Pancreas

APPROVED

Cynthia D. Guy, MD

Associate Professor of Pathology

DUMC

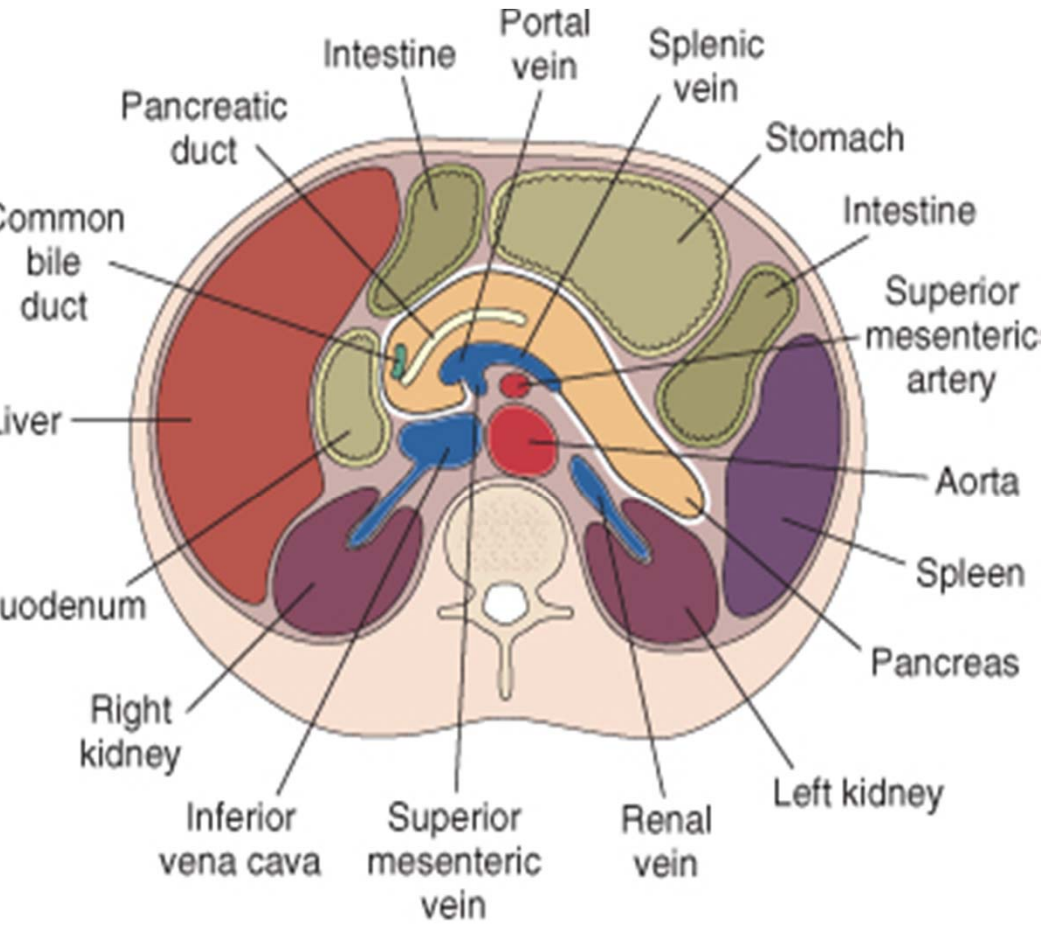
Pancreas
Lecture Overview

- Gross anatomy
  - Normal
  - Pancreatic divisum
- Microscopic anatomy and normal functions
- Pancreatitis
  - Acute
  - Chronic
- Diabetes mellitus
- Tumors of the pancreas
  - Ductal adenocarcinoma
  - Pancreatic endocrine tumors (Islet cell tumors)

also included: cystic neoplasms

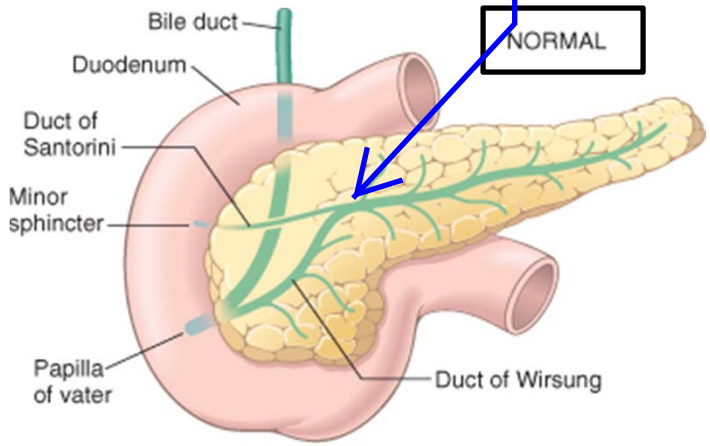
High yield nugget from FA: The pancreas is retroperitoneal except for the tail. What are the other retroperitoneal structures?

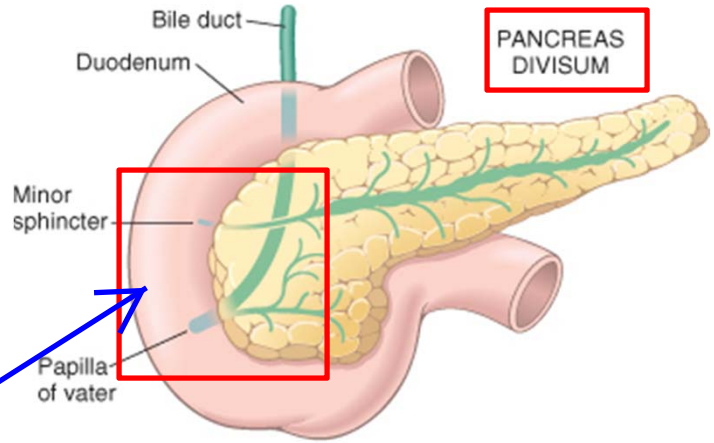
Gross Anatomy of the Pancreas



Q: What is the major function of the pancreas?
A: The main function is for 'proper

Pancreatic duct carries enzymes





The main pancreatic duct is not complete here. Accordingly, all the pancreatic fluids are forced out the minor sphincter. Because of the small caliber of this hole, pancreatic secretions build up and cause dysfunction.

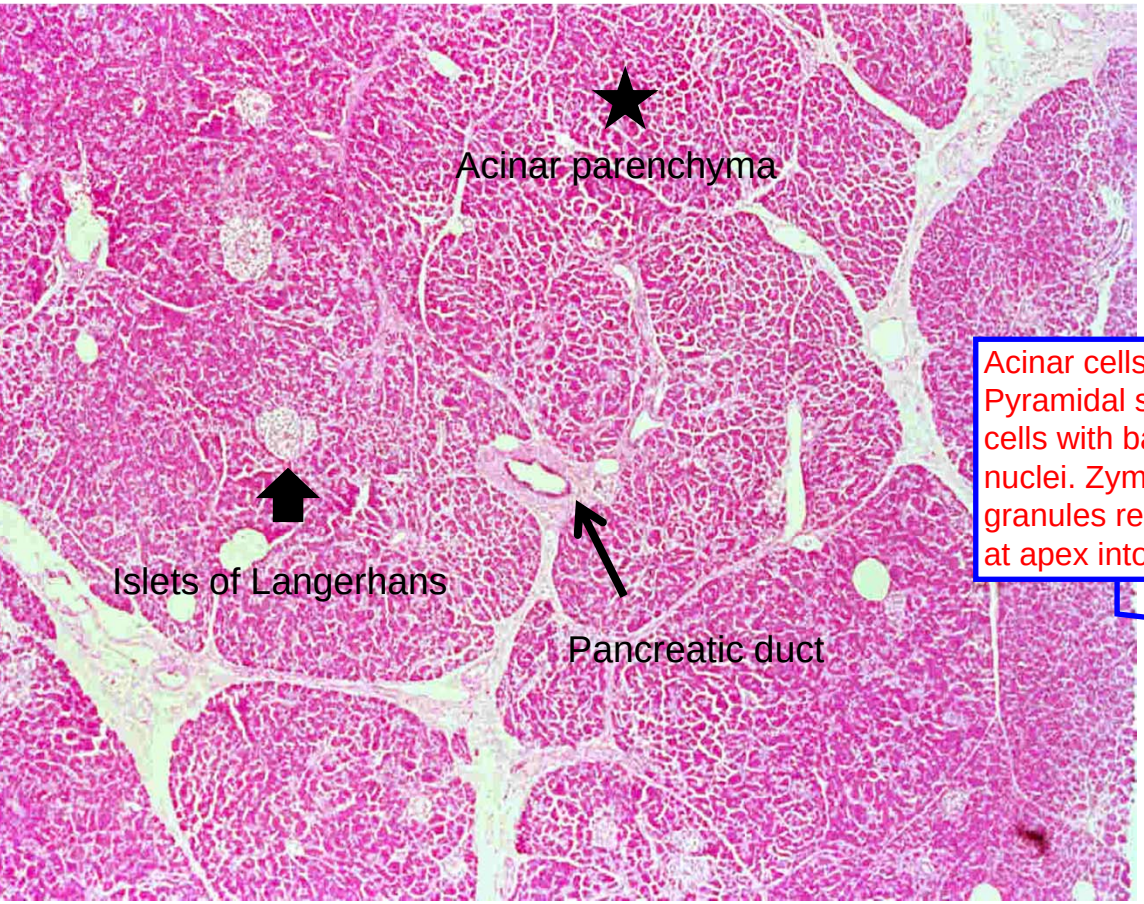
She just read the slide

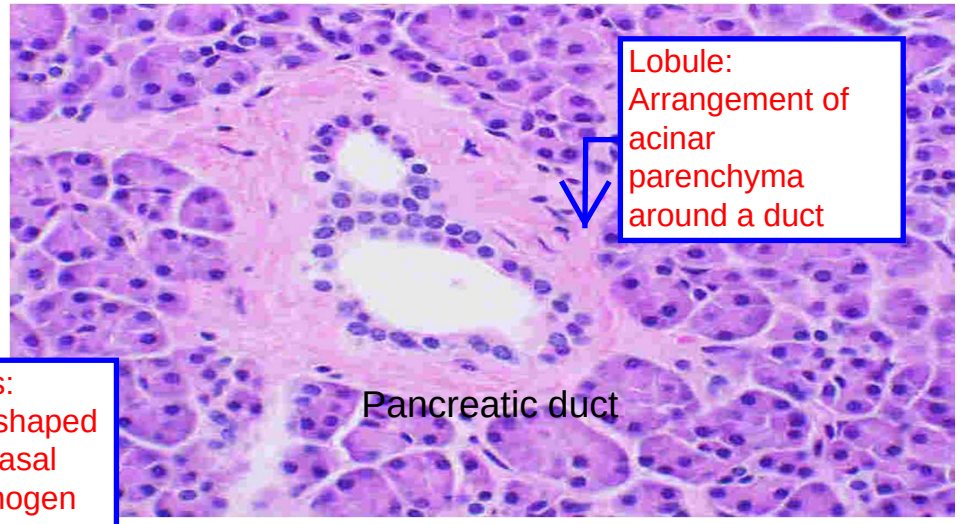
Pancreas: 2 distinct functions

- Pancreas can be thought of as “2 organs in 1”
  - **Exocrine portion**
    - Produces digestive enzymes (such as amylase and lipase) and delivers these to the lumen of the duodenum
    - Composed of acinar cells and ducts
    - Comprises 80-90% of the pancreas
  - **Endocrine portion**
    - Secretes hormones such as insulin and glucagon
    - Composed of Islets of Langerhans

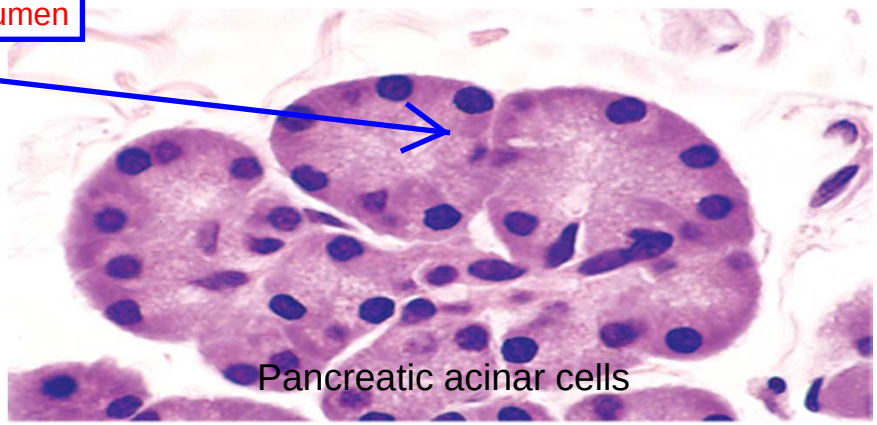
Nothing new here

Microscopic Anatomy of the Pancreas





Acinar cells: Pyramidal shaped cells with basal nuclei. Zymogen granules released at apex into lumen



More slide reading

Exocrine Pancreas

- Most of the exocrine secretions are produced and stored as enzymatically inert proenzymes to prevent autodigestion:
  - The acinar cells store the proenzymes in the cytoplasm as secretory granules (zymogen granules)
  - Trypsinogen, chymotrypsinogen, procarboxypeptidase, and proelastase
- Amylase and lipase are secreted in active forms

Regulation of pancreatic secretions

1 Neural stimulation: vagus nerve

2 Humoral factors:

Secretin and cholecystokinin from the duodenum

Secretin stimulates water and bicarbonate secretion from the duct cells

Cholecystokinin promotes discharge of the digestive enzymes from the acinar cells

PATHOLOGY OF THE PANCREAS

Major clinical problem of the pancreas

Pancreatitis

- Inflammation of the pancreas associated with acinar cell injury = pancreatitis

General pathogenesis: Acinar cell injury releases pancreatic enzymes that autodigest the parenchyma

- Occurs along a spectrum of severity

  (ranging from mild/self-limited to severe/life threatening)

  and a spectrum of duration

  (quick transient attack to chronic irreversible loss of function)

- Mechanism: autodigestion by inappropriately activated pancreatic enzymes

She read the slide

Two major forms of pancreatitis

- Acute pancreatitis
  - By definition, the gland can return to normal if the underlying cause is removed
- Chronic pancreatitis
  - By definition, there is irreversible destruction of predominately the exocrine pancreatic parenchyma

Acute pancreatitis: Reversible damage
Chronic pancreatitis: Permanent damage

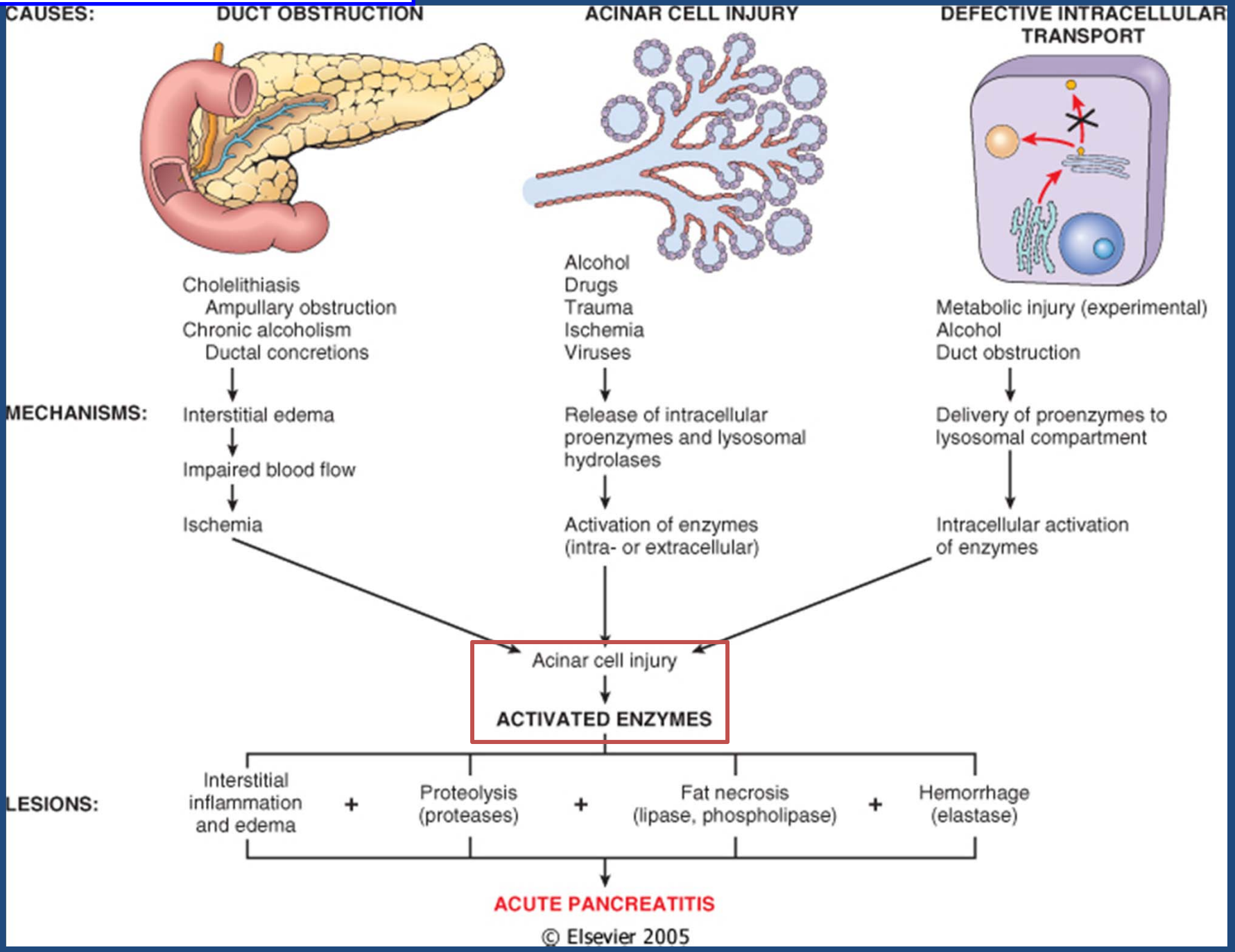
Acute Pancreatitis

- Relatively common
  - Annual incidence in Western countries is 10-20 cases/100,000 people
- 80% of cases in Western countries are associated with:
  - Biliary tract disease such as gallstones
    - Male to female ratio = 1:3
  - Alcoholism
    - Male to female ratio = 6:1
- Less common causes
  - Duct obstruction from tumor, medications (thiazide diuretics), infections (mumps, coxsackieviruses), and trauma (blunt trauma, iatrogenic/surgical)

Acute pancreatitis caused by biliary tract disease is female-dominant, while alcohol-related pancreatitis is male-dominant.

Mnemonic for acute pancreatitis: I GET SMASHED (allusion to heavy drinking)
I- idiopathic (maybe hypertensive sphincter or microlithiasis)
G-gallstone
E- ethanol
T- trauma
S- steroids
M - mumps (and other viruses such as EBV, CMV, Coxsackie)
A- autoimmune disease (Polyarteritis nodosa, SLE)
S- scorpion sting (snake bites, brown recluse spider0
H- hypercalcemia, hyperlipidemia/hypertriglyceridemia and hypothermia
E- ERCP (endoscopic retrograde cholangio-pancreatography)
D- Drugs (SAND- Steroids and Sulfonamides, Azathioprine, NSAIDS, Diuretics) and duodenal ulcers

Summary of different ways you can get pancreatitis.
Nothing added.



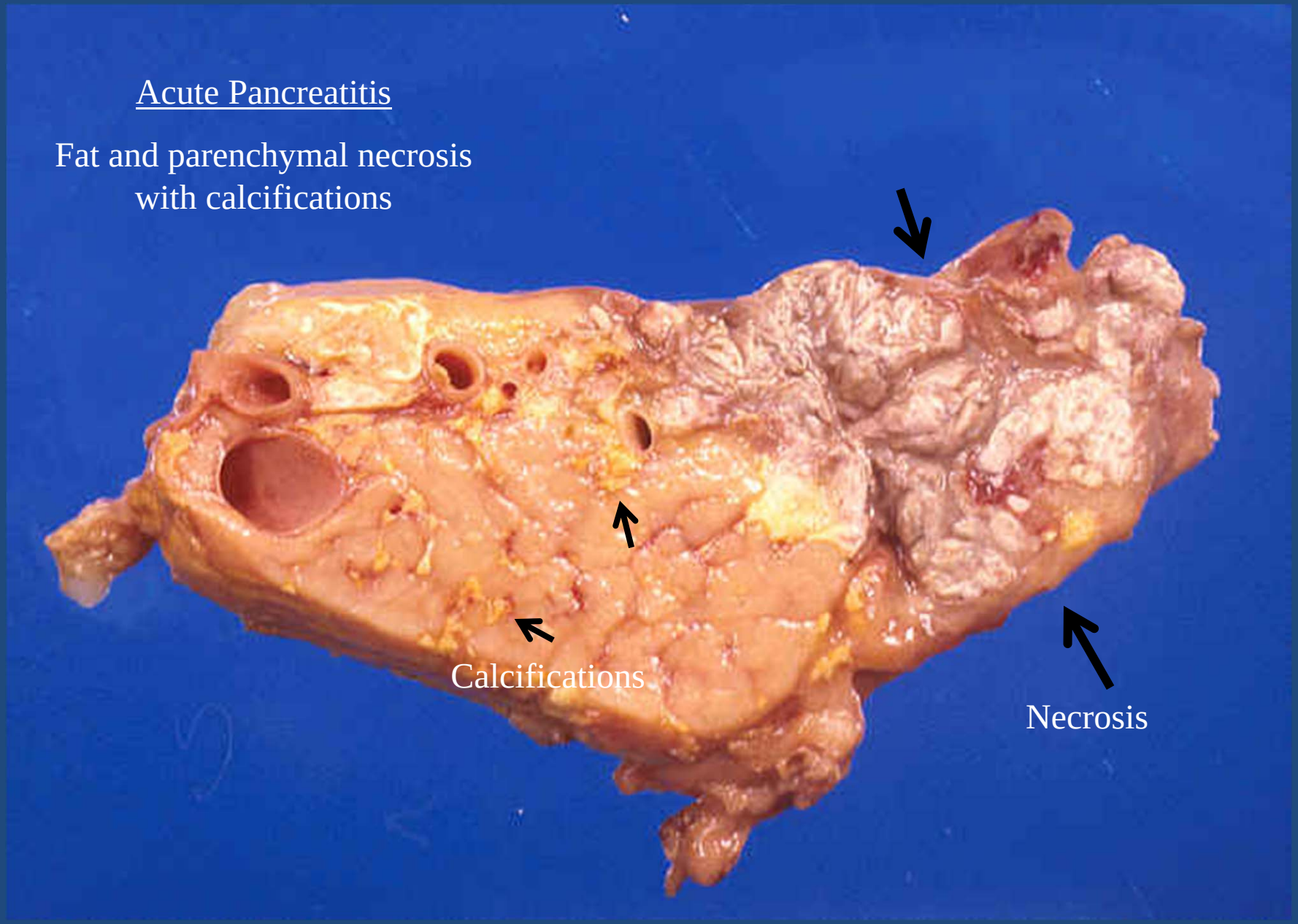
Clinical features of acute pancreatitis

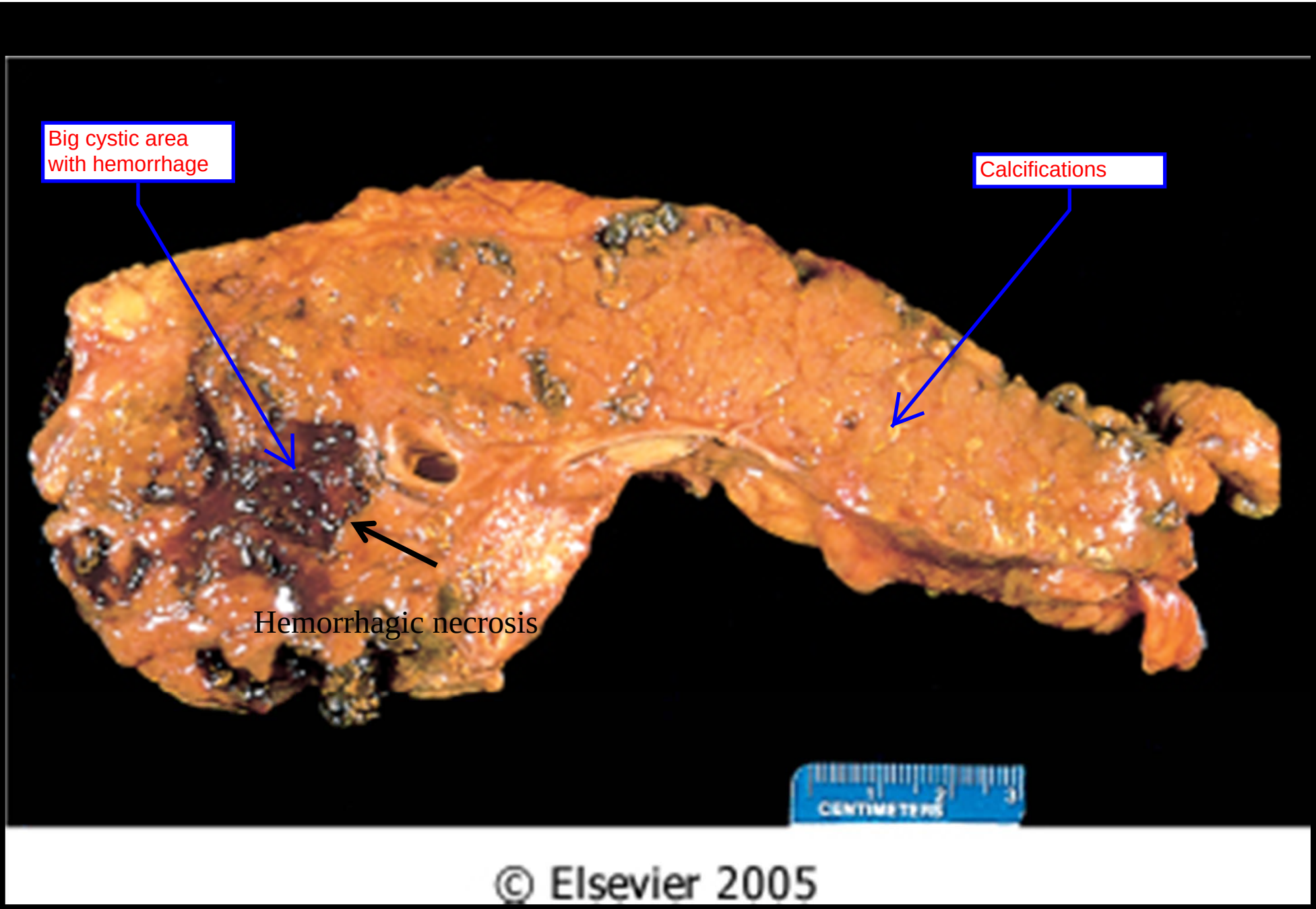
- Cardinal manifestation: abdominal pain
  - Ranges from mild to severe
- Full-blown acute pancreatitis (sudden calamitous onset of an “acute abdomen”) is a medical emergency because it can result in systemic organ failure, shock, acute renal failure, ARDS
- Characteristic laboratory values include: marked elevation of serum amylase and lipase
- Treatment: “resting” the pancreas by total restriction of food and fluids

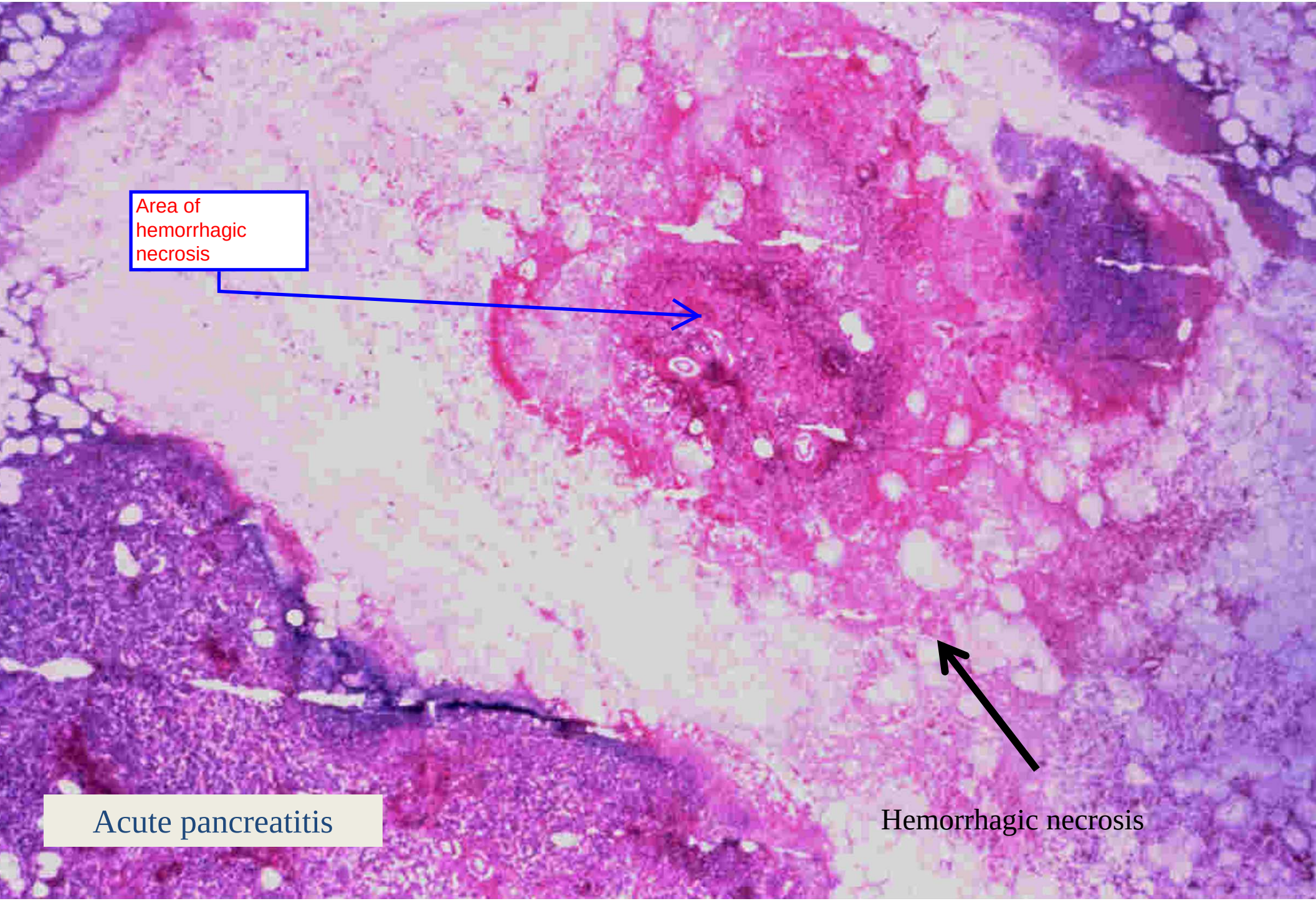
"Let me spell this out: Acute Respiratory Distress Syndrome"

Just let the patient rest. Calling the surgeons is not necessary here.

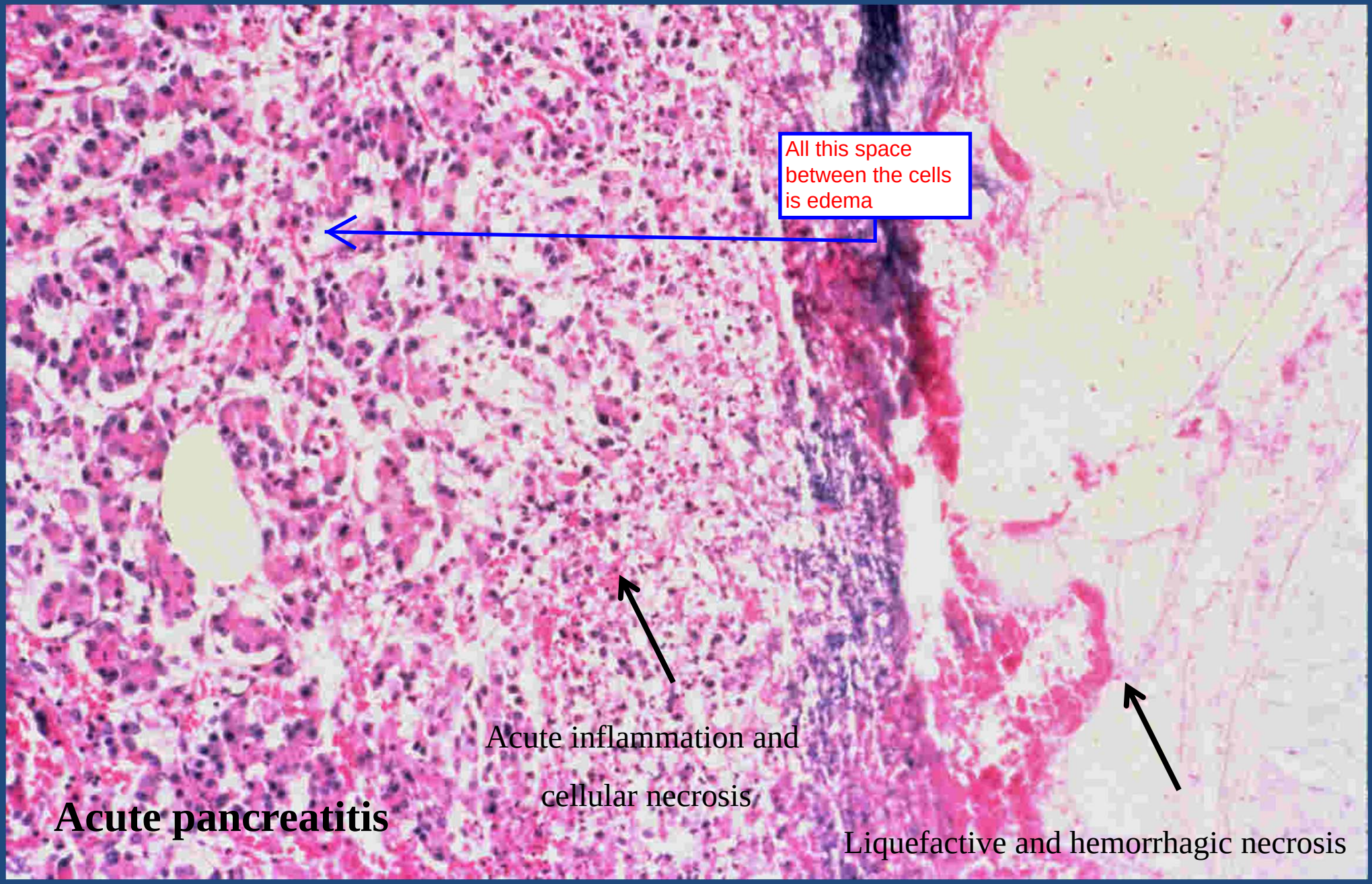
"A patient comes into the ER complaining of abdominal pain. What's the first thing you do?"
-Abdominal palpation: If it is rigid and board-like, that's bad. Next steps: Get a blood test. If a female, get a pregnancy test.
In the blood test, look for elevated levels of amylase and lipase.


Acute Pancreatitis
Fat and parenchymal necrosis
with calcifications
Calcifications
Necrosis





Acute pancreatitis



Acute pancreatitis

One major sequela of acute pancreatitis:

Pancreatic Pseudocyst

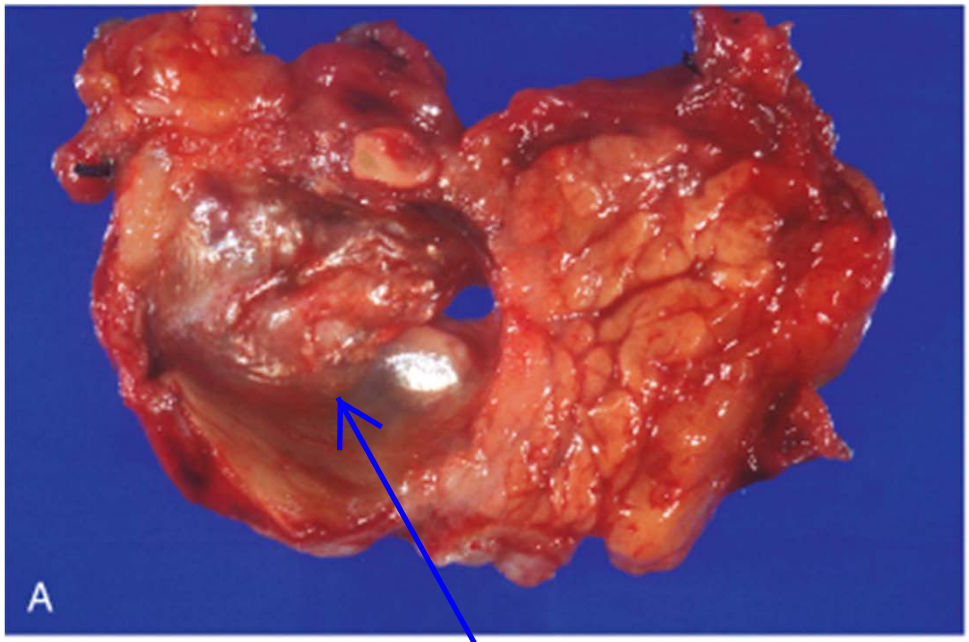
- A localized collection of necrotic-hemorrhagic material rich in pancreatic enzymes
- A cyst is by definition lined by epithelial cells; a pseudocyst has no true epithelial lining
- Pseudocysts usually arise following an episode of acute pancreatitis
- Pseudocysts are fairly common and account for 75% of the cysts in the pancreas
  - Differential diagnosis includes cystic pancreatic neoplasms
- May present as a mass lesion in the pancreas or more commonly is located in the peripancreatic soft tissues

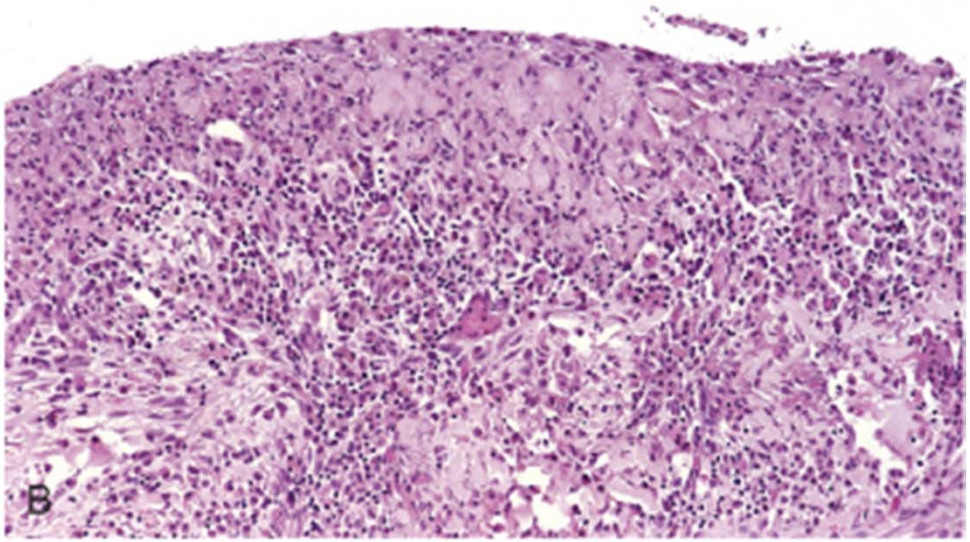
Persistent increase in serum amylase: consider pancreatic pseudocyst
From RR Path (Goljan)

Mass hangs off pancreas in imaging scan

Pancreatic Pseudocyst

No epithelial lining. All that fluid in the cyst would be here





The gross appearance doesn't tell you if this is a neoplasm or not. you need to take a biopsy

Chronic Pancreatitis

- Repeated bouts of pancreatitis
- Loss of pancreatic parenchyma and replacement by fibrosis
  - Relative sparing of the Islets of Langerhans until the late stages
- Resultant irreversible impairment of pancreatic exocrine function
  - Malabsorption
  - Steatorrhea
- Most common cause: long-term alcohol abuse

What does the body do when damaged? Answer: Make a scar (fibrosis)

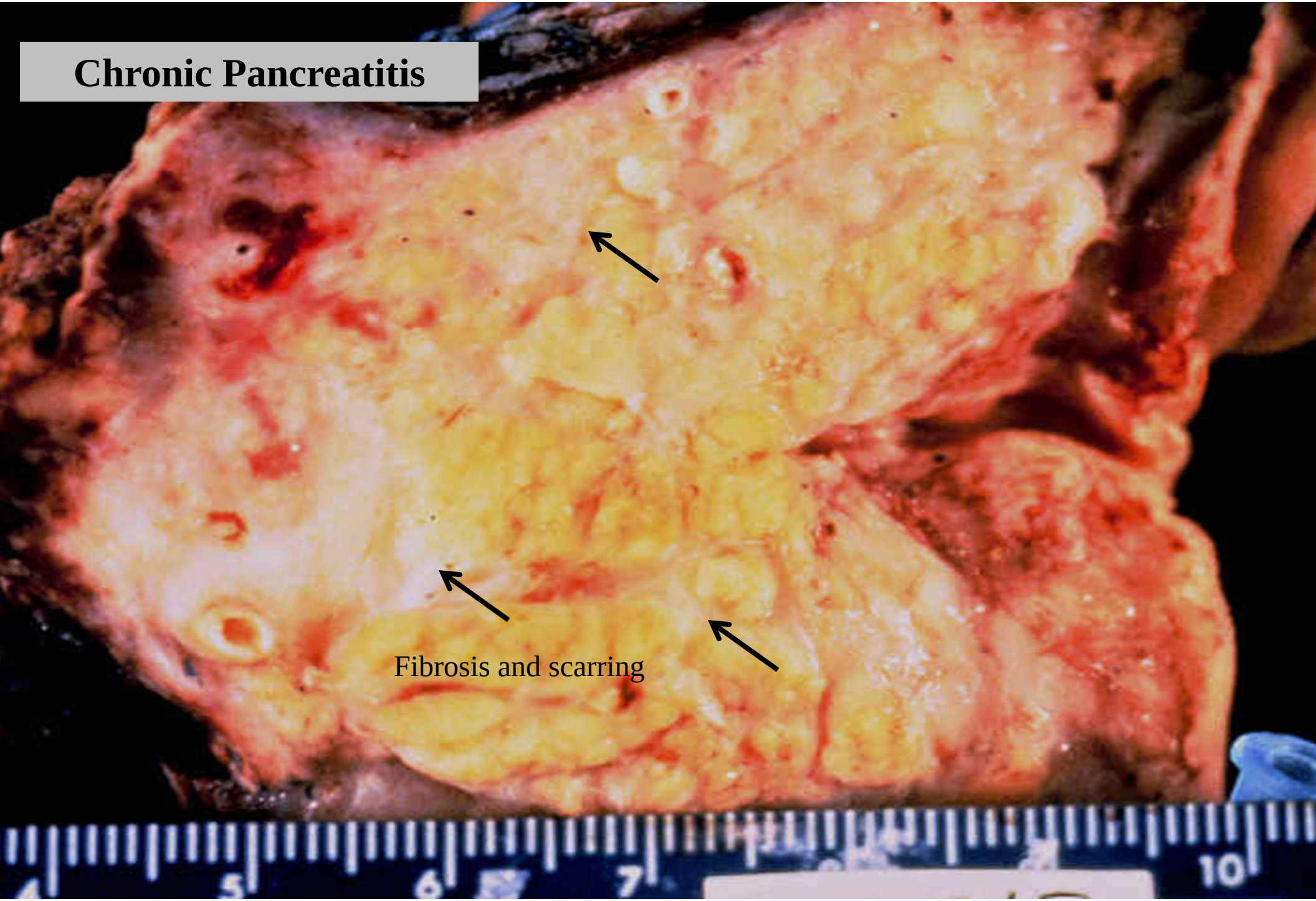
Due to lack of release of pancreatic enzymes

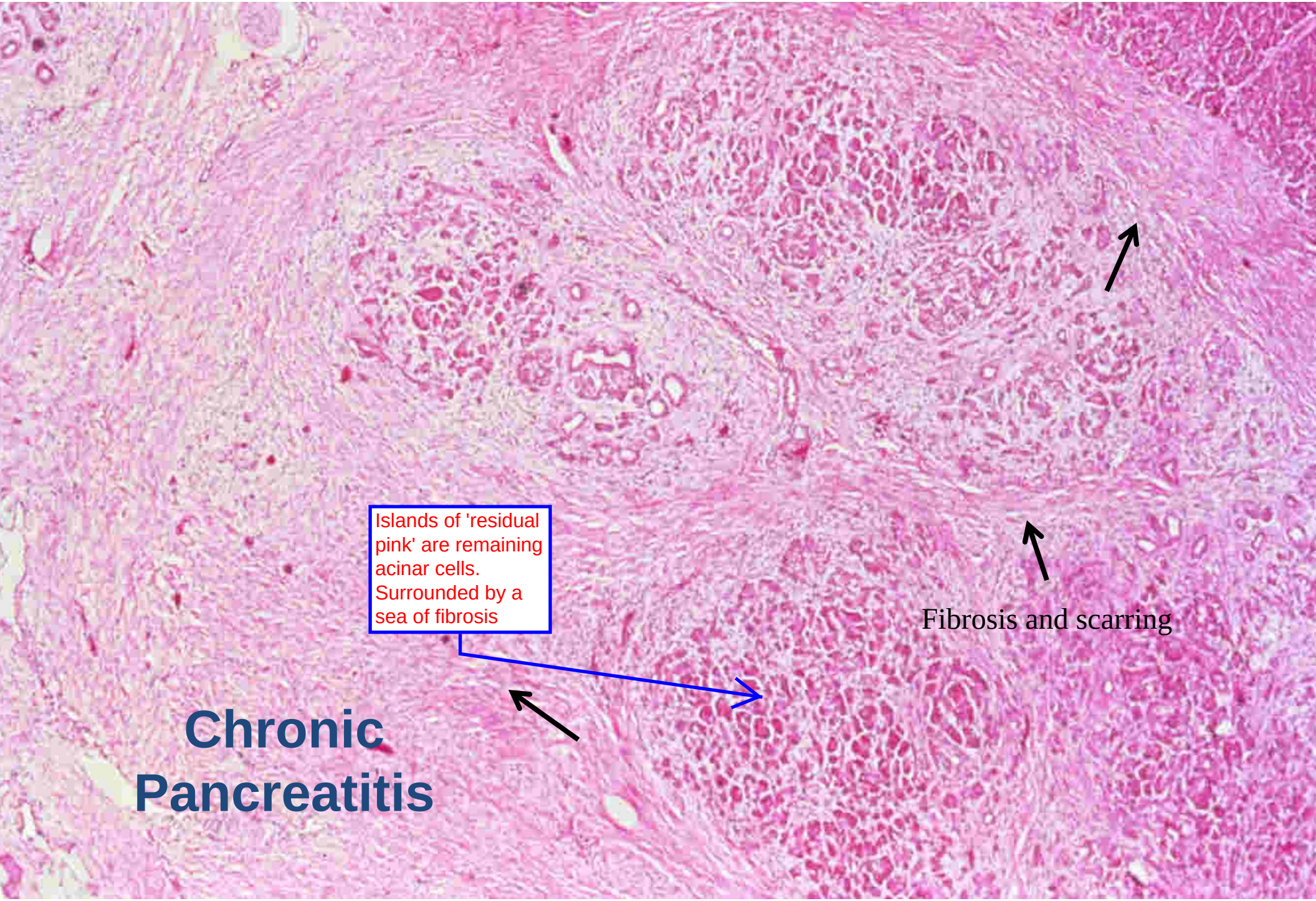
Not sure why this happens

Fatty diarrhea

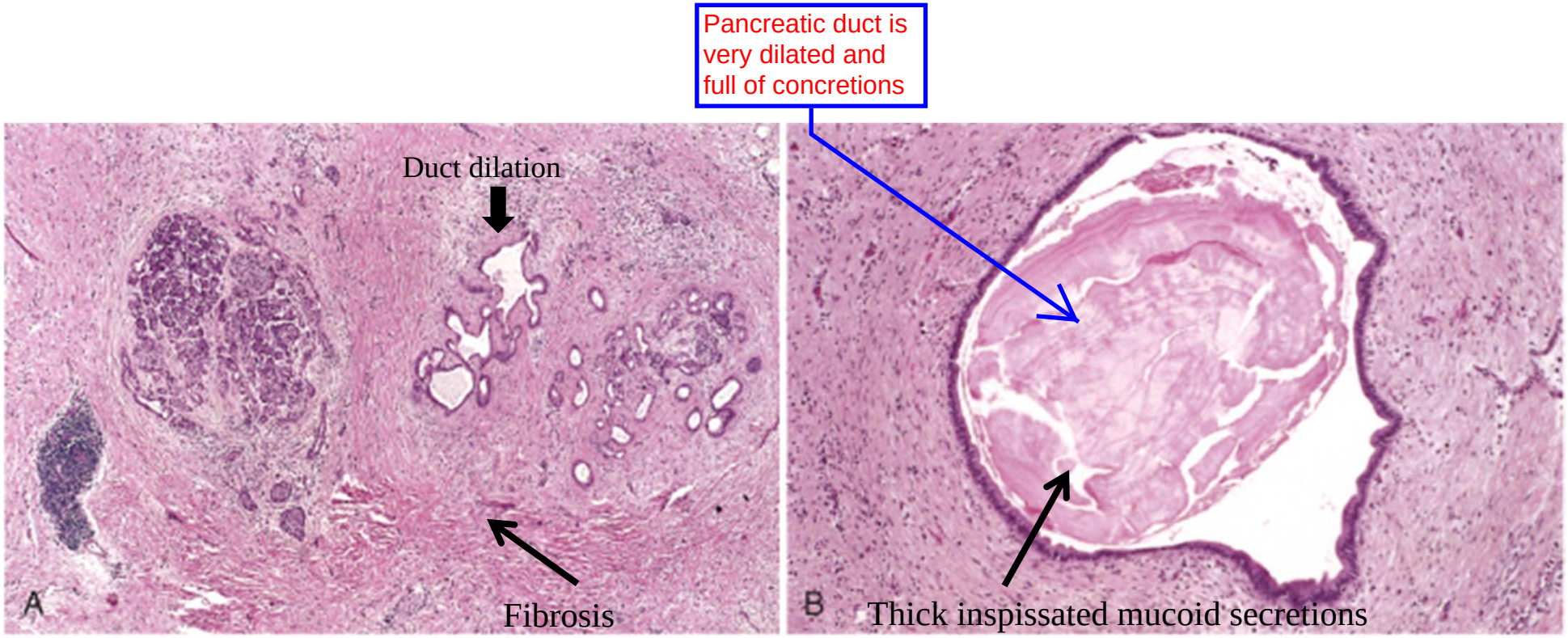
From Robbins: 65% of chronic pancreatitis in the US is from chronic alcohol abuse

Chronic Pancreatitis



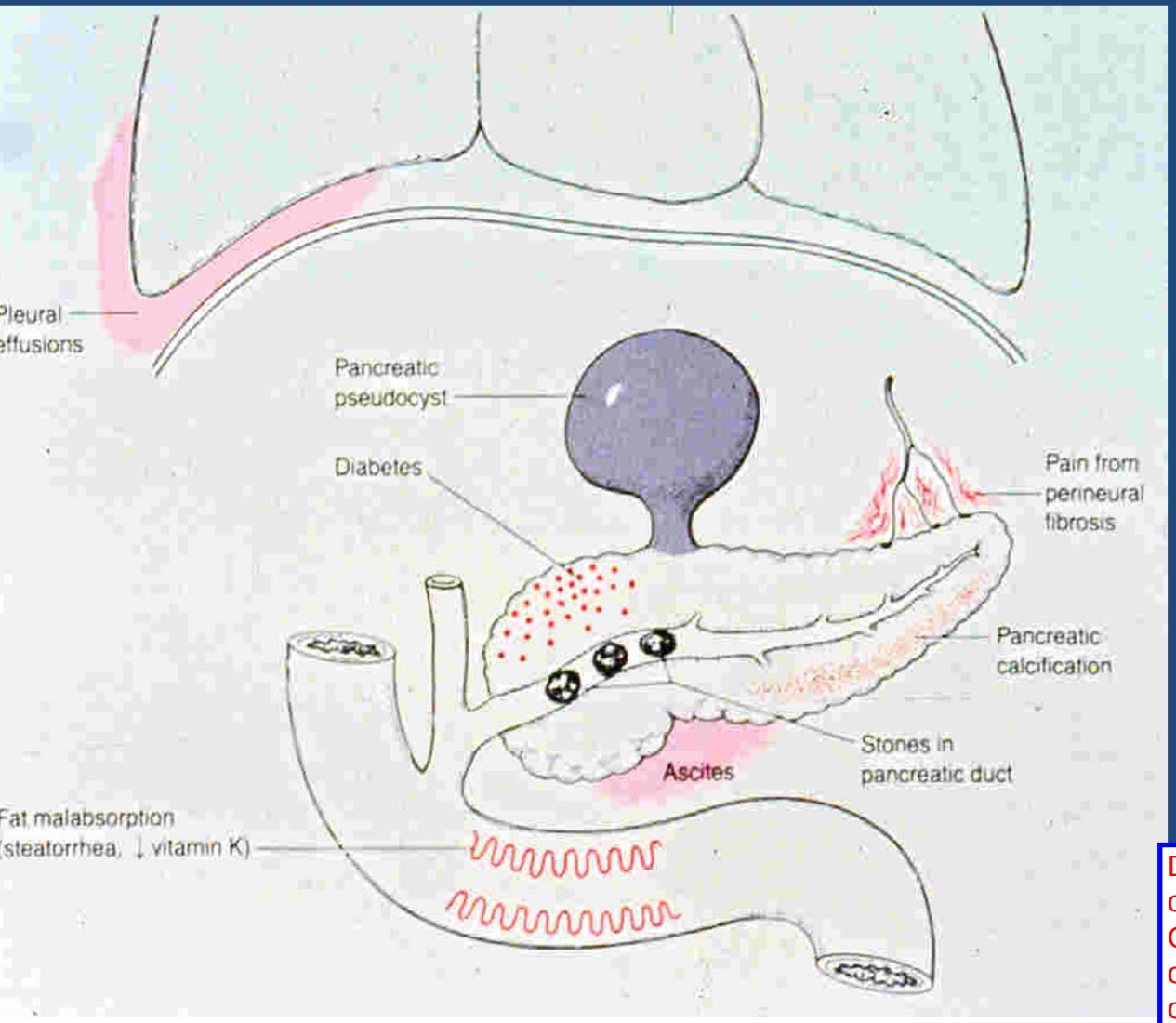

Islands of 'residual pink' are remaining acinar cells. Surrounded by a sea of fibrosis
Fibrosis and scarring
Chronic Pancreatitis

Chronic Pancreatitis



She read the slide. Summary: These are the complications of pancreatitis.

In review: Sequelae of pancreatitis



Due to endothelial damage cause by released enzymes, particularly trypsin

ACUTE PANCREATITIS

- Systemic organ failure
  - Shock
  - ARDS
  - Acute renal failure
- Disseminated intravascular coagulation
- Pancreatic abscess
- Pancreatic pseudocyst
- Duodenal obstruction

Commonly gram-negative sepsis

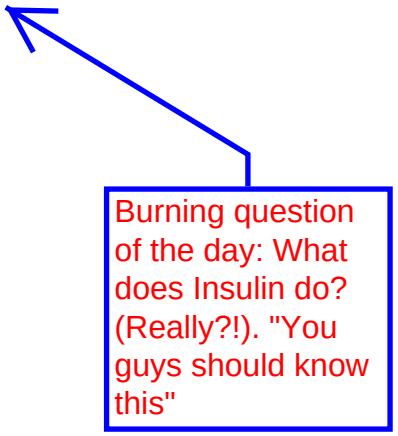
CHRONIC PANCREATITIS

- Pseudocyst
- Duct obstruction
- Malabsorption, steatorrhea
- Secondary diabetes

Destruction of Islets occurs. According to Goljan, type I diabetes occurs in 70% of cases of chronic pancreatitis

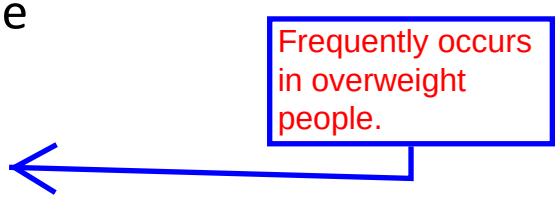
Diabetes Mellitus

- Heterogeneous group of chronic disorders involving carbohydrate, fat, and protein metabolism.
- Absolute or relative deficiency in insulin
- Unifying feature is hyperglycemia
- Common disease: 13 million Americans
- Annual mortality rate of 35,000



Diabetes Mellitus

- Two major types
  - **Type 1** or "Insulin dependent DM"
    - More commonly arises in children and adolescents
    - Autoimmune disease, autoantibodies against beta cells
    - Tends to be severe with marked insulin deficiency, and marked hyperglycemia, if not controlled results in ketoacidosis
  - **Type 2** or "Adult onset DM"
    - More common in adults, often obese
    - Normal or increased blood insulin
    - Target tissues are insulin resistance



Nothing new or added here...

Diabetes Mellitus

- Long term complications of DM can involve many organs systems with resultant high morbidity
- Atherosclerosis, peripheral vascular disease, myocardial infarcts, nephrosclerosis, peripheral neuropathy, microangiopathy and cerebrovascular infarcts and hemorrhages

Pancreatic Neoplasms

Ductal Adenocarcinoma
Cystic Neoplasms
and
Islet Cell Tumors

Pancreatic Adenocarcinoma

4th leading cause of cancer deaths in the US

Approximately 28,00 cases per year

One of the highest mortality rates of any cancer

- Less than 5% 5 year survival

Pancreatic Adenocarcinoma

- Often considered a disease of the elderly
  - 80% occur between the ages of 60 – 80
- Risk Factors
  - Smoking
    - The strongest environmental factor
    - Doubles the risk of developing pancreatic cancer (impact is significant due to large number of people who smoke)
  - Chronic pancreatitis

Familial Syndromes Predisposing to Pancreatic Cancer

- <u>Inherited genetic syndromes associated with increased risk of developing pancreatic cancer</u>
  - Peutz-Jeghers 130X increased risk
  - Hereditary Pancreatitis 50 – 80X increased risk
  - Familial Atypical Multiple Mole Melanoma Syndrome 25X increased risk

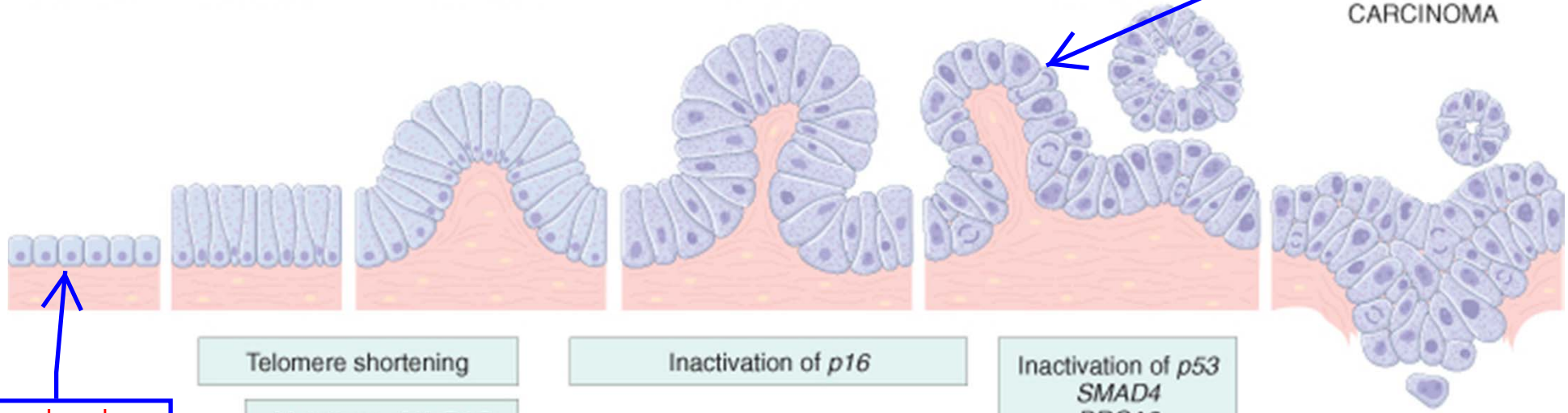
Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by multiple GI harmartomous polyps and mucocutaneous hyperpigementation. If a patient presents with Peutz-Jeghers, you should be very suspicious. Check for pancreatic cancer.

Another burning question from Dr. Guy: "How many of you know that many cancers occur in a stepwise manner? You should learn this"

Precursors to invasive pancreatic adenocarcinoma

- There is a stepwise progression from non-neoplastic ductal epithelium to precursor lesions to invasive adenocarcinoma
- The precursor lesions are called pancreatic intraepithelial neoplasia (PanIN)
- PanINs are microscopic/histologic cellular changes in the ductal epithelial cells.
- PanINs consist of a spectrum of progressively more severe histologic changes (PanIN-1, PanIN-2, and PanIN-3) that mirror molecular changes.

Progression model for pancreatic adenocarcinoma



N:C ratio is increasing and the cell morphology is changing. (Elongated). Cells are beginning to break through the basement membrane

Uniform basal nuclei in orderly cuboidal cells

Pancreatic Adenocarcinoma

Clinical Features

Often remains silent until it impinges on some other structure

- Pain is often one of the first symptoms

Pancreatic cancers like to invade nerves

- Obstructive jaundice is common

Due to increased bilirubin

Weight loss, anorexia, generalized malaise and weakness

Disease course is usually brief and progressive

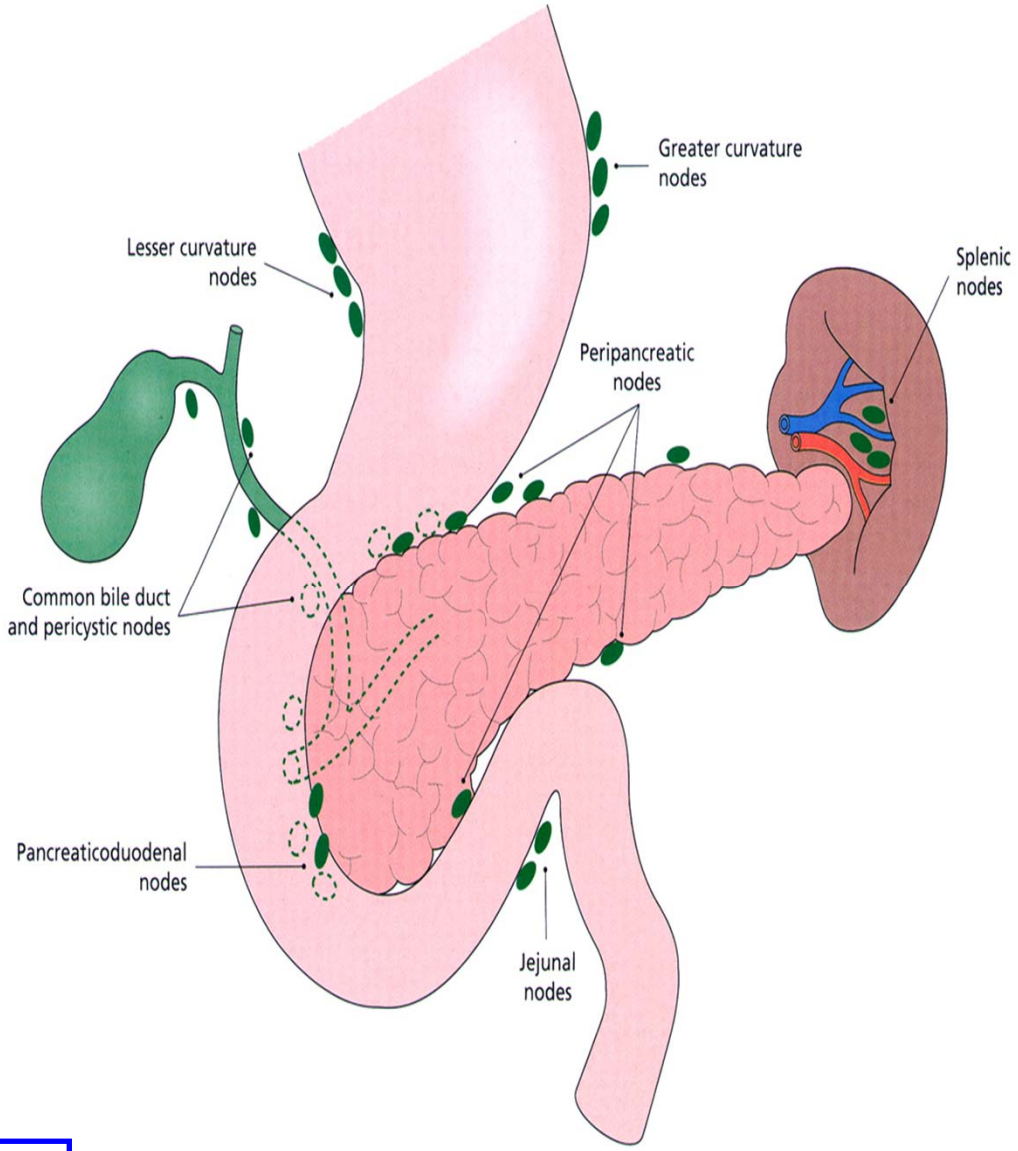
Fewer than 20% are resectable at the time of diagnosis

Pancreatic Cancer

Macroscopic Features

- 60% occur in the HOP
  - 15% body
  - 5% tail
  - 20% diffusely involves the pancreas
- Gross exam:
  - Hard, stellate, gray-white, poorly defined

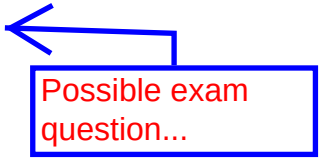
- Carcinoma in the HOP often leads to obstruction
- Carcinoma of the body and tail may remain silent for a longer period of time
- Infiltrative nature often leads to extension into retroperitoneal space and lymphovascular invasion
- Metastasis to liver is common



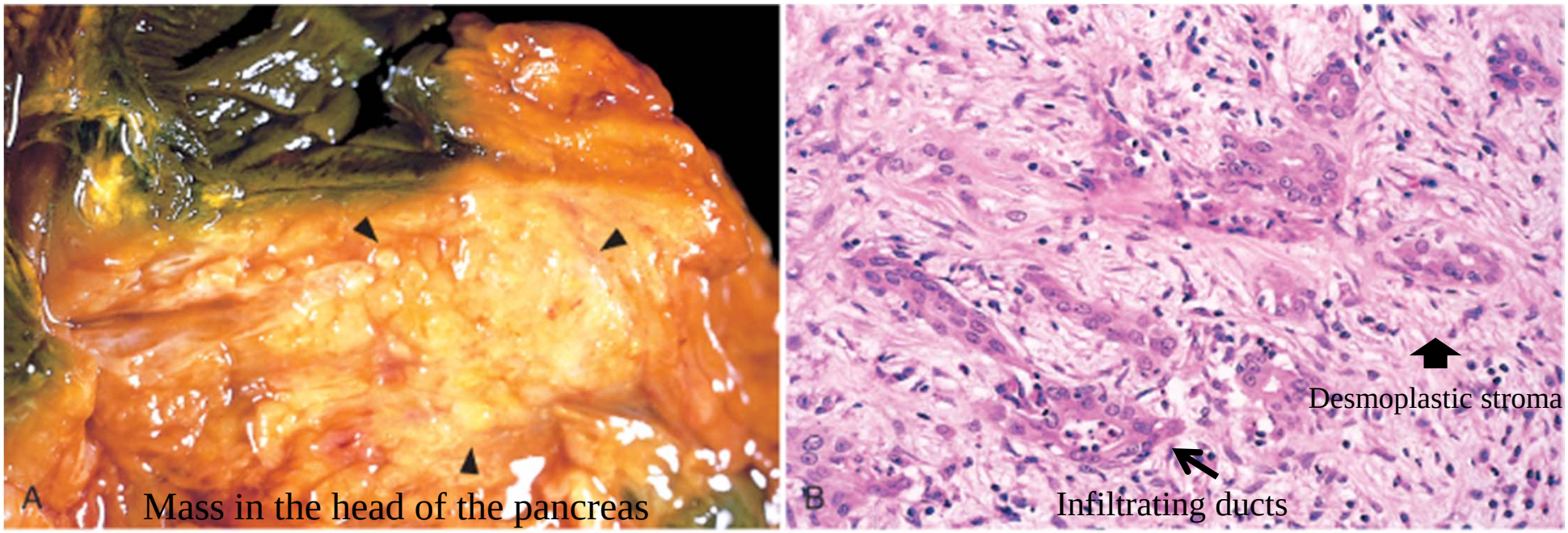
And to the supraclavicular nodes on the left side and the periumbilical region (Goljan)

Microscopic Findings

- Ductal adenocarcinomas
  - recapitulate to some degree the normal ductal epithelium by forming glands and secreting mucin
- 2 features highly characteristic of pancreatic ductal adenocarcinoma
  - Highly infiltrative
  - Elicits an intense non-neoplastic host response comprised of fibroblasts, chronic inflammatory cells, and matrix "desmoplastic response"

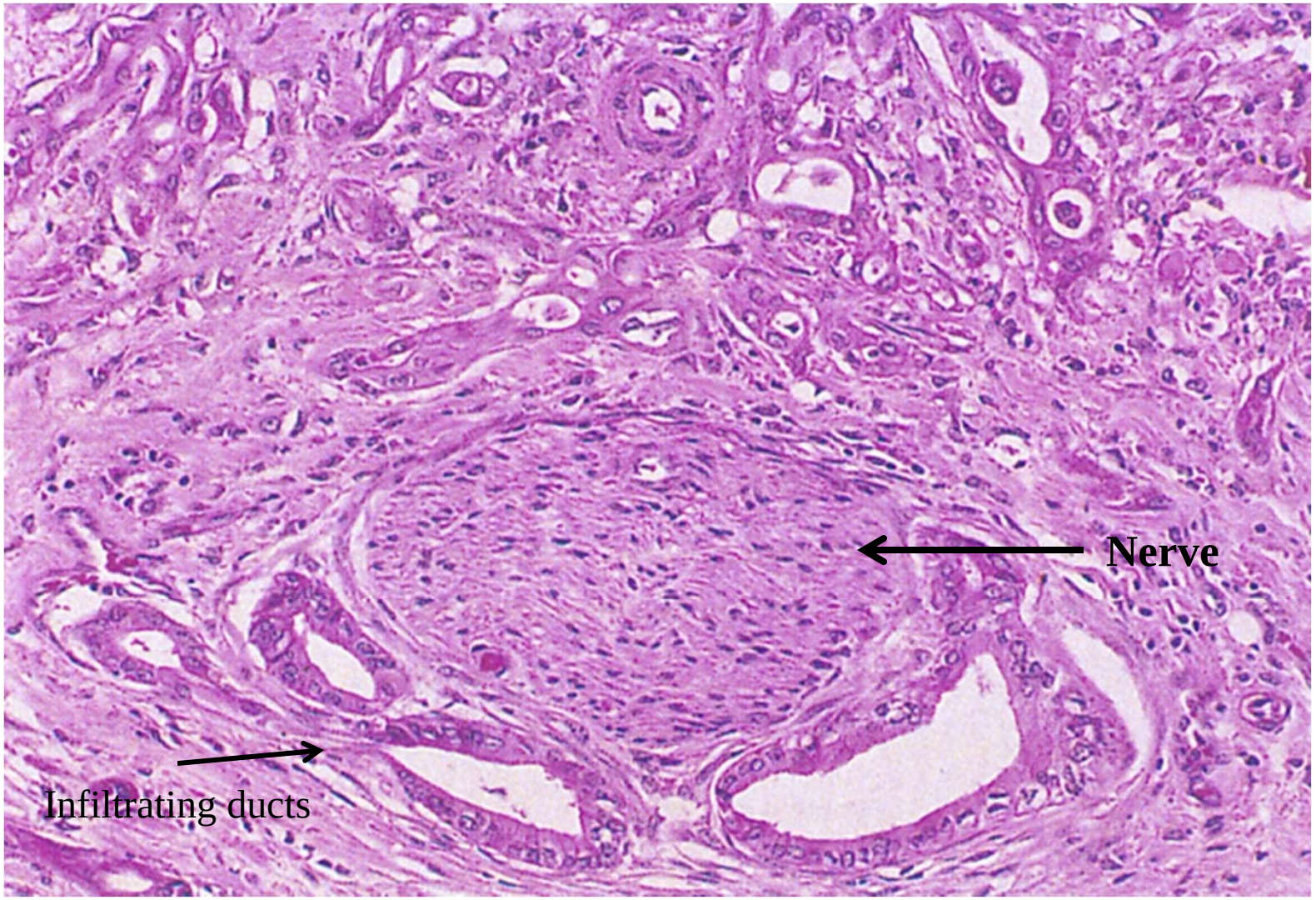


Carcinoma of the Pancreas



Pancreatic adenocarcinoma

Perineural invasion



Cystic Pancreatic Neoplasms

- Cystic neoplasm with serous epithelium
  - Serous cystadenoma
- Cystic neoplasms with mucinous epithelium
  - Mucinous cystic neoplasms
  - Intraductal papillary mucinous neoplasm (IPMN)

Pancreatic cysts

- Of all pancreatic cysts, about 10% are neoplastic
  - Pseudocyts comprise the vast majority
- Of all pancreatic neoplasms, less than 5% are cystic

Serous cystadenoma

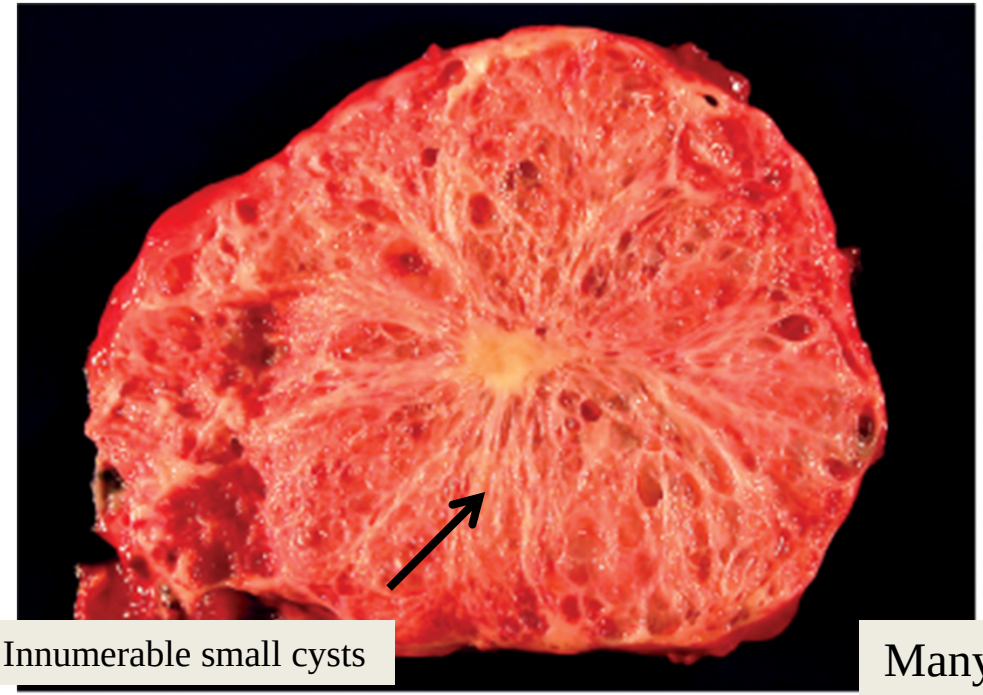
- About 25% of all cystic pancreatic neoplasms are serous cystadenomas
- The cyst lining is comprised of serous epithelium
- Serous epithelial cells are glycogen-rich and cuboidal
- The cystic spaces are filled with thin glycogen-rich fluid
- Clinical presentation
  - 7^{th} decade
  - Female to male ratio is 2:1

Serous cystadenomas

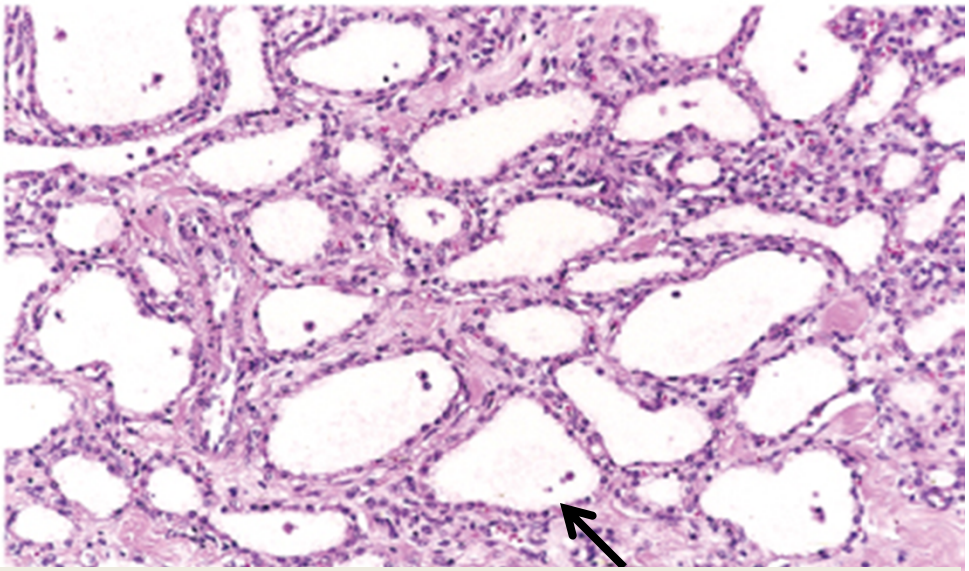
- Clinical presentation
  - 7^{th} decade
  - Female to male ratio is 2:1
- Presenting symptoms
  - Abdominal pain
- Serous cystadenomas are benign
  - They will not progress to malignancy
  - Therefore surgical resection is not mandatory

She's running out of time. From here on out, verbatim slide reading.

Serous cyst adenoma



Innumerable small cysts



Many small cysts lined by serous cuboidal epithelium

Surgical removal of these cysts are curative in most cases.

Cystic Tumors that are mucinous

- Mucinous cystic neoplasms
- Intraductal papillary mucinous neoplasms

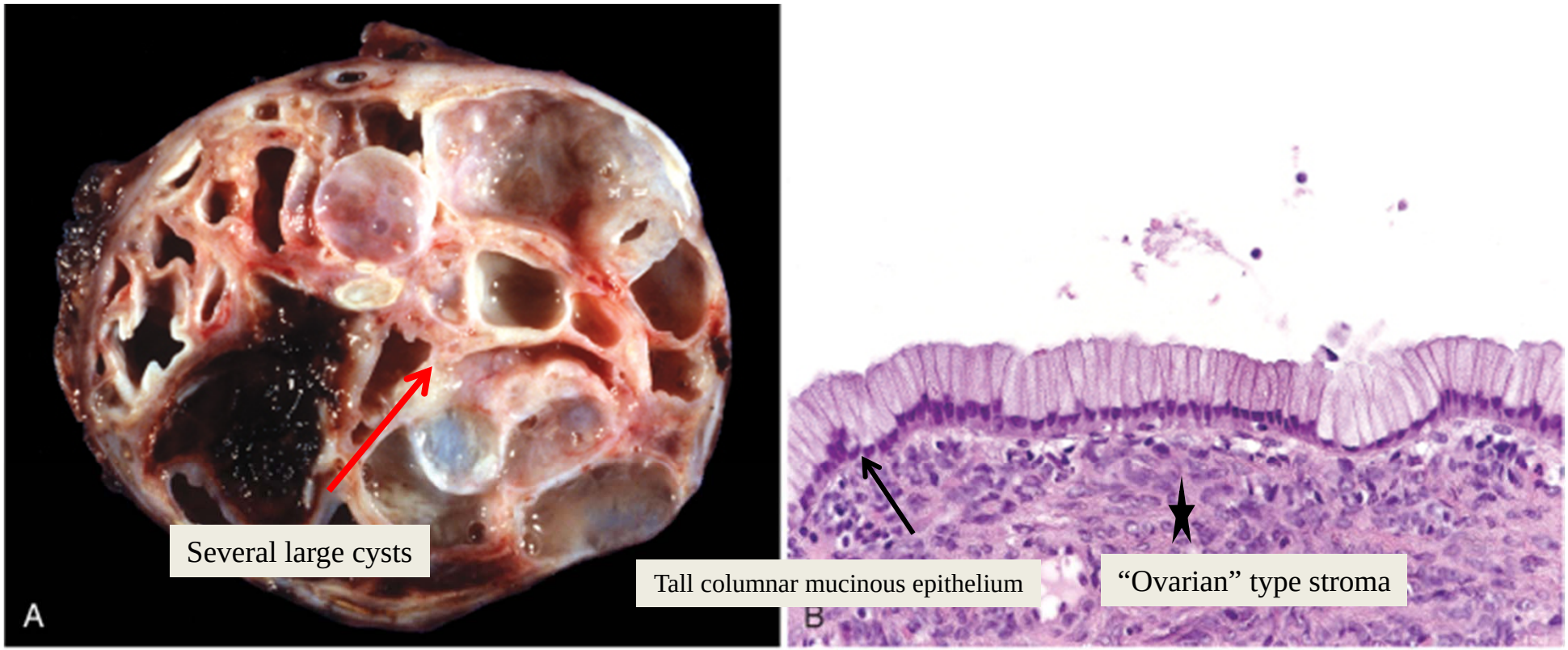
Mucinous cystic neoplasms

- Almost always arise in women
- Often arise in the body or tail of the pancreas
- Essentially never arise from or involve the pancreatic duct system
- The epithelial lining is made up of columnar mucinous cells and the supporting stroma is cellular and has an "ovarian" stromal phenotype
  - Histologically looks like ovarian stroma
  - Expresses similar markers (estrogen receptors, progesterone receptors)

Mucinous cystic neoplasms

- These tumors can be benign, borderline or malignant
  - Benign: no epithelial dysplasia
  - Borderline: epithelial dysplasia
  - Malignant: invasive adenocarcinoma
- These tumor have malignant potential and if at all possible surgical resection is advised

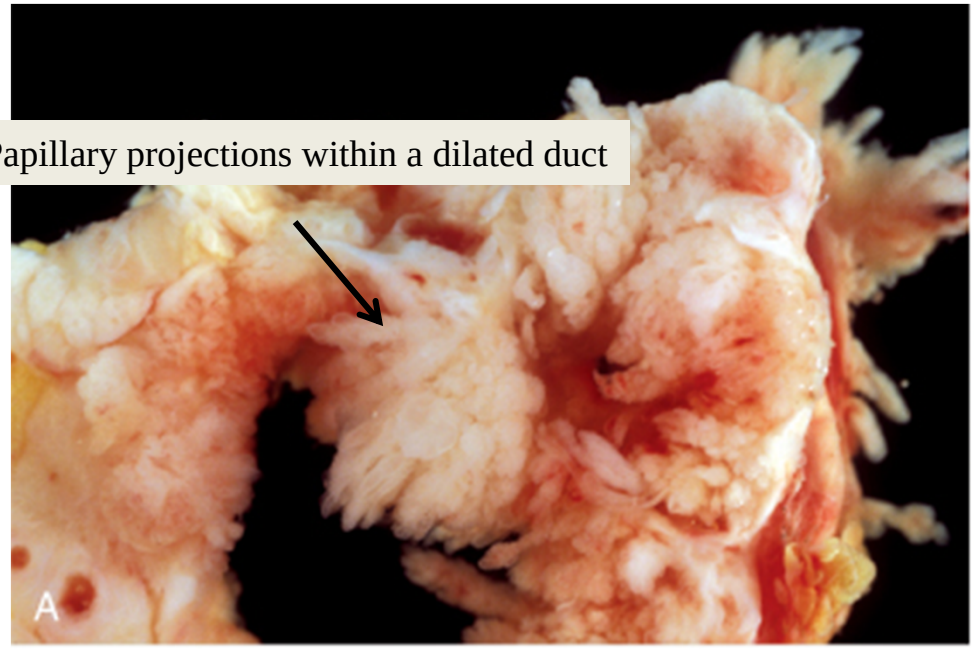
Mucinous cystic neoplasms



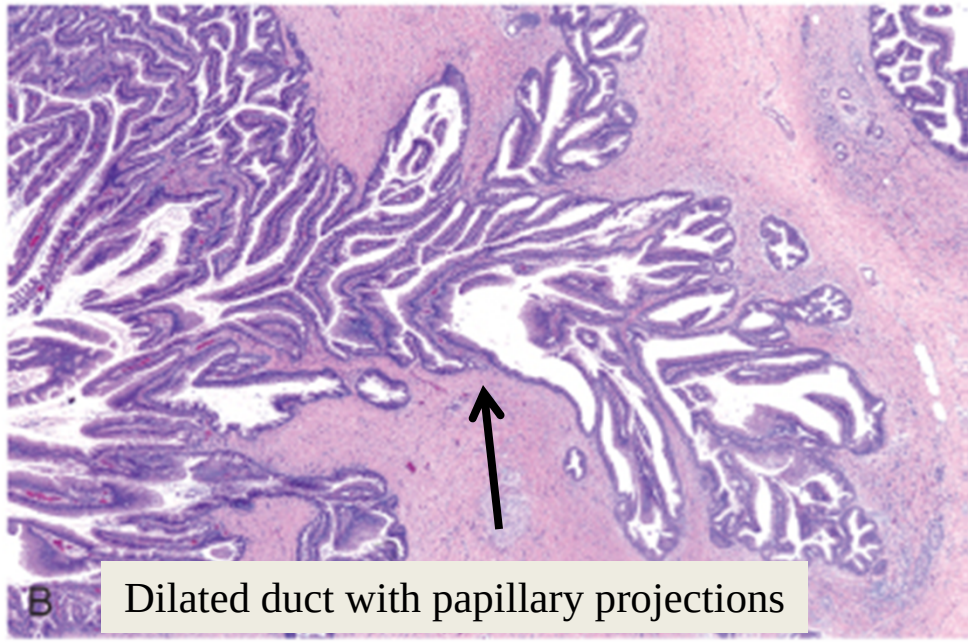
Intraductal papillary mucinous cystic neoplasm

- Arise more frequently in men
- Arise more frequently in the head of pancreas
- Arise from and involve the major and minor pancreatic ducts
- The epithelial lining is comprised of mucinous columnar cells
- Can be benign, borderline or malignant
  - Thus have malignant potential and should be resected

Intraductal papillary mucinous neoplasm



Papillary projections within a dilated duct



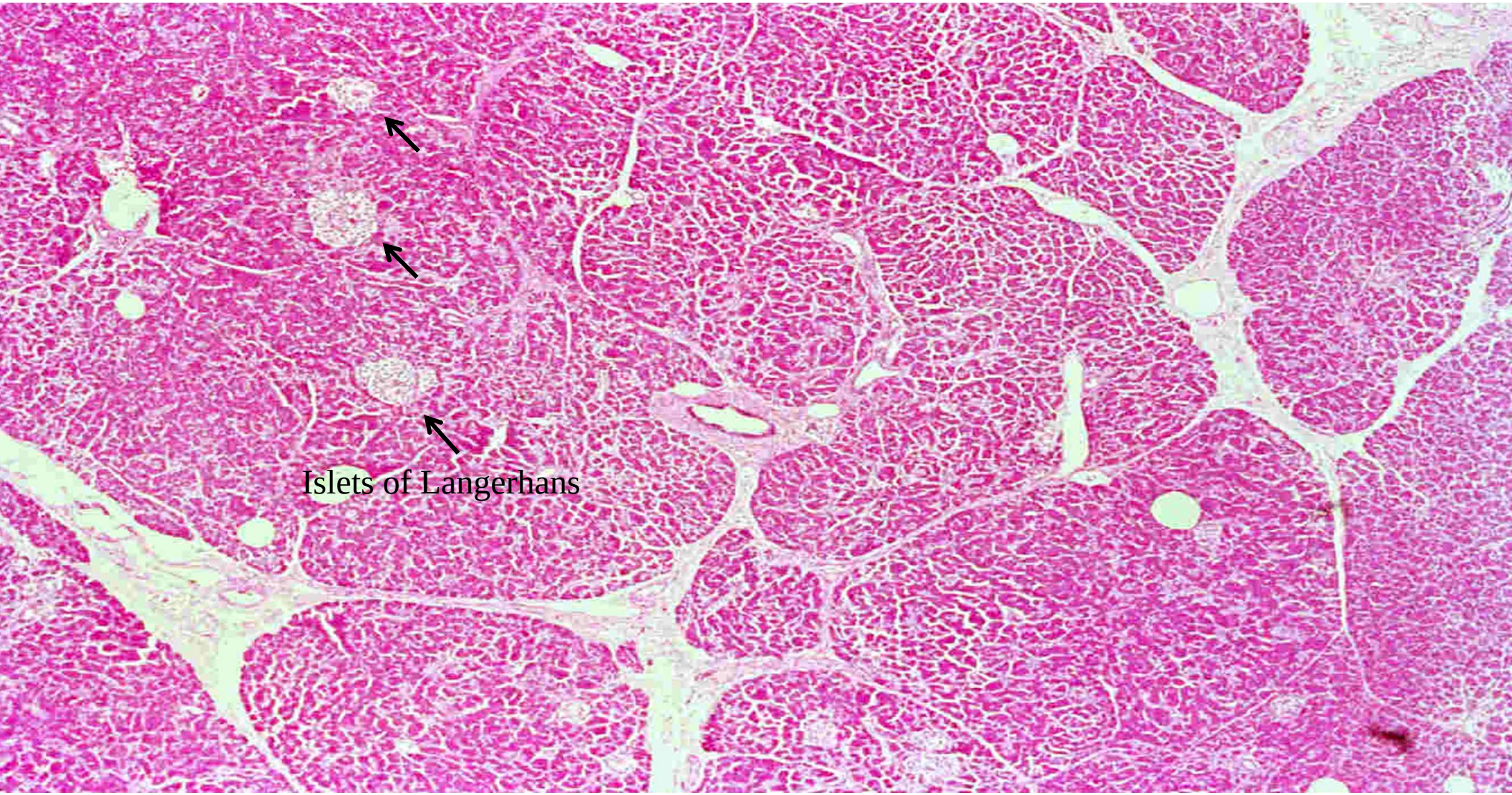
Dilated duct with papillary projections

Islet Cell Tumors

(Pancreatic Endocrine Tumors or
Pancreatic Neuroendocrine Tumors)

Normal pancreas

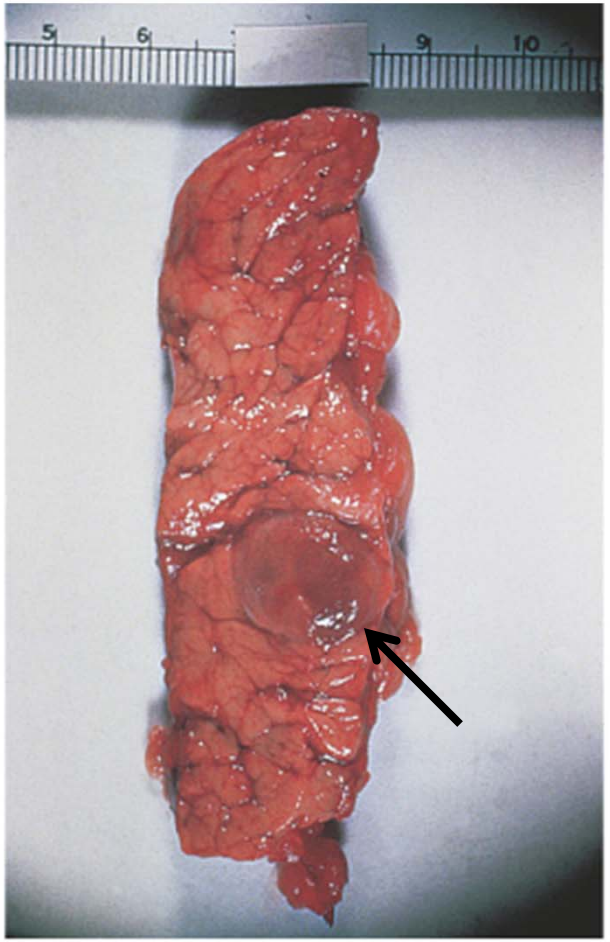
Small groups of endocrine cells (Islets of Langerhans) which secrete hormones such as insulin, glucagon and gastrin

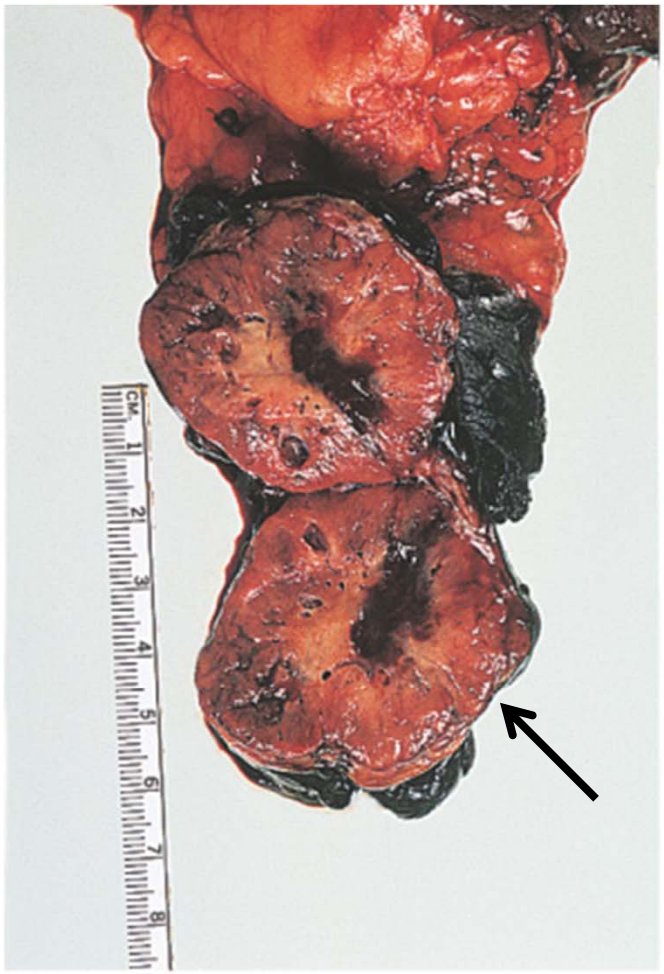


Pancreatic Neuroendocrine Tumors

- Rare compared to adenocarcinoma
- Clinical presentation
  - May present with symptoms related to increased hormone secretion
    - Hyperinsulinemia causing hypoglycemia
    - Hypergastrinemia causing increased gastric acid production and severe ulcers (Zollinger-Ellison syndrome)
  - May present as a non-functional (non-secreting) mass
    - This is the most common

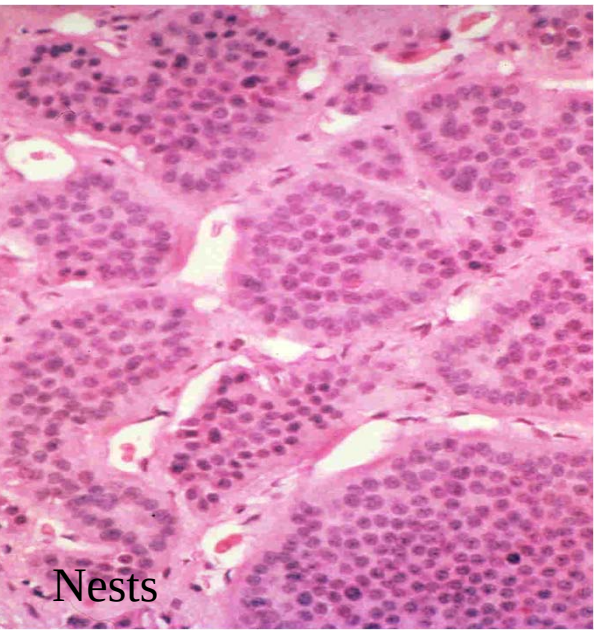
Pancreatic endocrine tumor

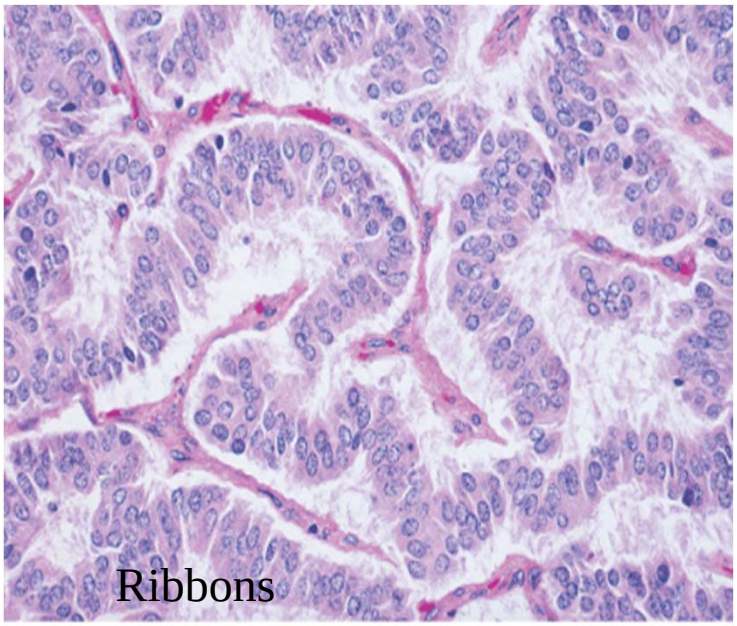


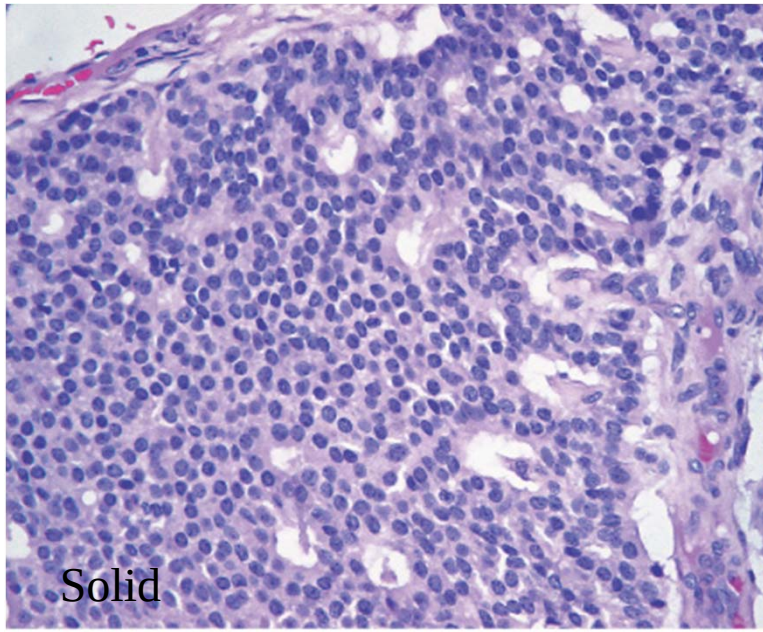


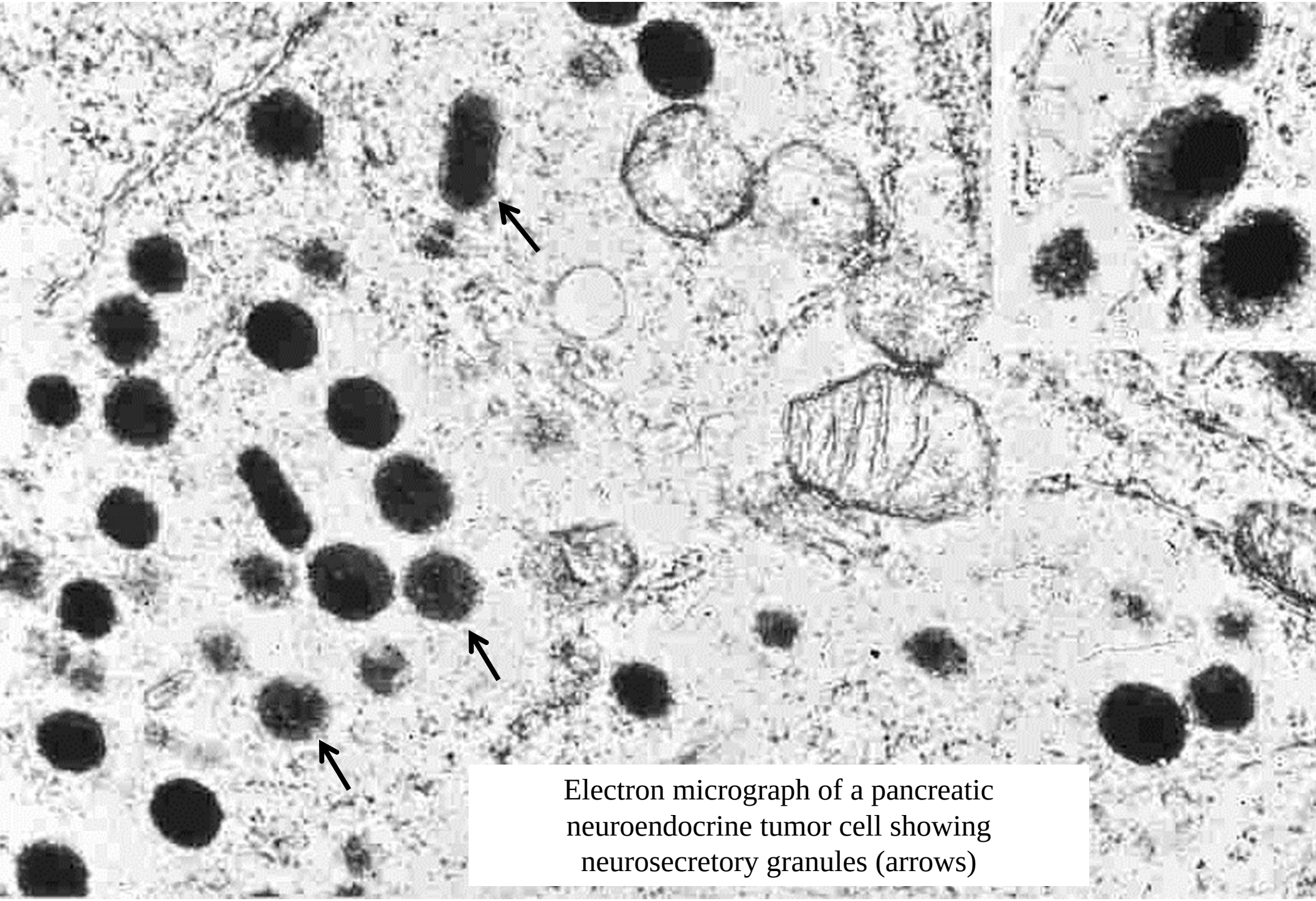
Pancreatic endocrine tumors

Histologic features/growth patterns









Electron micrograph of a pancreatic neuroendocrine tumor cell showing neurosecretory granules (arrows)

The end

Parting words from Dr. Guy: "Thanks. Read the book."