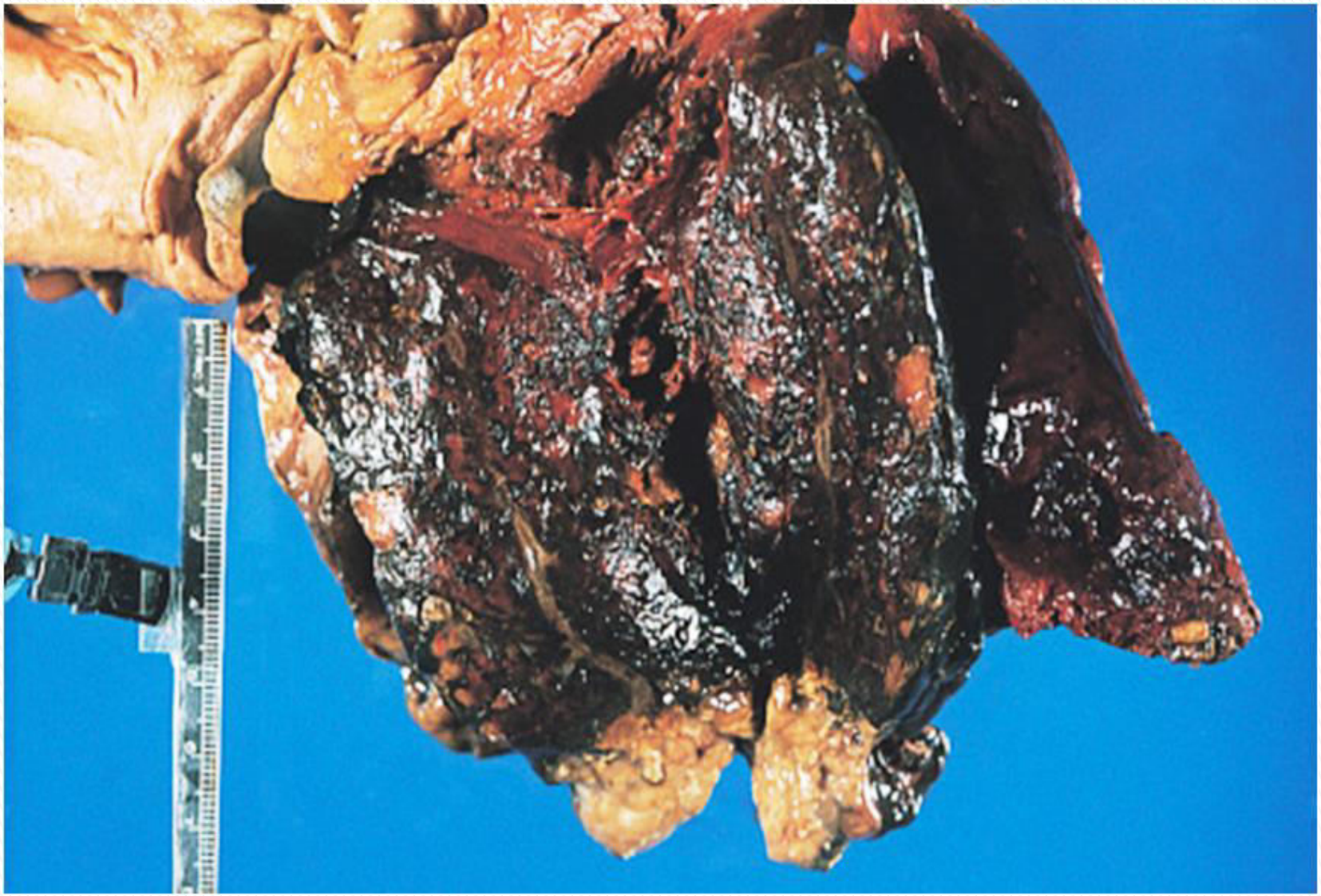


Morphology of acute pancreatitis

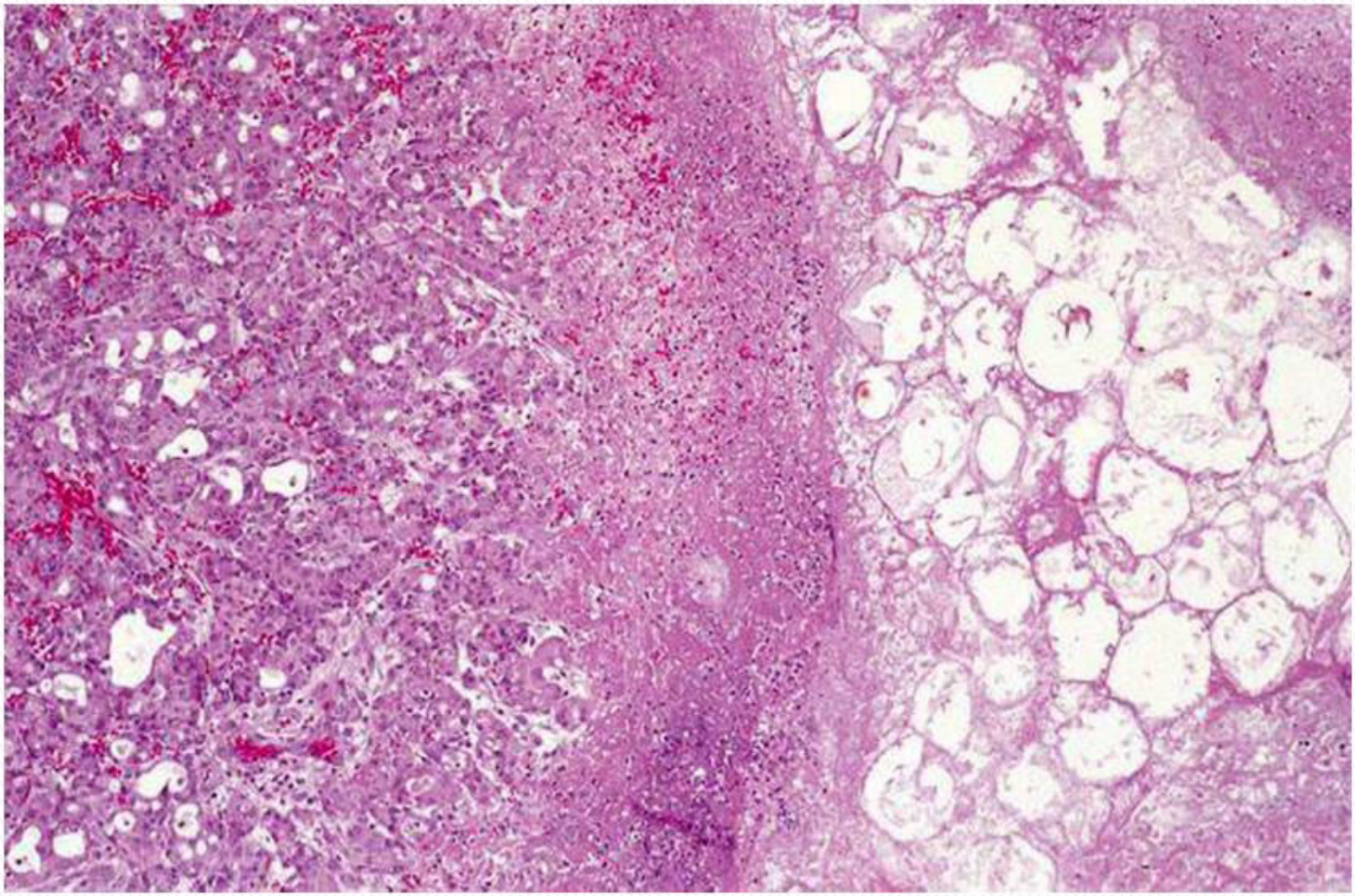
- **Acute necrotizing pancreatitis**
  - Proteolytic destruction of pancreatic parenchyma including acinar + ductal tissue + islets.

- **Hemorrhagic pancreatitis (most severe):**
  - Extensive necrosis, destruction of BVs with hemorrhage.

Acute hemorrhagic pancreatitis



Acute pancreatitis

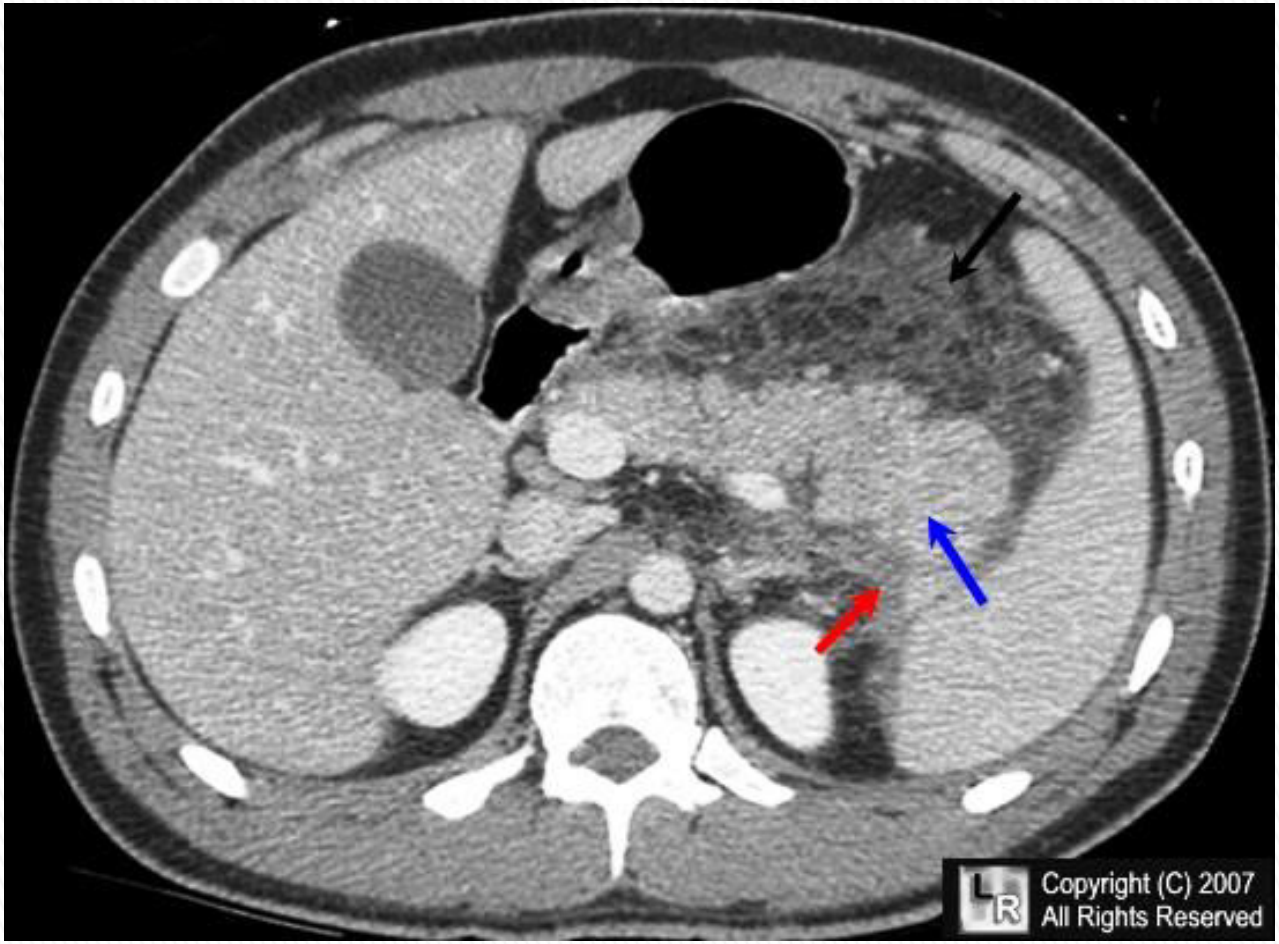


Fat necrosis on the right and focal pancreatic parenchymal necrosis *(center)*

Clinical Features of acute pancreatitis

- A medical emergency
  - Abdominal pain is the cardinal manifestation*.
- LAB findings
  - Elevated plasma levels of amylase** during first 24 hrs followed (within 72-96 Hrs) by lipase.
  - Hypocalcemia***.
- CT scan or MRI to visualize the enlarged inflamed pancreas.

Acute pancreatitis–CT scan



The pancreas is enlarged (blue arrow) with indistinct and shaggy margins. There is peripancreatic fluid (red arrow) and extensive peripancreatic infiltration of the surrounding fat (black arrow).

Complications of acute pancreatitis

- **Due to systemic release of digestive enzymes & systemic inflammatory response:**
  - Electrolyte disturbances.
  - Peripheral vascular collapse (shock).
  - Disseminated intravascular coagulation.
  - ARDS (due to alveolar capillary injury).
  - Acute renal failure.
  - Endotoxemia (from breakdown of the barriers between GI flora and the bloodstream).

Complications of acute pancreatitis

- Duodenal obstruction.
- Widespread metastatic fat necrosis*.
- Infected pancreatic necrosis:
  - In 40% – 60% of cases of acute necrotizing pancreatitis become infected, usually by gram-negative organisms from the GI without abscess
- Pancreatic abscess.
  - A collection of pus resulting from tissue necrosis, liquefaction ± infection
- Pancreatic pseudocyst.

Treatment and prognosis of acute pancreatitis

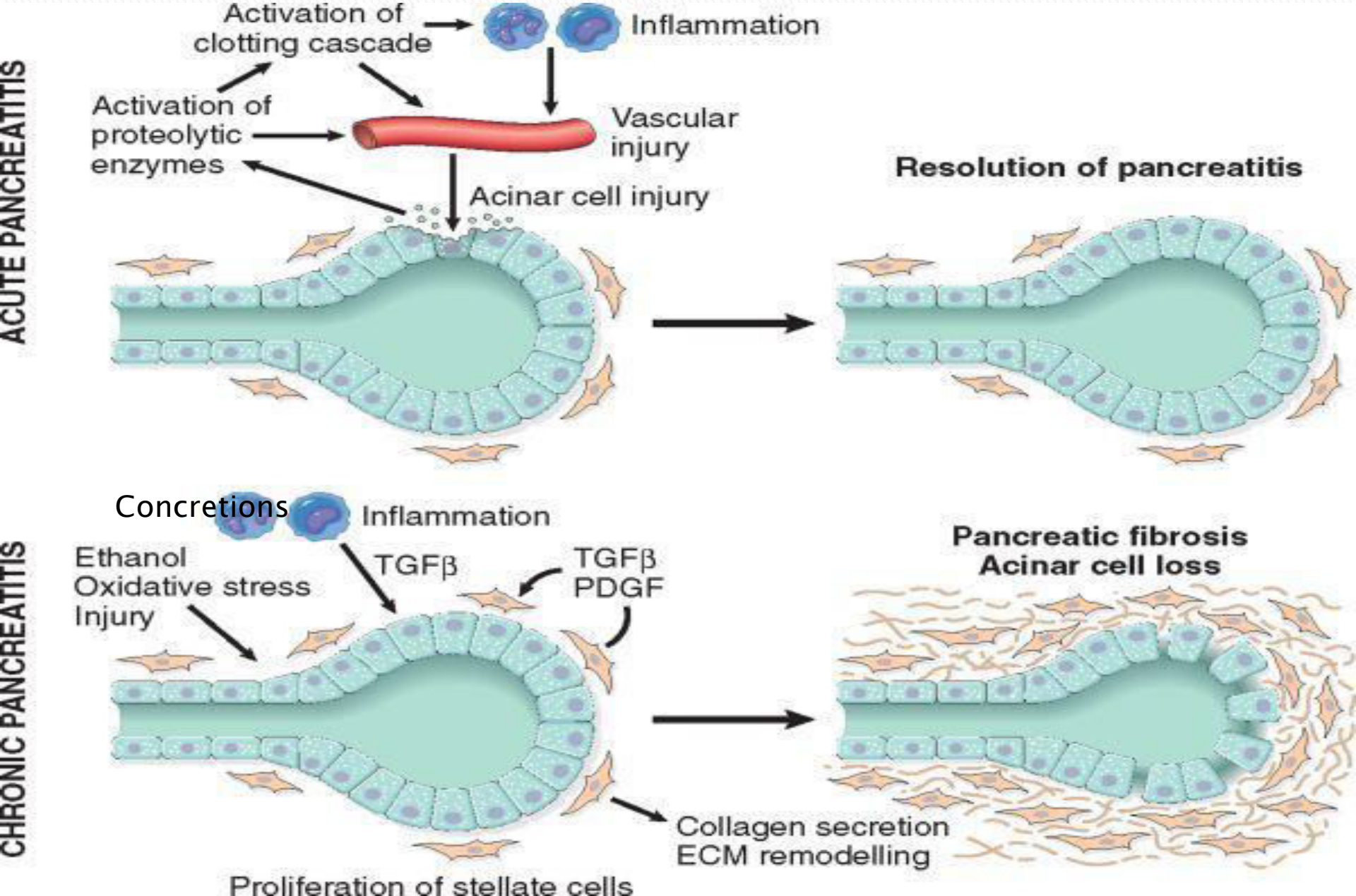
- Supportive therapy & resting of pancreas.
- Most individuals eventually *recover*.
- *5% die* from shock during the first week due to complications*.
- In surviving patients, outcomes include:
  - Sterile pancreatic abscesses.
  - Pancreatic pseudocysts.

Chronic Pancreatitis

- Characterized by longstanding **inflammation** and **fibrosis** of the pancreas with **irreversible** destruction of the exocrine pancreas.
- The endocrine parenchyma is lost *late*.
- Chronic pancreatitis can result from recurrent bouts of acute pancreatitis.
- Common in *middle age men*.

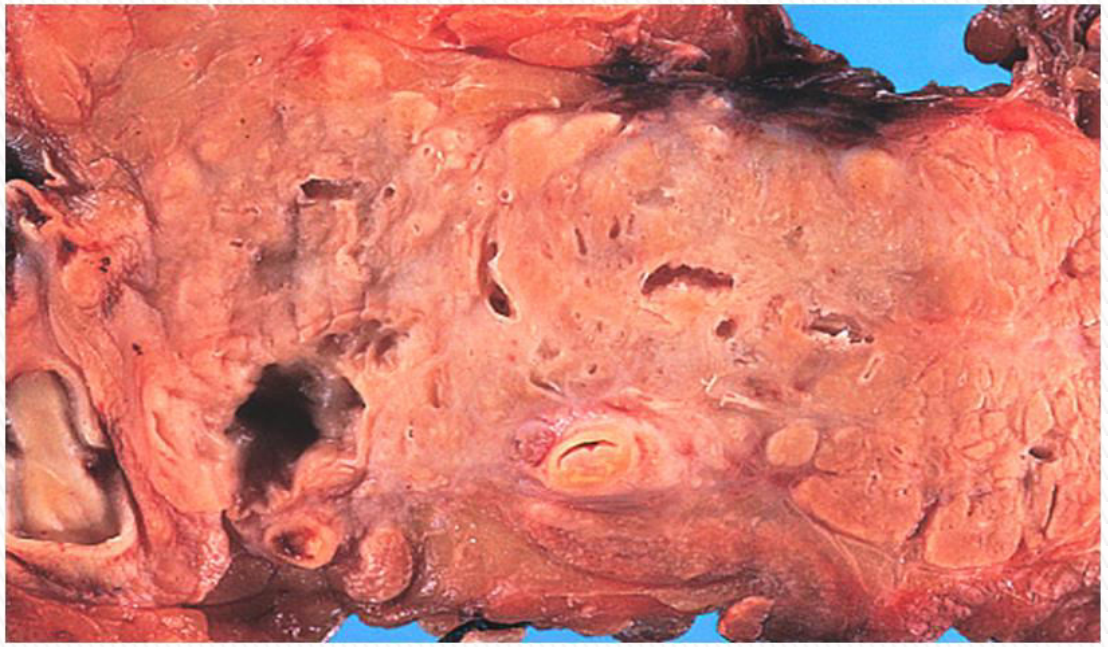
Causes of chronic pancreatitis	
Metabolic	The most common cause is prolonged alcohol abuse
Long-standing pancreatic duct obstruction	Pseudocysts Calculi Neoplasms Pancreas divisum
Tropical pancreatitis	In Africa and Asia Due to malnutrition
Genetic	PRSS1 mutations (hereditary pancreatitis) SPINK1 mutations **CFTR mutations** ↓ bicarbonate secretion and protein plugging
Idiopathic	40% of cases*

Pathogenesis



Chronic Pancreatitis

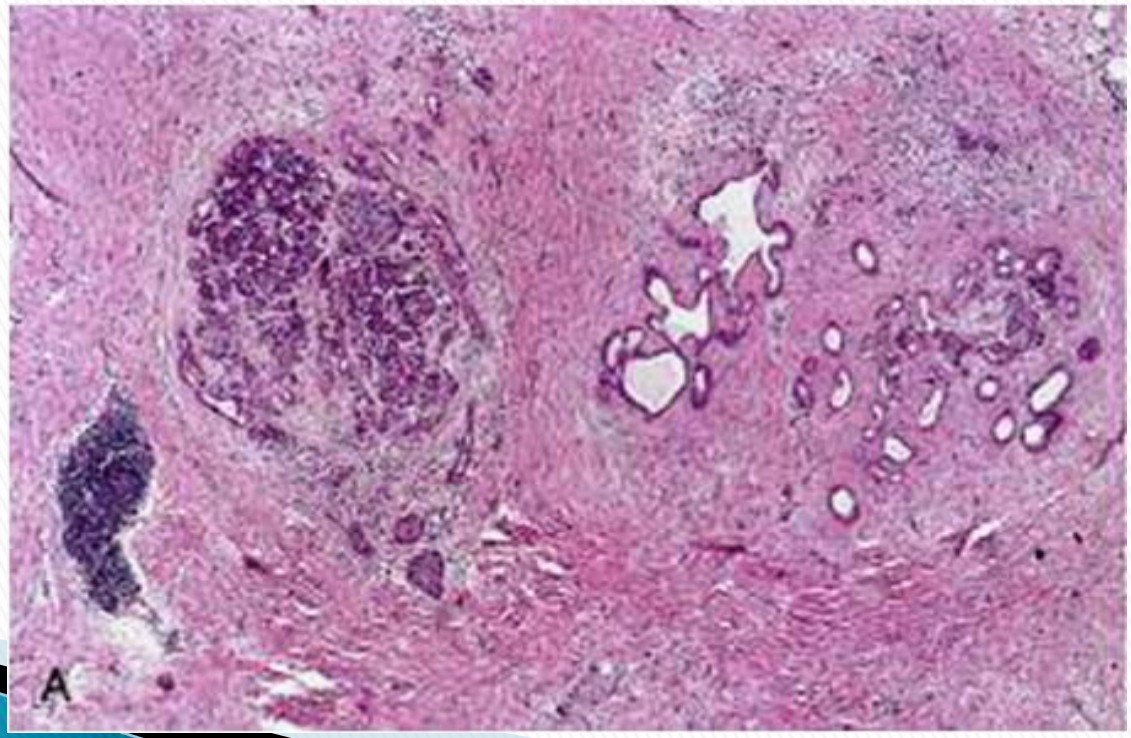
- **Gross appearance:**
  - The gland is hard due to fibrosis.
  - The ducts may be extremely dilated with visible calcified concretions.



Fibrosis, duct dilation & concretions

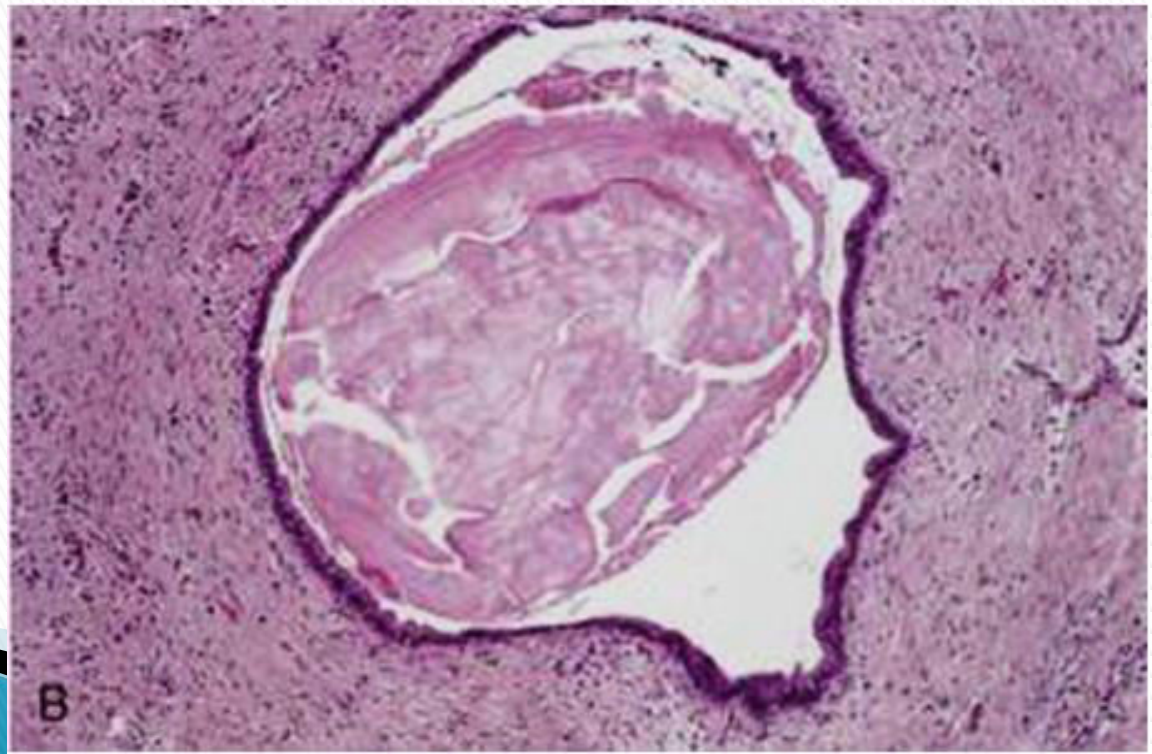
Microscopic appearance

- Parenchymal fibrosis:
- Acinar loss, ↓ number and size of acini:
  - Chronic inflammatory infiltrate around remaining lobules and ducts



Microscopic appearance

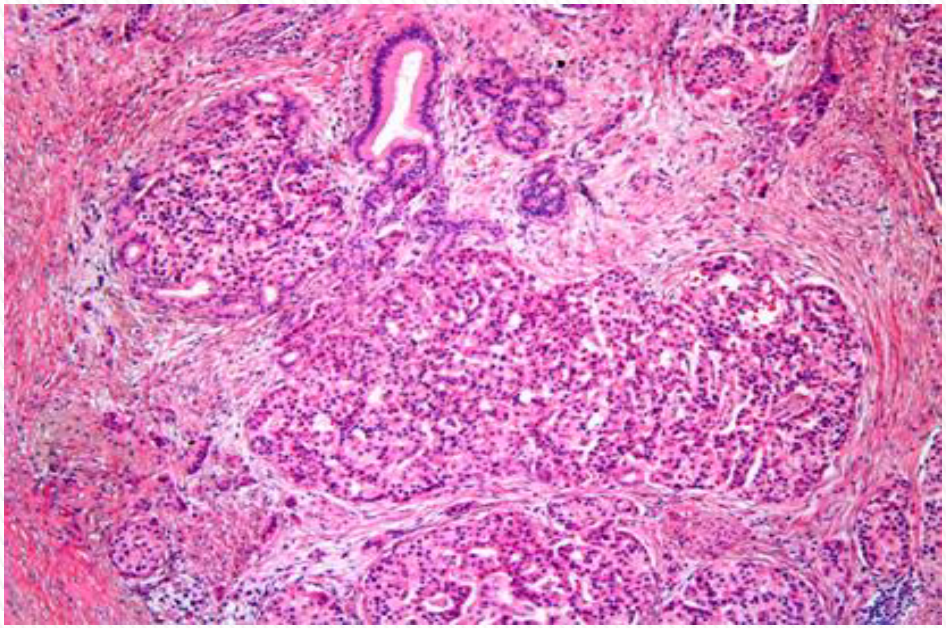
- Variable **dilation of the pancreatic ducts**
  - The ductal epithelium may be atrophied, hyperplastic, or exhibit squamous metaplasia
  - Ductal concretions.



Microscopic appearance

- **Islets of Langerhans**
  - Relatively spared early in the disease and may appear enlarged*.
  - Lost late in the disease.

Large islets aggregate



Clinical Features

- Recurrent vague abdominal pain & jaundice.
- Mild fever & modest ↑ of sreum amylase*.
- Attacks can be precipitated by:
  - Alcohol abuse
  - Overeating
  - Opiates (contraction of sphincter of Oddi)
- May be entirely **silent** until pancreatic insufficiency and diabetes mellitus develop.

Prognosis

- **Not** an acutely life-threatening condition.
- The long-term outlook is poor, with a 50% mortality rate over 20 to 25 years.

- **Complications:**
  - Chronic malabsorption*.
  - Diabetes mellitus.
  - Wide spread metastatic fat necrosis.
  - Pancreatic pseudocysts develop in 10%.
  - Individuals with hereditary pancreatitis have a 40% lifetime risk of pancreatic cancer.

Neoplasms of exocrine pancreas

- May be cystic or solid
- **Cystic neoplasms**
- 5% to 15% of all pancreatic cysts
- < 5% of all pancreatic neoplasms
  - Serous cystadenoma (microcystic cystadenoma)
  - Mucinous cystic neoplasm
  - Intraductal papillary mucinous neoplasm (IPMN)

Pancreatic Carcinoma

- Pancreatic carcinoma is the **4th** leading cause of cancer death → High mortality rates.
- It is a disease of the **elderly, 60-80 years** (in 80%), commoner in **blacks.**

Pathogenesis

- Precancerous lesions
- Molecular carcinogenesis
- Environmental factors

Multifactorial

- Familial syndromes

Molecular carcinogenesis

- There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive lesions in to invasive carcinoma.

- The more common molecular alterations in pancreatic carcinogenesis affect ***K-RAS, p16, SMAD4,*** **and** ***p53***

Environmental factors

- Smoking (strongest influence).
- Alcohol.
- Chronic pancreatitis.
- ?? DM is the result rather than the cause.

Familial syndromes

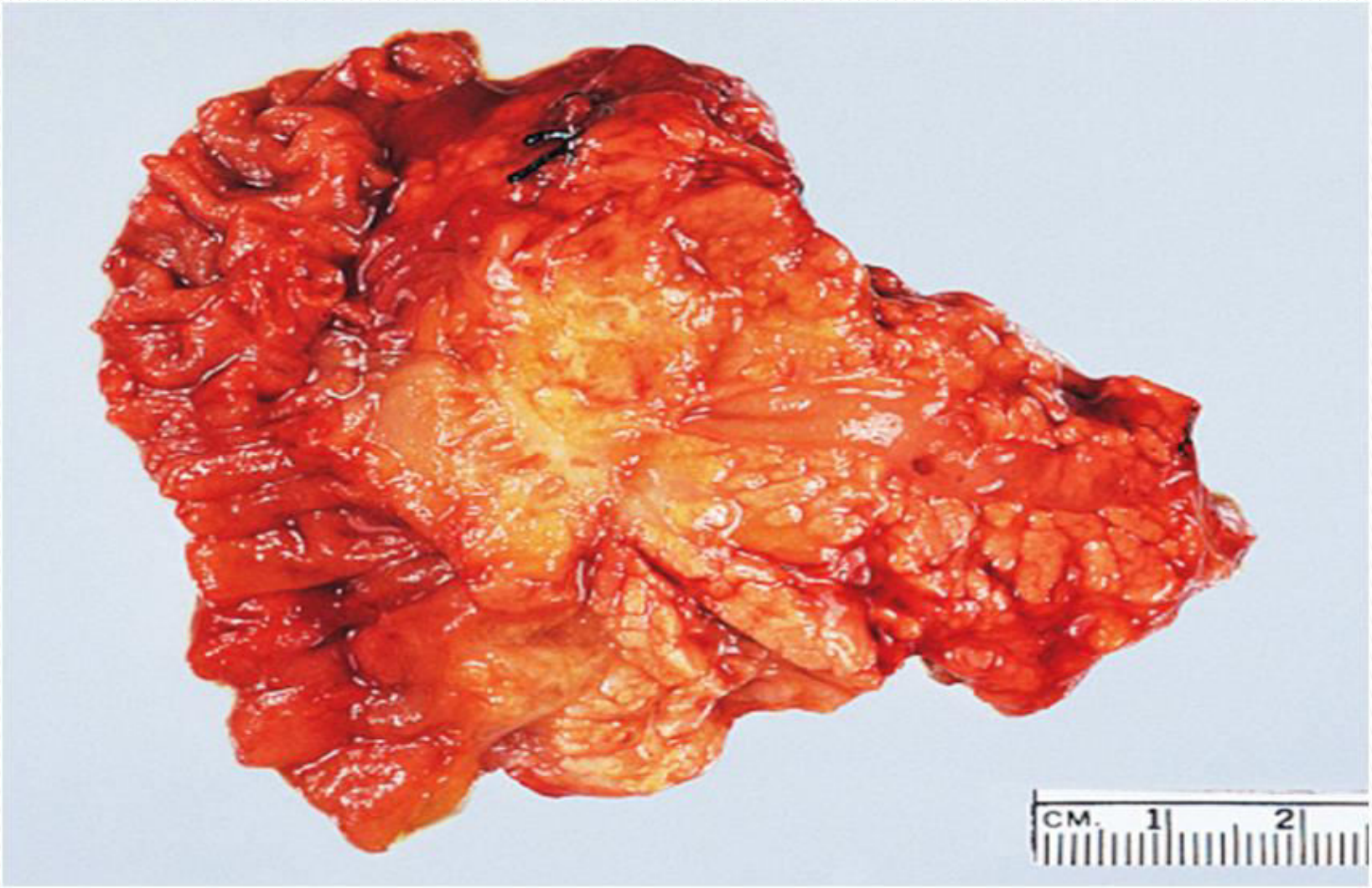
- Familial clustering of pancreatic cancer

Disorder	Gene
Hereditary nonpolyposis colorectal cancer (Lynch II)	hMSH2, hMLH1
Hereditary breast and ovarian cancer	BRCA2
Familial atypical multiple mole melanoma syndrome (FAMMM)	p16
Hereditary pancreatitis	PRSS1
Peutz-Jeghers syndrome	STK11/LKB1

Gross appearance

- **60% of arise in the head.**
  - Obstruct the CBD, present early with jaundice.
- **15% in the body, 5% in the tail.**
  - Remain silent until large & widely disseminated
- **In 20%, diffusely involves the entire organ.**
- **Gross:**
  - Hard, stellate, gray-white, poorly defined masses.
  - Extrapancreatic extension is common.

Carcinoma of head of pancreas

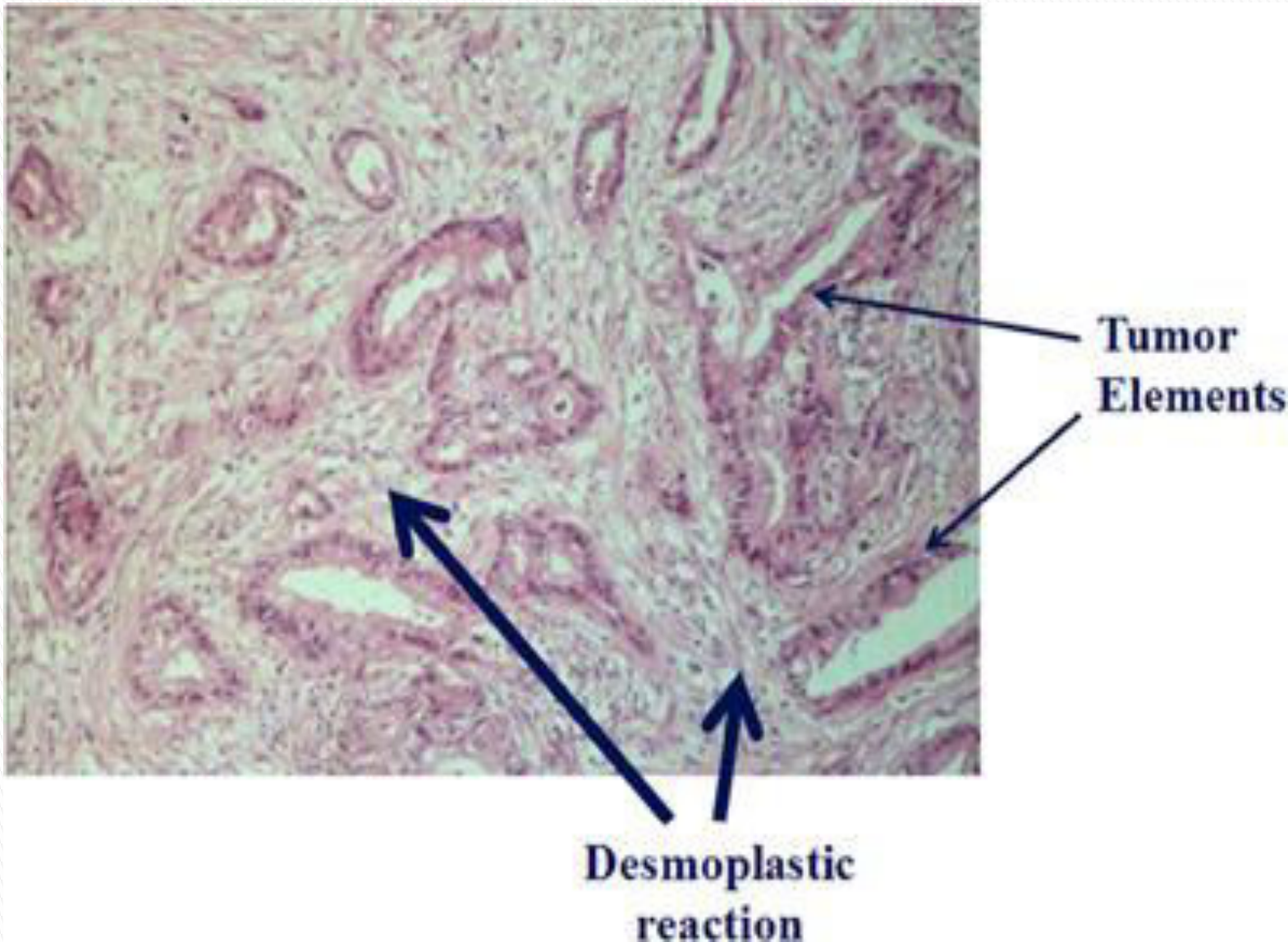


The tumor protrude into duodenal lumen

Microscopic appearance

- **Ductal adenocarcinoma**
  - Malignant glands with dense desmoplastic reaction.
  - Perineural invasion & lymphovascular invasion is common

Pancreatic ductal adenocarcinoma



Tumor spread

- **Direct spread** → Entrapping adjacent organs and nerves.
- **Lymphatic spread.**
- **Distant mets.** (esp. liver).

Clinical Features

- Early lesions are **asymptomatic.**
- Symptoms appear in advanced tumors:
  - Pain is usually the first symptom.
  - Obstructive jaundice if carcinoma is in the head of the pancreas.
  - Migratory thrombophlebitis (Trousseau syndrome) in 10% of patients.
- ↑ serum level of CEA & CA19.9

Prognosis

- The prognosis is poor
- The most important prognostic factor is **stage**
- The 5-year survival rate is dismal < 5%

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