Diseases of the Pancreas

Dr. Gary Mumaugh

- The pancreas has critical endocrine functions, and the exocrine portion of the pancreas is a major source of potent enzymes that are essential for digestion.
- Diseases affecting the pancreas can be the source of significant morbidity and mortality.
- The retroperitoneal location of the pancreas and the generally vague nature of signs and symptoms associated with its injury or dysfunction allow many pancreatic diseases to progress undiagnosed for extended periods of time.

- The epithelial cells lining the ducts also are active participants in pancreatic secretion.
- The cuboidal cells lining the smaller ductules secrete bicarbonate-rich fluid, while the columnar cells lining the larger ducts produce mucin.
- The epithelial cells of the larger ducts also express the cystic fibrosis transmembrane conductance regulator (CFTR).
  - Aberrant function of this membrane protein affects the viscosity of the pancreatic secretions and has a fundamental role in the pathophysiology of pancreatic disease in persons with cystic fibrosis.

- Autodigestion of the pancreas (e.g., in pancreatitis) can be a catastrophic event.
- A number of “fail-safe” mechanisms have evolved to minimize the risk of occurrence of this phenomenon:
  - Most pancreatic enzymes are synthesized as inactive proenzymes
  - Activation of proenzymes requires conversion of trypsinogen to trypsin
  - Trypsin inhibitors also are secreted by acinar and ductal cells

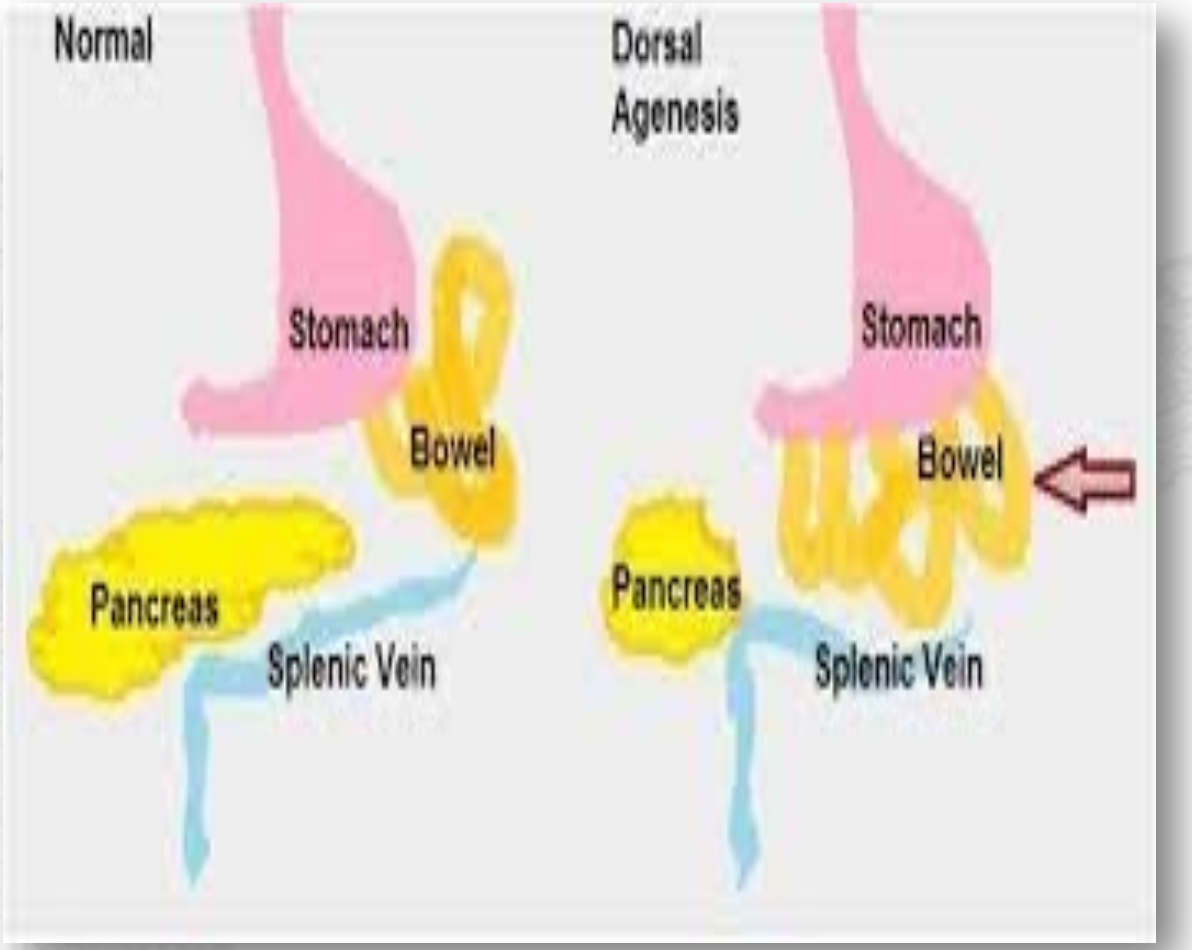
- Trypsin cleaves and inactivates itself, a negative feedback mechanism that normally puts a limit on local levels of activated trypsin.
- Acinar cells are remarkably resistant to the action of activated enzymes such as trypsin, chymotrypsin.

Congenital Anomalies

- Pancreatic development is a complex process involving fusion of dorsal and ventral primordia; subtle deviations in this process frequently give rise to congenital variations in pancreatic anatomy.
- While most of these do not cause disease, these anatomical variants (especially in ductal anatomy) can present challenges to the endoscopist and the surgeon.

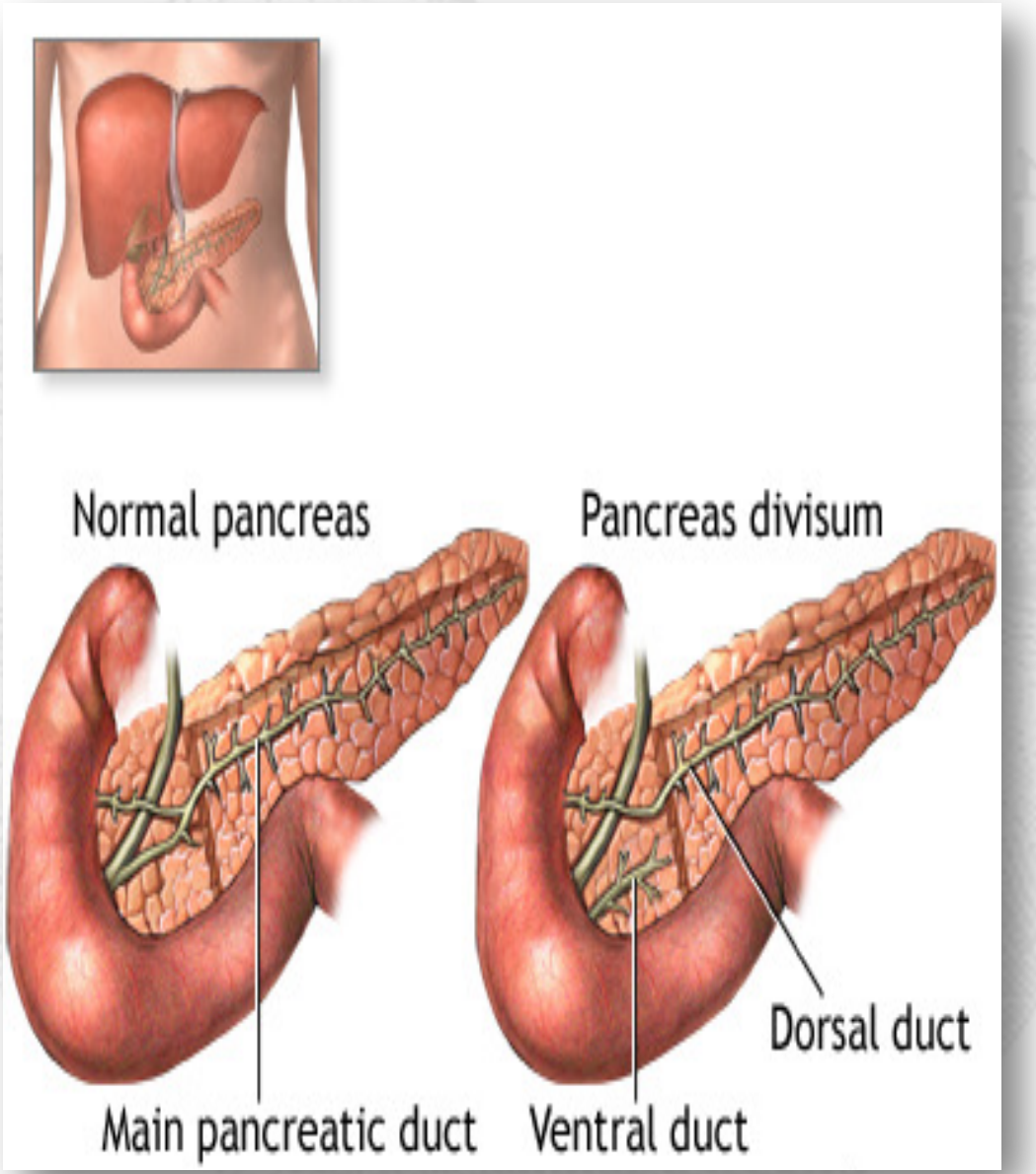
Agenesis

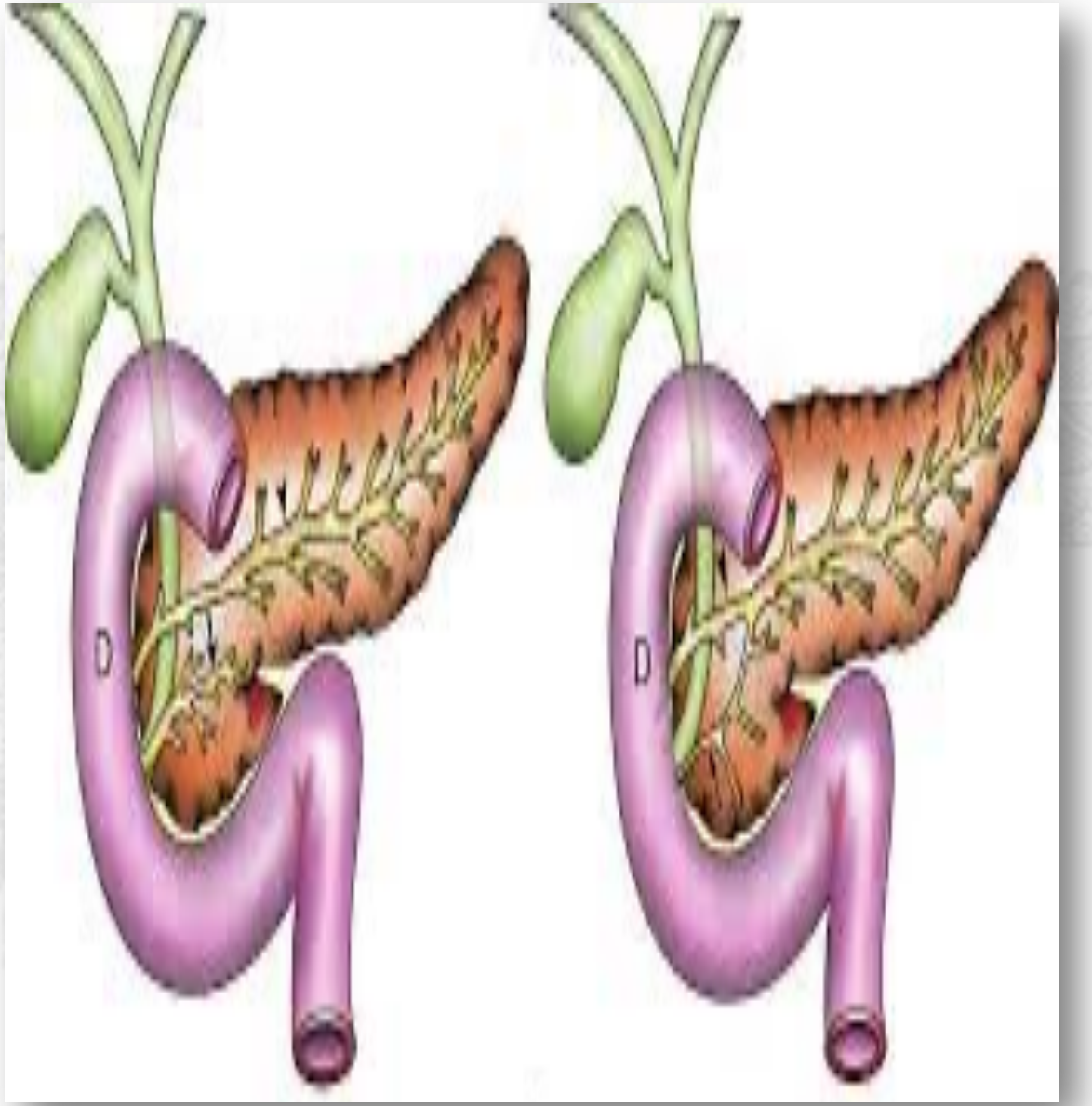
- Very rarely, the pancreas may be totally absent.
- Usually (but not invariably) associated with additional severe malformations.
- Incompatible with life,



Pancreas Divisum

- Pancreas divisum is the most common clinically significant congenital pancreatic anomaly.
- Incidence of 3% to 10% in autopsy series.
- It occurs when the duct systems fail to fuse.
- As a result, the main pancreatic duct drains only a small portion of the head of the gland, while the bulk of the pancreas drains through the minor sphincter, which has a narrow opening.
- As a result of this defect in drainage, persons with pancreas divisum have elevated intraductal pressures throughout most of the pancreas and are at increased risk for chronic pancreatitis.


Normal pancreas
Pancreas divisum
Dorsal duct
Main pancreatic duct
Ventral duct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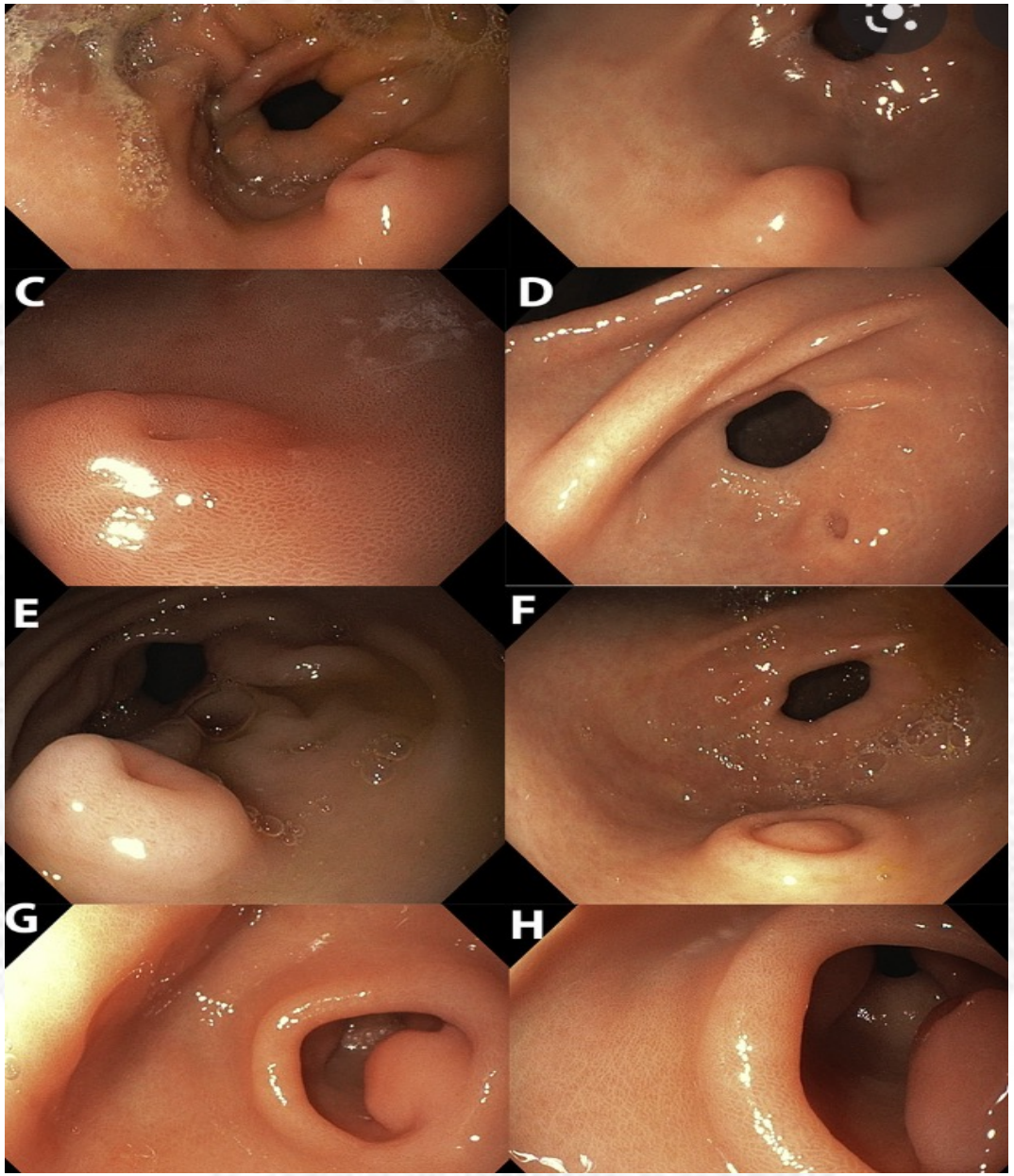
Ectopic Pancreas

- Aberrantly situated, or ectopic, pancreatic tissue occurs in about 2% of the population.
- Main sites are the stomach and duodenum, followed by the jejunum, Meckel diverticulum, and ileum.
- They are composed of normal pancreatic acini with occasional islets.
- Though usually incidental and asymptomatic, ectopic pancreas can cause pain from localized inflammation, or can cause mucosal bleeding.
- Approximately 2% of pancreatic neuroendocrine tumors arise in ectopic pancreatic tissue.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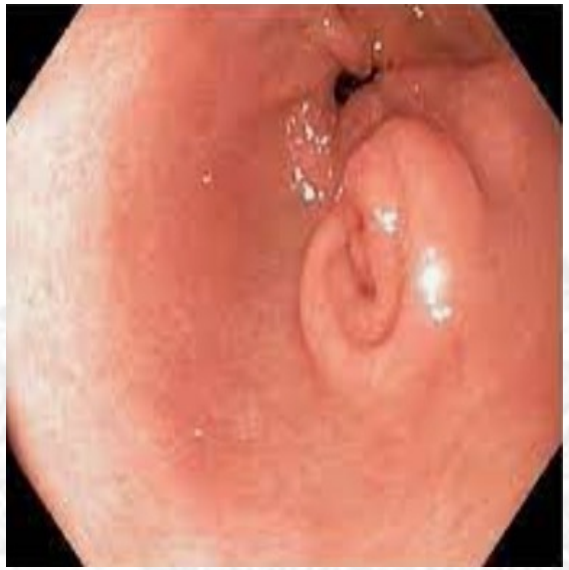
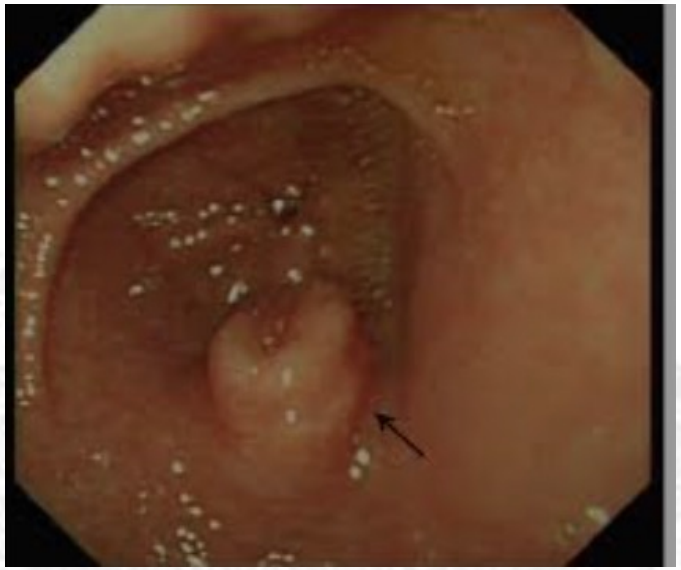
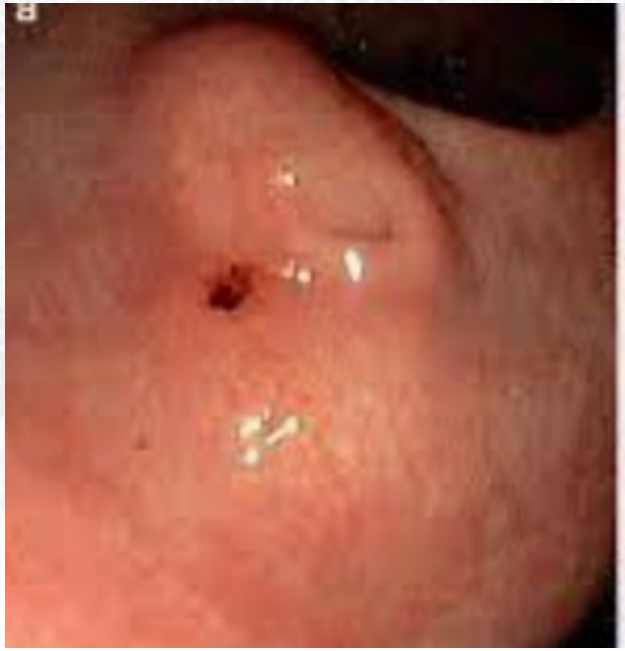
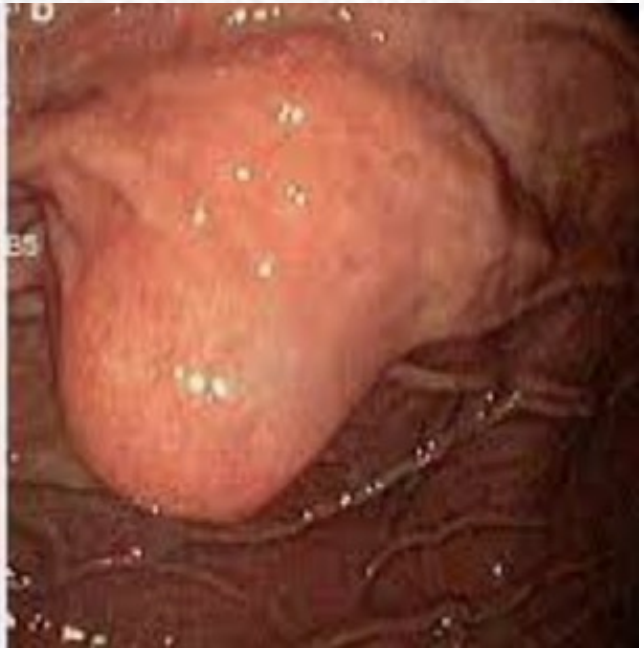


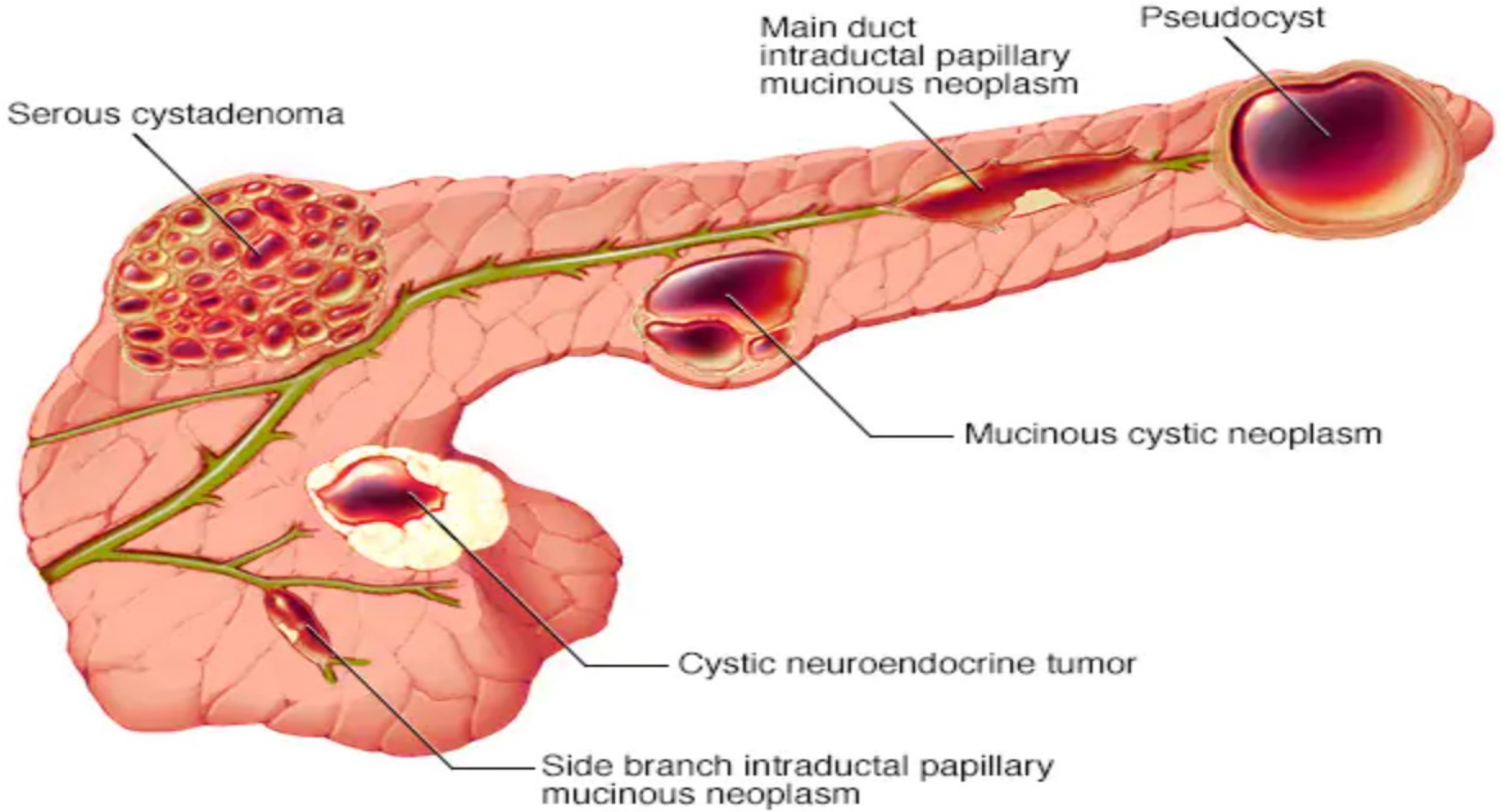






Congenital Cysts

- Congenital pancreatic cysts probably result from anomalous development of the pancreatic ducts.
- In polycystic disease, the kidneys, liver, and pancreas can all contain cysts.
- Congenital cysts generally are from microscopic to 5 cm in diameter.
- These benign cysts contain clear serous fluid.
  - This is an important point of distinction from pancreatic cystic neoplasms, which often are mucinous.


Main duct
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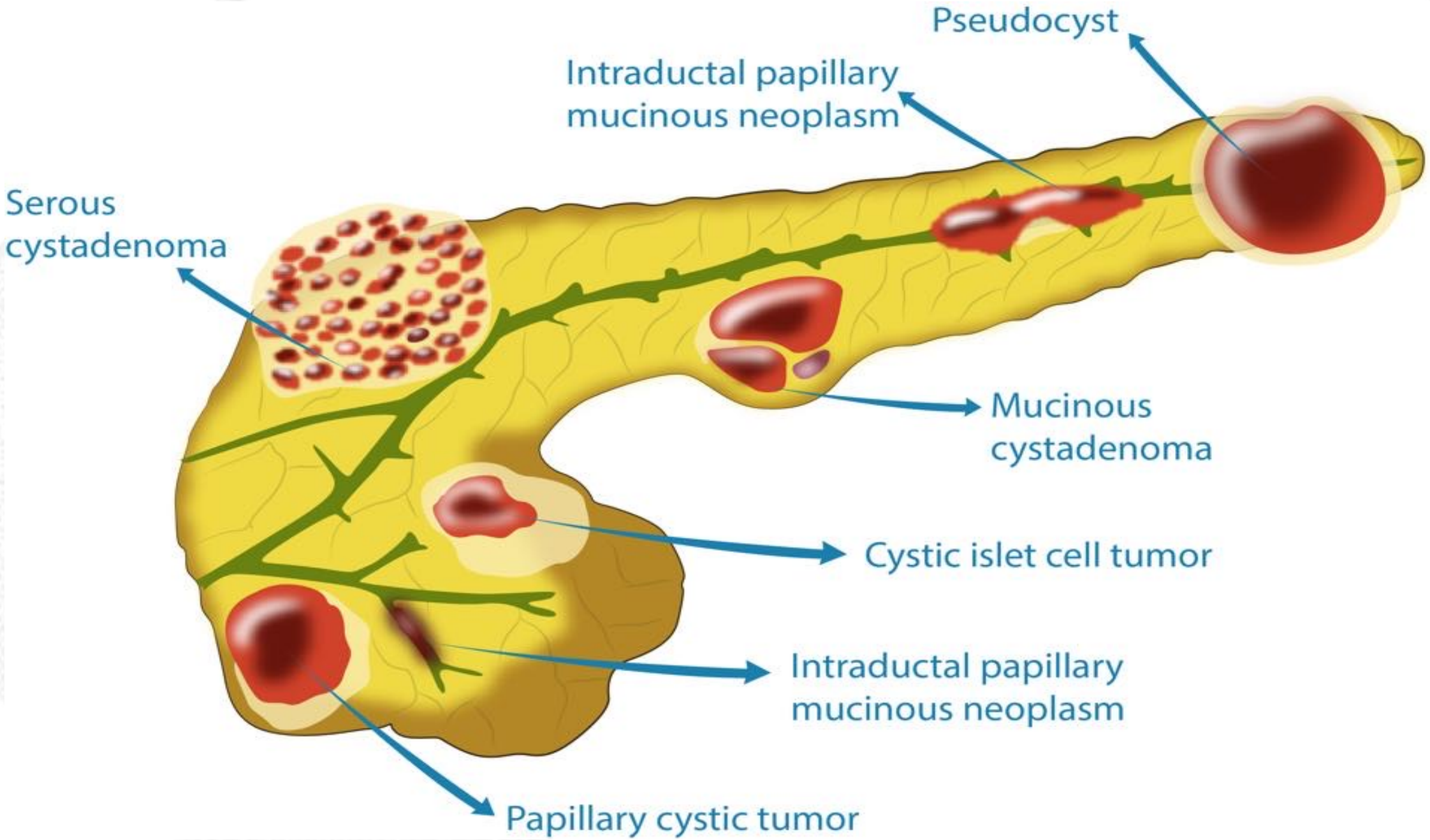
Pseudocyst
Serous cystadenoma
Mucinous cystic neoplasm
Cystic neuroendocrine tumor
Side branch intraductal papillary
mucinous neoplasm


Pseudocyst
Intraductal papillary mucinous neoplasm
Serous cystadenoma
Mucinous cystadenoma
Cystic islet cell tumor
Intraductal papillary mucinous neoplasm
Papillary cystic tumor

Pancreatitis

- Inflammatory disorders of the pancreas range in severity from mild, self-limited disease to life-threatening.
- Pancreatitis is very destructive pathology, and can be serious and permanent.
- In acute pancreatitis, function can return to normal if the underlying cause of inflammation is removed, and the diagnosis is caught early.
- By contrast, chronic pancreatitis is defined by irreversible destruction of exocrine pancreatic parenchyma.

Acute Pancreatitis

- Acute pancreatitis is a reversible inflammatory disorder that varies in severity, ranging from local edema and fat necrosis to widespread hemorrhagic parenchymal necrosis.
- Acute pancreatitis is relatively common, with an annual incidence of 10 to 20 per 100,000 people in the Western world.
- Approximately 75% of the cases are attributable to alcoholism.
- 35% to 60% of the cases have gallstones.
- Roughly 5% of patients with gallstones develop acute pancreatitis.

Etiology of Acute Pancreatitis

- Metabolic
  - Alcoholism - most common in USA
  - Hyperlipoproteinemia
  - Hypercalcemia
  - Drugs (e.g., azathioprine)

- Mechanical
  - Gallstones - most common in USA
  - Trauma
  - Iatrogenic injury
  - Perioperative injury
  - Endoscopic procedures with dye injection

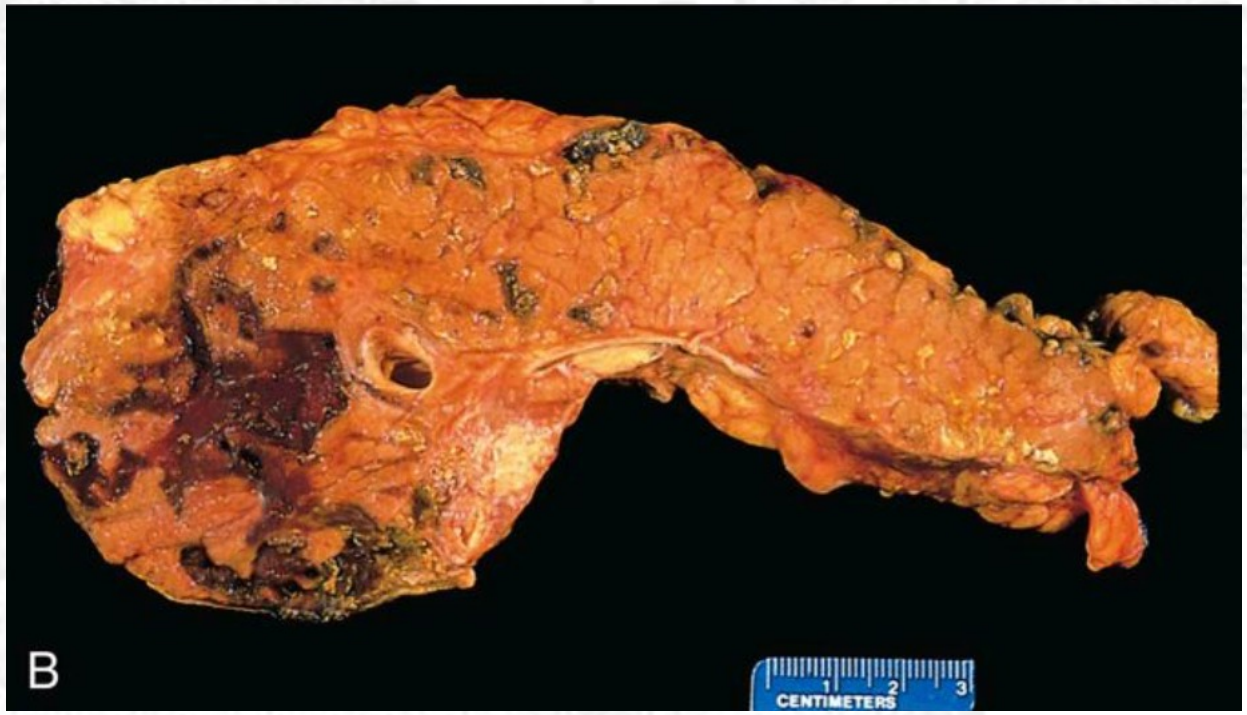
Etiology of Acute Pancreatitis

- Vascular
  - Shock
  - Atheroembolism
  - Polyarteritis nodosa
- Infectious
  - Mumps
  - Coxsackievirus
- Genetic mutations

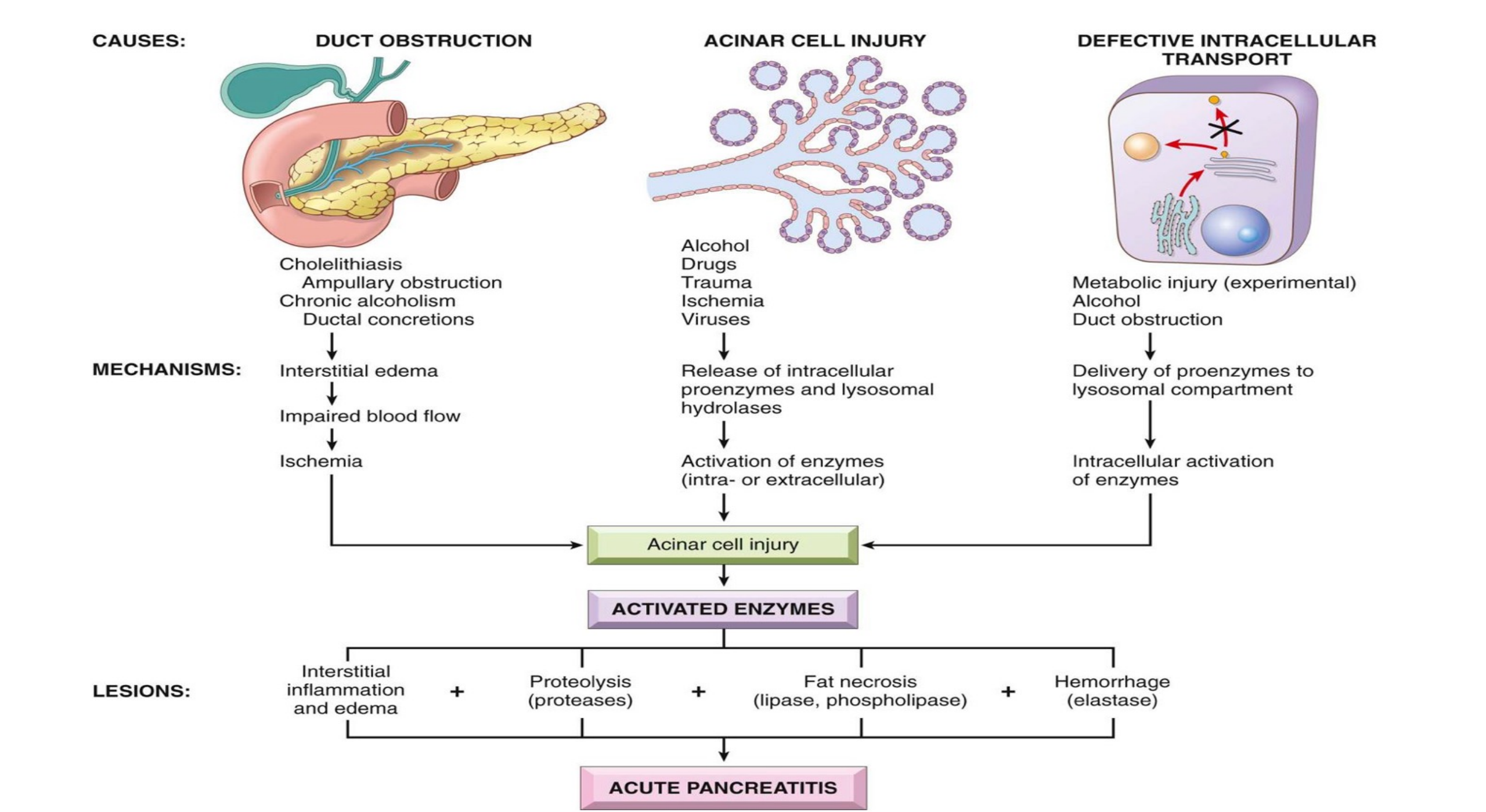
Other Causes of Pancreatitis

- Non–gallstone related obstruction of the pancreatic ducts
  - Due to neoplasms, pancreas divisum, or parasites.
- Medications including anticonvulsants, cancer chemotherapeutic agents, diuretics, estrogens, and more than 85 others in clinical use
- Infections with mumps virus or coxsackievirus
- Metabolic disorders, including hypertriglyceridemia, hyperparathyroidism, and other hypercalcemic states
- Ischemia due to vascular thrombosis, embolism, vasculitis, or shock
- Trauma, both blunt force and iatrogenic during surgery or endoscopy
- Inherited mutations

- 10% to 20% of cases of acute pancreatitis have no identifiable cause (idiopathic pancreatitis).



The pancreas has been sectioned longitudinally to reveal dark areas of hemorrhage in the pancreatic substance and a focal area of pale fat necrosis


CAUSES:
DUCT OBSTRUCTION
ACINAR CELL INJURY
DEFECTIVE INTRACELLULAR TRANSPORT
Cholelithiasis
Ampullary obstruction
Chronic alcoholism
Ductal concretions
Alcohol
Drugs
Trauma
Ischemia
Viruses
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

Changes in Pancreatitis

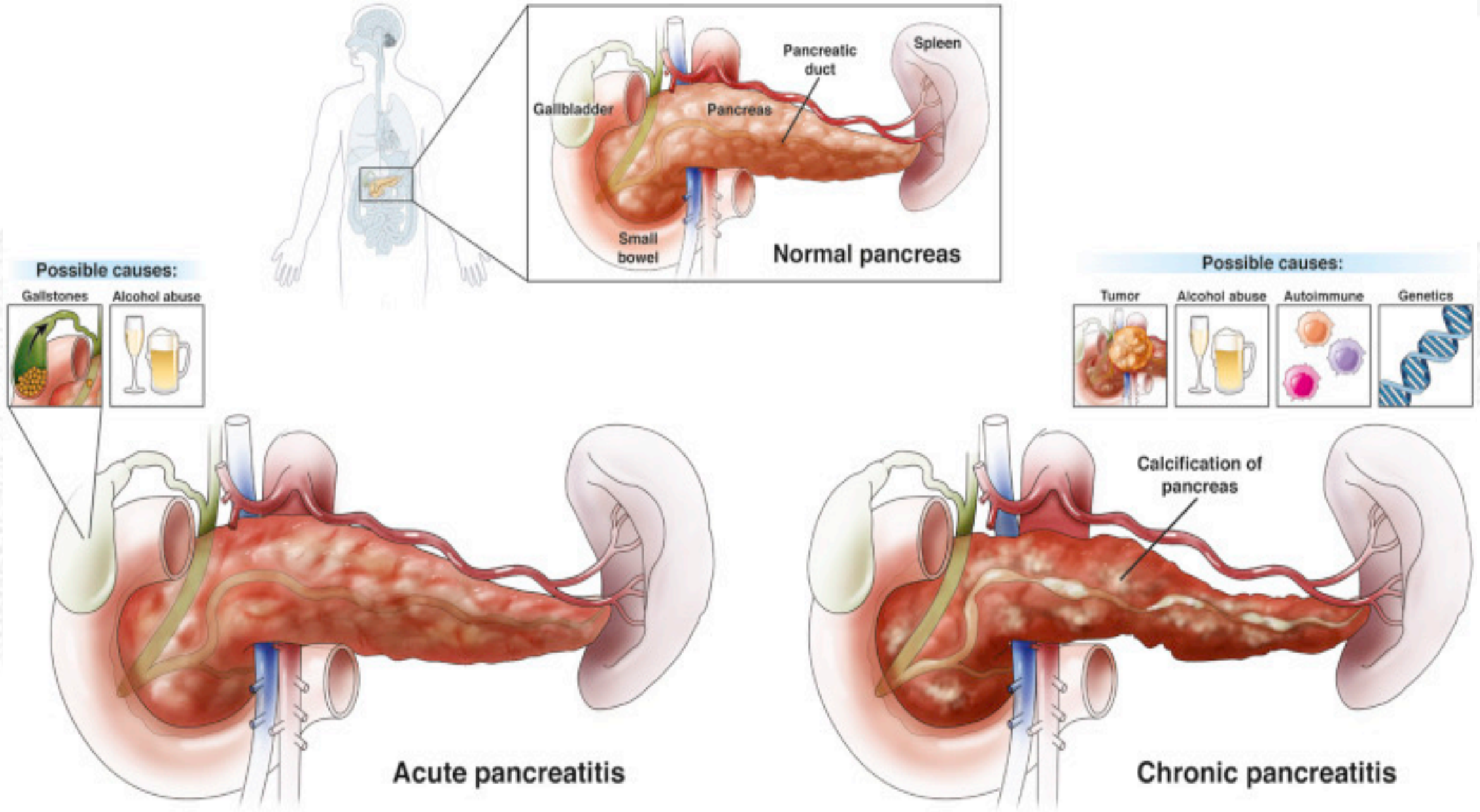
- The basic alterations in acute pancreatitis are
  - (1) microvascular leakage causing edema
  - (2) necrosis of fat by lipases
  - (3) an acute inflammatory reaction
  - (4) proteolytic destruction of pancreatic parenchyma, and
  - (5) destruction of blood vessels leading to interstitial hemorrhage

- In more severe forms, such as acute necrotizing pancreatitis, necrosis of pancreatic tissue affects acinar and ductal tissues as well as the islets of Langerhans; vascular damage causes hemorrhage into the parenchyma of the pancreas.
- In the most severe form, hemorrhagic pancreatitis, extensive parenchymal necrosis is accompanied by diffuse hemorrhage within the substance of the gland.

Pancreatitis Pathogenesis

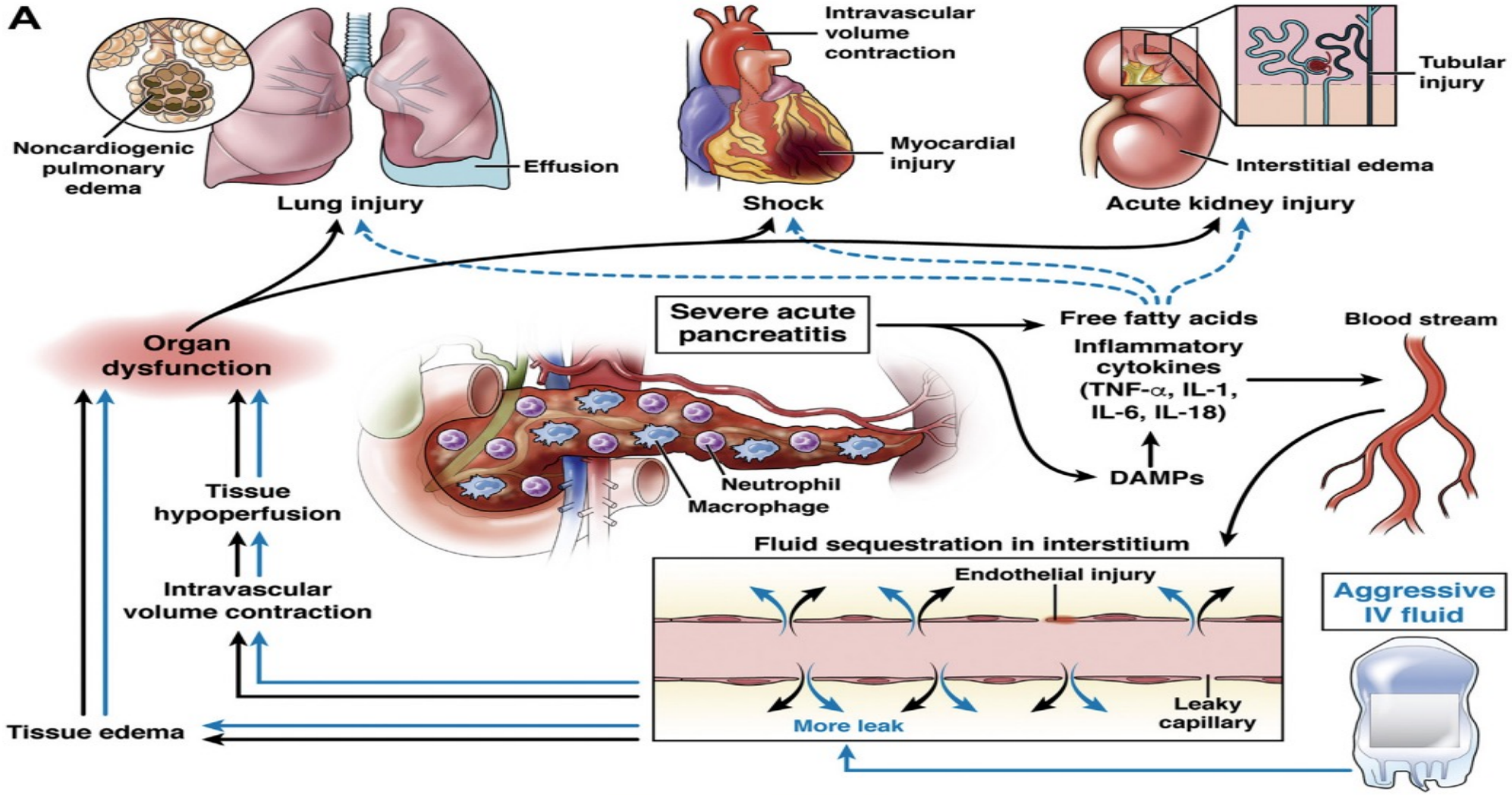
- Pancreatic duct obstruction.
- Impaction of a gallstone or biliary sludge, or extrinsic compression of the ductal system increases intraductal pressure, and allows accumulation of an enzyme-rich interstitial fluid.
- Since lipase is secreted in an active form, local fat necrosis may result.
- Injured tissues, myofibroblasts, and leukocytes then release pro-inflammatory cytokines that promote local inflammation and interstitial edema through a leaky microvasculature.

- Edema further compromises local blood flow, causing vascular insufficiency and ischemic injury to acinar cells.
- Primary acinar cell injury.
  - This pathogenic mechanism comes into play in acute pancreatitis caused by ischemia, viral infections (e.g., mumps), drugs, and direct trauma to the pancreas.


Pancreatic duct
Spleen
Gallbladder
Pancreas
Small bowel
Normal pancreas
Possible causes:
Gallstones
Alcohol abuse
Acute pancreatitis
Possible causes:
Tumor
Alcohol abuse
Autoimmune
Genetics
Calcification of pancreas
Chronic pancreatitis

Alcohol Consumption

- Alcohol consumption may cause pancreatitis by several mechanisms.
- Alcohol transiently increases pancreatic exocrine secretion and contraction of the sphincter of Oddi.
- Alcohol also has direct toxic effects on acinar cells, which leads to membrane damage.
- Chronic alcohol ingestion results in the secretion of protein-rich pancreatic fluid, which leads to the deposition of protein plugs and obstruction of small pancreatic ducts.


A
Noncardiogenic pulmonary edema
Effusion
Lung injury
Intravascular volume contraction
Myocardial injury
Shock
Tubular injury
Interstitial edema
Acute kidney injury
Severe acute pancreatitis
Free fatty acids
Inflammatory cytokines (TNF-α, IL-1, IL-6, IL-18)
DAMPs
Blood stream
Organ dysfunction
Tissue hypoperfusion
Intravascular volume contraction
Tissue edema
Neutrophil
Macrophage
Fluid sequestration in interstitium
Endothelial injury
More leak
Leaky capillary
Aggressive IV fluid
B
Mild acute pancreatitis
Preserved neurohumoral mechanisms & intact capillary circulation
No systemic inflammation
Minimal fluid deficit, no capillary leak
If given aggressive fluids
Potentially no significant harm, diuresis
No organ dysfunction

Clinical Features of Pancreatitis

- Abdominal pain is the cardinal manifestation of acute pancreatitis.
- Its severity varies from mild and uncomfortable to severe and incapacitating.
- Suspected acute pancreatitis is diagnosed primarily by the presence of elevated plasma levels of amylase and lipase and the exclusion of other causes of abdominal pain.
- In 80% of cases acute pancreatitis is mild and self limiting; the remaining 20% develop severe disease.

- Full-blown acute pancreatitis constitutes a medical emergency of the first magnitude.
- Affected persons usually experience the sudden calamitous onset of an “acute abdomen” with pain, abdominal guarding, and the ominous absence of bowel sounds.
- Characteristically, the pain is constant and intense and often is referred to the upper back.

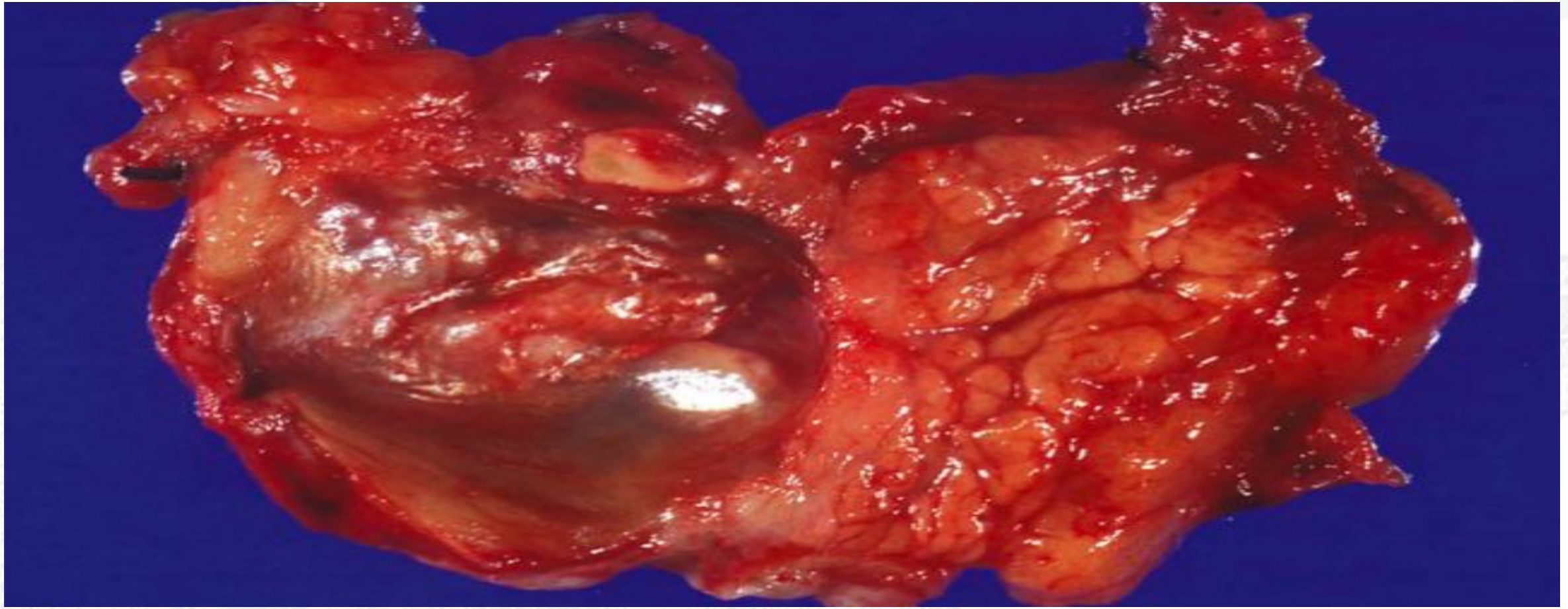
- The manifestations of severe acute pancreatitis are attributable to systemic release of digestive enzymes and explosive activation of the inflammatory response. The initial clinical evaluation may reveal leukocytosis.
- Peripheral vascular collapse (shock) can rapidly ensue as a result of increased microvascular permeability and resultant hypovolemia.

- Laboratory findings include markedly elevated serum amylase during the first 24 hours, followed (within 72 to 96 hours) by rising serum lipase levels.
- The enlarged inflamed pancreas can be visualized by computed tomography (CT) or magnetic resonance imaging (MRI).

- Management of acute pancreatitis is supportive therapy (e.g., maintaining blood pressure and alleviating pain) and “resting” the pancreas by total restriction of food and fluids.
- In 40% to 60% of cases of acute necrotizing pancreatitis, the necrotic debris becomes infected.
- Most persons with acute pancreatitis eventually recover, some 5% die from shock during the first week.

Pancreatic Pseudocysts

- A common sequela of acute pancreatitis (and in particular, alcoholic pancreatitis) is a pancreatic pseudocyst.
- Liquefied areas of necrotic pancreatic tissue become walled off by fibrous tissue to form a cystic space, lacking an epithelial lining (hence the designation pseudo).
- The cyst contents are rich in pancreatic enzymes, and a laboratory assessment of the cyst aspirate can be diagnostic.
- Pseudocysts account for approximately 75% of all pancreatic cysts.
- While many pseudocysts spontaneously resolve, they can become secondarily infected, and larger pseudocysts can compress or even perforate into adjacent structures.



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

Chronic Pancreatitis

- Chronic pancreatitis is characterized by long-standing inflammation, fibrosis, and destruction of the exocrine pancreas.
- The chief distinction between acute and chronic pancreatitis is the irreversible impairment in pancreatic function in chronic pancreatitis.
- The prevalence of chronic pancreatitis is difficult to determine but probably ranges between 1% and 5% of the U.S. population.
- By far the most common cause of chronic pancreatitis is long-term alcohol abuse.

- Less common causes of chronic pancreatitis include
  - Pancreatic duct obstruction (e.g., by pseudocysts, calculi, neoplasms, or pancreas divisum)
  - Tropical pancreatitis in Africa and Asia
  - Hereditary pancreatitis
  - Chronic pancreatitis associated with Cystic Fibrosis mutations
- As many as 40% of persons with chronic pancreatitis have no recognizable predisposing factors.
- A growing number of these “idiopathic” cases are associated with genetic mutations.

Clinical Features of Chronic Pancreatitis

- Chronic pancreatitis manifests in several different ways.
- Repeated bouts of jaundice
- Vague indigestion
- Persistent or recurrent abdominal and back pain
- It may be entirely silent until pancreatic insufficiency and diabetes mellitus develop.

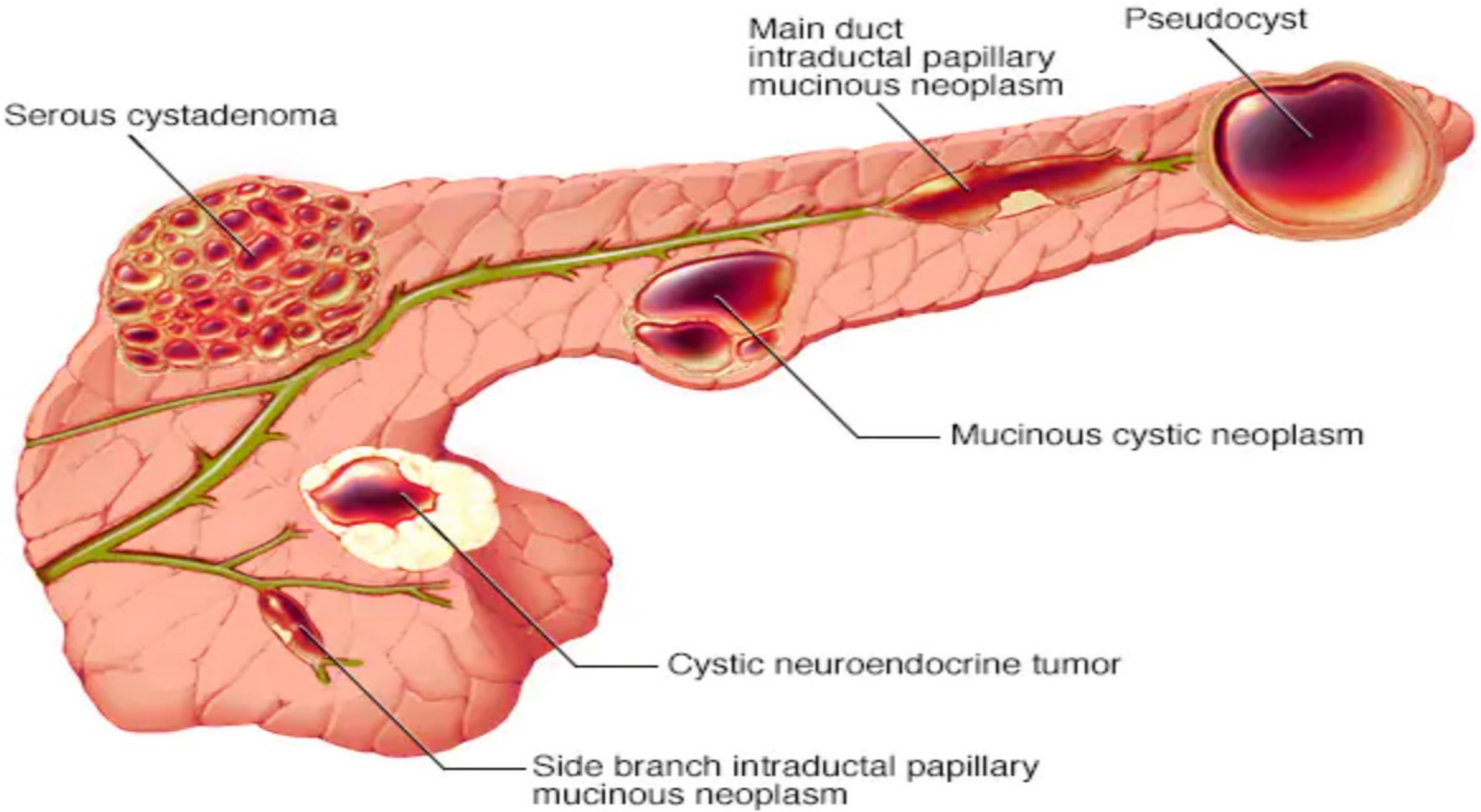
- Attacks can be precipitated by alcohol abuse, overeating (increases demand on pancreatic secretions), or opiates or other drugs that increase the muscle tone of the sphincter of Oddi.
- Although chronic pancreatitis is usually not acutely life-threatening, the long-term outlook is poor, with a 50% mortality rate over 20 to 25 years.
- Severe pancreatic exocrine insufficiency and chronic malabsorption may develop, as can diabetes mellitus.

Pancreatic Neoplasms

- Pancreatic exocrine neoplasms can be cystic or solid.
- Some tumors are benign, while others are among the most lethal of all malignancies.

Cystic Neoplasms

- Only 5% to 15% of all pancreatic cysts are neoplastic.


Main duct
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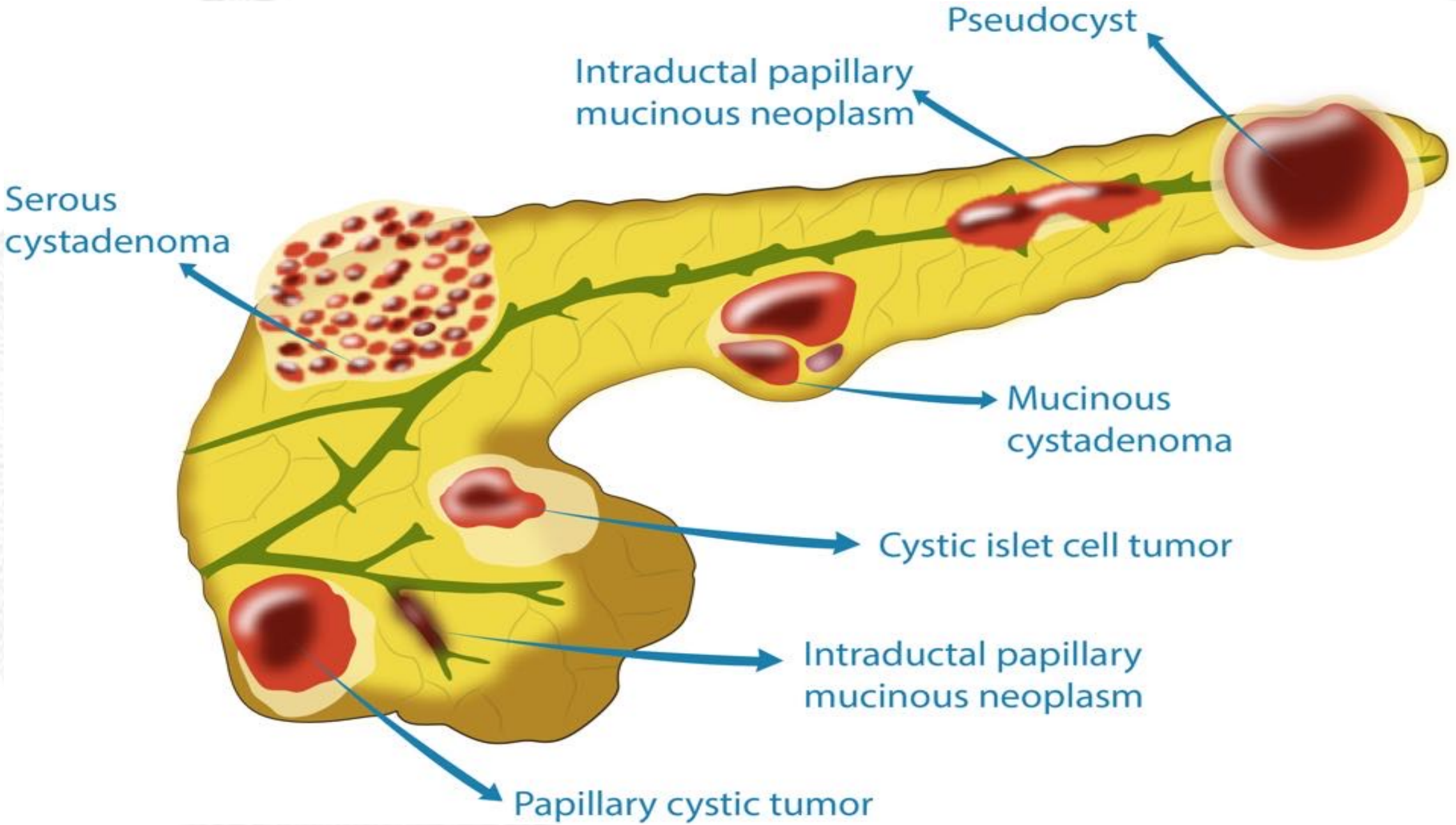
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Serous cystadenoma
Mucinous cystadenoma
Cystic islet cell tumor
Intraductal papillary mucinous neoplasm
Papillary cystic tumor

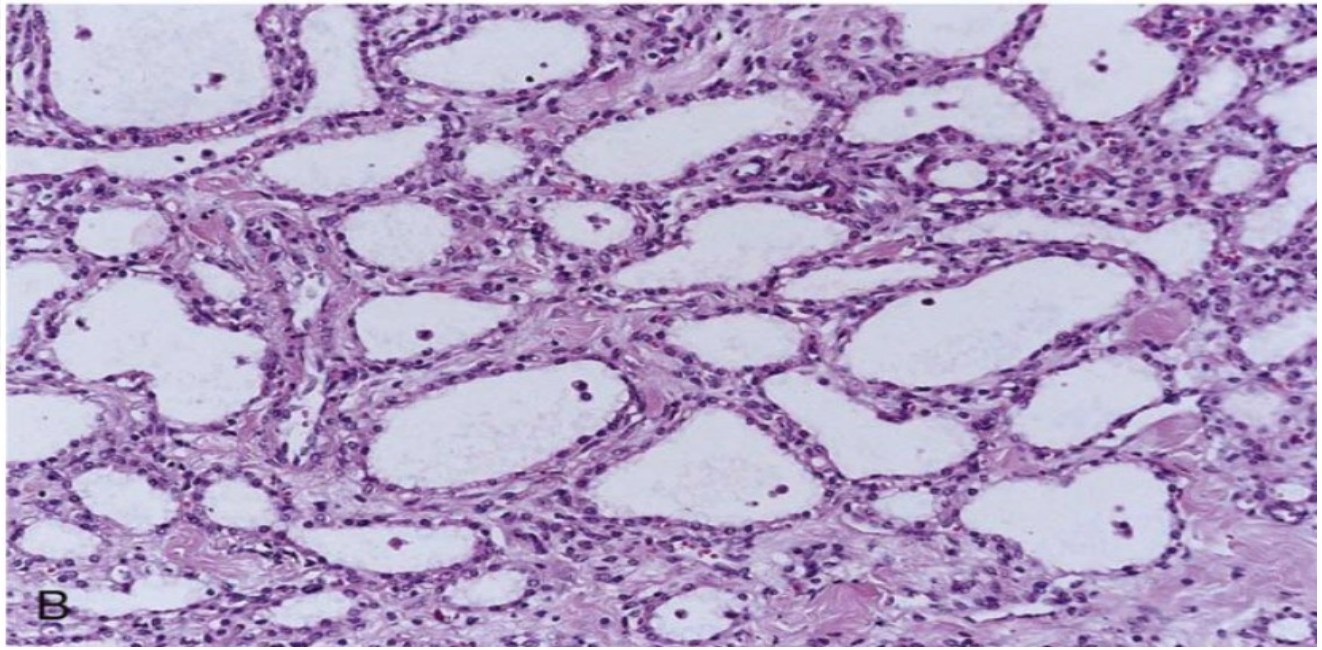
Serous Cystadenomas

- Serous cystadenomas account for approximately 25% of all pancreatic cystic neoplasms.
- They are composed of cuboidal cells surrounding small cysts containing clear, straw-colored fluid.
- The tumors typically manifest in the seventh decade of life with nonspecific symptoms such as abdominal pain; the female-to-male ratio is 2:1.

Serous cystadenoma

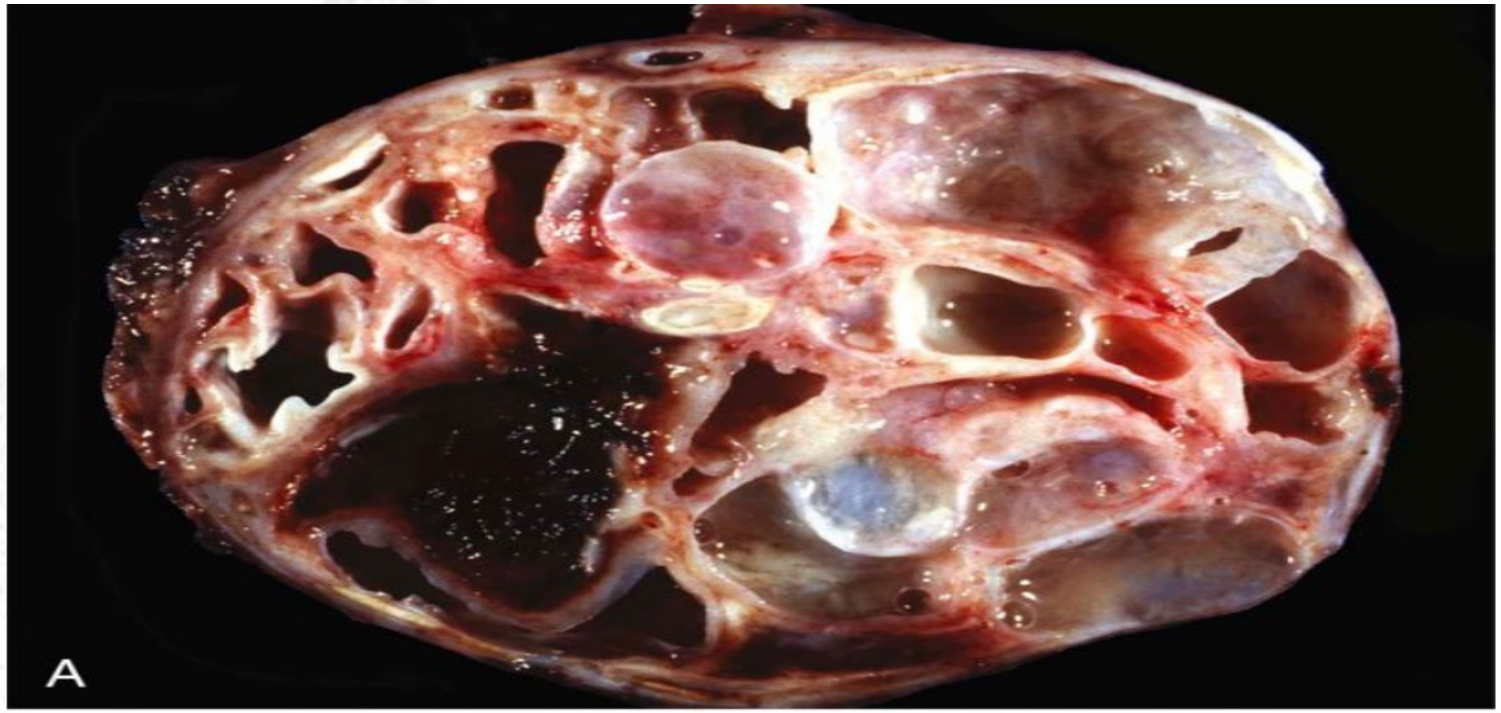
Cross-section through a serous cystadenoma. Only a thin rim of normal pancreatic parenchyma remains. The cysts are relatively small and contain clear, straw-colored fluid.

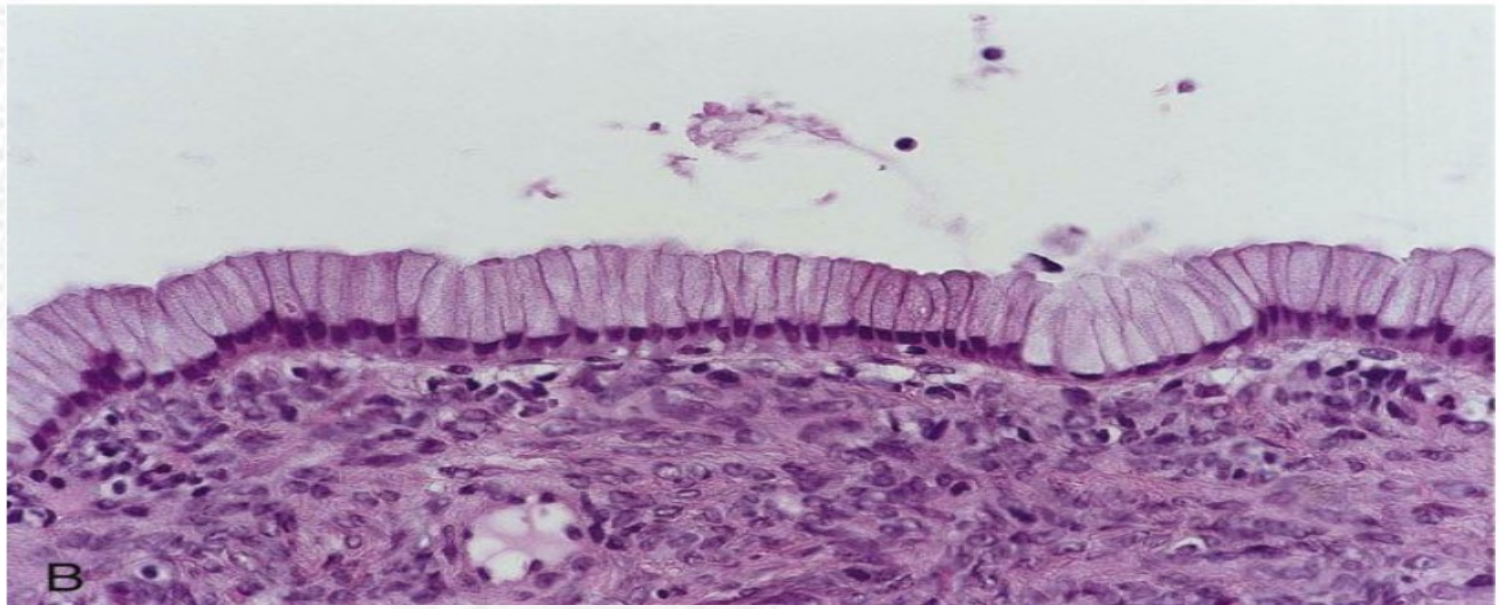
The cysts are lined by cuboidal epithelium without atypia.



Mucinous Cystic Neoplasms

- Close to 95% of mucinous cystic neoplasms arise in women, usually in the body or tail of the pancreas, and manifest as painless, slow-growing masses.
- Up to one third of these cysts can be associated with an invasive adenocarcinoma.





Mucinous cystic neoplasm

Cross-section through a mucinous multiloculated cyst in the tail of the pancreas. The cysts are large and filled with tenacious mucin.

The cysts are lined by columnar mucinous epithelium, with a densely cellular “ovarian” stroma.

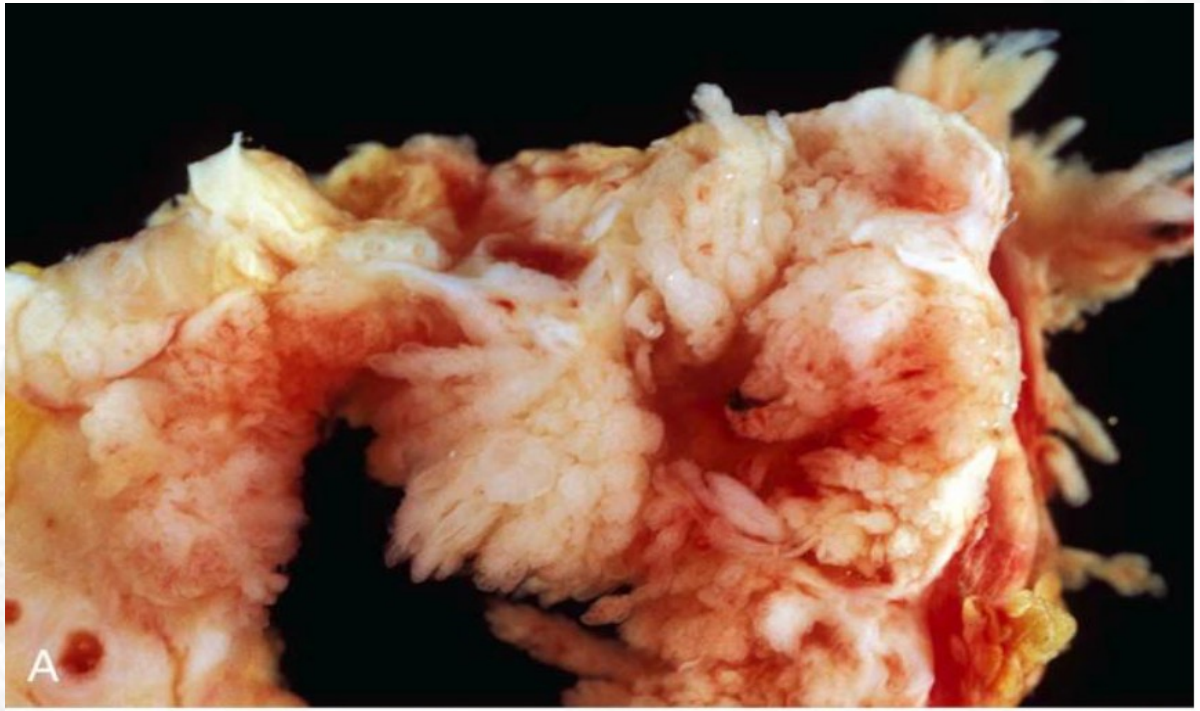
Intraductal Papillary Mucinous Neoplasms

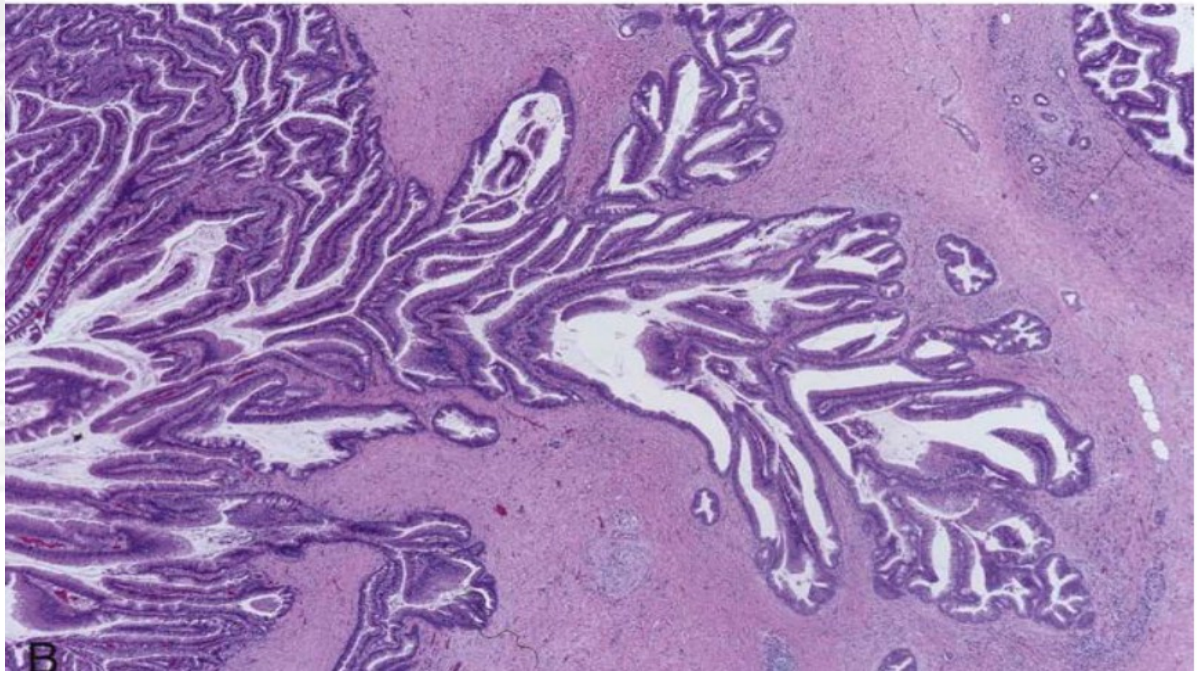
- Intraductal papillary mucinous neoplasms are mucin-producing intraductal neoplasms.
- In contrast with mucinous cystic neoplasms, they occur more frequently in men than in women and more frequently involve the head of the pancreas.

Intraductal papillary mucinous neoplasm

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

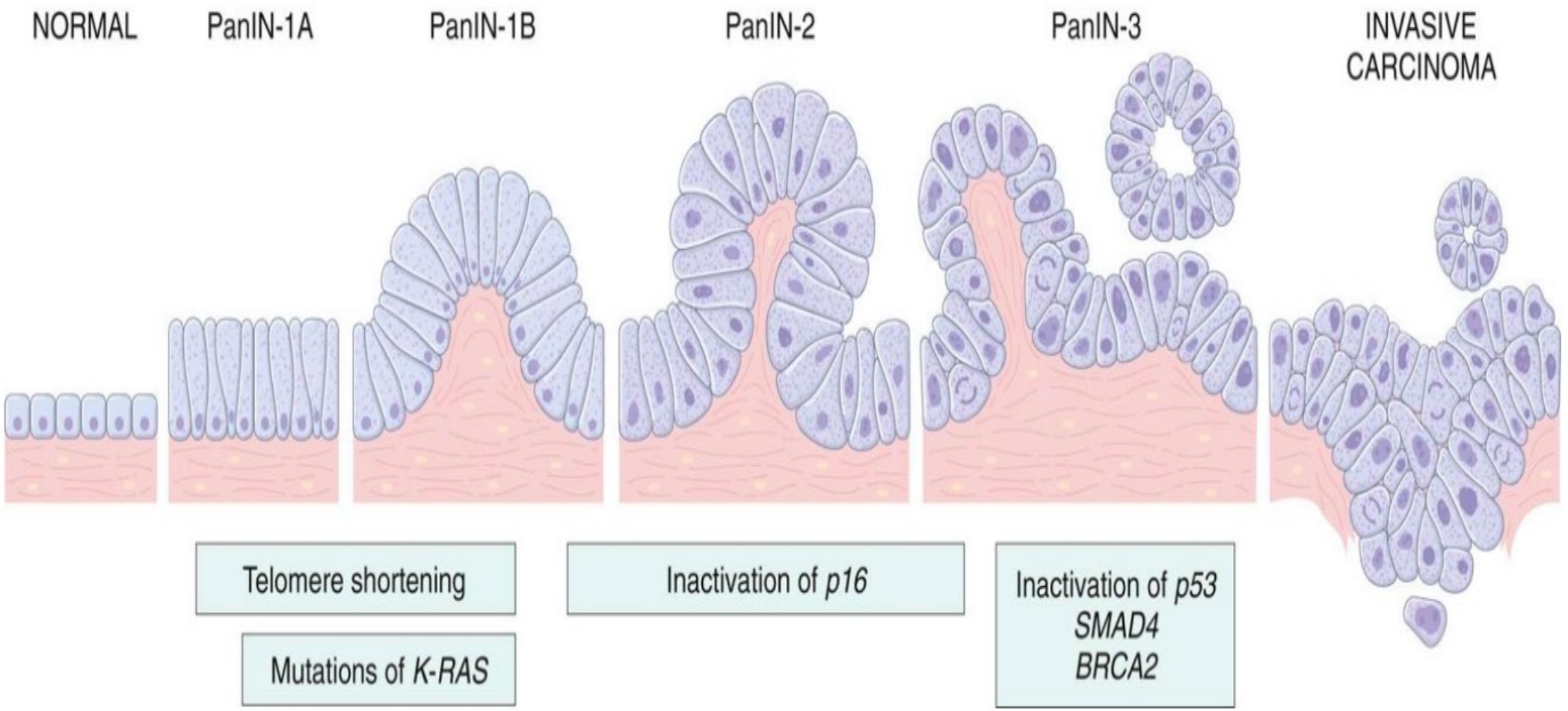
The papillary mucinous neoplasm involved the main pancreatic duct (left) and is extending down into the smaller ducts and ductules (right).





Pancreatic Carcinoma

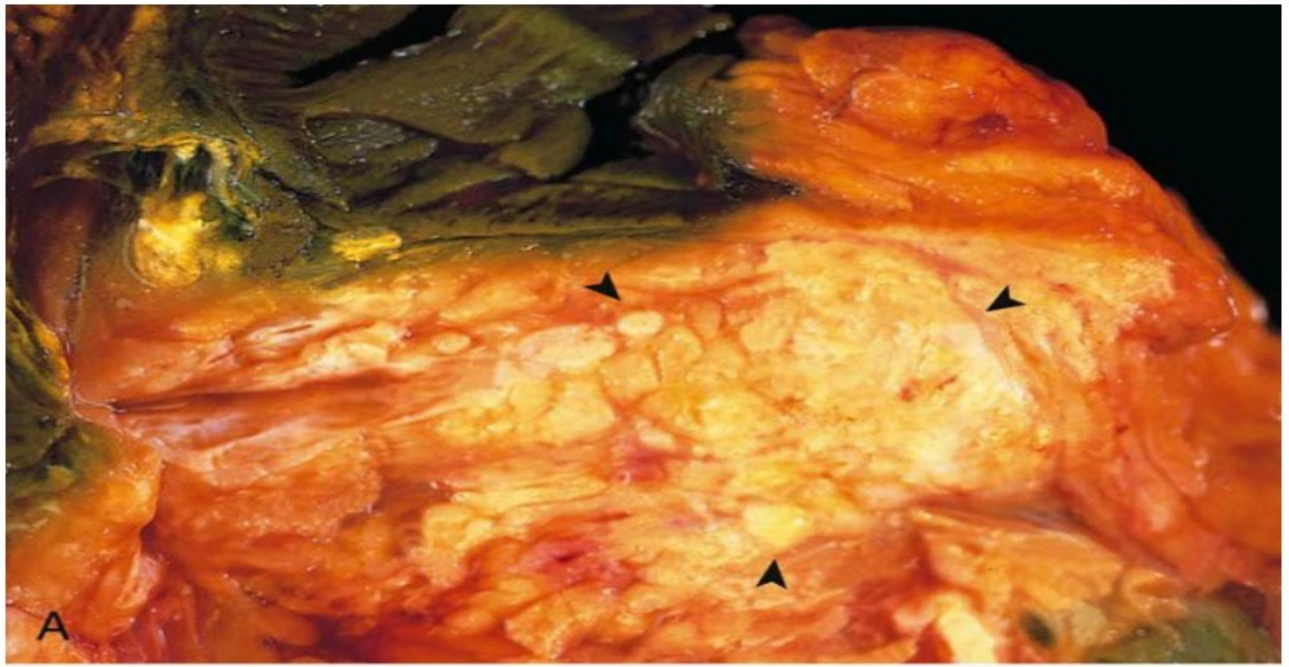
- Infiltrating ductal adenocarcinoma of the pancreas (more commonly referred to as “pancreatic cancer”) is the fourth leading cause of cancer death in the United States, preceded only by lung, colon, and breast cancers. Although it is substantially less common than the other three malignancies, pancreatic carcinoma is near the top of the list of killers because it carries one of the highest mortality rates. Over 44,000 Americans were diagnosed with pancreatic cancer in 2010, and virtually all will die of it; the 5-year survival rate is dismal—less than 5%.

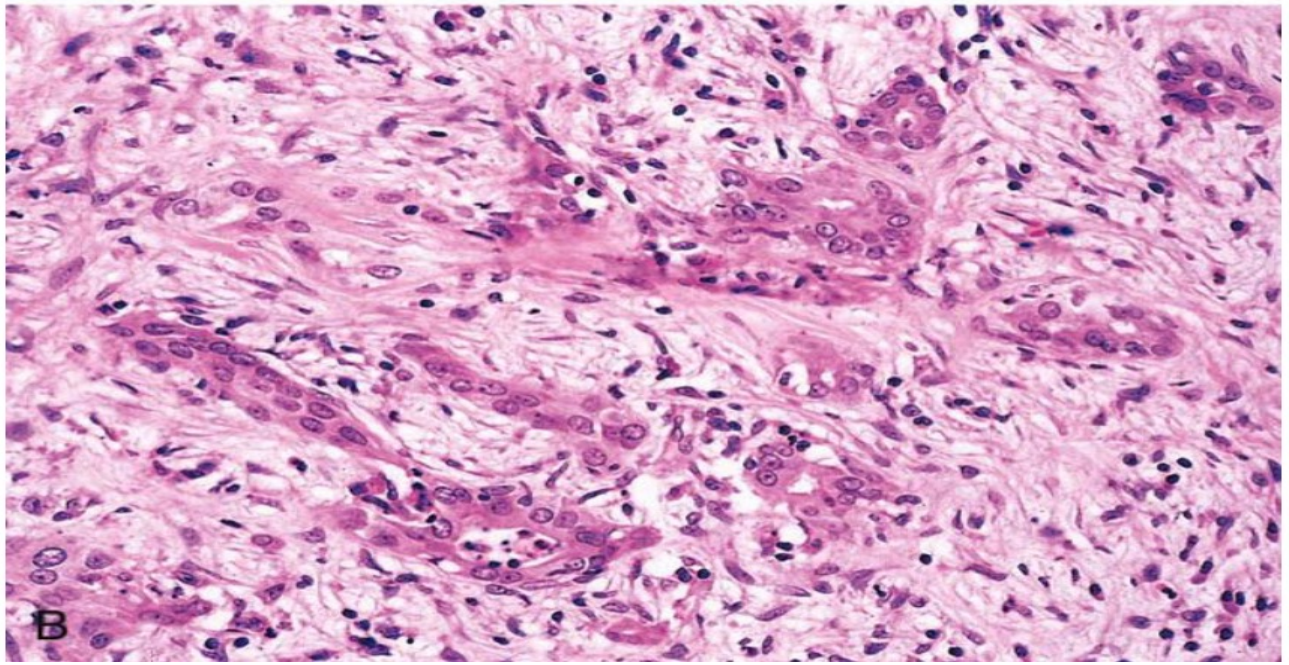

NORMAL
PanIN-1A
PanIN-1B
PanIN-2
PanIN-3
INVASIVE CARCINOMA
Telomere shortening
Mutations of K-RAS
Inactivation of p16
Inactivation of p53
SMAD4
BRCA2

Carcinoma of the pancreas

A cross-section through the head of the pancreas and adjacent common bile duct showing both an ill-defined mass in the pancreatic substance (arrowheads) and the green discoloration of the duct resulting from total obstruction of bile flow.

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





Pathogenesis

- Like all cancers, pancreatic cancer arises as a consequence of inherited and acquired mutations in cancer-associated genes.
- Both intraductal papillary mucinous neoplasms and mucinous cystic neoplasms can progress to invasive adenocarcinoma and are thus considered bona fide precursors of cancer.
- The most common lesions of pancreatic cancer arise in small ducts and ductules, and are called pancreatic intraepithelial neoplasias (PanINs).

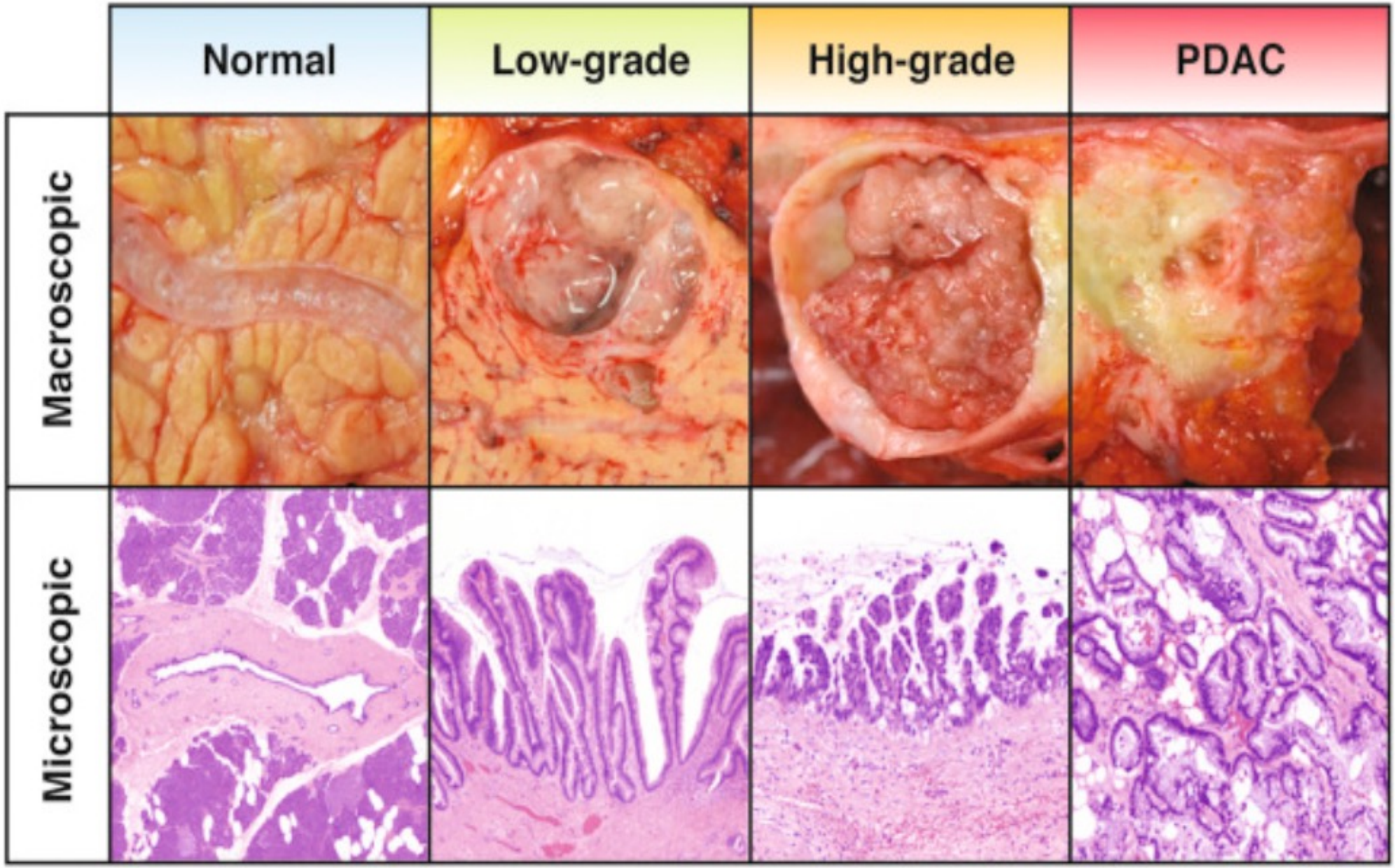
- What causes these molecular changes is unknown.
- Pancreatic cancer is primarily a disease of the elderly population, with 80% of cases occurring between the ages of 60 and 80.
- The strongest environmental influence is smoking, which doubles the risk.
- Chronic pancreatitis and diabetes mellitus are also both associated with an increased risk of pancreatic cancer.

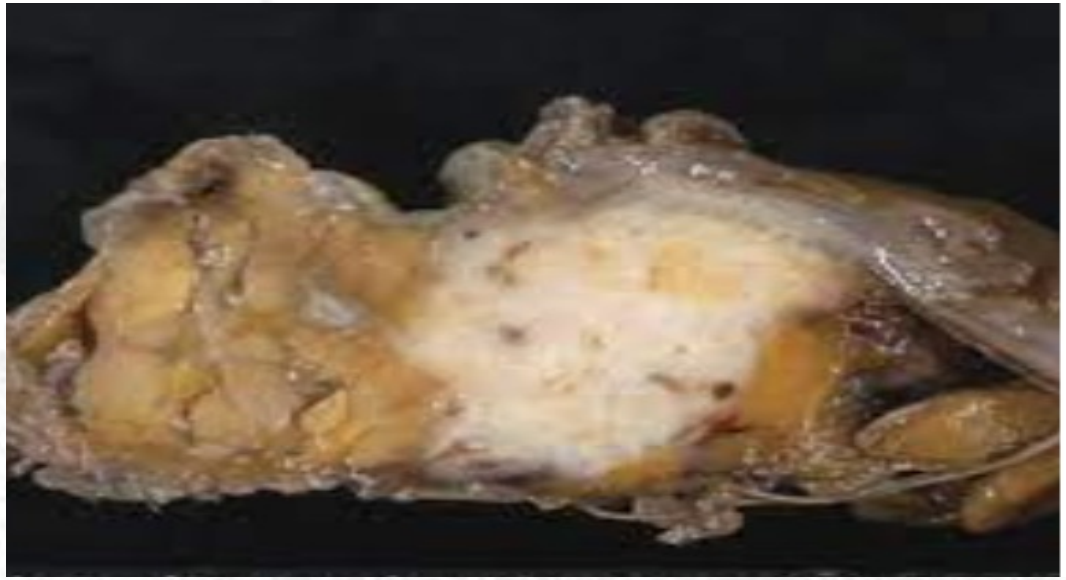
- The basis of the association of diabetes mellitus with pancreatic cancer is also unclear, since diabetes can occur as a consequence of pancreatic cancer, and in fact, new-onset diabetes in an elderly patient may be the first sign of this malignancy.
- The vast majority of carcinomas are ductal adenocarcinomas.
- It is highly invasive (even “early” invasive pancreatic cancers invade peripancreatic tissues extensively), and it elicits an intense non-neoplastic host reaction composed of fibroblasts, lymphocytes, and extracellular matrix.

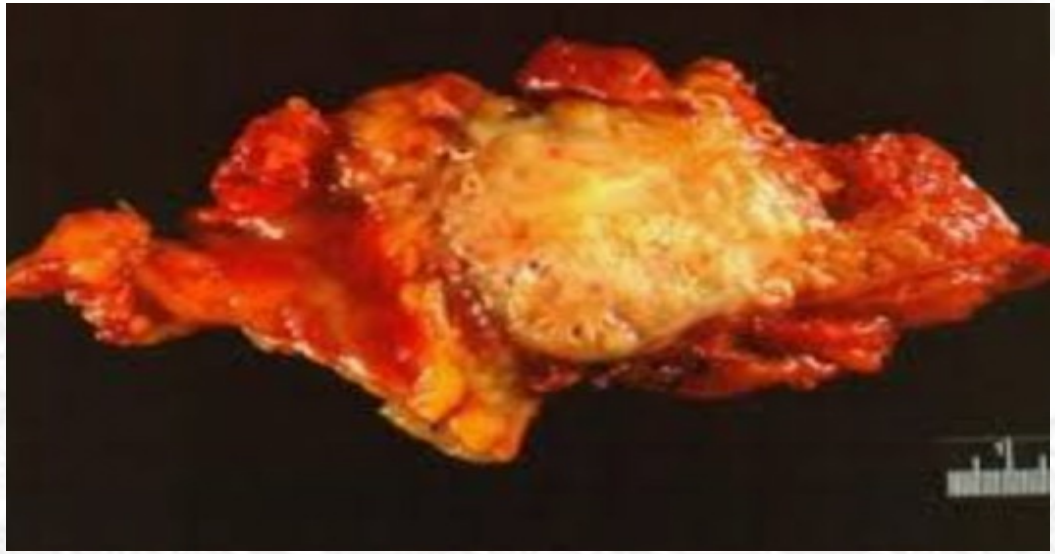
Clinical Features of Adenocarcinoma

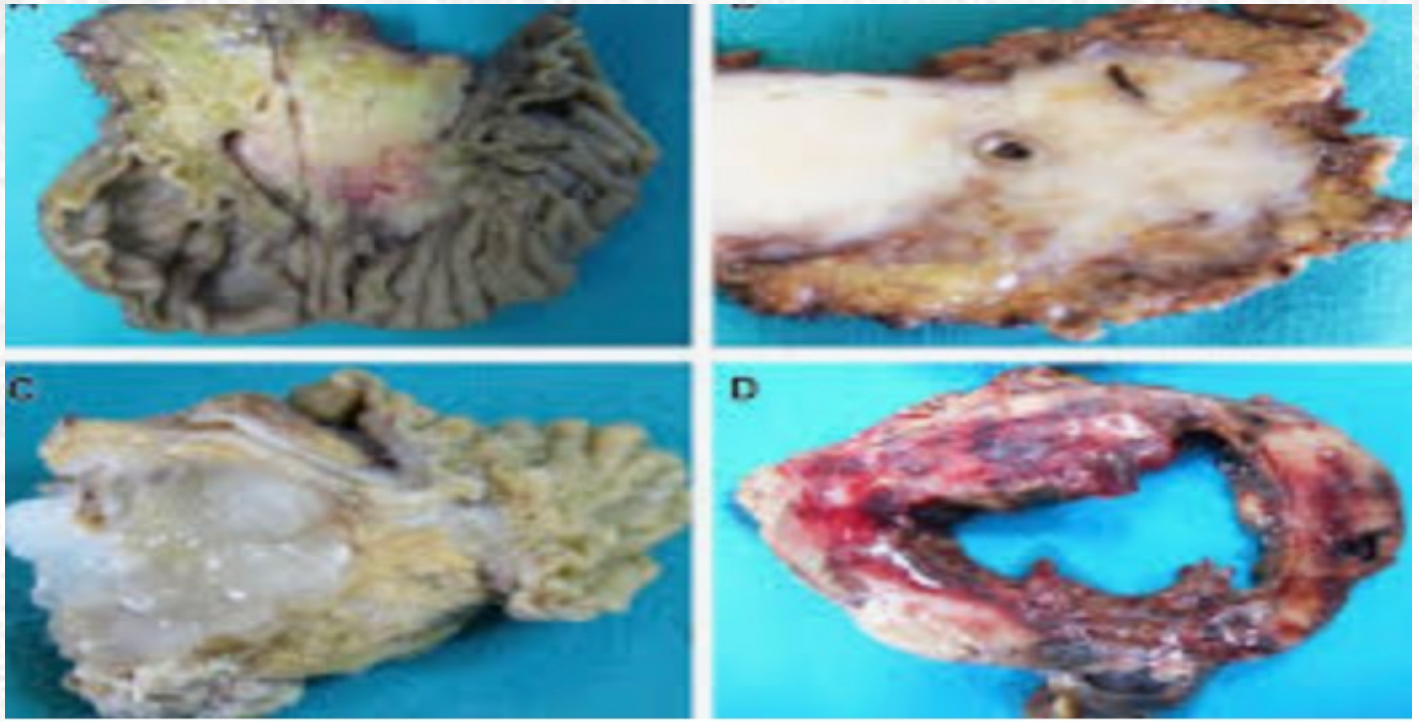
- Carcinomas of the pancreas typically remain silent until their extension impinges on some other structure.
- Pain usually is the first symptom, but by that point these cancers are often beyond cure.
- Obstructive jaundice can be associated with carcinoma in the head of the pancreas.
- Weight loss, anorexia, and generalized malaise and weakness are manifestations of advanced disease.

- Migratory thrombophlebitis occurs in about 10% of patients and is attributable to the elaboration of platelet-aggregating factors and pro-coagulants from the tumor or its necrotic products.
- The clinical course of pancreatic carcinoma is rapidly progressive and distressingly brief.
- Less than 20% of pancreatic cancers are resectable at the time of diagnosis.


Normal
Low-grade
High-grade
PDAC
Macroscopic
Microscopic






C
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