GALLBLADDER DISEASES

Cholelithiasis (Gallstones)

Gallstones afflict 10% to 20% of adults residing in Western countries in the Northern Hemisphere, 20% to 40% in Latin American countries, and only 3% to 4% in Asian countries.

In the United States, about 1 million new cases of gallstones are diagnosed annually, and two thirds of persons so

- affected undergo surgery, There are two main types of gallstones: cholesterol stones, containing crystalline cholesterol monohydrate (80% of stones in the West),
- and pigment stones, made of bilirubin calcium salts.

- PATHOGENESIS Bile formation is the only significant pathway for elimination of excess cholesterol from the body, either as free cholesterol or as bile salts.
- Cholesterol is rendered water-soluble by aggregation with bile salts and lecithins. When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and crystallizes out of solution. Cholesterol gallstone formation is enhanced by hypomobility of the gallbladder (stasis), which promotes nucleation, and by mucus hypersecretion, with consequent trapping of the crystals, thereby enhancing their aggregation into stones.

- Formation of pigment stones is more likely in the presence of unconjugated bilirubin in the biliary tree, as occurs in

- hemolytic anemias and infections of the biliary tract.
- The precipitates are primarily insoluble calcium bilirubinate salts.

Up to 80% of people with gallstones, however, have no identifiable risk factors other than age and gender.

• The prevalence of gallstones increases throughout life.

The prevalence in women of all ages is about twice as high as in men. •

Ethnic and geographic. Cholesterol gallstone prevalence approaches 50% to 75% in certain Native American populations—the Pima, Hopi, and Navajos—whereas pigment stones are rare;

the prevalence seems to be related to biliary cholesterol hypersecretion. •

Heredity.

• Environment. Estrogenic influences, including oral contraceptives and pregnancy, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol.

Obesity, rapid weight loss, and treatment with the hypocholesterolemic agent clofibrate also are strongly associated with increased biliary cholesterol secretion. •

Acquired disorders. Any condition in which gallbladder motility is reduced predisposes to gallstones, such as pregnancy, rapid weight loss, and spinal cord injury. In most cases, however, gallbladder hypomotility is present without obvious cause.

Cholecystitis

- Inflammation of the gallbladder may be acute, chronic, or acute superimposed on chronic, and almost always occurs in association with gallstones. Its epidemiologic distribution closely parallels that of gallstones.
- MORPHOLOGY
- In acute cholecystitis, the gallbladder usually is enlarged and tense, and it assumes a bright red or blotchy, violaceous color, the latter imparted by subserosal hemorrhages. The serosa frequently is covered by a fibrinous, or in severe
- cases, fibrinopurulent exudate.
- In 90% of cases, stones are present, often obstructing the neck of the gallbladder or the cystic duct. The gallbladder lumen is filled with cloudy or turbid bile that may contain fibrin, blood, and frank pus.

- When the contained exudate is mostly pus, the condition is referred to as empyema of the gallbladder.
- In mild cases the gallbladder wall is thickened, edematous, and hyperemic.
- In more severe cases the gallbladder is transformed into a green-black necrotic organ—a condition termed gangrenous cholecystitis.
- On histologic examination,
- the inflammatory reactions are not distinctive and consist of the usual patterns of acute inflammation (i.e., edema, leukocytic infiltration, vascular congestion, frank abscess formation, or gangrenous necrosis).
- The morphologic changes in chronic cholecystitis are extremely variable ز
- The mere presence of stones within the gallbladder, even in the absence of acute inflammation, often is taken as sufficient justification for the diagnosis.
- The gallbladder may be contracted, of normal size, or enlarged.; the submucosa and subserosa often are thickened from fibrosis. In the absence of superimposed acute cholecystitis, mural lymphocytes are the only signs of inflammation.

- DISORDERS OF EXTRAHEPATIC BILE DUCTS
- Choledocholithiasis and Cholangitis
- Choledocholithiasis and cholangitis are considered together because these conditions frequently go hand in hand. Choledocholithiasis is the presence of stones within the biliary tree.
- Choledocholithiasis may not immediately obstruct major bile ducts; asymptomatic stones are found in about 10% of patients at the time of surgical cholecystectomy. Symptoms may develop because of (1) biliary obstruction, (2) cholangitis, (3) hepatic abscess, (4) chronic liver disease with secondary biliary cirrhosis, or (5) acute calculous cholecystitis.
- Cholangitis is the term used for acute inflammation of the wall of bile ducts, almost always caused by bacterial infection of the normally sterile lumen. It can result from any lesion obstructing bile flow, most commonly choledocholithiasis, and also from surgery involving the biliary tree.

- Ascending cholangitis refers to the propensity of bacteria, once within the biliary tree, to infect intrahepatic biliary ducts. The usual pathogens are E. coli, Klebsiella, Enterococci, Clostridium, and Bacteroides. Two or more organisms are found in half of the cases.
- In some world populations, parasitic cholangitis is a significant problem.

- Secondary Biliary Cirrhosis Prolonged obstruction of the extrahepatic biliary tree results in profound damage to the liver itself. The most common cause of obstruction is extrahepatic cholelithiasis. Other obstructive conditions include biliary atresia , malignancies of the biliary tree and head of the pancreas, and strictures resulting from previous surgical procedures. The initial morphologic features of cholestasis were described earlier and are entirely reversible with correction of the obstruction. However, secondary inflammation resulting from biliary obstruction initiates periportal fibrogenesis, which eventually leads to scarring and nodule formation, generating secondary biliary cirrhosis.

- Biliary Atresia Biliary atresia is a major cause of neonatal cholestasis, accounting for one third of the cases of cholestasis in infants and occurring in approximately 1 in 10,000 live births. Biliary atresia is defined as a complete obstruction of bile flow caused by destruction or absence of all or part of the extrahepatic bile ducts. It is the most frequent cause of death from liver disease in early childhood and accounts for more than half of the referrals of children for liver transplantation. The salient features of biliary atresia include • Inflammation and fibrosing stricture of the hepatic or common bile ducts • Inflammation of major intrahepatic bile ducts, with progressive destruction of the intrahepatic biliary tree • Florid features of biliary obstruction on liver biopsy (i.e., ductular reaction, portal tract edema and fibrosis, and parenchymal cholestasis) • Periportal fibrosis and cirrhosis within 3 to 6 months of birth

- Clinical Course ,Infants with biliary atresia present with neonatal cholestasis; there is a slight female predominance. Affected infants have normal birth weights and postnatal weight gain. Stools become acholic as the disease evolves. Laboratory findings do not distinguish between biliary atresia and intrahepatic cholestasis, but a liver biopsy provides evidence of bile duct obstruction in 90% of cases of biliary atresia. Liver transplantation is the definitive treatment. Without surgical intervention, death usually occurs within 2 years of birth.

TUMORS

Carcinoma of the Gallbladder

- Although uncommon, carcinoma of the gallbladder is the most frequent malignant tumor of the biliary tract.
- It is 2 to 6 times more common in women and occurs most frequently in the seventh decade of life.
- Only rarely is it discovered at a resectable stage, and the mean 5-year survival rate is a dismal 5%. Gallstones are present in 60% to 90% of cases.
- gallbladders containing stones or infectious agents develop cancer as a result of recurrent trauma and chronic inflammation.
- The role of carcinogenic derivatives of bile acids is unclear.

MORPHOLOGY

Cancers of the gallbladder may exhibit exophytic or infiltrating growth patterns. The infiltrating pattern is more common and usually appears as a poorly defined area of diffuse thickening and induration of the gallbladder wall that may cover several square centimeters or involve the entire gallbladder.

These tumors are scirrhous and very firm.

The exophytic pattern grows into the lumen as an irregular, cauliflower-like mass but at the same time also invades the underlying wall .

Most are adenocarcinomas, which may be papillary or poorly differentiated.

About 5% are squamous cell carcinomas or demonstrate adenosquamous differentiation,

and rare neuroendocrine tumors also occur.

By the time gallbladder cancers are discovered, most have invaded the liver or have spread to the bile ducts or to the portal hepatic lymph nodes.

. Onset of symptoms is insidious, and presenting manifestations typically are indistinguishable from those associated with cholelithiasis:

abdominal pain, jaundice, anorexia, and nausea and vomiting.

The fortunate person develops early obstruction and acute cholecystitis or undergoes cholecystectomy for coexistent symptomatic gallstones before the tumor spreads to other sites.

Cholangiocarcinomas

Cholangiocarcinomas are adenocarcinomas that arise from cholangiocytes lining the intrahepatic and extrahepatic biliary ducts.

Extrahepatic cholangiocarcinomas constitute approximately two thirds of these tumors and may develop at the hilum (known as Klatskin tumors) or more distally in the biliary tree.

Cholangiocarcinomas occur mostly in persons of 50 to 70 years of age.

Because both intra- and extrahepatic cholangiocarcinomas generally are asymptomatic until they reach an advanced stage,

the prognosis is poor, and most patients have unresectable tumors.

Risk factors include, primary sclerosing cholangitis, fibropolycystic diseases of the biliary tree, and infestation by Clonorchis sinensis or Opisthorchis viverrini.

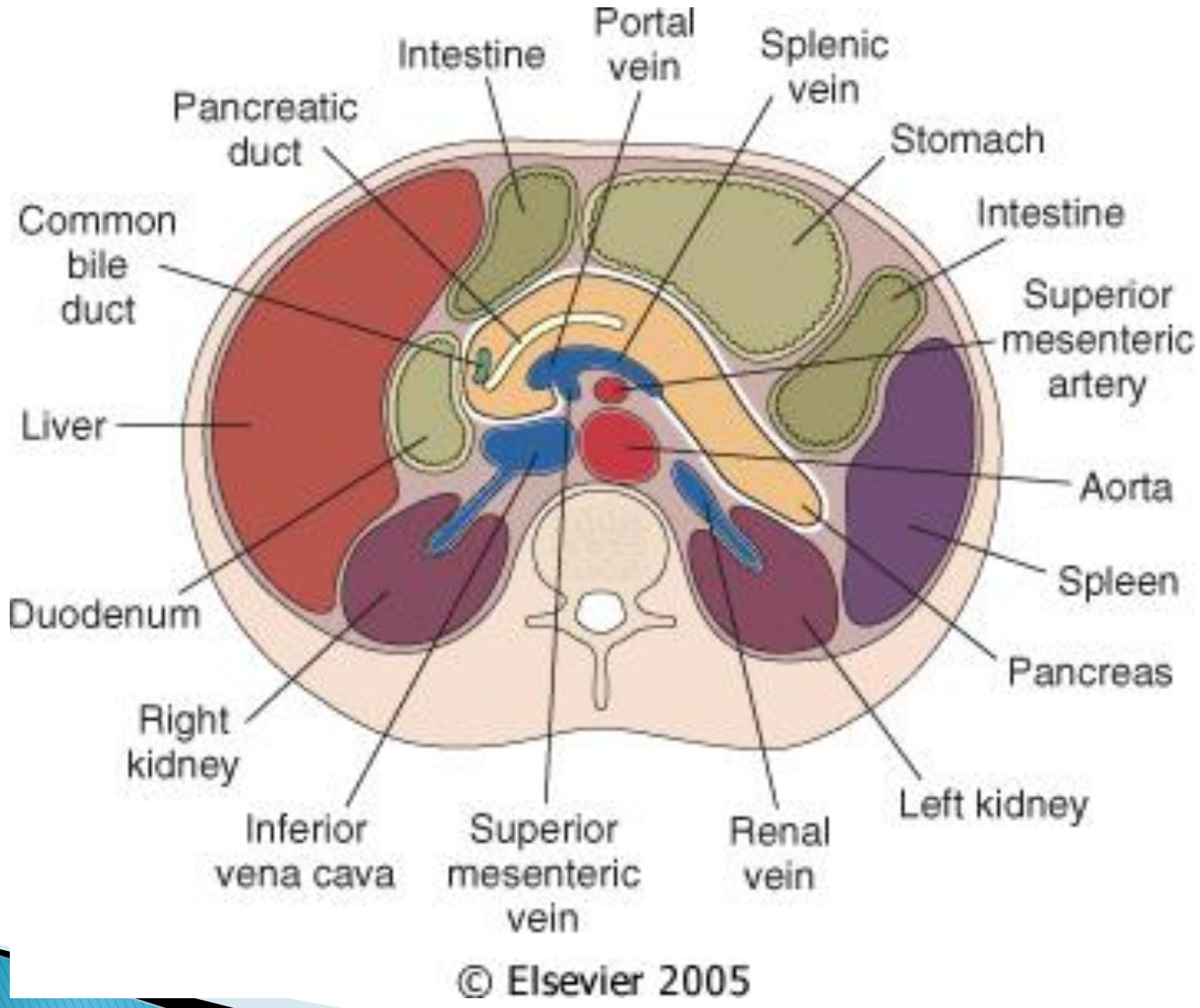
All risk factors for cholangiocarcinomas cause chronic cholestasis and inflammation, which presumably promote the occurrence of somatic mutations in cholangiocytes.

MORPHOLOGY

- Cholangiocarcinomas are typical adenocarcinomas with more or less well-formed glands often accompanied by abundant fibrous stroma (desmoplasia) yielding a firm, gritty consistency. Bile pigment and hyaline inclusions are absent from the tumor cells, while intracellular mucin may be prominent. Because partial or complete obstruction of bile ducts rapidly leads to jaundice, extrahepatic biliary tumors tend to be relatively small at the time of diagnosis,
- whereas intrahepatic tumors may cause symptoms only when much of the liver is replaced by tumor.
- Cholangiocarcinomas may spread to extrahepatic sites such as regional lymph nodes, lungs, bones, and adrenal glands. Invasion along peribiliary nerves is another route of spread to the abdomen.
- Cholangiocarcinoma has a greater propensity for extrahepatic spread than does hepatocellular carcinoma.

ANATOMY & HISTOLOGY OF THE PANCREAS

- **15 cm in length, 60-140 gm, consists of head, body & tail; pancreatic duct empty into duodenum or common bile duct**
- **Histologically, consists of 2 components:**
  - **1) Exocrine: 80-85%, consists of numerous glands (acini) lined by columnar basophilic cells containing zymogen granules, which form lobules; ductal system**
    - **Trypsin, chemotrypsin, aminopeptidase, amylase**
  - **2) Endocrine: islets of Langerhans, which are invaded by capillaries. Islets consist of:**
    - **4 main cell types: B (insulin), A (glucagon), D (somatostatin), PP cells (pancreatic polypeptide)**
    - **2 minor cell types: D1 (VIP) & enterochromaffin cells (serotonin)**


Intestine
Portal vein
Splenic vein
Pancreatic duct
Stomach
Common bile duct
Intestine
Superior mesenteric artery
Liver
Aorta
Spleen
Duodenum
Pancreas
Right kidney
Left kidney
Inferior vena cava
Superior mesenteric vein
Renal vein
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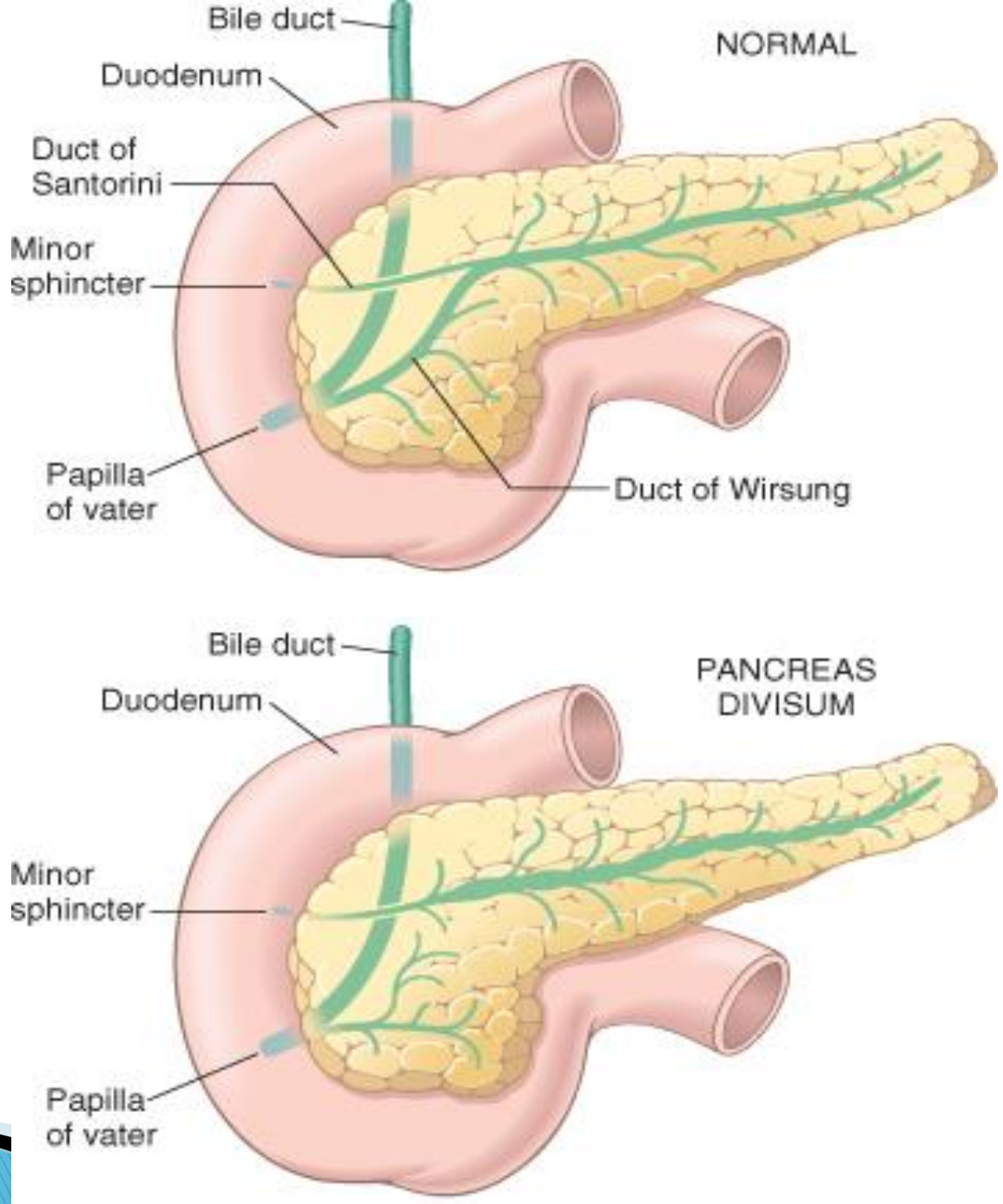
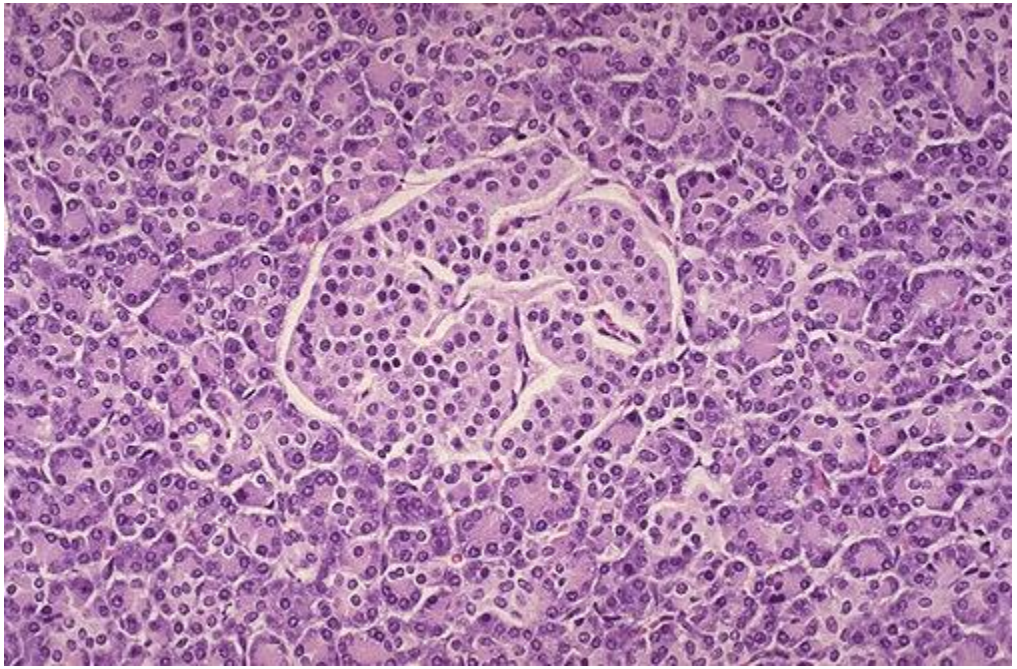




DISEASES OF THE PANCREAS

- **Congenital anomalies:**
  - **Agenesis, hypoplasia, ectopia, duct anomalies**
- **Exocrine pancreas:**
  - **Cystic fibrosis**
  - **Acute pancreatitis**
  - **Chronic pancreatitis**
  - **Carcinoma of the pancreas**
- **Endocrine pancreas:**
  - **Diabetes mellitus**
  - **Islet cell tumors**

CONGENITAL ANOMALIES OF THE PANCREAS

- **Agenesis:** usually associated with widespread severe malformations that are incompatible with life
- **Hypoplasia:** both endocrine & exocrine elements may be involved
- **Annular pancreas:** pancreas head encircle duodenum & may cause obstruction
- **Aberrant (ectopic) pancreas:** 2%; mostly in stomach, duodenum, jejunum, Meckel's diverticulum & ileum
- **Ducts anomalies:** duct of Wirsung may drain into common bile duct or an orifice high in the duodenum

DISEASES OF THE EXOCRINE PANCREAS
CYSTIC FIBROSIS

- **CF is the most common lethal genetic disease that affects white populations (1 in 2000 live births)**
- **Charcterized by abnormally viscid mucous secretions that block airways & pancreatic ducts & are responsible for:**
  - **1) Recurrent chronic pulmonary infections**
  - **2) Pancreatic insufficiency**
- **High level of NaCl in sweat**
- **Pathognesis: primary defect in transport of Cl^- across epithelia. The cAMP-dependent Cl^- channels (CF transmembrane conductance regulator [CFTR]) are defective.**

DISEASES OF THE EXOCRINE PANCREAS
CYSTIC FIBROSIS

- **CF gene is located on chromosome 7 with up to 300 mutations identified in this gene so far.**
- **Pancreatic pathology: abnormalities are seen in 85% of patients:**
  - **mucus accumulation,**
  - **duct dilation & plugging,**
  - **exocrine gland atrophy. Islets usually spared.**
  - **Ducts may be converted into cysts seperated only by islets of Langerhans & fibrous stroma (fibrocystic disease of pancreas)**
  - **Malabsorption syndrome: paticularly fat**
  - **Squamous metaplasia of duct lining**
- **Meconium ileus, pulmonary problems**
- **Rx: gene therapy**

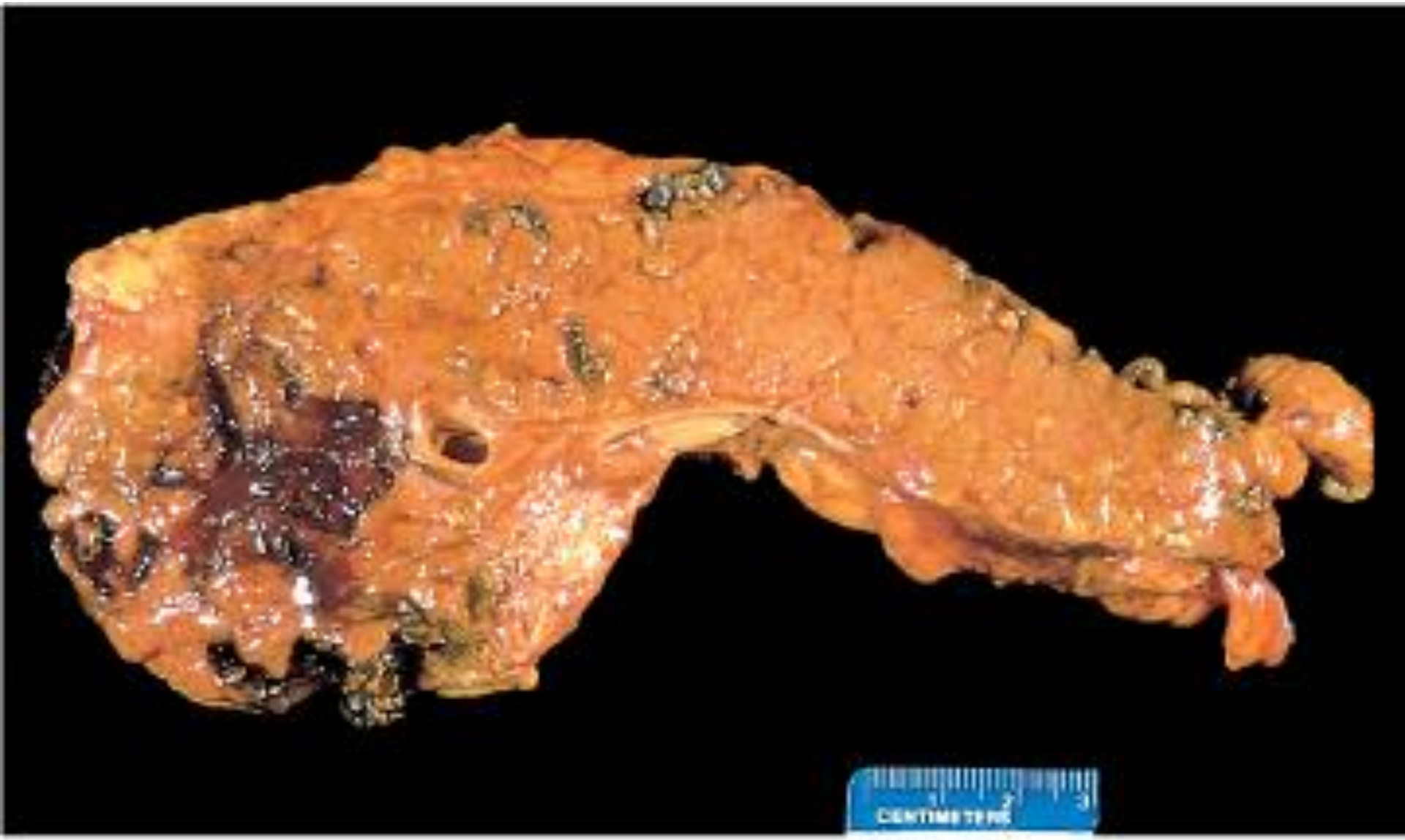
DISEASES OF THE EXOCRINE PANCREAS
ACUTE PANCREATITIS

- **Inflammation of the pancreas, which is almost always associated with acinar cell injury**
- **A clinical & histologic spectrum of severity & duration**
- **Etiologic factors:**
  - **1) Metabolic: alcohol, hyperlipoproteinemia, hypercalcemia, drugs (e.g. thiazides), genetic**
  - **2) Mechanical: gallstones, traumatic & perioperative injury**
  - **3) Vascular: shock, atheroembolism, polyarteritis nodosa**
  - **4) Infections: Mumps, Coxsackie virus, Mycoplasma**
  - **5) Idiopathic : 10-20% ; ? Genetic basis**

DISEASES OF THE EXOCRINE PANCREAS

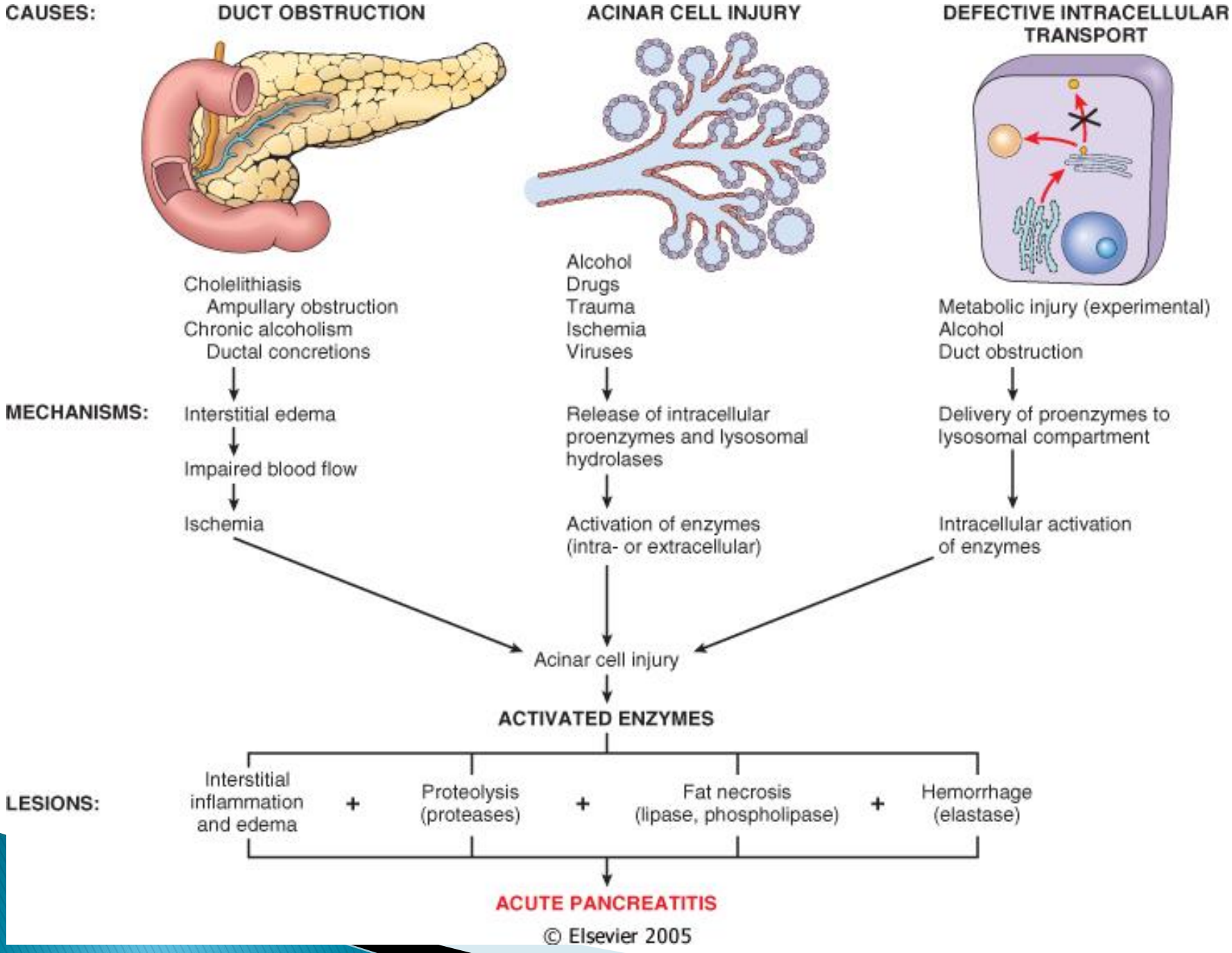
ACUTE PANCREATITIS

- **Pathology:**
  - **4 basic alterations:**
    - **1) Proteolytic destruction of pancreatic substance**
    - **2) Necrosis of blood vessels & interstitial hemorrhage**
    - **3) Fat necrosis by lipolytic enzymes**
    - **4) Associated acute inflammatory reaction**
  - **Pathologic lesions:**
    - **a. Acute pancreatic necrosis**
    - **b. Acute hemorrhagic pancreatitis**
    - **c. Suppurative peritonitis**
    - **d. Pancreatic pseudocysts**



DISEASES OF THE EXOCRINE PANCREAS
ACUTE PANCREATITIS

- **Pathogenesis:**
  - **Autodigestion of pancreatic tissue by inappropriately activated pancreatic enzymes**
  - **Trypsin has a major role:**
    - **a. Activates other proenzymes (proelastase ,prophospholipase)**
    - **b. Converts prekallikrein to kallikrein (Kinin system)**
    - **c. Hageman factor is activated**
  - **Mechanisms of pancreatic enzyme activation:**
    - **1) Pancreatic duct obstruction**
    - **2) Primary acinar cell injury**
    - **3) Defective intracellular transport of proenzymes within acinar cells**


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
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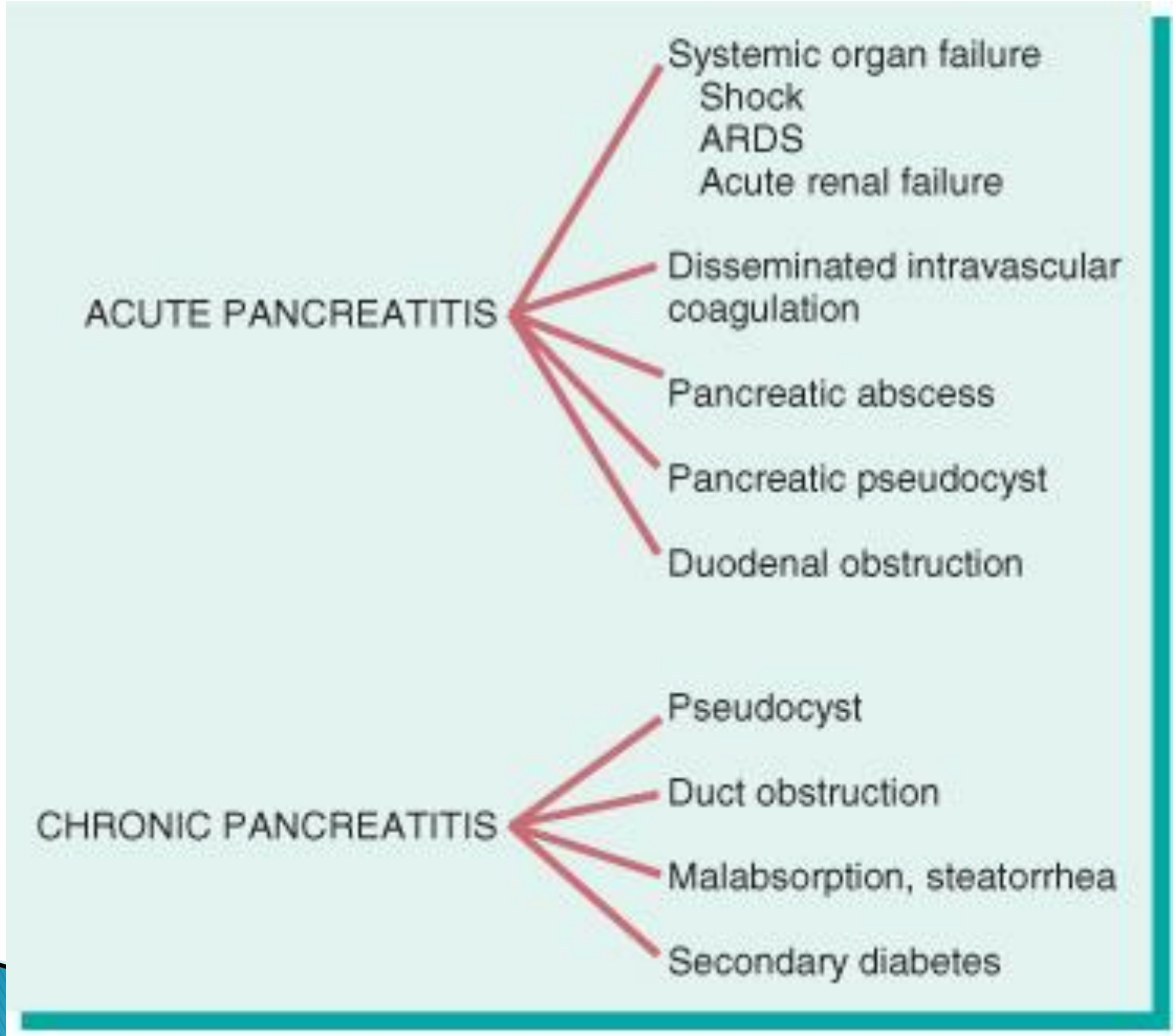
DISEASES OF THE EXOCRINE PANCREAS
ACUTE PANCREATITIS

- **Clinical features:**
  - **Abdominal pain is the cardinal manifestation: epigastric, radiating to back, variable in severity**
  - **Shock: due to pancreatic hemorrhage & release of vasodilatory agents (BK & PGs)**
- **Lab: ↑ serum amylase and lipase; ↓ Ca; ↑ bilirubin, ↑ glucose & glycosuria**
- **CT scan: inflammation, pseudocysts**
- **Px: severe cases have high mortality rate (20-40%)**
- **Death due to: 1) shock, 2) secondary abdominal sepsis, 3) adult respiratory distress syndrome**

DISEASES OF THE EXOCRINE PANCREAS
CHRONIC PANCREATITIS

- **Repeated bouts of mild to moderate pancreatic inflammation, with continued loss of pancreatic parenchyma & replacement by fibrous tissue**
- **Distinction from acute pancreatitis may be difficult; distinction is made if there is evidence of previous attacks**
- **Middle-aged men, mostly in alcoholics but may due to biliary tract disease, hyperlipoproteinemia & hypercalcemia; no apparent cause in 50% of cases**
- **Pathogenesis:**
  - **Protein hypersecretion from acinar cells**
  - **Precipitation of proteins forming ductal plugs**
  - **Plugs enlarge forming laminar aggregates**



DISEASES OF THE EXOCRINE PANCREAS
CHRONIC PANCREATITIS

- **Pathology:**
  - **Hard organ with dilated ducts & calcified concretions**
  - **Fibrosis, chronic inflammatory cells, obstruction of ducts by protein plugs**
  - **Extensive atrophy of exocrine glands**
  - **Pseudocysts**
- **Clinical features:**
  - **Repeated attacks of abdominal pain or may be silent**
- **Dx: clinical suspicion, lab & CT**
- **Px: chronic disabling disease due to its major complications: pancreatic insufficiency & diabetes mellitus**

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DISEASES OF THE EXOCRINE PANCREAS

PANCREATIC CARCINOMA

- **Malignant epithelial neoplasm of exocrine portion of pancreas**
- **5th most frequent cause of death from cancer**
- **Increasing in incidence in the West**
- **Peak incidence: 60 - 80 years**
- **Cause is unknown; more frequent in smokers**
- **Location:**
  - **Head of pancreas 60%**
  - **Body of pancreas 15%**
  - **Tail of pancreas 5%**
  - **Diffuse involvement 20%**

DISEASES OF THE EXOCRINE PANCREAS

PANCREATIC CARCINOMA

- Gritty gray hard masses
- Vast majority are adenocarcinomas, with poorly formed glands and densely fibrous stroma
- Carcinoma of pancreatic head: invasion of ampullary region with bile outflow obstruction, & distension of biliary tree
- Carcinoma of body & tail: no impingement on biliary tract & remain silent for longer periods
- Extends into retroperitoneal spaces, infiltrate nerves, abdominal organs & lymph nodes
- Distant metastasis to lungs, bone, ..

DISEASES OF THE EXOCRINE PANCREAS

PANCREATIC CARCINOMA

- **Clinical features:**
  - **Usually silent until its extension impinges on other structures**
  - **Pain is usually the first symptom**
  - **Obstructive jaundice**
  - **Trousseau's syndrome: Migratory thrombophlebitis (phlebothrombosis)**
- **Lab: tumor markers, e.g. CEA, CA19-9 Ag are nonspecific**
- **Dx: CT scan & percutaneous biopsy**
- **Px: 1 year survival is 10%; 5 yr survival is 2.5%**