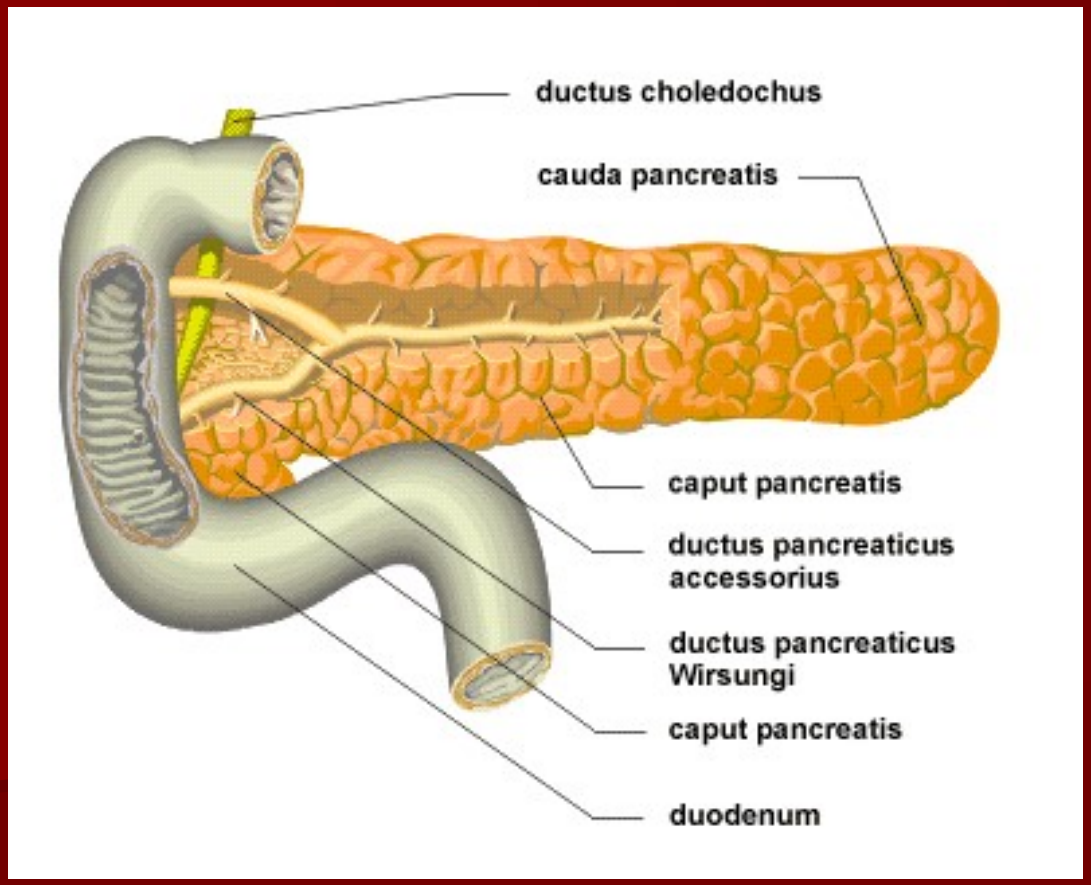
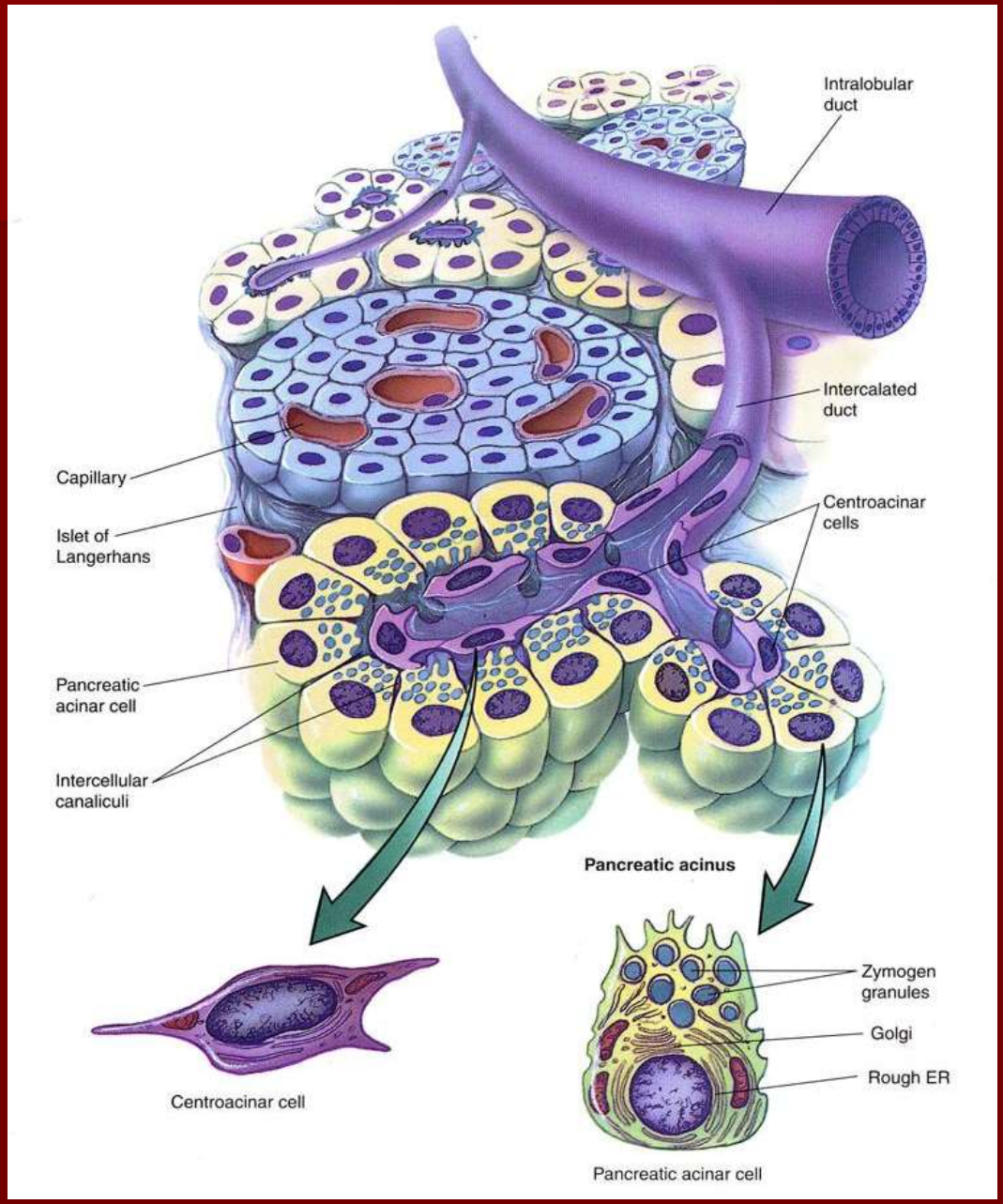
Pathophysiology of the exocrine pancreas



Anatomy of the pancreas



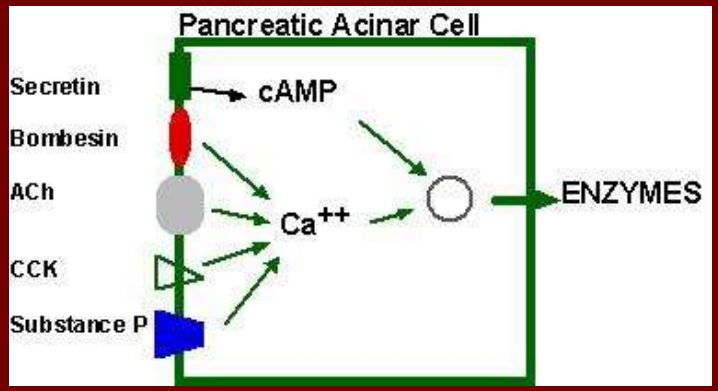
Cell types in the pancreas

- Endocrine – islets of Langerhans

α-cells – producing glucagon
β-cells – producing insulin and amylin
δ-cells – producing somatostatin
ε-cells – producing ghrelin
PP-cells – producing pancreatic polypeptide
G-cells – producing gastrin

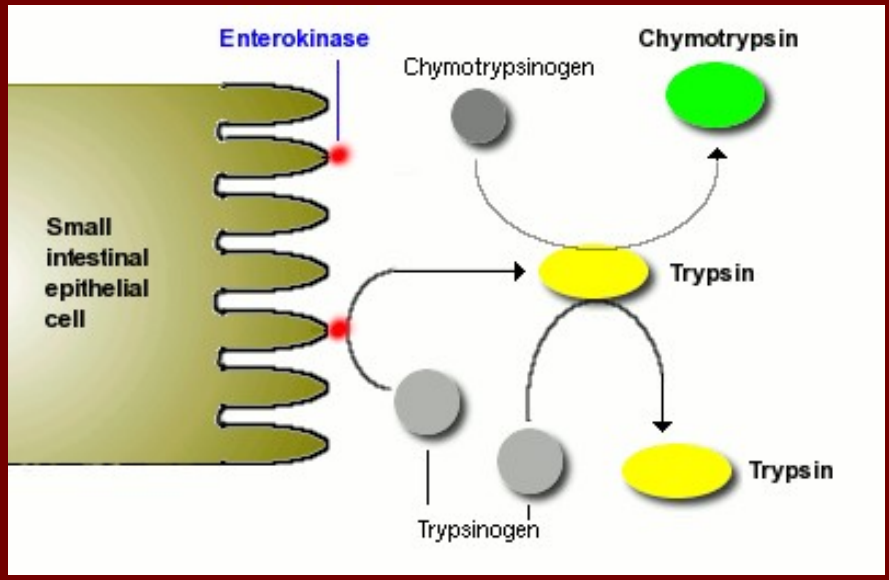
- Exocrine – acini and ducts

acinar (basophilic) cells – producing pancreatic enzymes (trypsin, amylase, lipase)
centroacinar cells – producing HCO_3^-
ductal cells – producing HCO_3^-



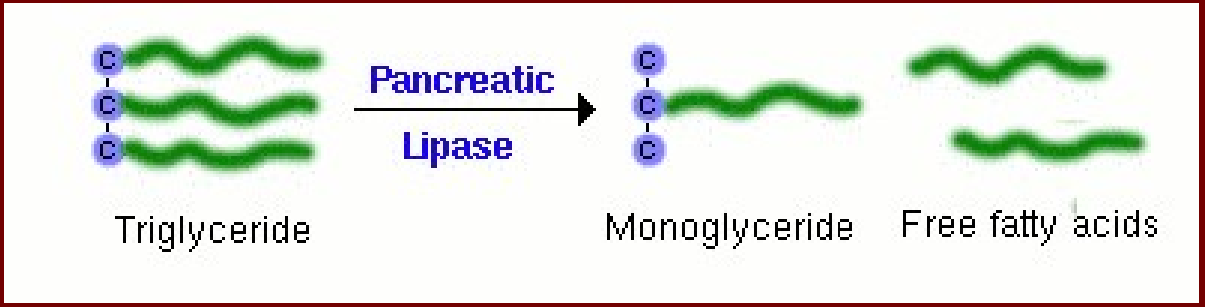
Exocrine pancreas in protein digestion

- Proteases – are secreted in inactive form: trypsinogen, chymotrypsinogen
- Trypsinogen is converted into trypsin by enterokinase in the small intestine
- Trypsin then converts chymotrypsinogen into chymotrypsin
- Each enzyme then cleaves peptidic bonds between different aminoacids
- Both act inside the protein - endopeptidases



Exocrine pancreas in lipid digestion

- Pancreatic lipase (LPS)
  - converts TAG into monoacylglycerol and FFA
  - acts together with bile acids, which emulsify lipids
- Lysophospholipase, Phospholipase A2
  - cleave phospholipids
- Cholesterol esterase
  - de-esterifies cholesterol and helps its transport into enterocytes



Exocrine pancreas and saccharide digestion

- Pancreatic amylase (AMS-pancr.)

  - catalyses cleavage of starch or glycogen into oligosaccharides (dextrin, maltotriose, maltose)

  - cleavage by both salivary and pancreatic AMS represents the initial stage in saccharide digestion

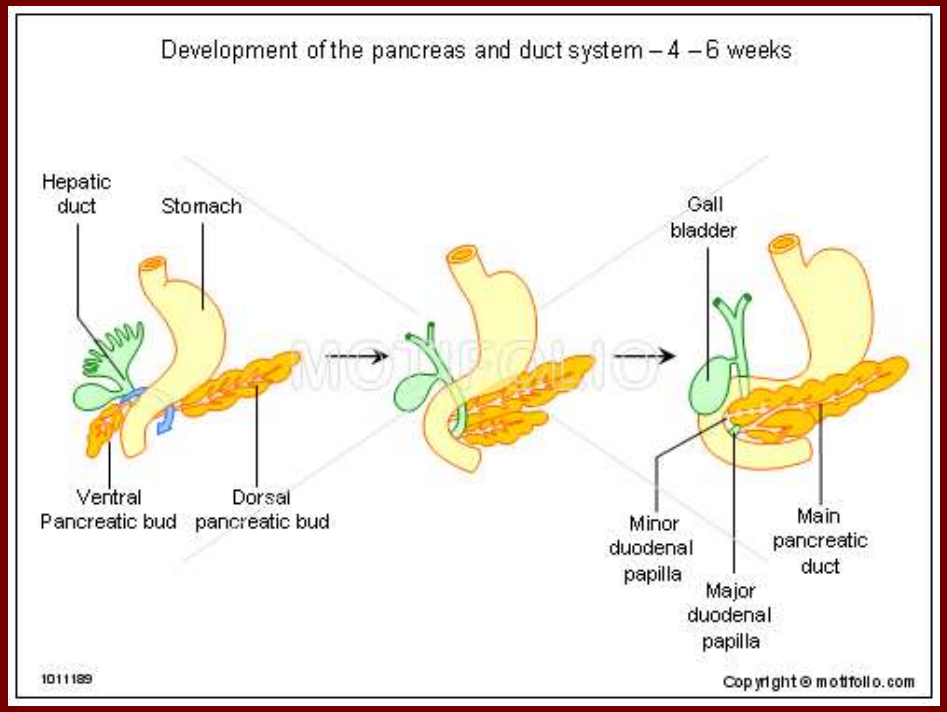
  - Its products are further cleaved by intestinal enzymes (glucosidases, maltase) into monosaccharides, which are transported into blood

Diseases of exocrine pancreas

- Congenital malformations
- Acute pancreatitis
- Chronic pancreatitis
- Cystic fibrosis
- Tumours

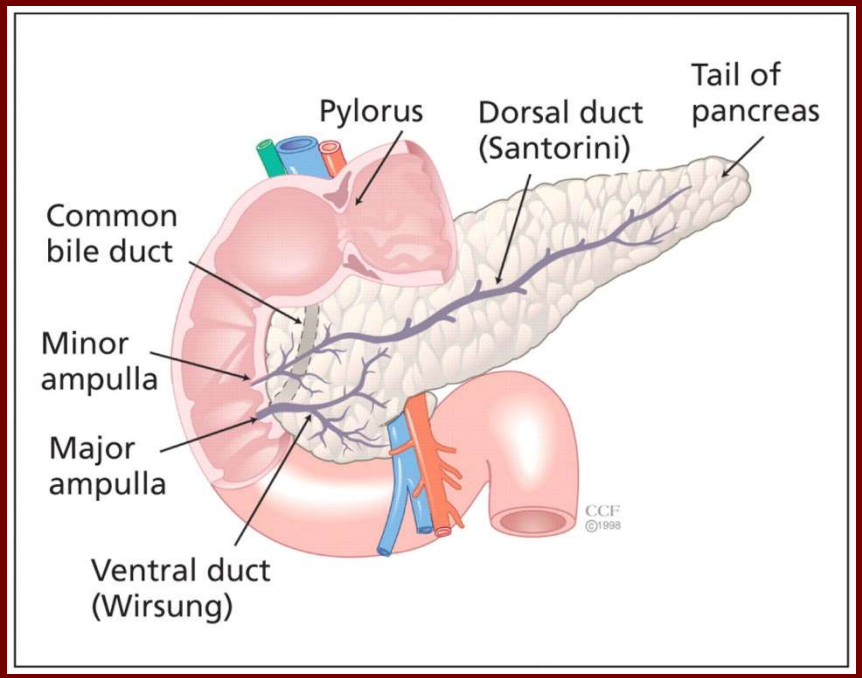
Congenital malformations

- During development, pancreas is formed through the fusion of ventral and dorsal bud
- Ventral bud turns into most of the head of pancreas, while dorsal bud turns into its body and tail
- Initially, they both have separate ducts, in most cases, the ducts are joint together during development. Ventral duct (duct of Wirsung) drains most of pancreas.
- Usually, it has common orifice with biliary duct



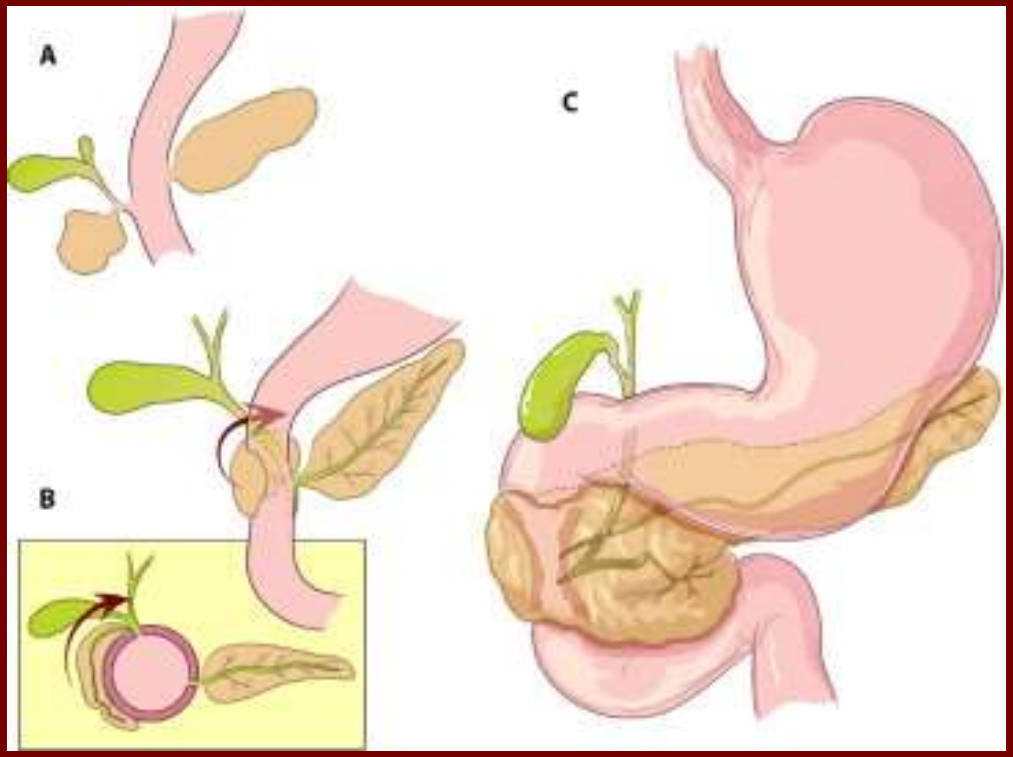
Pancreas divisum

- In some cases, the fusion of both buds is incomplete
- Smaller dorsal duct is sometimes incapable to drain pancreatic juice effectively
- The condition can lead into repeated acute pancreatitis



Annular pancreas

- In other cases, ventral bud can pinch the duodenum during its abnormal rotation and fusion, causing vomiting and duodenal ulcers



Acute pancreatitis

- Various factors lead into the damage of acinar cells
- Granules with trypsinogen are overpresented in cells and trypsinogen can react with lysosomal enzymes
- The reaction can lead into conversion of a small amount of trypsinogen into trypsin
- Trypsin can activate other enzymes (as chymotrypsin or phospholipase A)
- This leads into the autodigestion of the pancreas and consequent complications

Causes of acute pancreatitis

- Obstruction of pancreatic ducts (most often)
  - obstruction of common biliary and pancreatic orifice (ampulla Vateri) – usually together with icterus
  - tumours
  - pancreas divisum
- Alcoholic excess
- Metabolic causes (e.g.hypertriglyceridemia)
- Idiopatic

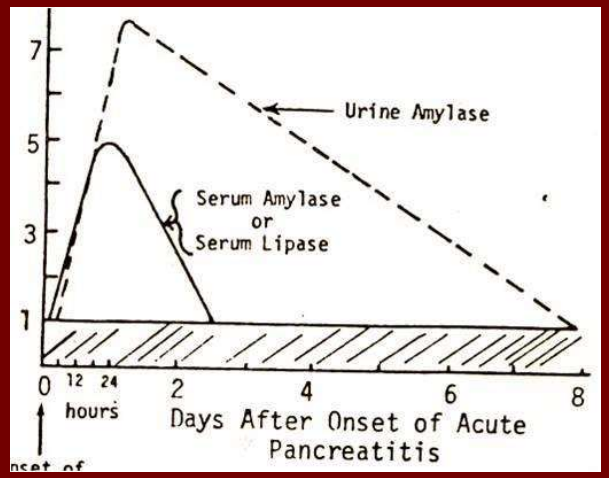
Manifestation of acute pancreatitis

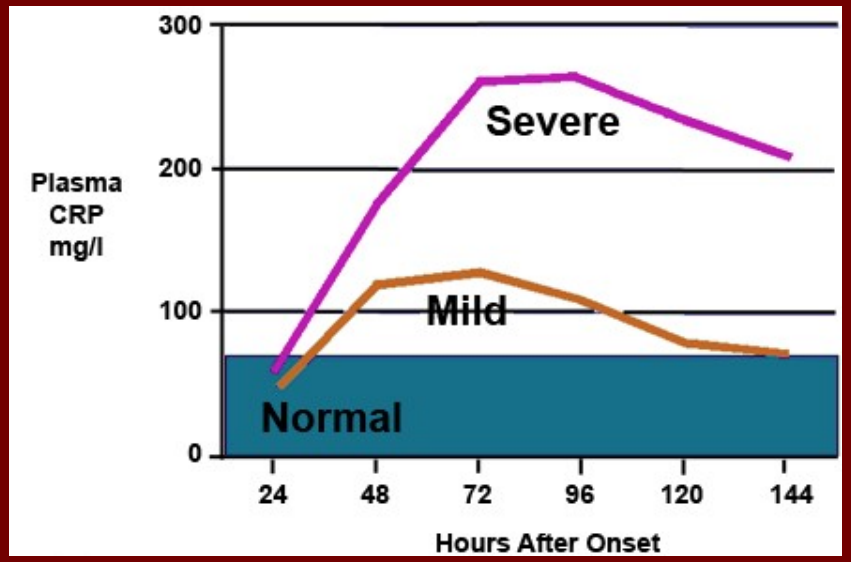
Mild form
- interstitial oedema
- inflammation of interstitium

Severe form
- necrosis
- haemorrhage
- necrosis of surrounding tissue
- sepsis
- circulatory shock
- DIC

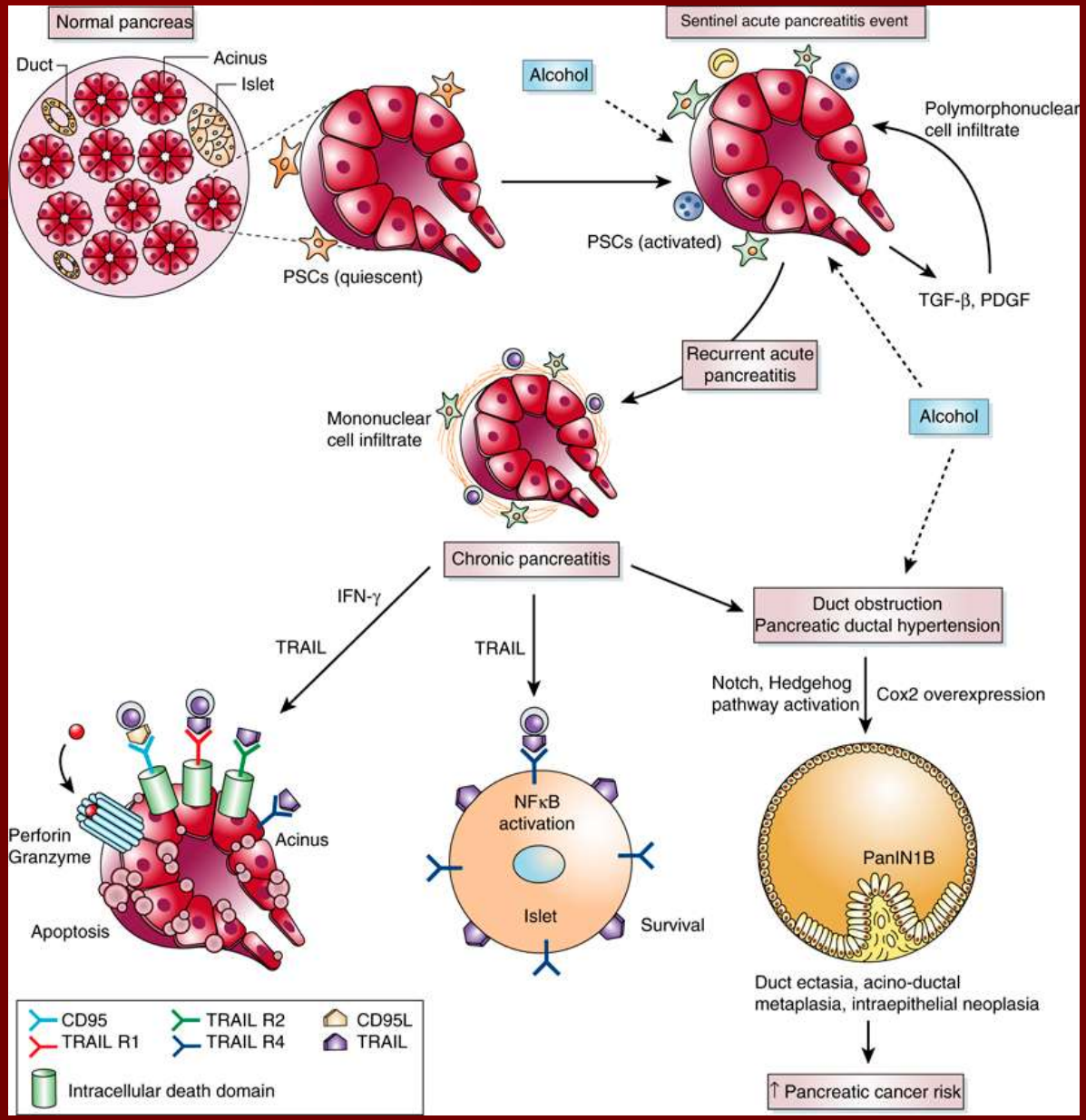
Clinical and laboratory findings

- Severe stomach ache (usually after alcohol intake or fatty meal)
- Fever, CRP and leukocytes elevation
- Elevation of LPS, pancreatic AMS (within several hours after onset



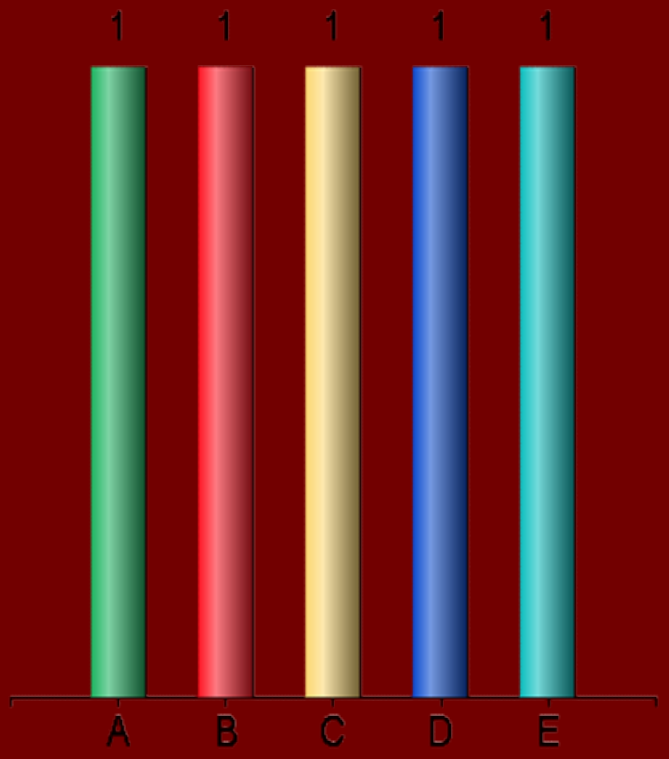


Late complications



Pancreas divisum...

A. Results from an abnormal rotation of the ventral pancreatic bud
B. Leads into the hyperviscosity of pancreatic juices
C. Manifests by obstructive icterus
D. Manifests by obstructive acute pancreatitis without the icterus
E. Leads regularly to the ulcerations of upper duodenum



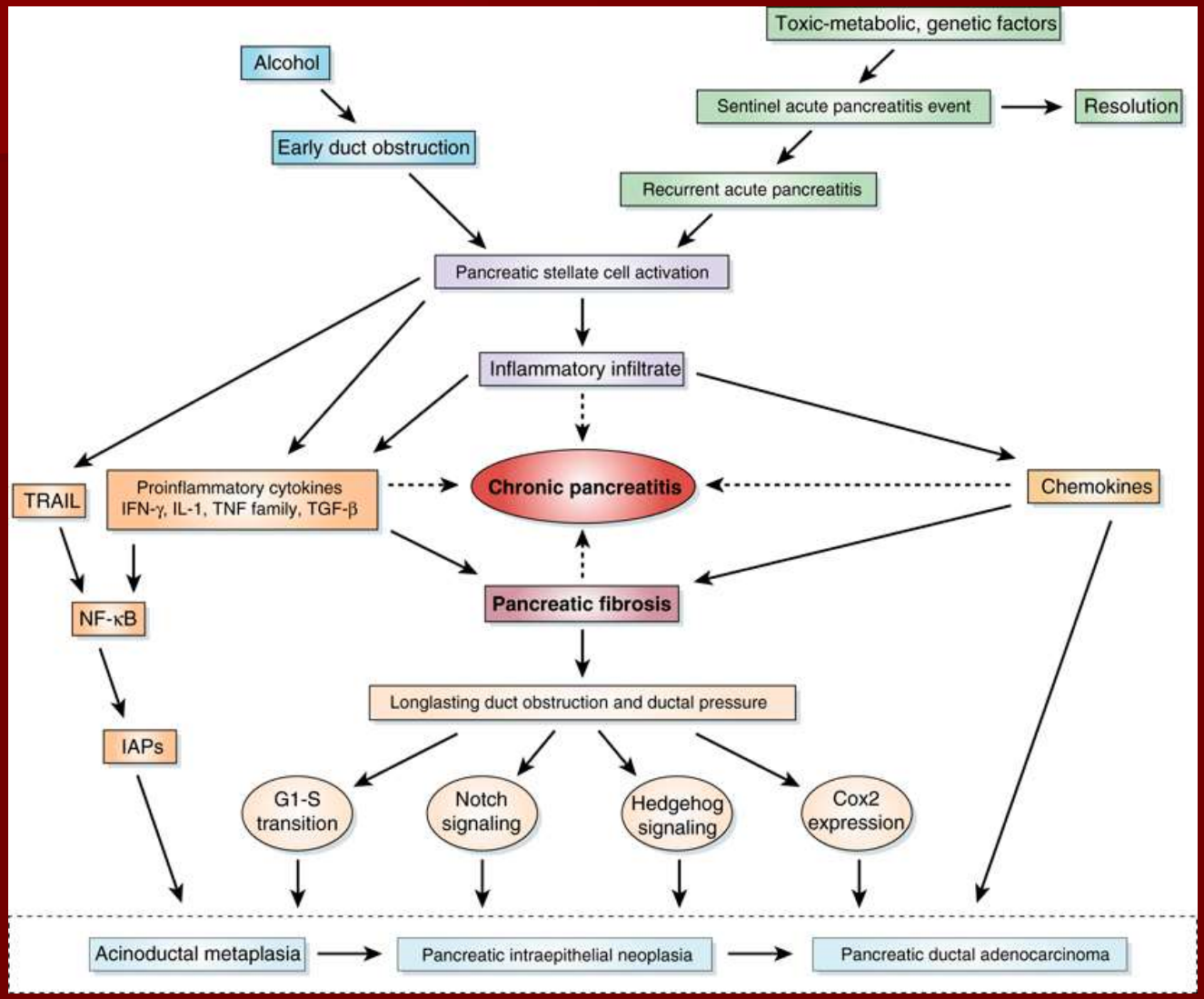
Chronic pancreatitis

- Various causes, exact pathophysiology is not always clear
- Chronic irritation of pancreas by alcohol or other causes leads into chronic monocyte and lymfocyte infiltration
- Occassional reaction of pancreatic proenzymes with lysosome hydrolases (as in acute pancr.)
- Necrosis of acinar cells and subsequent fibrosis is present
- In final stage, endocrine pancreas is also affected

Causes of chronic pancreatitis

- Abuse of alcohol (most often)
- Idiopatic
- Toxic or radiation damage
- Hereditary
  - congenital anomalies (e.g. pancreas divisum)
  - cystic fibrosis
  - α-1 antitrypsin deficiency
- Acute pancreatitis

Development of chronic pancreatitis

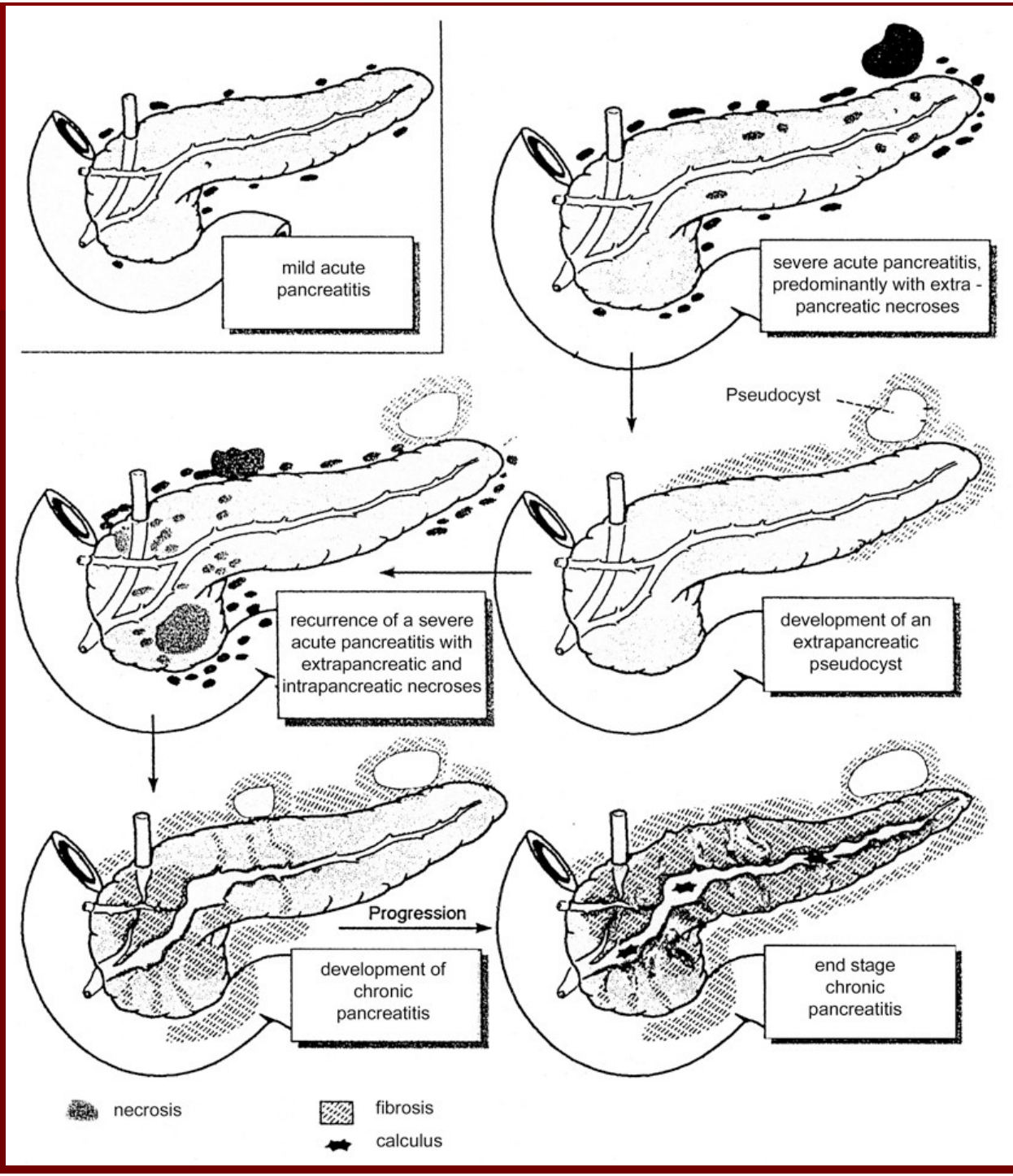


Clinical finding

- Stomach ache (very variable)
- Diarrhoea, steatorrhoea
- Malabsorption
  - vitamin carence
  - hypoproteinemia with oedemas
- Secondary diabetes
- Obstruction of biliary duct with icterus
- Ascites (rare)

Chronic pancreatitis - diagnosis

- Pancreatic AMS or LPS are useless (elevated just in acute exacerbations)
- Imaging methods: ultrasonography, CT, MR
- Secretin-CCK test (invasive, measures amylase, trypsin and acidity in the duodenum)
- Secretin and CCK can be replaced by lipid-saccharide-protein solution (but with lower sensitivity and specifity)


mild acute pancreatitis
severe acute pancreatitis, predominantly with extra - pancreatic necroses
Pseudocyst
development of an extrapancreatic pseudocyst
recurrence of a severe acute pancreatitis with extrapancreatic and intrapancreatic necroses
Progression
development of chronic pancreatitis
end stage chronic pancreatitis
necrosis
fibrosis
calculus

Choose a suitable marker of acute pancreatitis

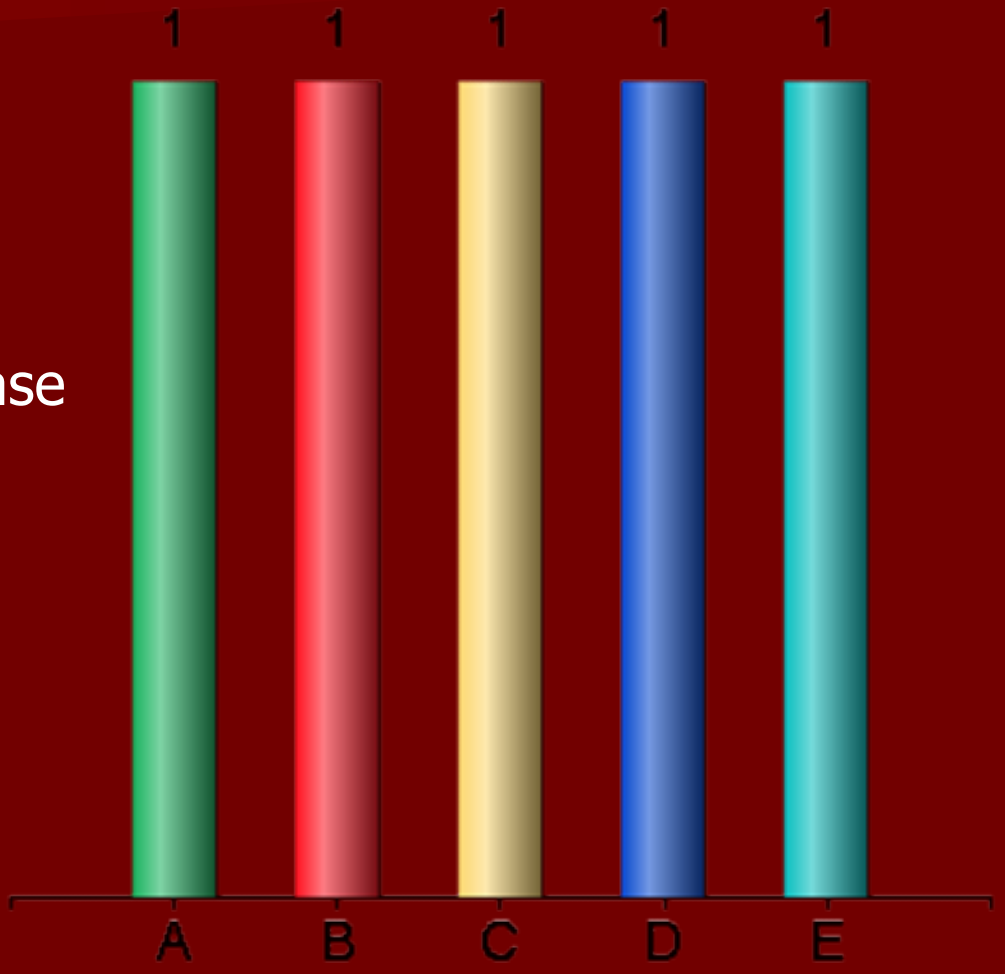
A. Total amylase

B. α1-antitrypsin

C. Pancreatic alkaline phosphatase

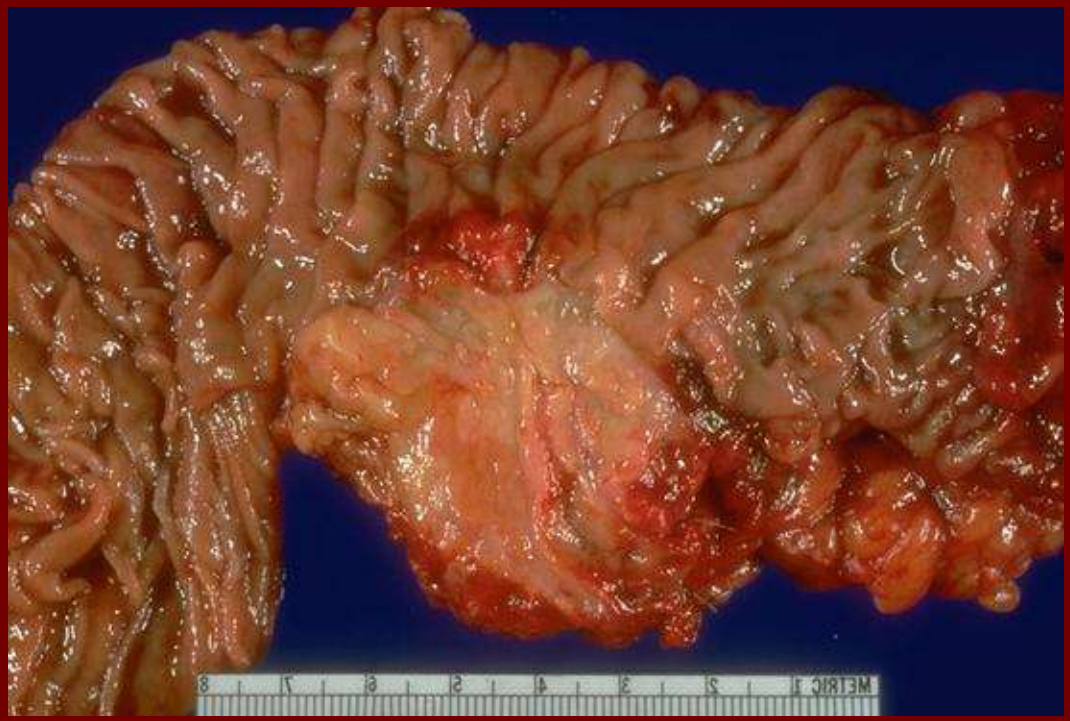
D. Enterokinase

E. Lipase



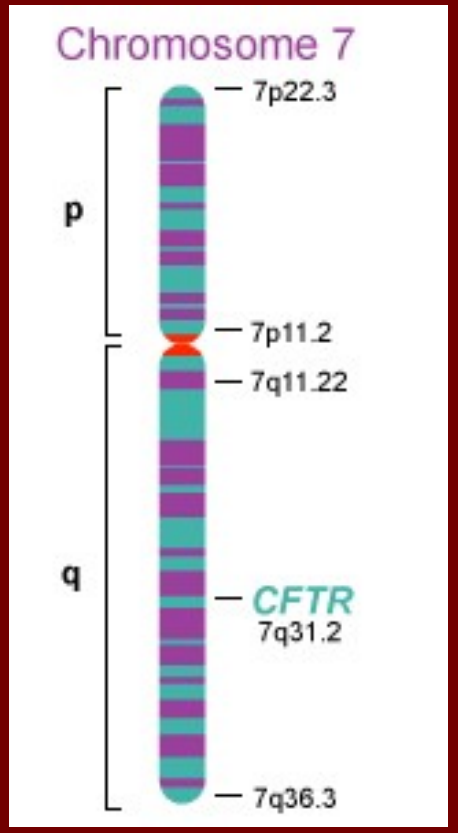
Tumours of pancreas

- Exocrine: adenocarcinoma
  - bad prognosis (5-years survival <10%)
  - 90% of tumours are practically untreatable due to late diagnosis
- Endocrine: both benign or malign
  - usually with endocrine activity



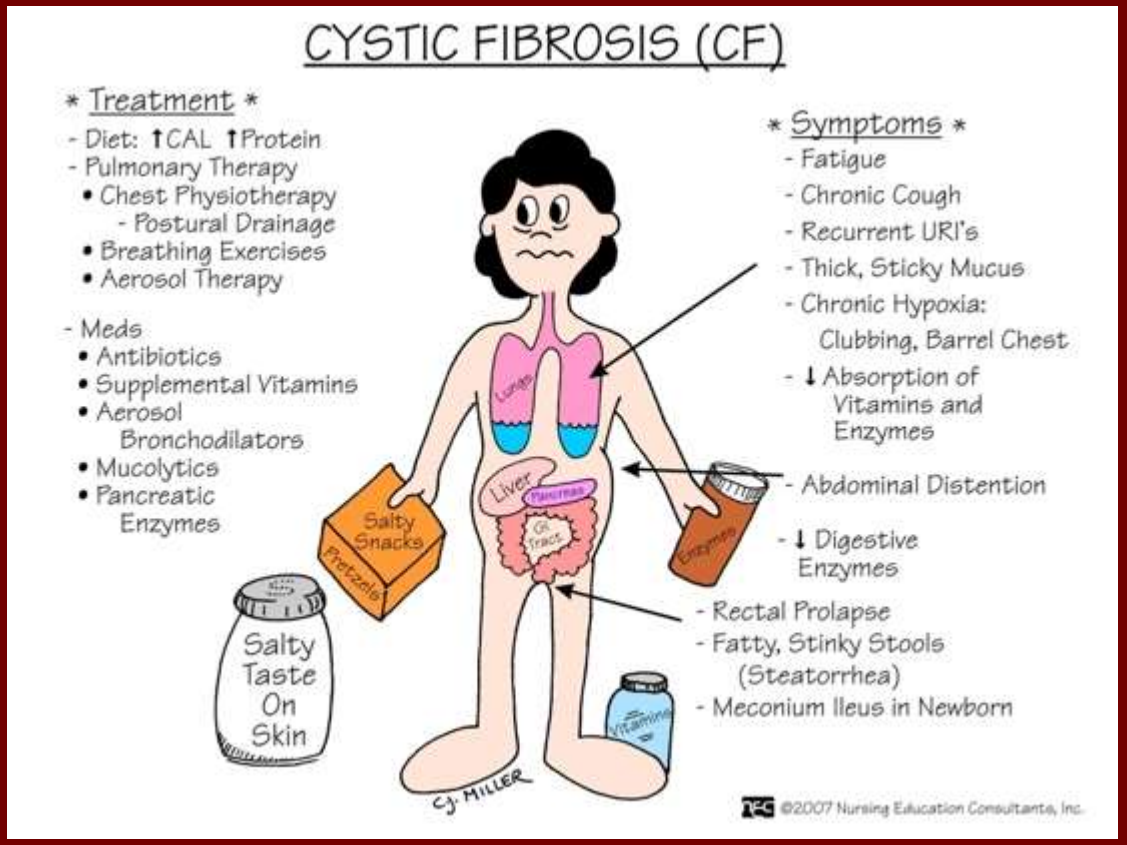
Cystic fibrosis (mucoviscidosis)

- Monogenic disease with autosomal recessive inheritance
- Mutation in the gene for CFTR (Cystic Fibrosis Transmembrane conductance Regulator)
- Its product is a chloride channel, present in most tissues
- Gene for CFTR is located in 7q31.2. locus
- In Czech and most other European populations, approximately 4% of population are carriers of mutated allele



Various manifestations of CF

- The retention of chlorides leads into increased viscosity of secretions
- In the sweat glands, chloride (and sodium) re-uptake is blocked



Cystic fibrosis in the pancreas

- The viscous secretion blocks pancreatic ducts
- This leads into chronic pancreatitis and malabsorption
- In late stages, the disease leats to total obstruction of the ducts, fibrosis and atrophy
- Average life expectancy is less than 40 years