Cholecystitis
- acute
- chronic

Gallbladder tumors
- Adenomyoma (benign)
- Adenocarcinoma

Pancreatitis
- acute
- chronic

Pancreatic tumors

Intro to Gallbladder & Pancreas Pathology

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Gallstones
(Cholelithiasis)

- 10 - 20% Adults
- 35% Autopsy: Over 65

- Over 20 Million
- 600,000 Cholecystectomies
- #2 reason for abdominal operations

Cholesterol/mixed stones

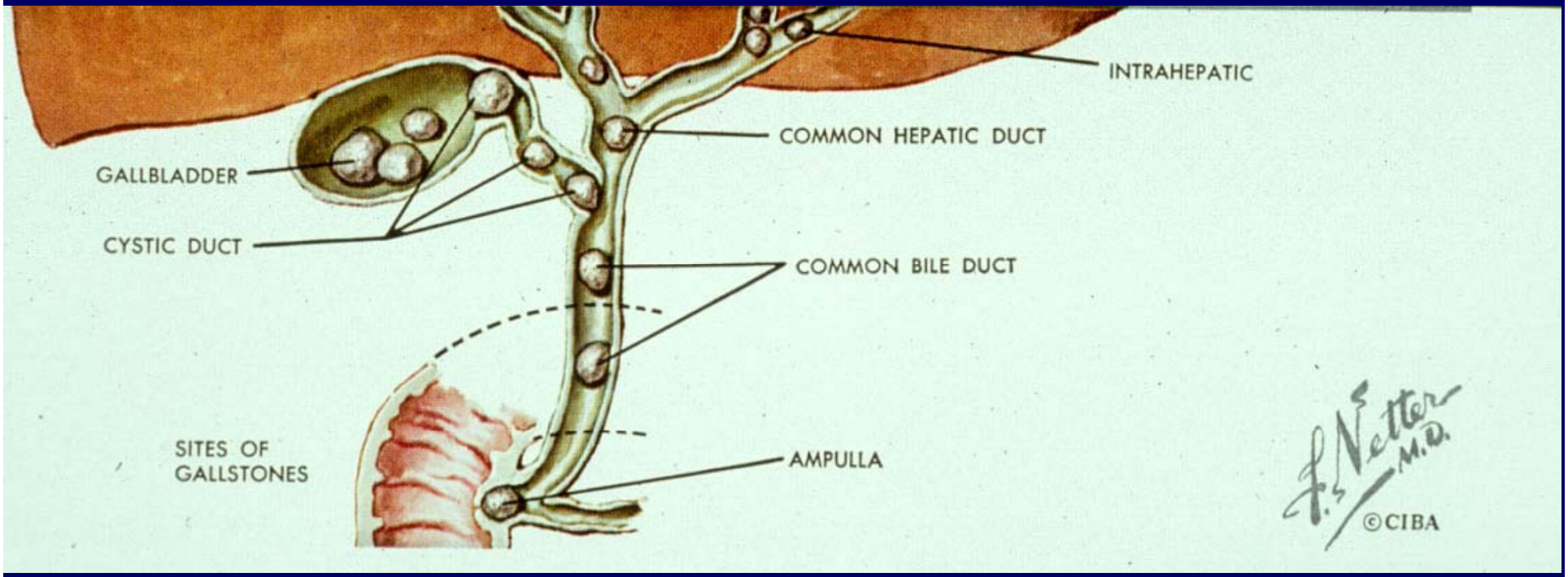
Choledocholithiasis
(Stones in the common bile duct)

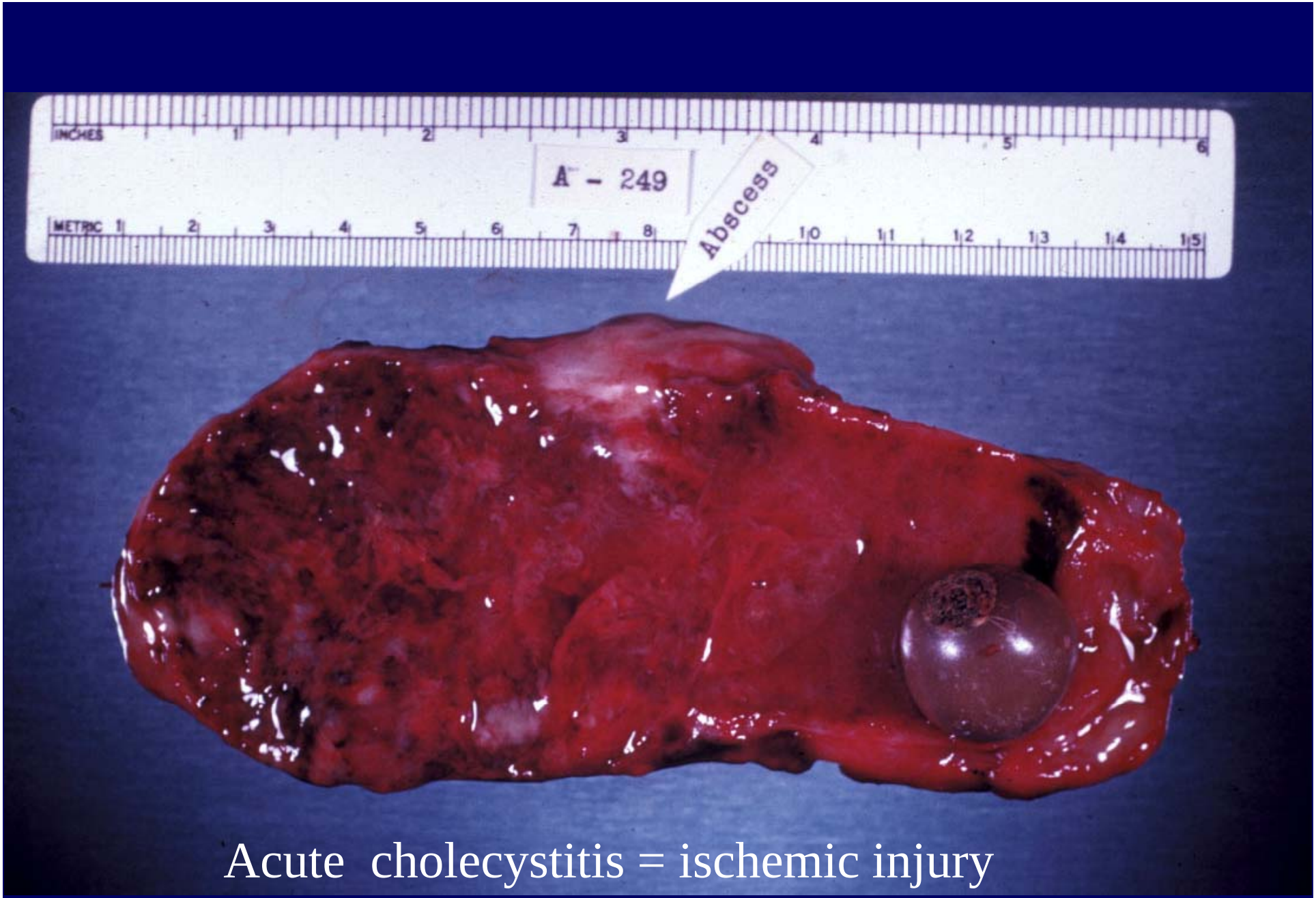
Pain: Epigastric, RUQ-stones may be passed

Obstructive Jaundice-may be intermittent

Ascending Cholangitis- Infection: to liver

20%: No pain; 25% no jaundice

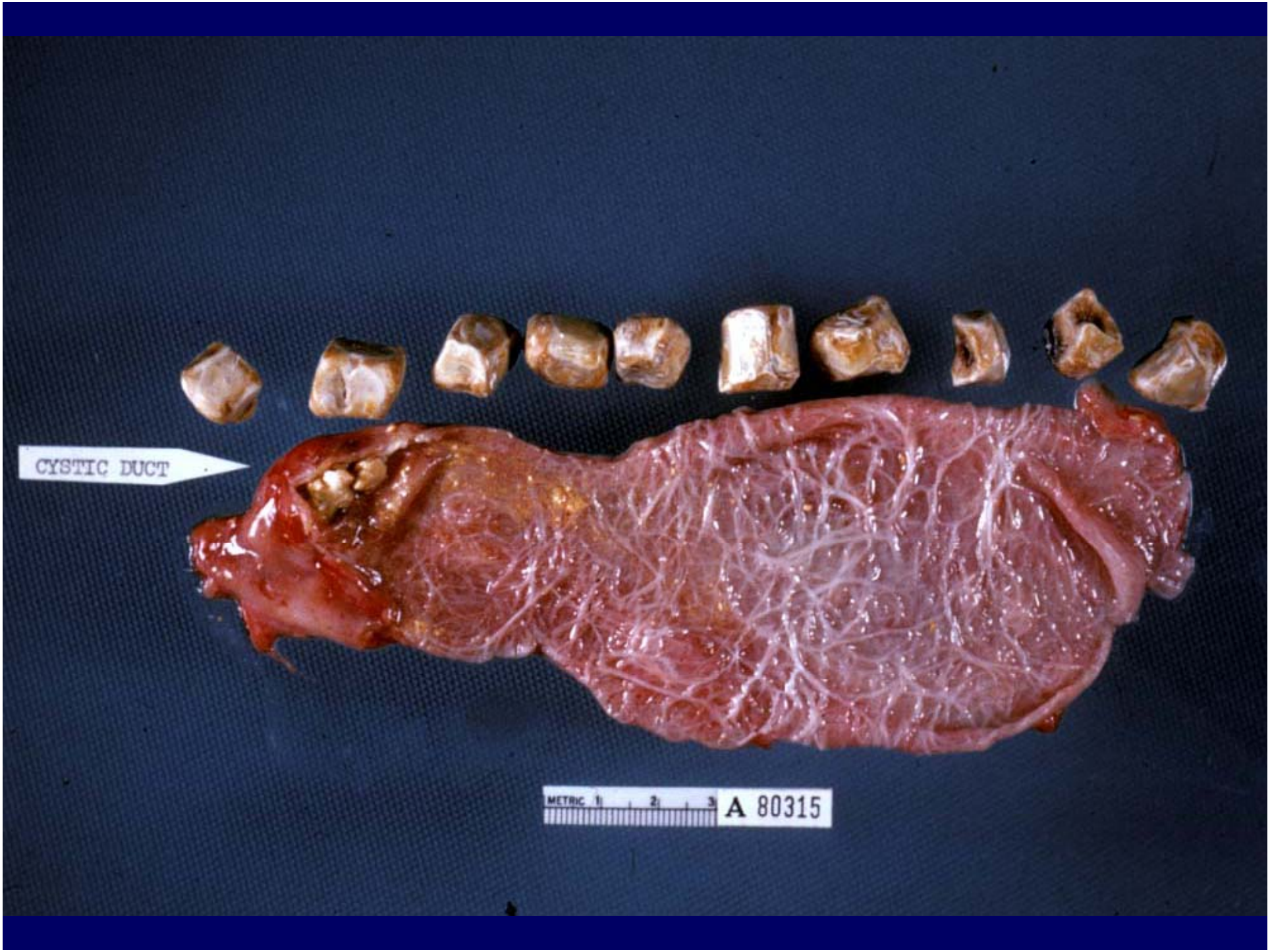




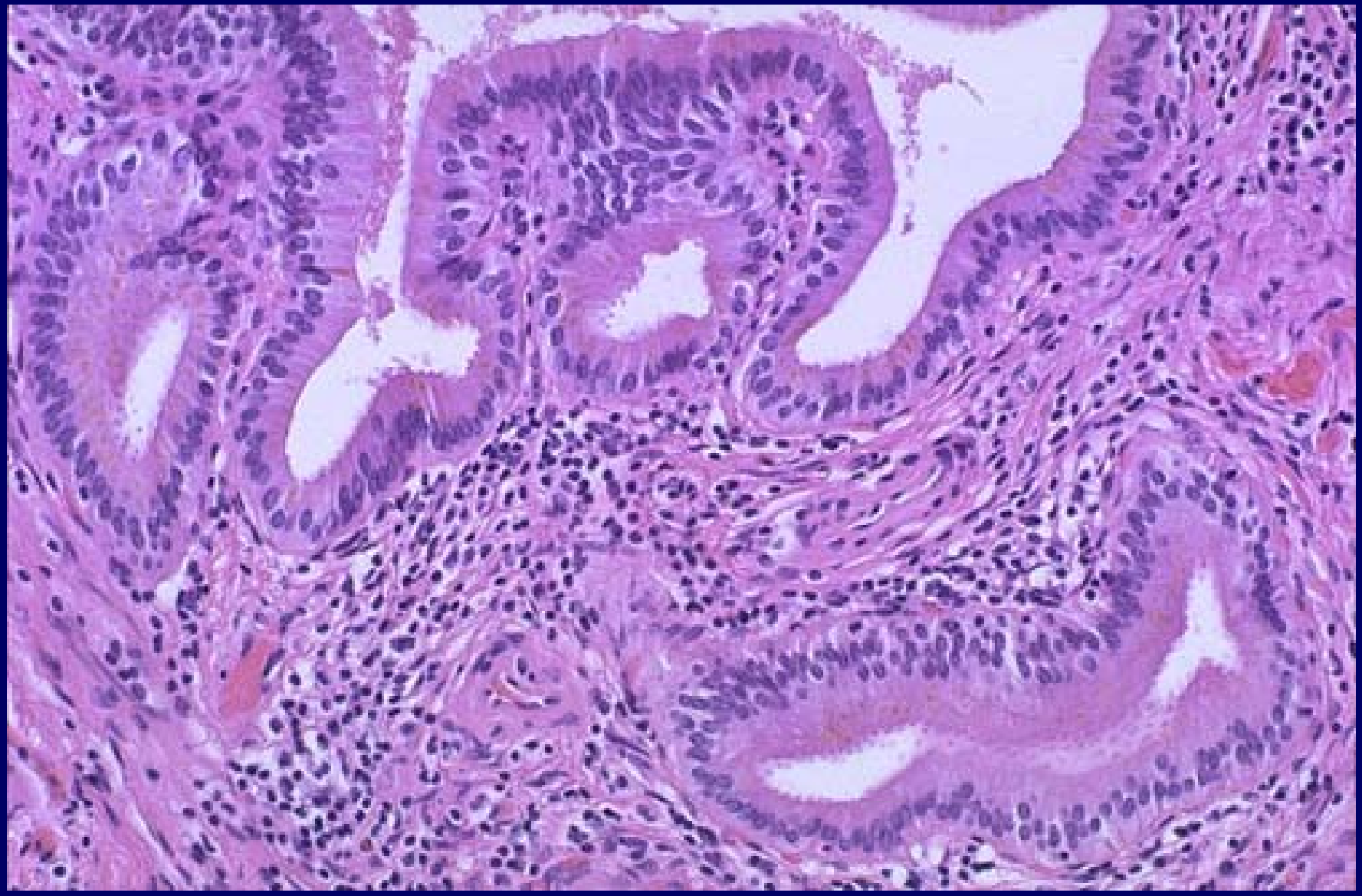
Acute cholecystitis = ischemic injury

Chronic Cholecystitis

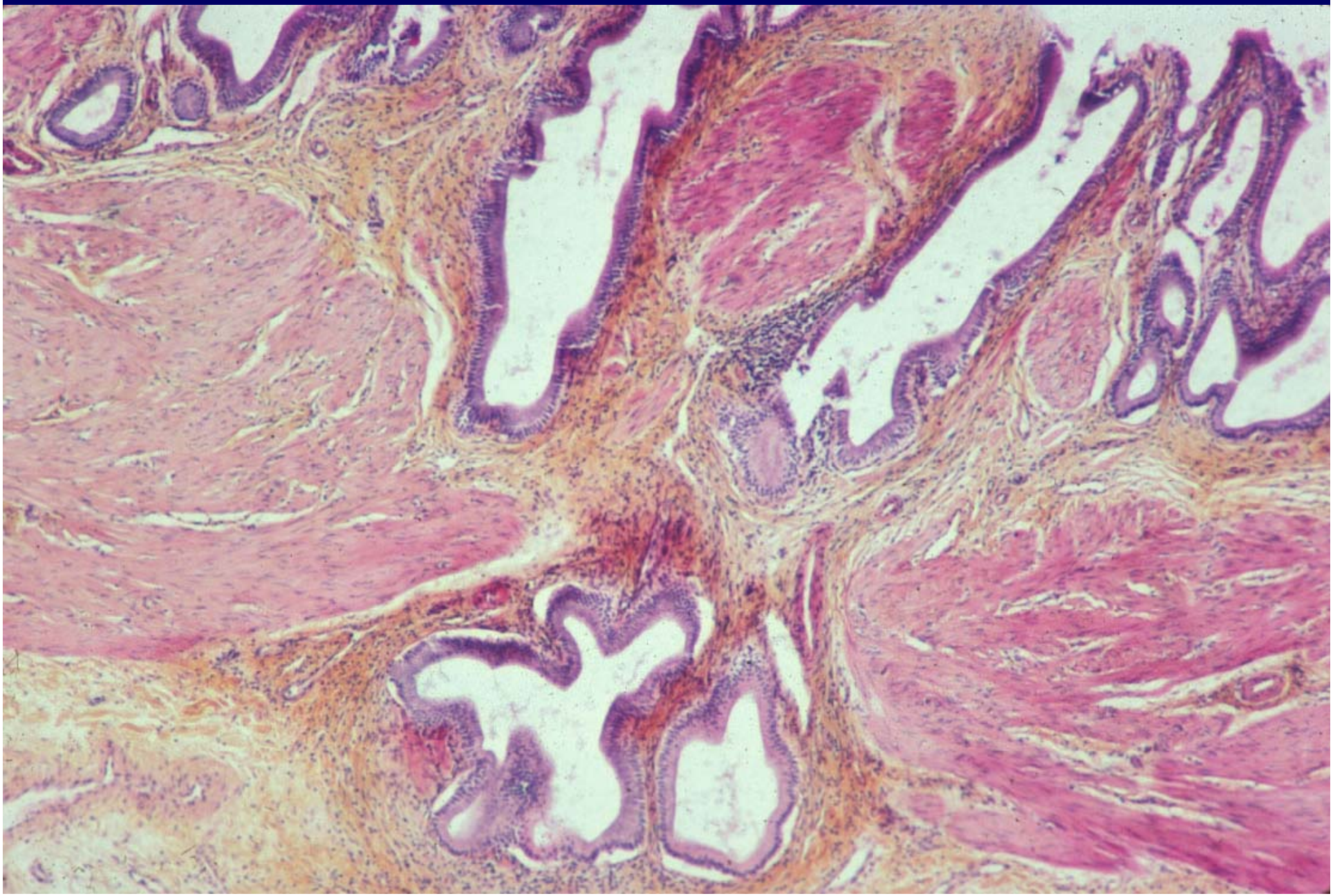
- Associated with calculi in 95% of cases.
- Multiples episodes of inflammation cause GB thickening with chronic inflammation/ fibrosis and muscular hypertrophy.
- Rokitansky - Aschoff Sinuses (mucosa herniates through the muscularis mucosae)
- With longstanding inflammation GB becomes fibrotic and calcified “porcelain GB”


CYSTIC DUCT
METRIC 1 2 3
A 80315

Chronic cholecystitis



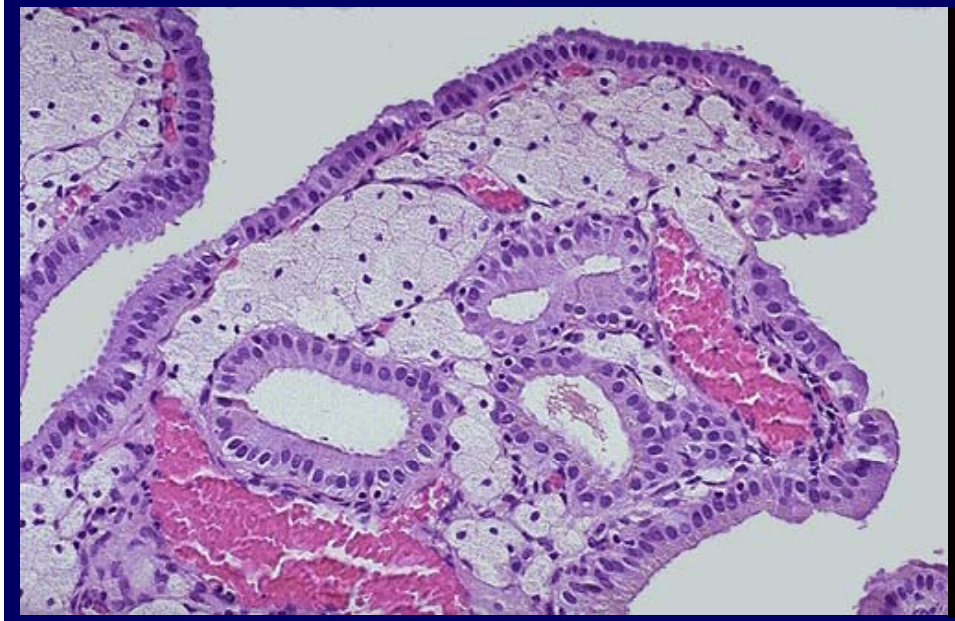
Rokitansky-Aschoff sinuses

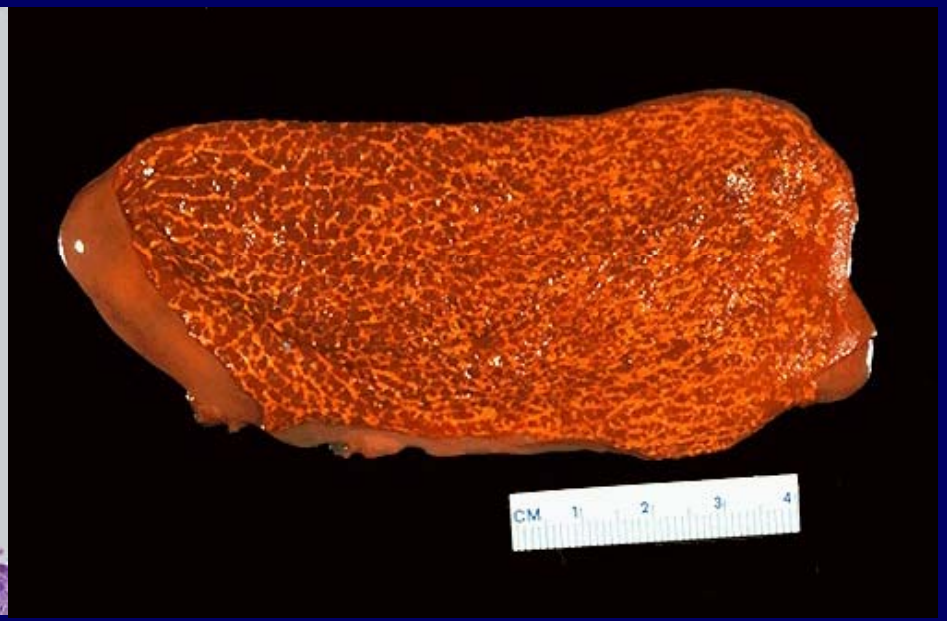


Chronic Cholecystitis

- Fibrosis
- Chronic Inflammation
- Rokitansky - Aschoff Sinuses
- Hypertrophy: Muscularis

Cholesterolosis

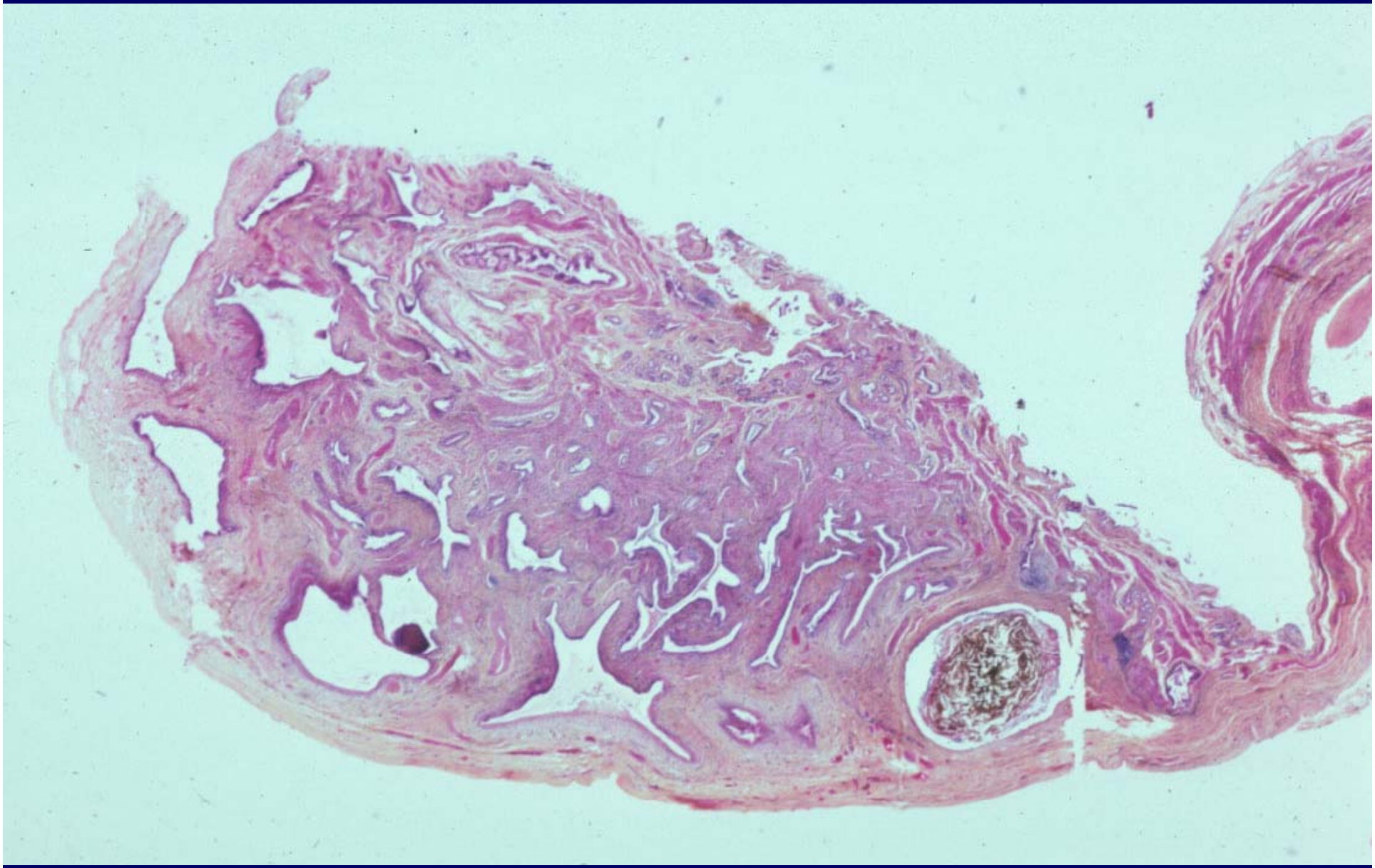


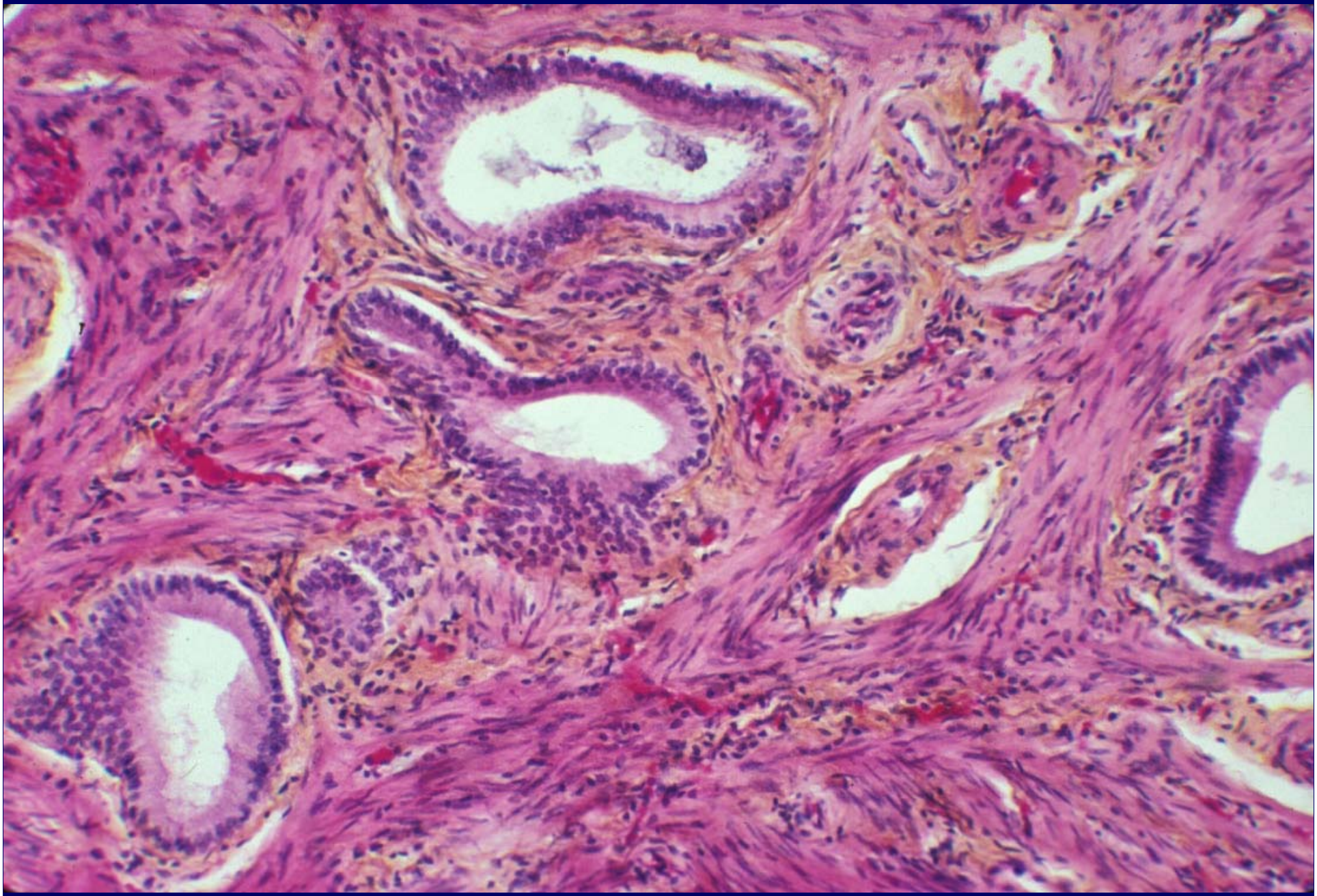


Focal accumulation of cholesterol-laden macrophages in lamina propria of gallbladder (incidental finding).

Adenomyoma of Gall Bladder


Fundus
Cystic Duc
A-56792
METRIC 1 2 3 4 5





Carcinoma: Gall Bladder

Uncommon: 5,000 cases / year

Fewer than 1% resected G.B.

Sx: same as with stones

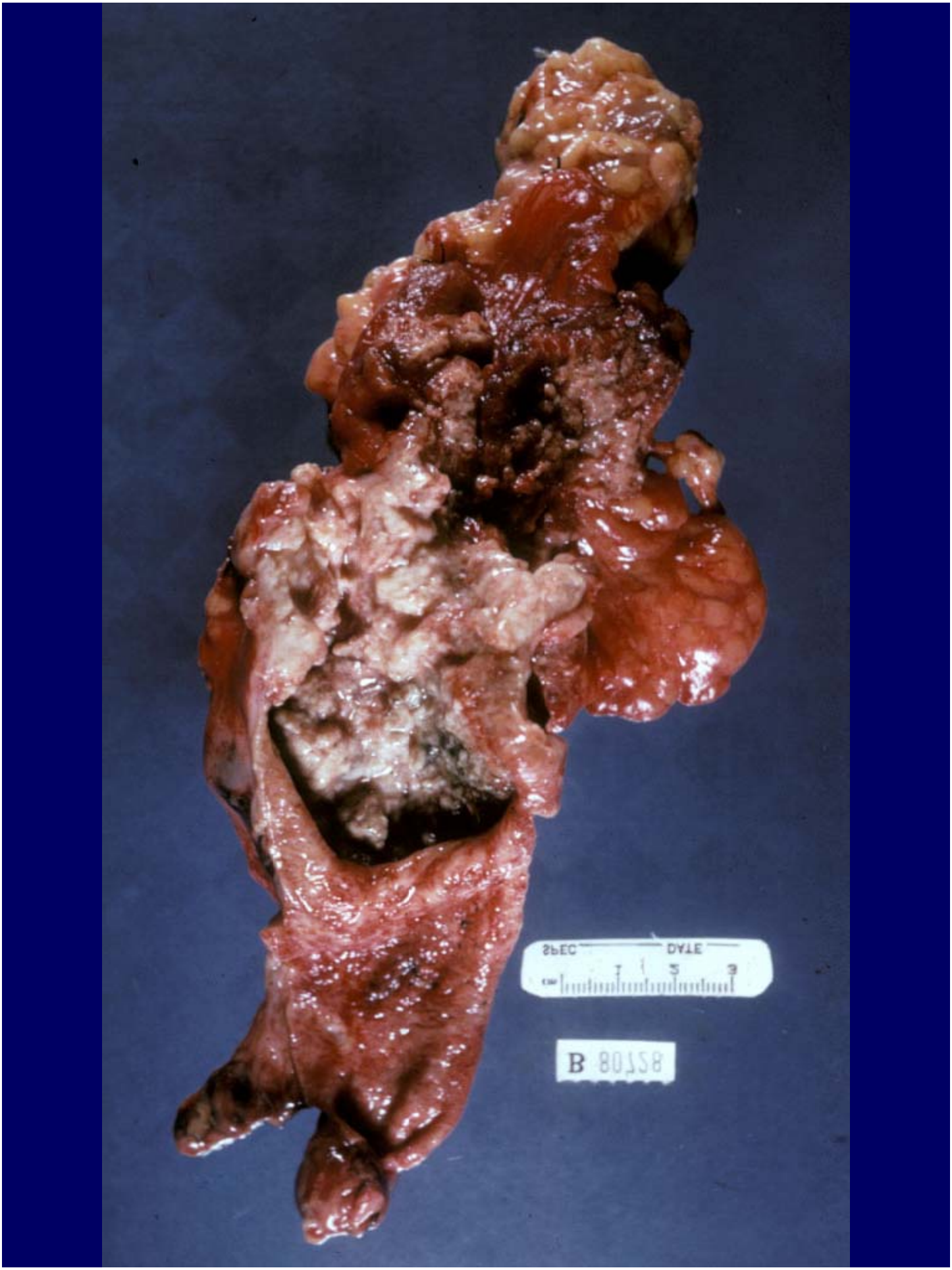
5 yr. survival: Less than 5%

(survival relates to stage)

90%: Stones

Long Hx: symptomatic stones

Stones: predispose to CA., but uncommon complication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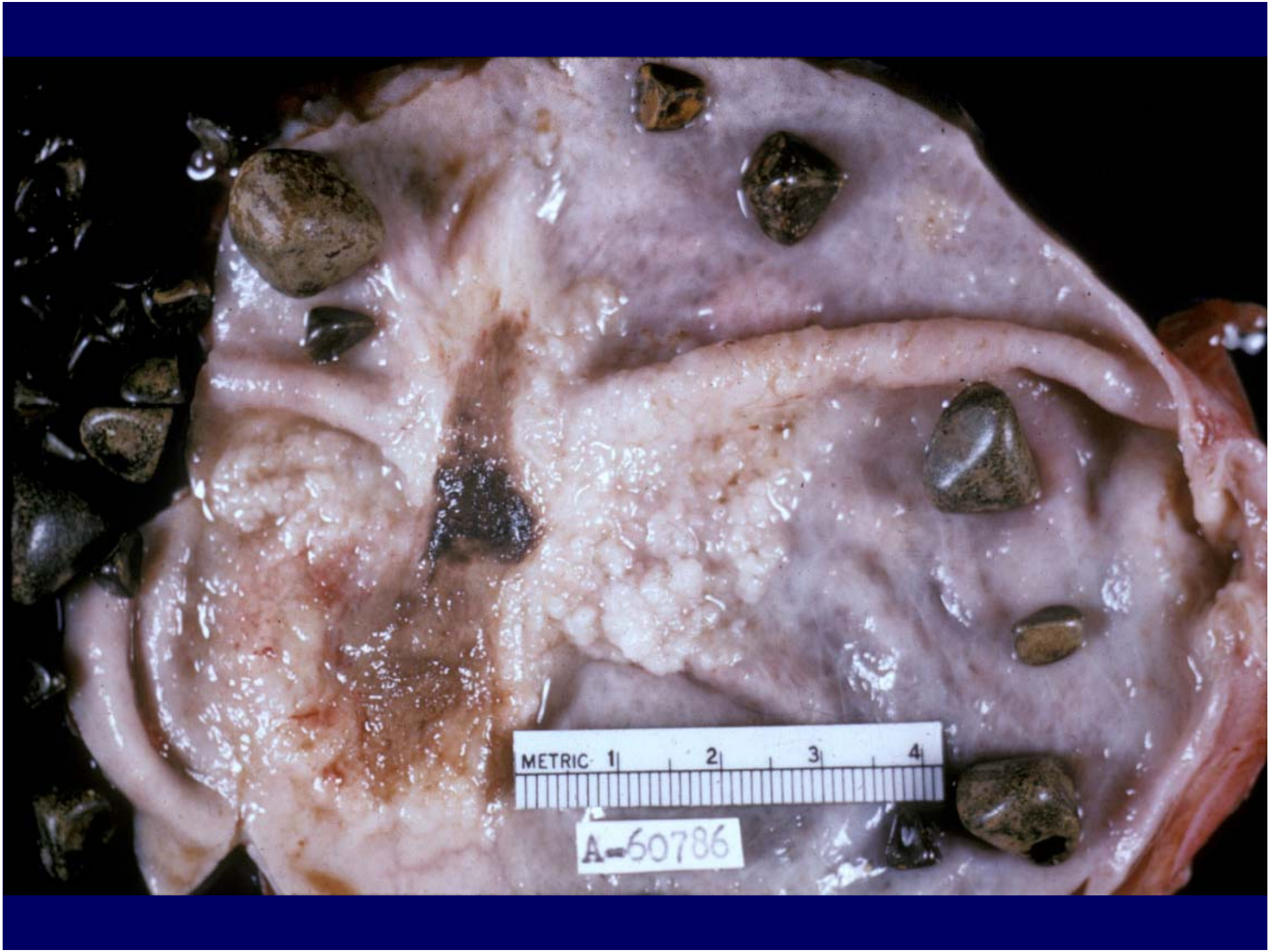
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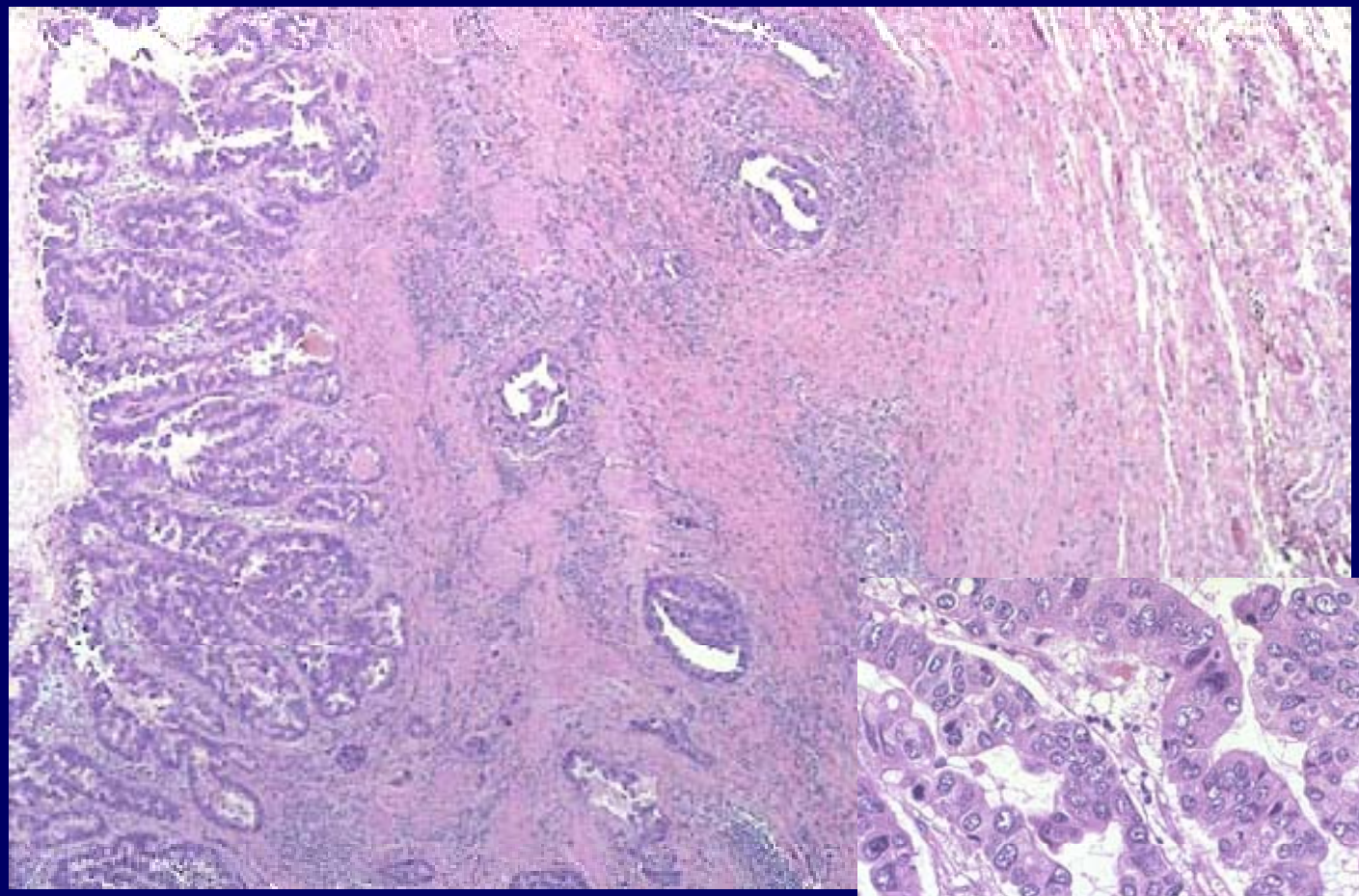
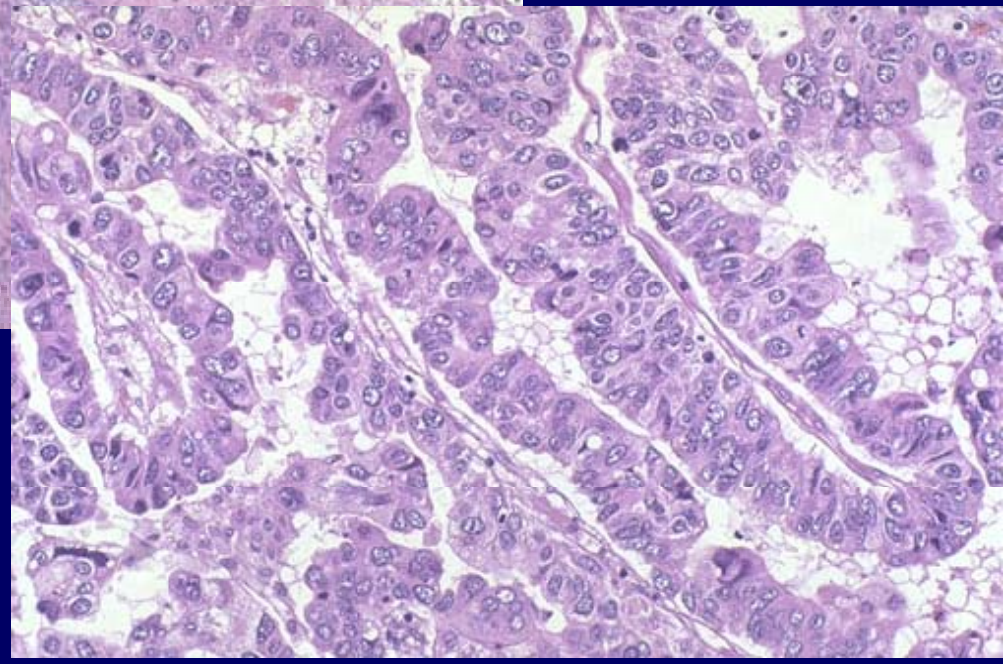
Gallbladder carcinoma





Case 1

56 year old woman presents to ER in shock, following rapid onset of severe upper abdominal pain, developing over the previous day.

Hx: heavy alcohol use.

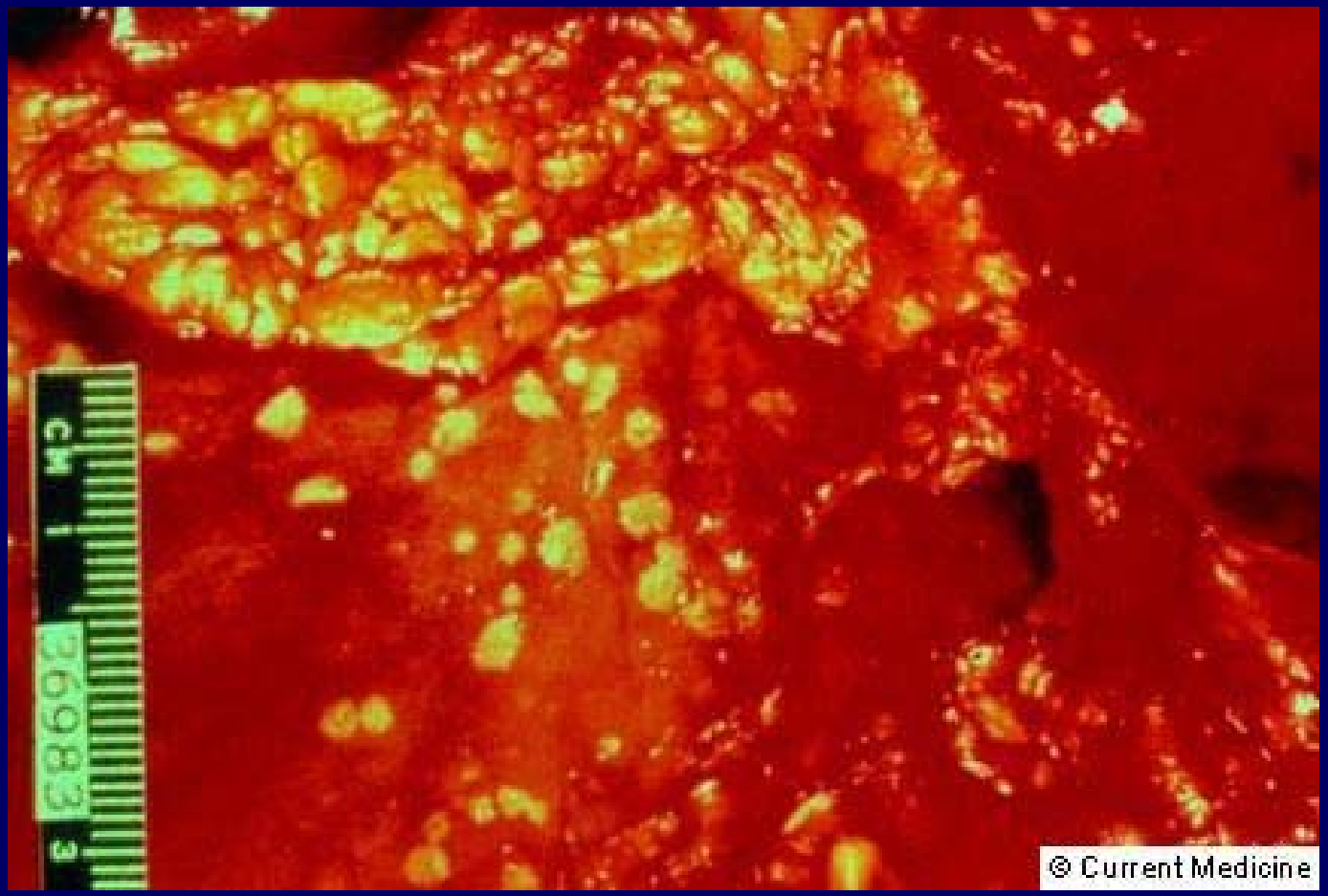
LABs: Elevated serum amylase and elevated peritoneal fluid lipase

Acute Pancreatitis

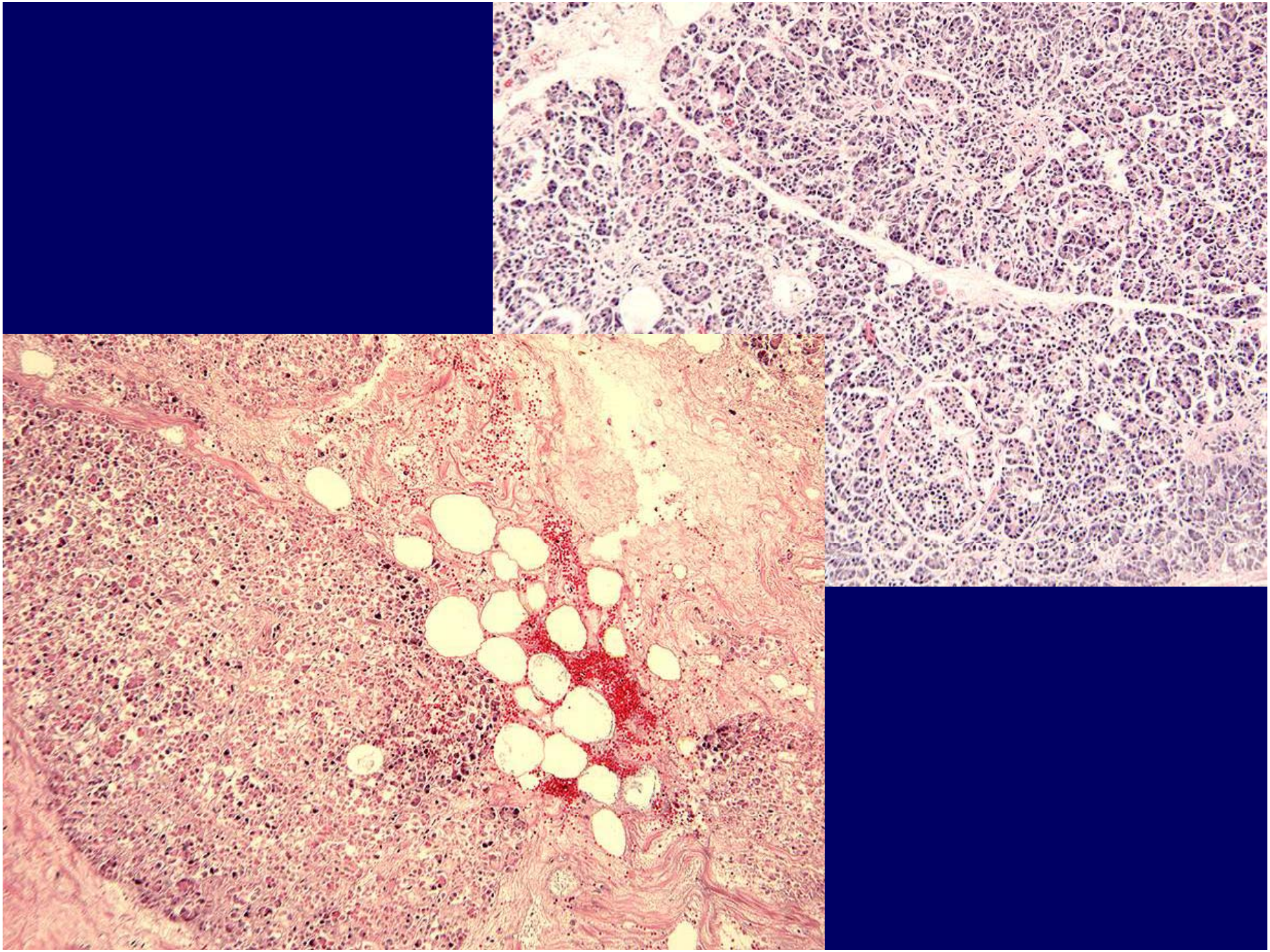
Patient developed rapid onset of respiratory failure necessitating intubation and mechanical ventilation.

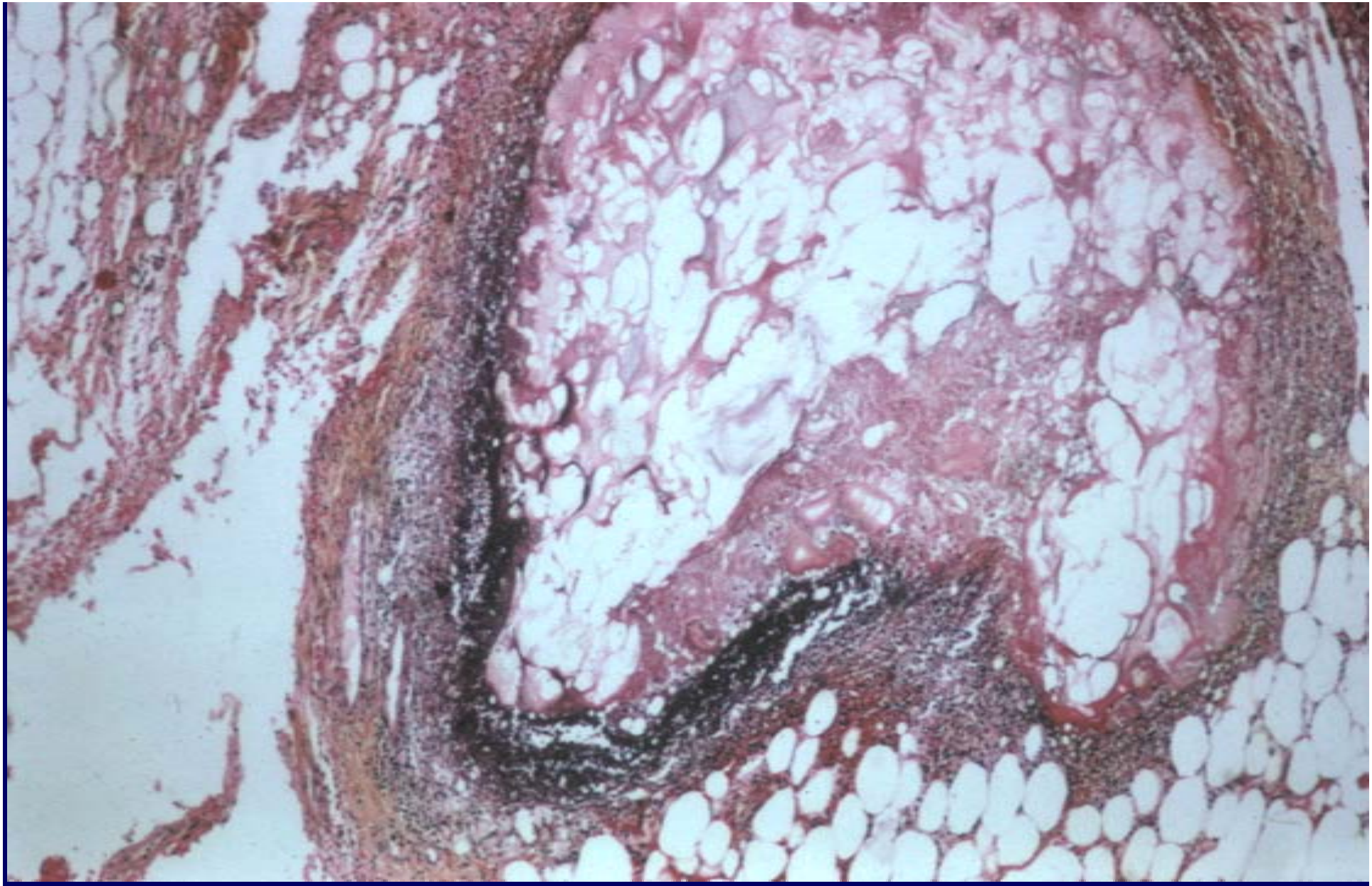
Over 48 hours, she was increasingly unstable, with evolution to multi-organ failure, and she expired 82 hours after admission.

An autopsy was performed.



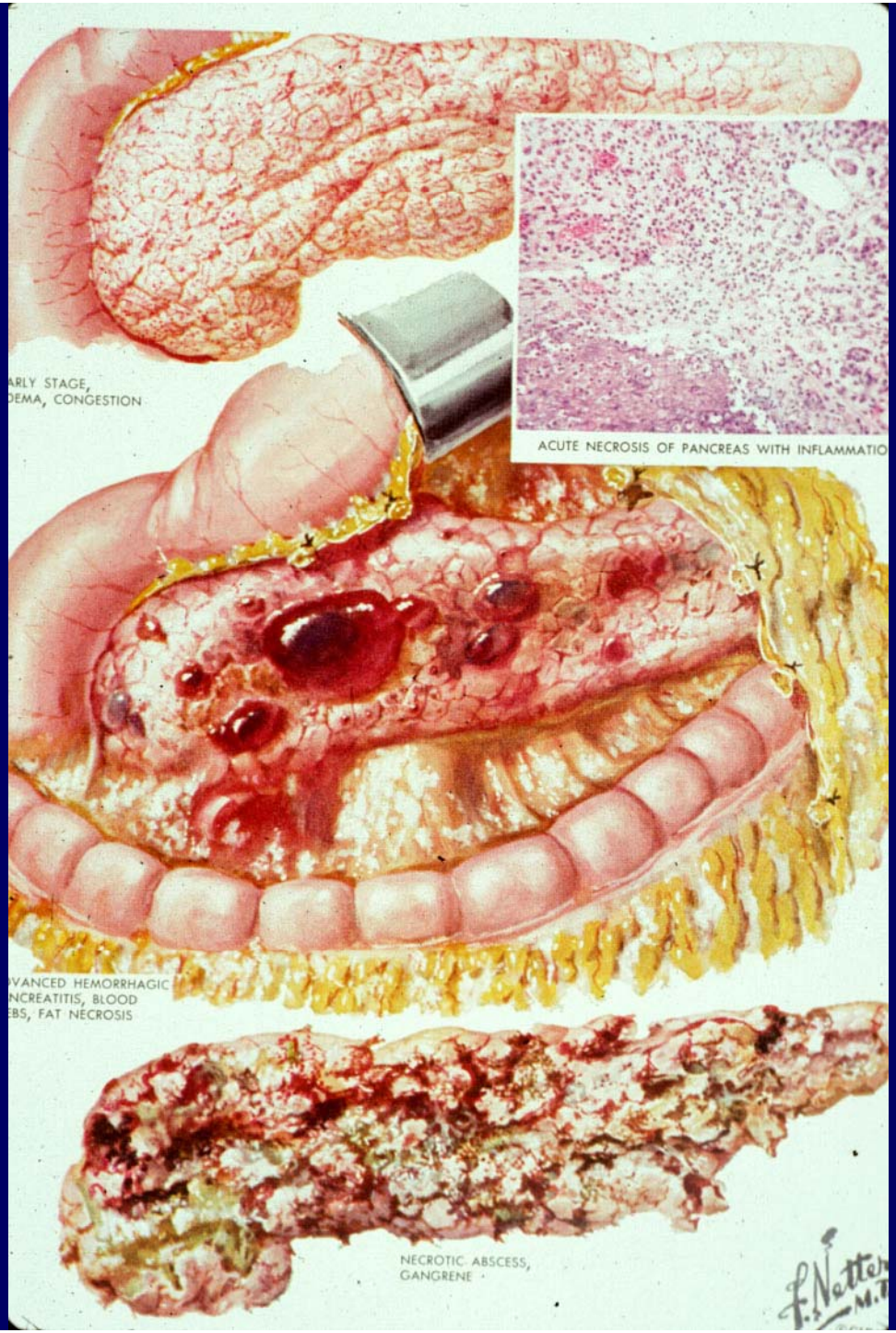
Acute pancreatitis





Elastase destruction of blood vessels – with hemorrhage

Acute Pancreatitis

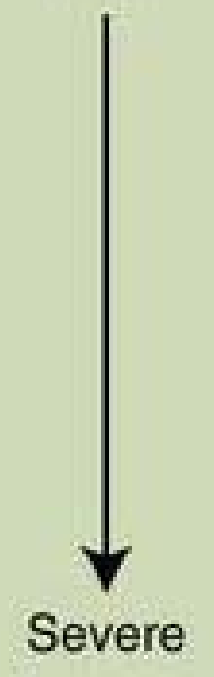


Edema, congestion

Advanced hemorrhagic pancreatitis, fat necrosis

Necrotic abscess, gangrene

Pathophysiology of acute pancreatitis



Stage 1. Pancreatic injury

Edema, inflammation, fat necrosis, variable necrosis of pancreatic secretory cells

Stage 2. Local (peripancreatic) effects

Retroperitoneal edema, extensive fat necrosis, ileus with "third-spacing" of fluid and electrolytes

Stage 3. Systemic complications

Hypotension/shock, metabolic disturbances, organ failure, sepsis

Acute Pancreatitis

US: 45% of cases have gallstones and choledocholithiasis;

35% associated with heavy alcohol ingestion

Pathology: Enzyme release is triggered with digestion of pancreas, necrosis of fat and lobules, hemorrhage from damaged blood vessels.

Variable severity: may lead to liquefactive necrosis, hemorrhage.

Mild cases – may have local complications: abscess, pseudocyst.

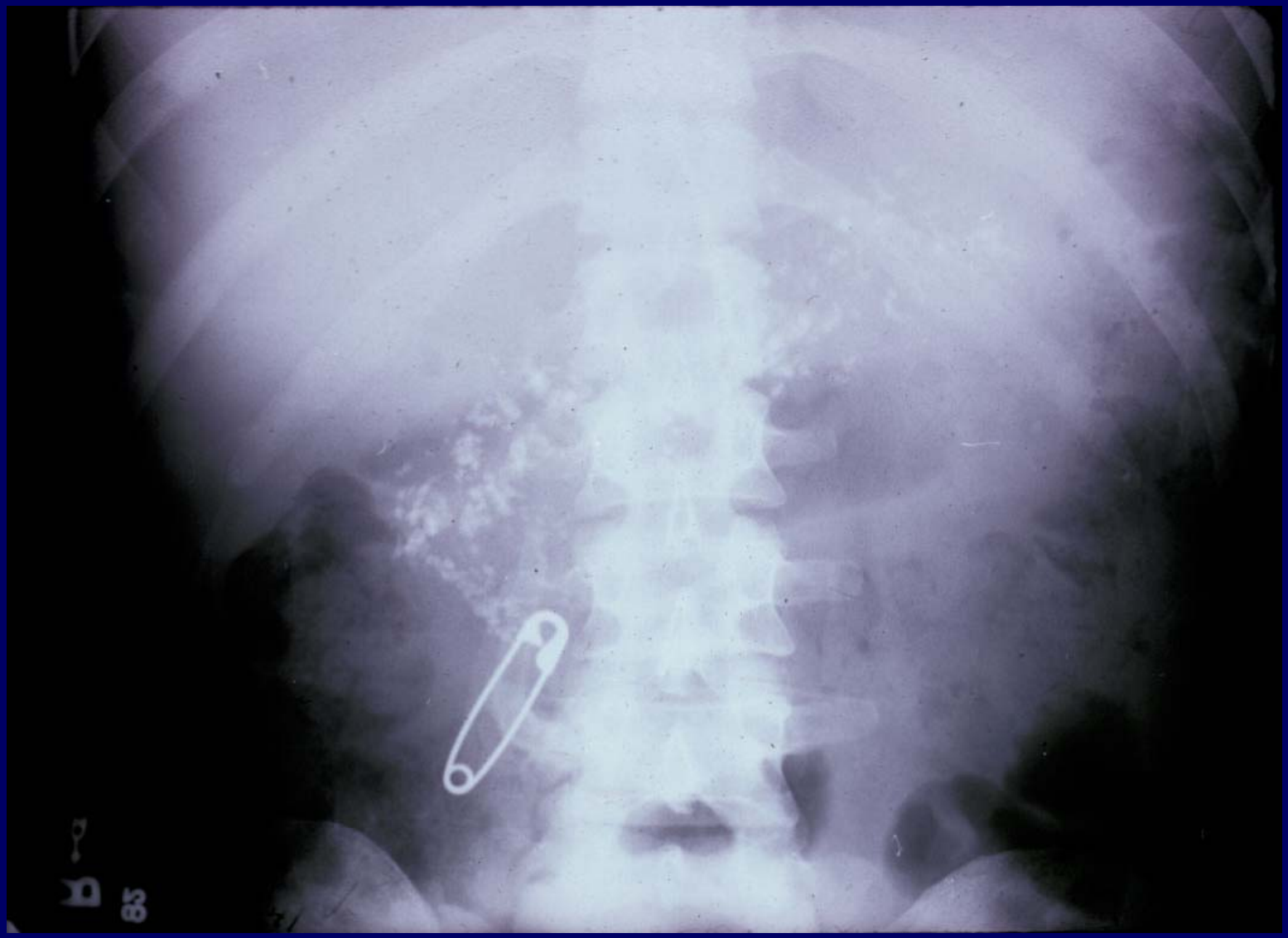
Chronic Pancreatitis

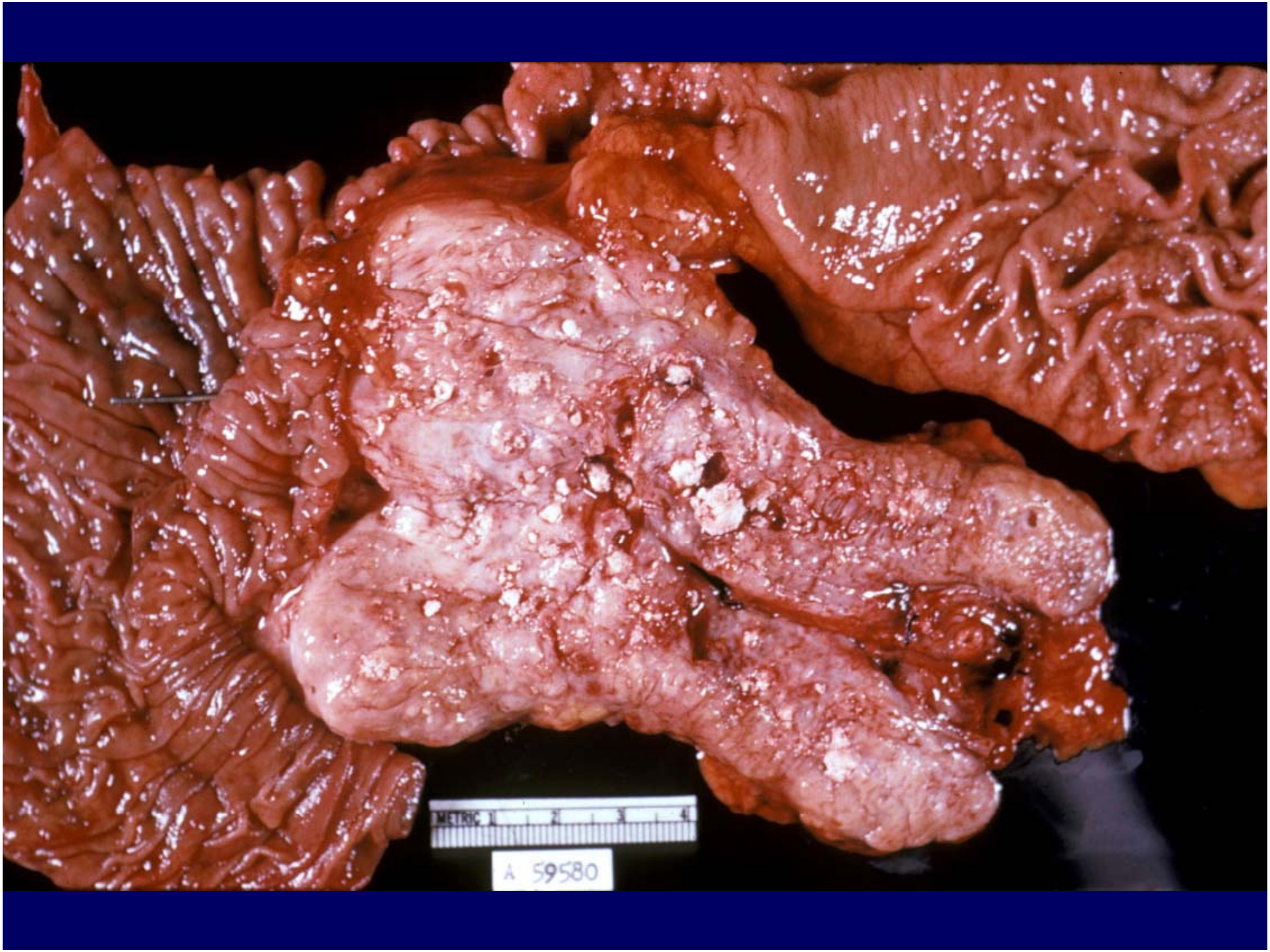
Continuing inflammation with irreversible changes in architecture, structure and function.

Fibrosis of parenchyma with distortion of duct architecture, loss of exocrine secretory function.

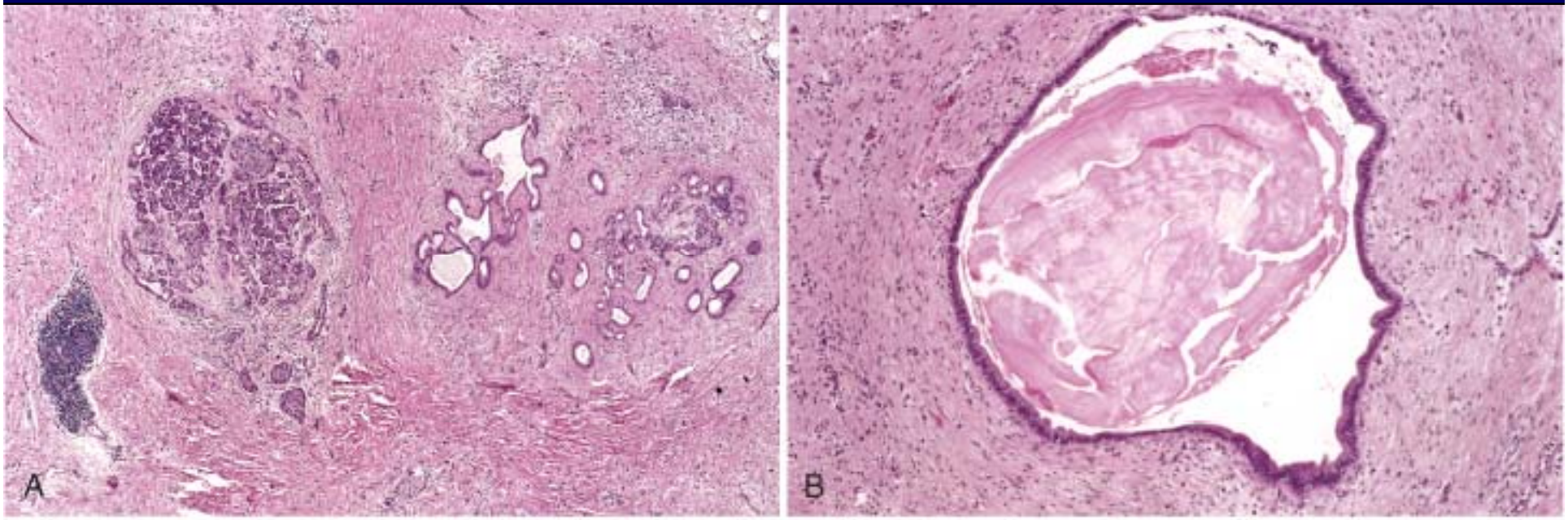
Changes may be focal or widespread.

Chronic pancreatitis with Stones

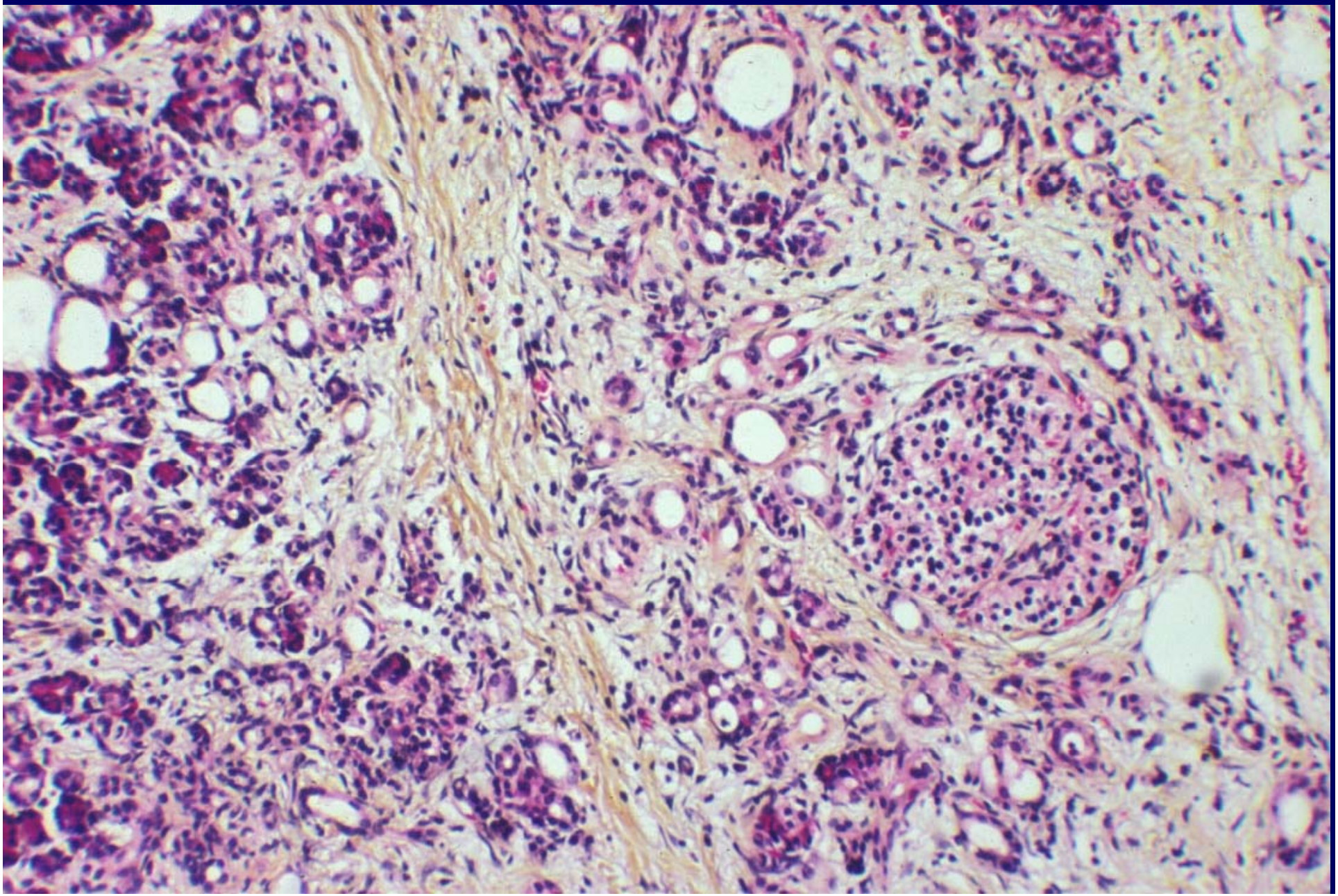



METRIC
A 59580

Chronic pancreatitis



Chronic Pancreatitis



Complications of Chronic Pancreatitis

Chronic abdominal pain, severe and unremitting, radiating to back

Malabsorption due to reduced enzyme secretion. (After 90% of pancreas is fibrotic, reduced lipase and trypsin secretion lead to steatorrhea) .

Pancreatic diabetes associated with decreased islets.

Pancreatic pseudocysts with extension or rupture in adjacent organs.

Case 2

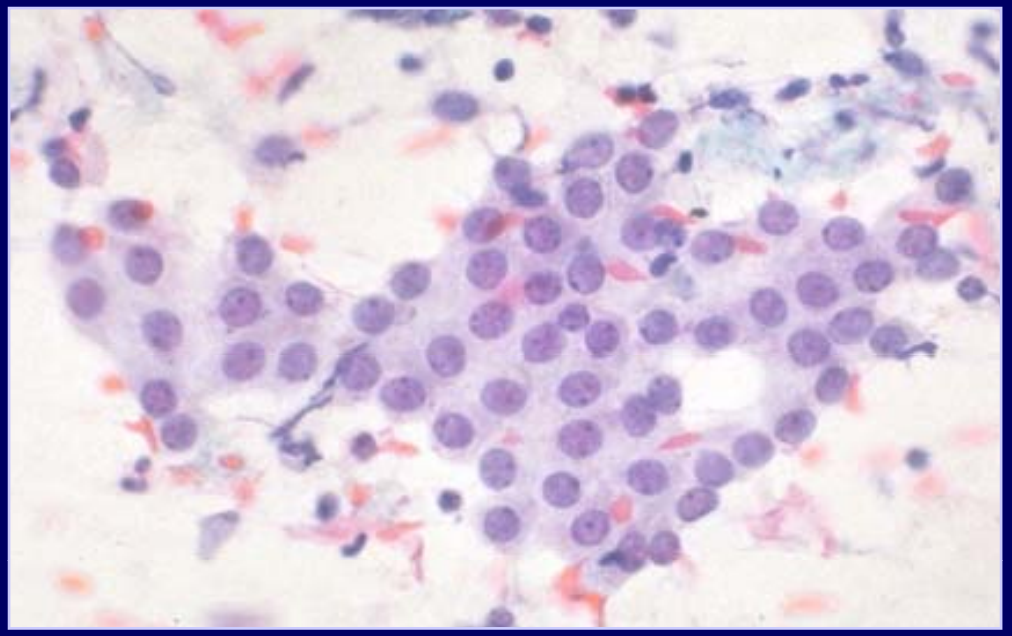
67 year old woman with recent onset painless jaundice.

History of 15lb weight loss over last 3 months.

She smoked 1 pack per day x 35 years.
Physical exam: palpable GB

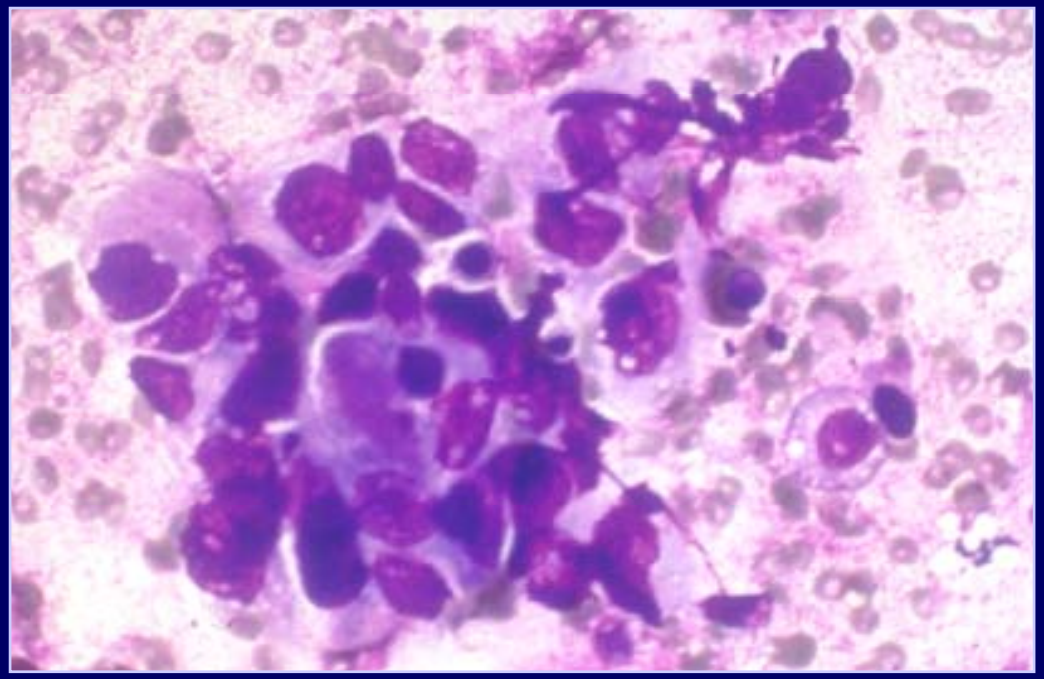
ERCP was performed with Endoscopic Ultrasound (EUS) evidence of a large mass in the head of the pancreas.

An endoscopic FNA was performed.



Normal pancreas

ductal epithelium



Patient’s FNA

Dx: Adenocarcinoma

Curvoissier's Law – enlarged palpable GB

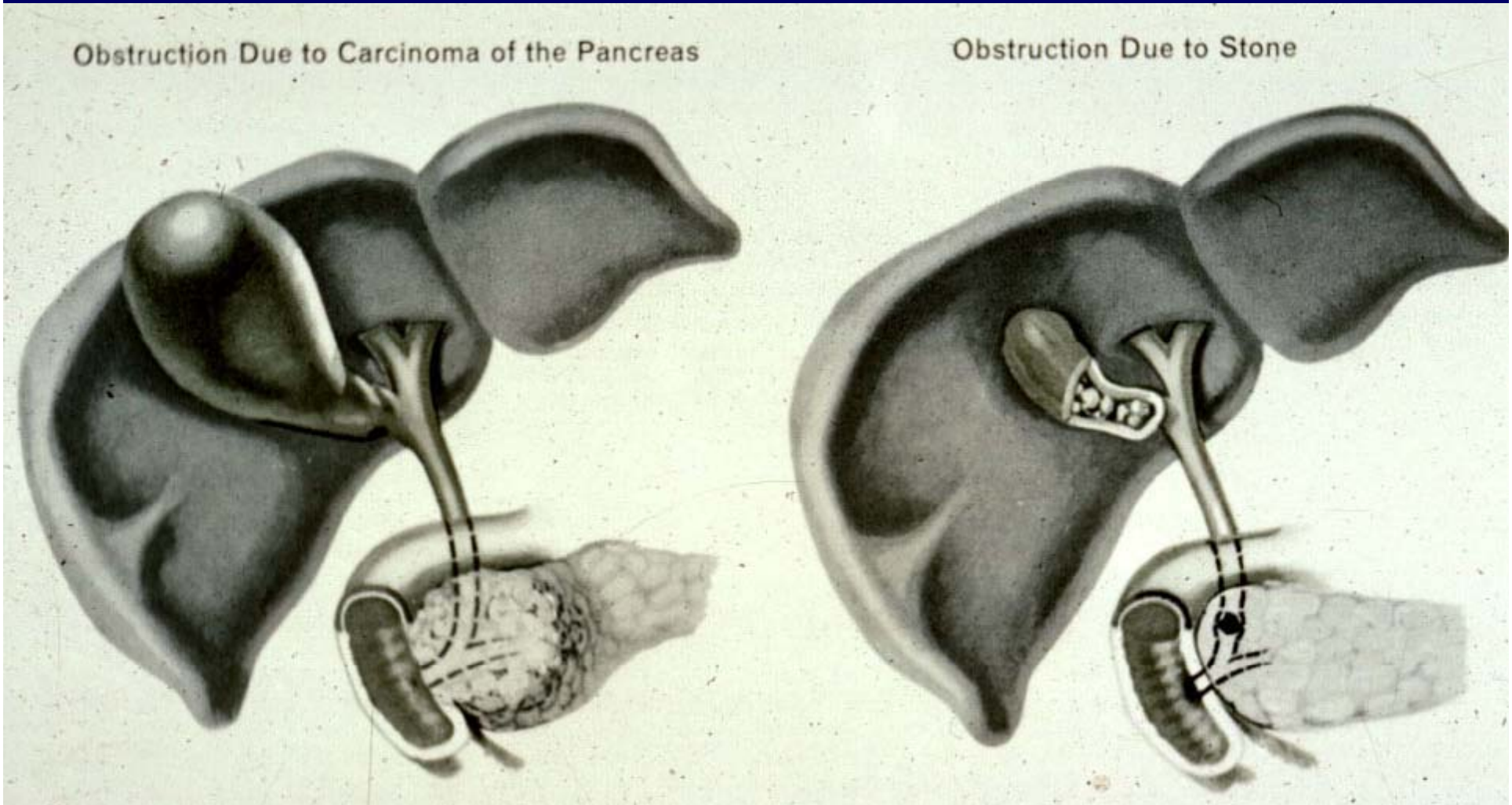
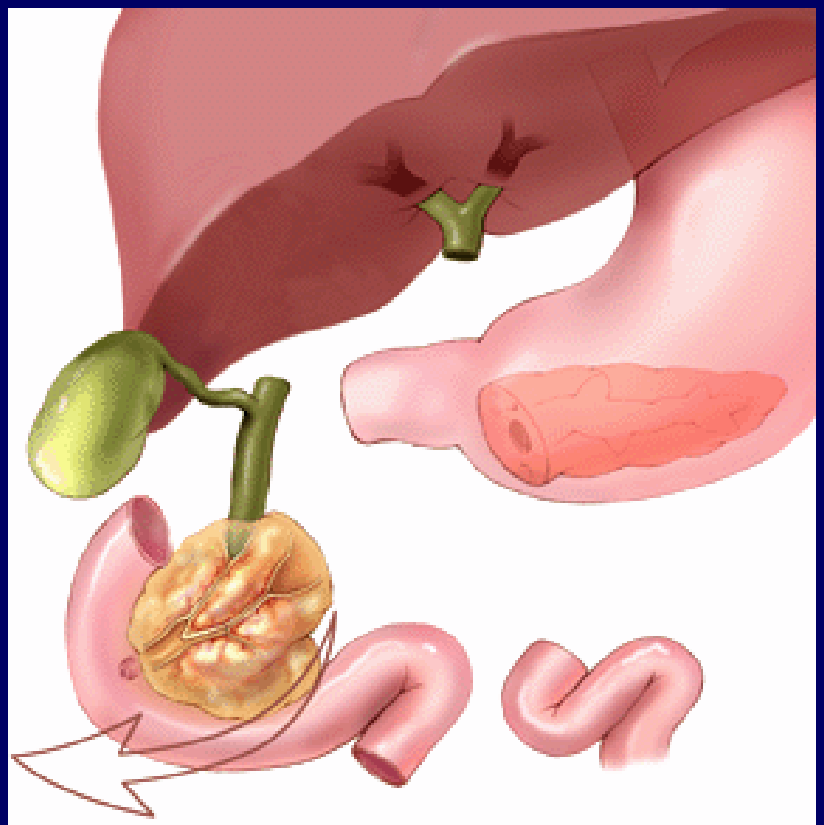


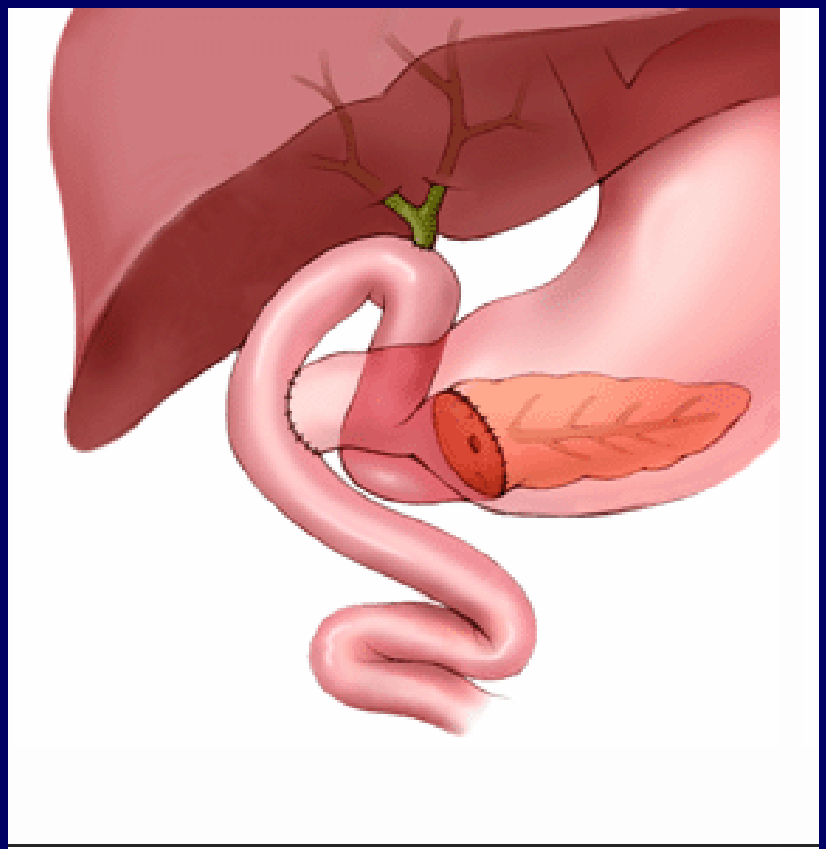
Figure 1. *Representation of Courvoisier's law. In obstruction of the biliary tract due to carcinoma of the pancreas, the gall bladder is often palpable; with obstruction due to stone, it is usually small.*

Pancreatic Ductal Adenocarcinoma: Clinical

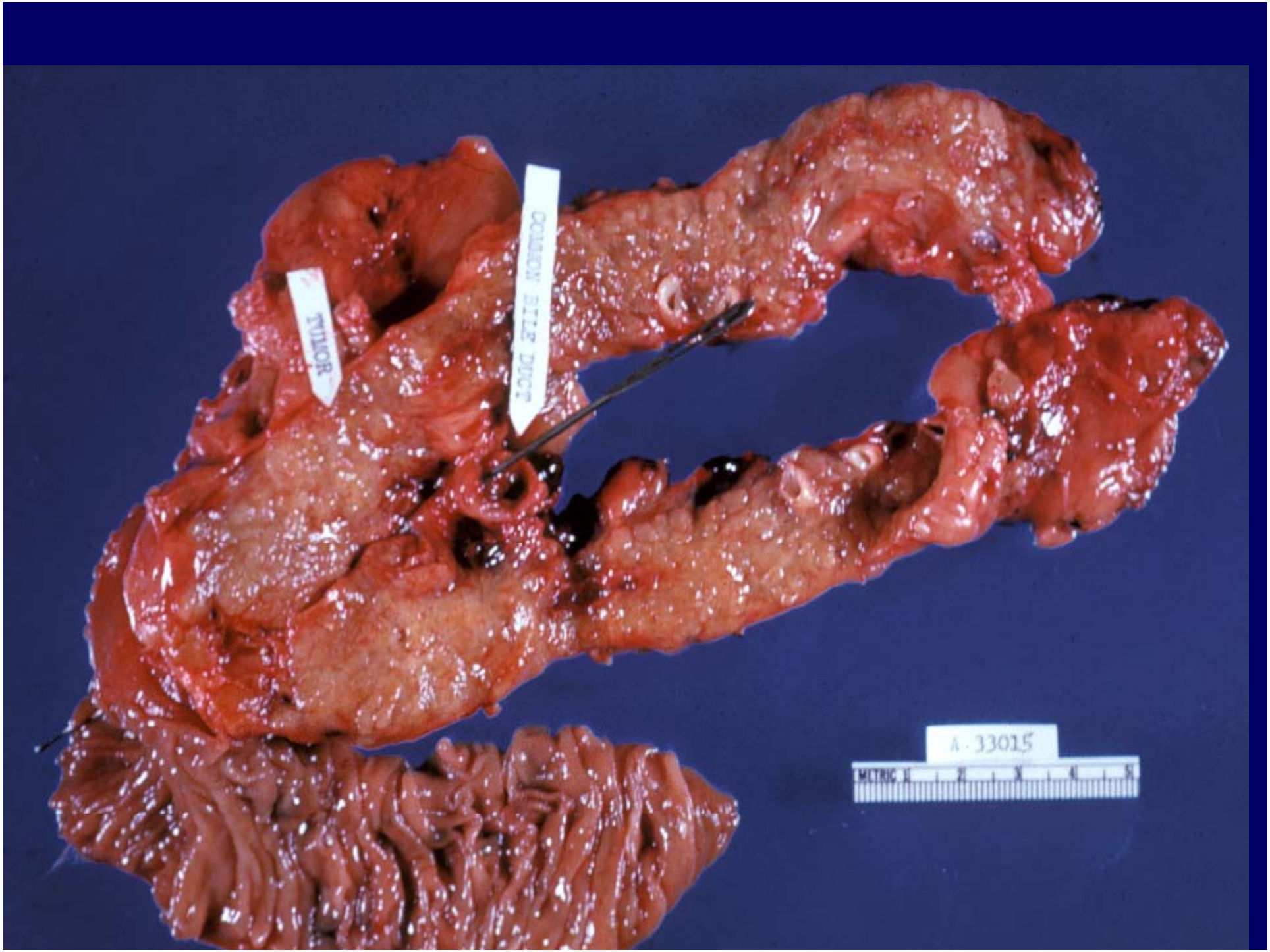
- Represents the most common pancreatic neoplasm
  - 2nd most common GIT cancer
- 4th leading cause of cancer death
- M > F; > 50 years at initial presentation usually
- Symptoms:
  - Abdominal pain, weight loss, jaundice, pancreatic insufficiency, malabsorption; Migratory thrombophlebitis (hypercoagulable state) – “Trousseau’s sign”
- Site:
  - head (60-70%) > body (10-15%) > tail (5-10%)
- Contributing factors:
  - smoking, carcinogens, genetics



Organs removed during a Whipple



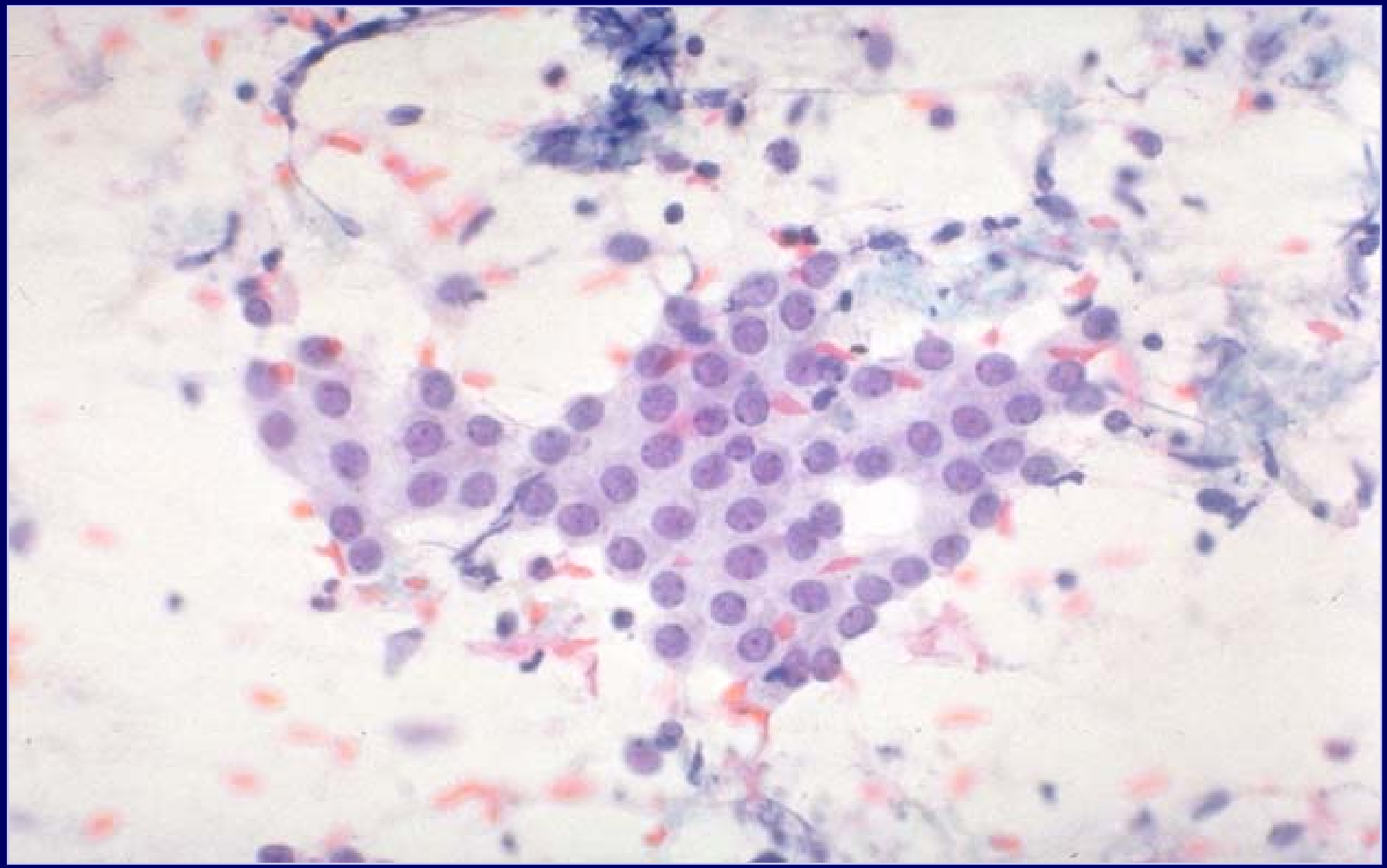
Most common anatomy after Whipple


TUMOR
COMMON BILE DUCT
A-33015
METRIC

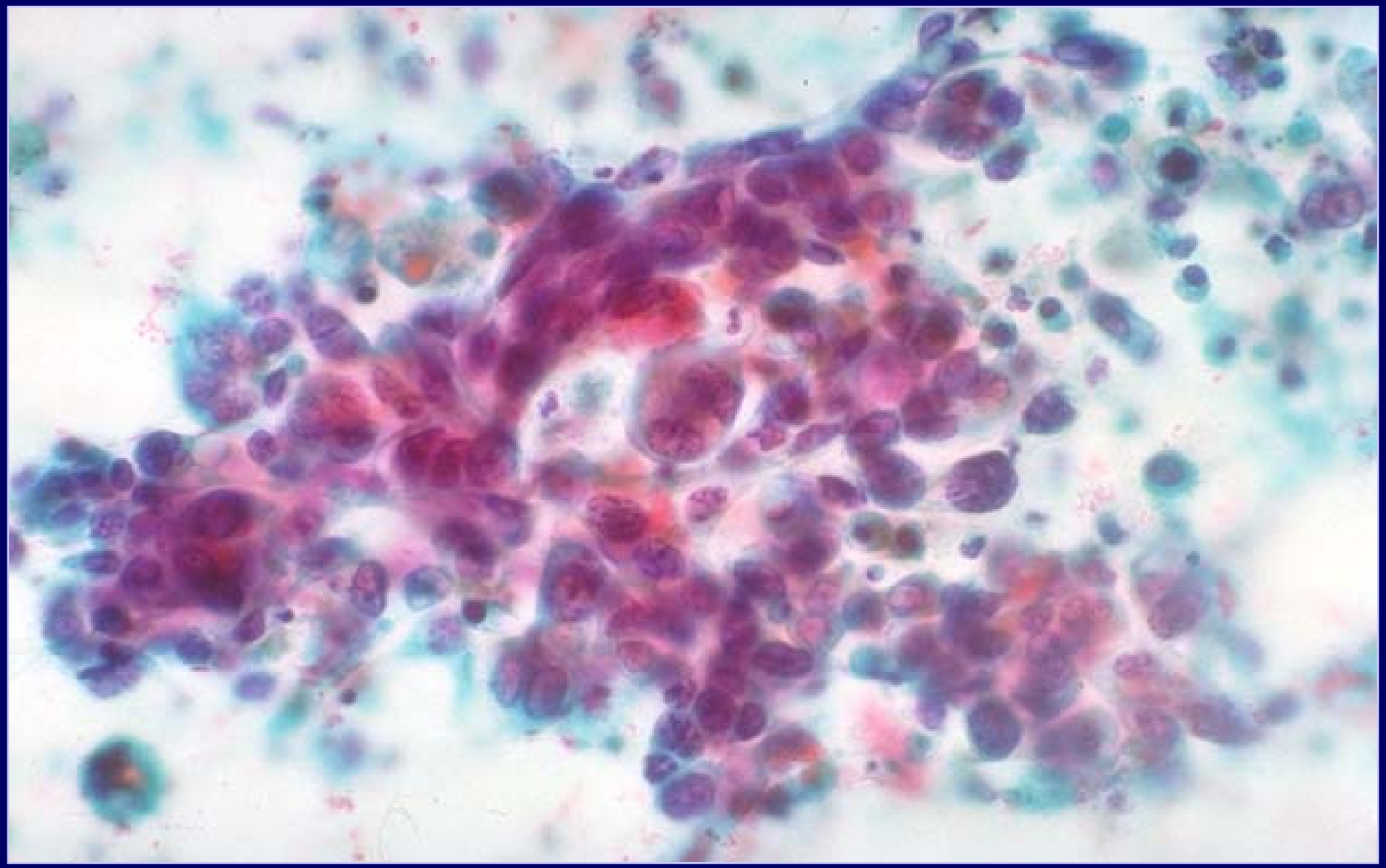
Pancreatic Ductal Adenocarcinoma: Pathology

- Macroscopic:
  - Usually a solitary mass
  - poor demarcation
  - firm to gritty consistency
  - depends upon location, but bile stasis specifically for the head of pancreas neoplasms

Chronic Pancreatitis:

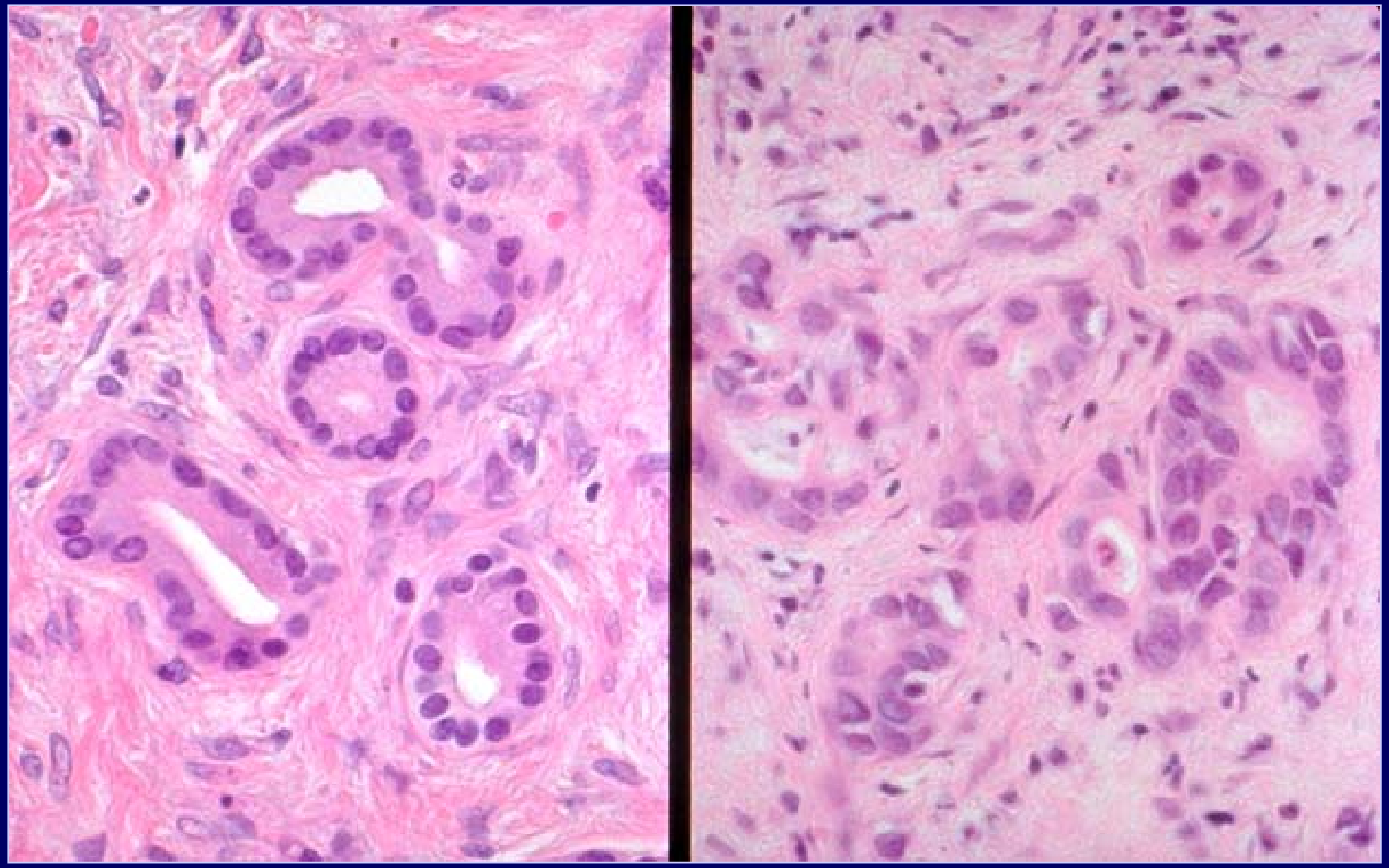


Pancreatic Ductal Adenocarcinoma: FNA



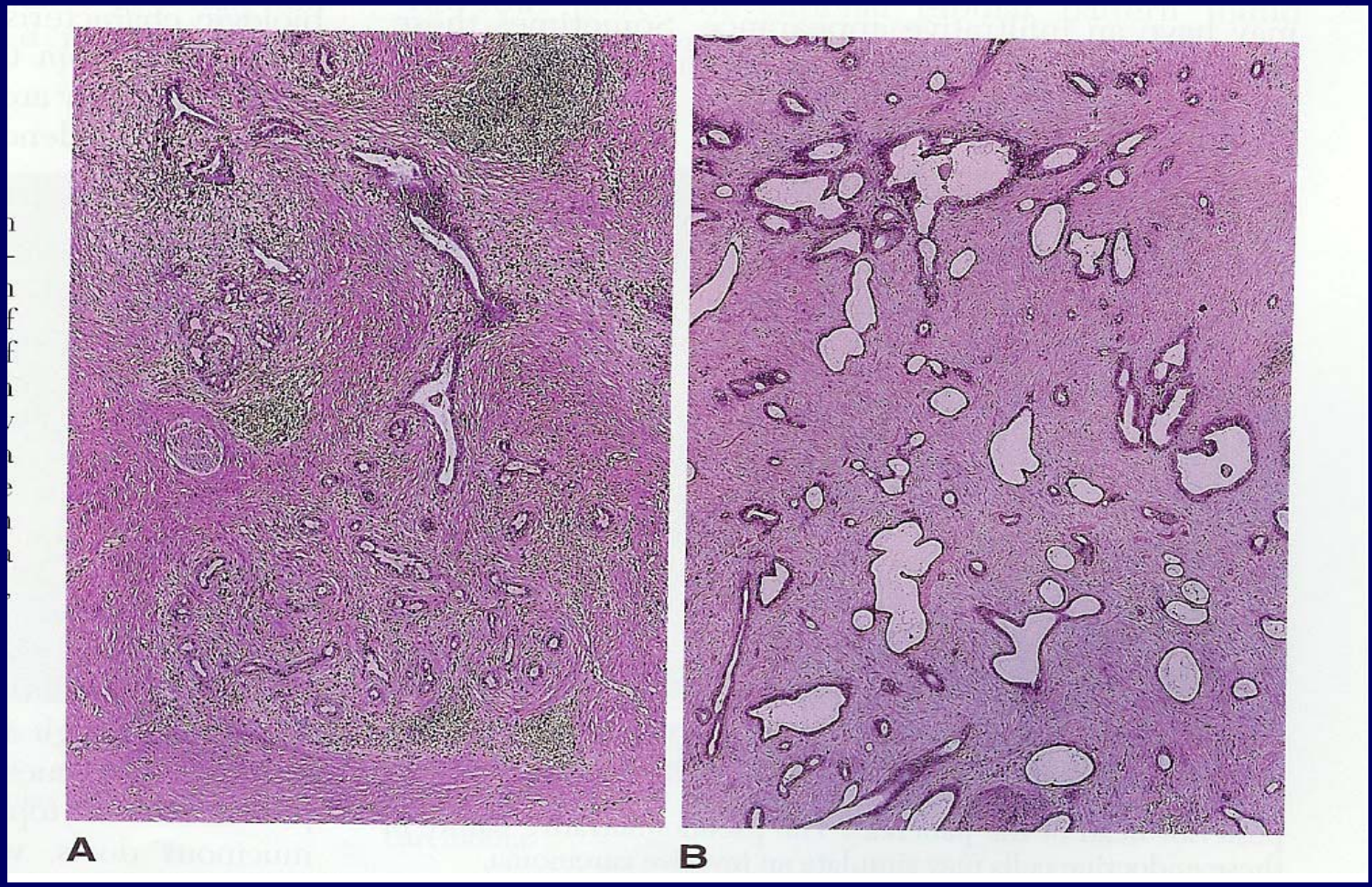
Normal

AdenoCA

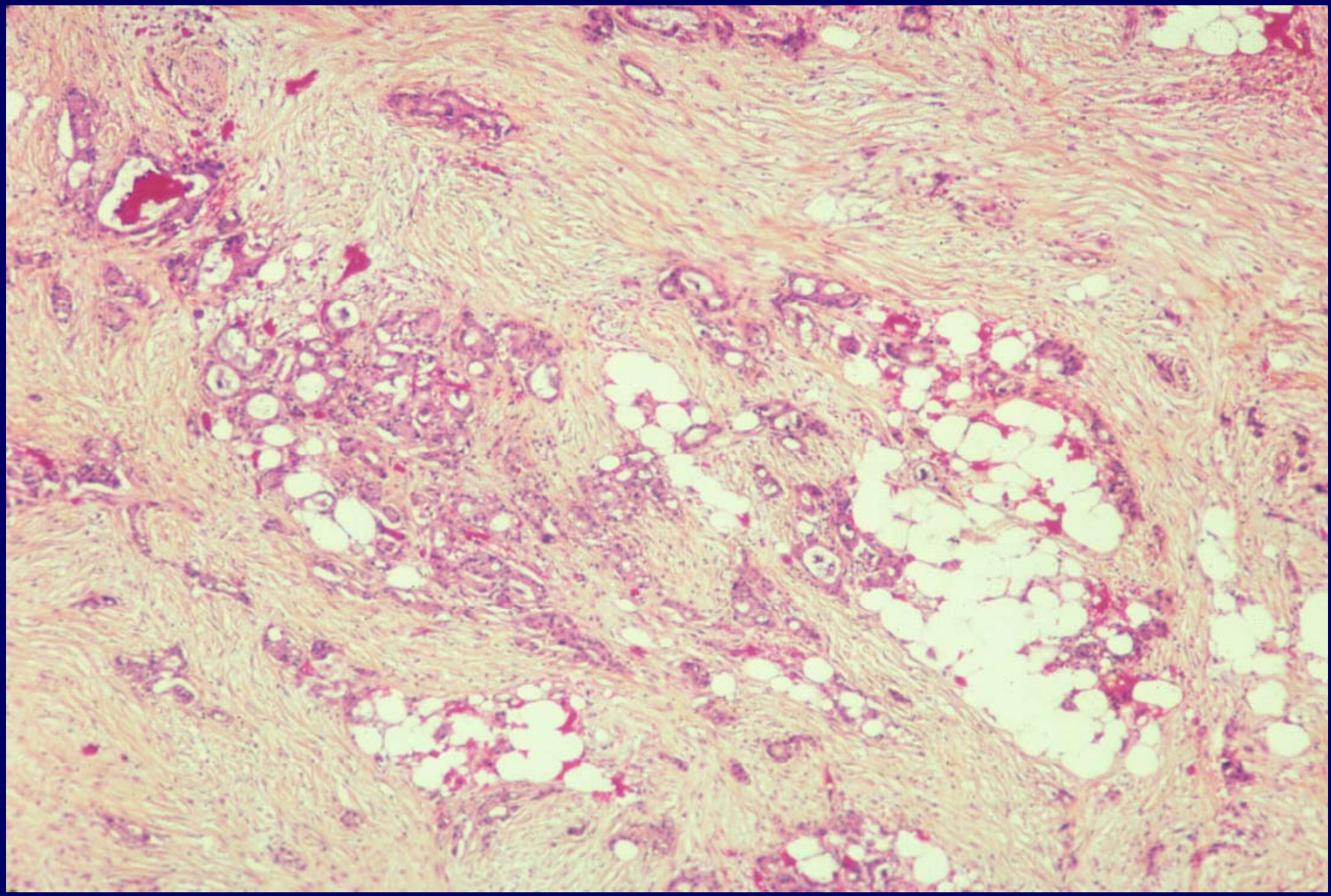


Benign – lobular

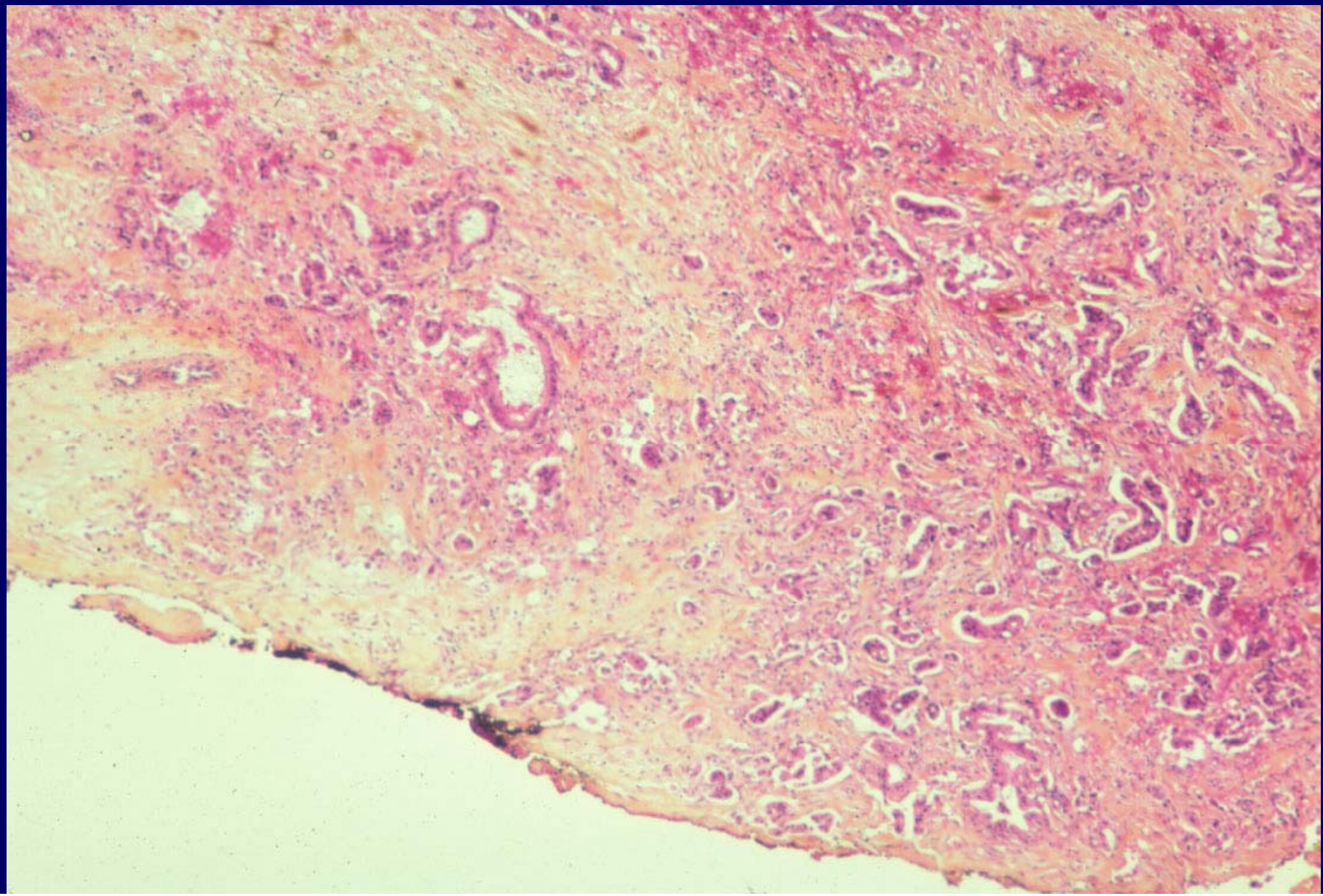
Malignant- haphazard



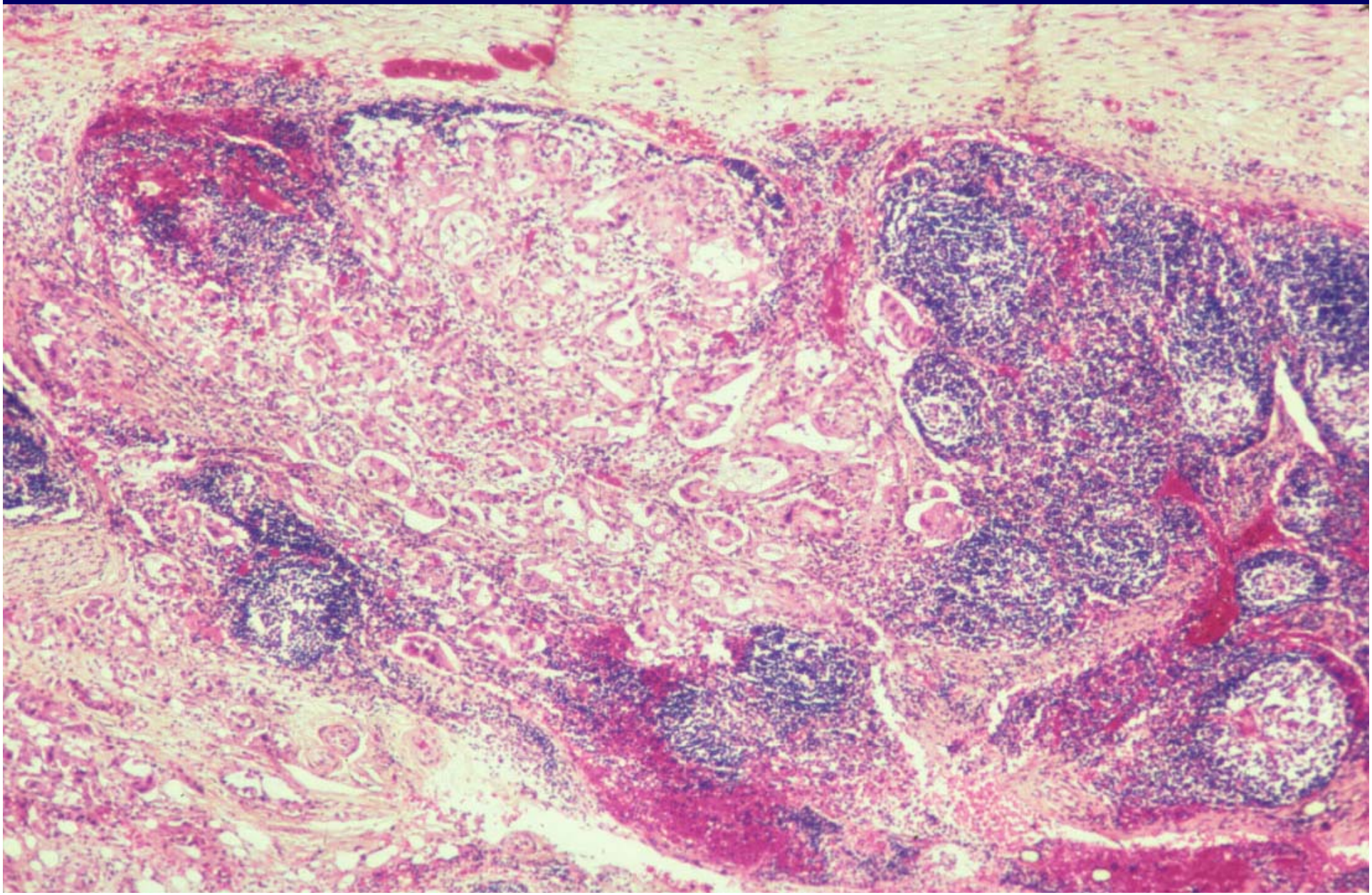
Invasive growth with associated desmoplasia



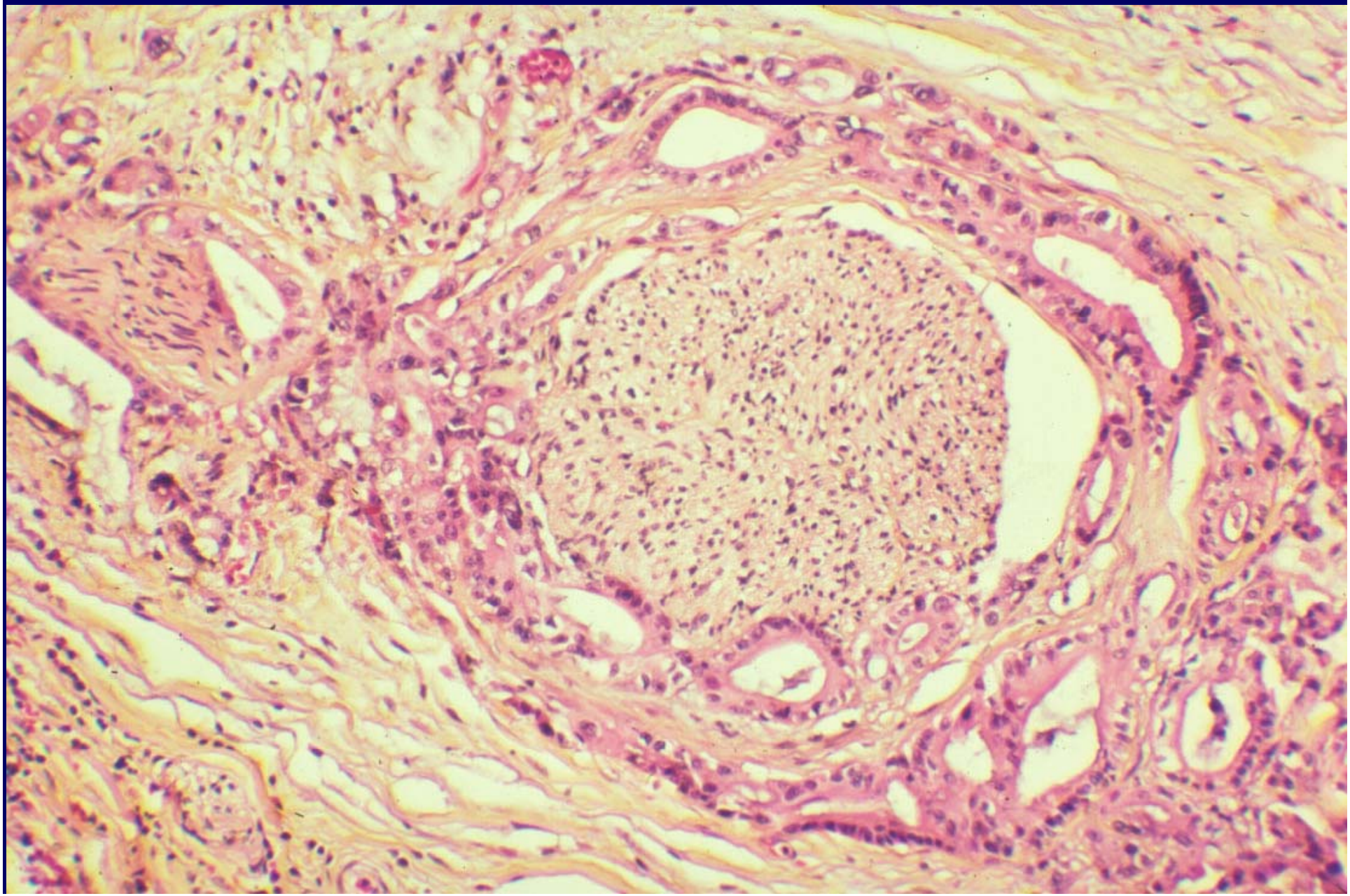
Invasion into peripancreatic soft tissue



Pancreatic adenocarcinoma – Lymph node metastases



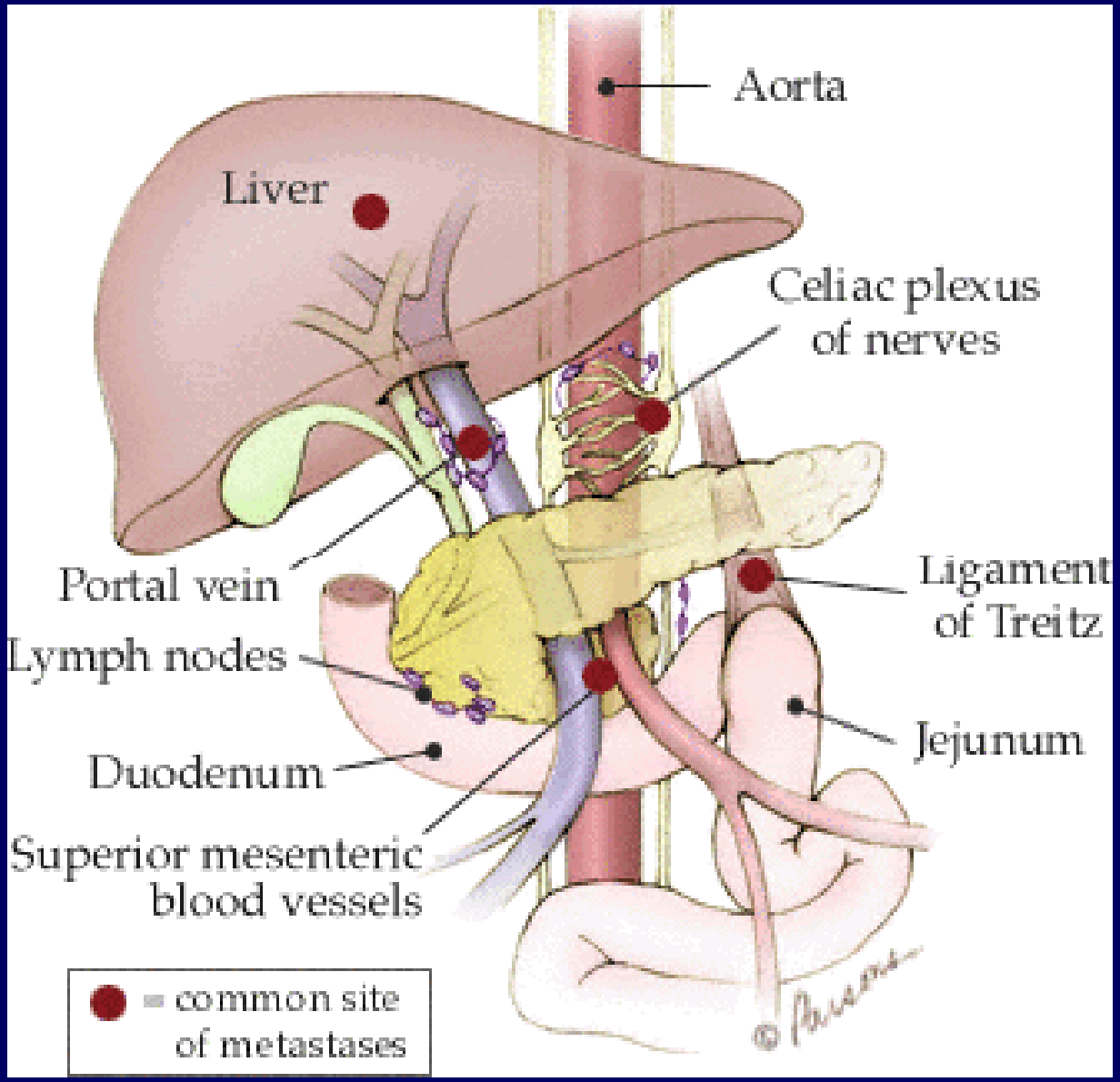
Pancreatic adenocarcinoma – perineural invasion



Pancreatic Ductal Adenocarcinoma: Pathology

- Microscopic:
  - loss of lobular architecture
  - architectural and cytomorphologic features indicative of malignancy:
    - loss of cell differentiation, hyperchromatic nuclei, increased N:C, prominent nucleoli, mitotic activity
  - intraductal carcinoma
  - invasive growth associated with desmoplasia
  - neurotropism, extratumoral vascular invasion
  - extension into peripancreatic soft tissue
  - secondary pancreatitis due to obstruction

Critical area to evaluate- uncinate margin

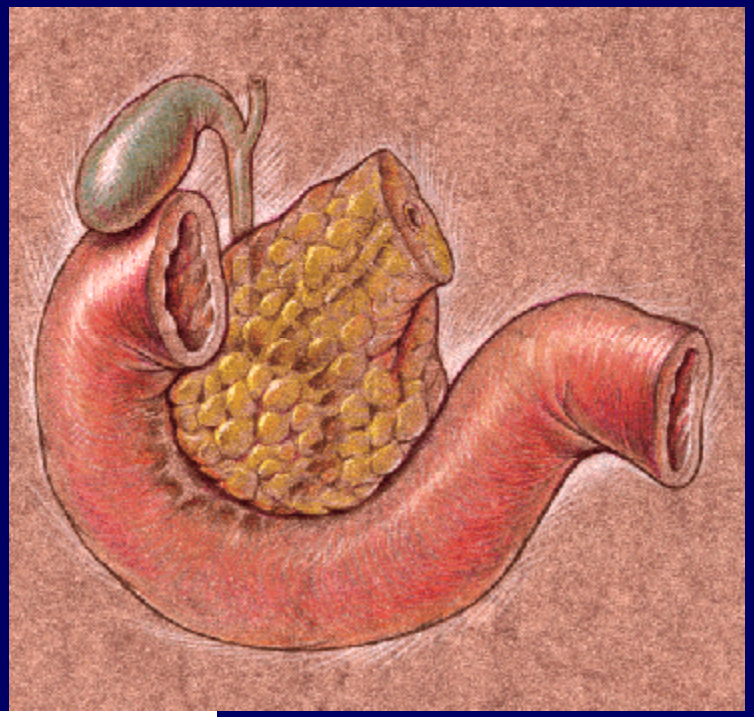


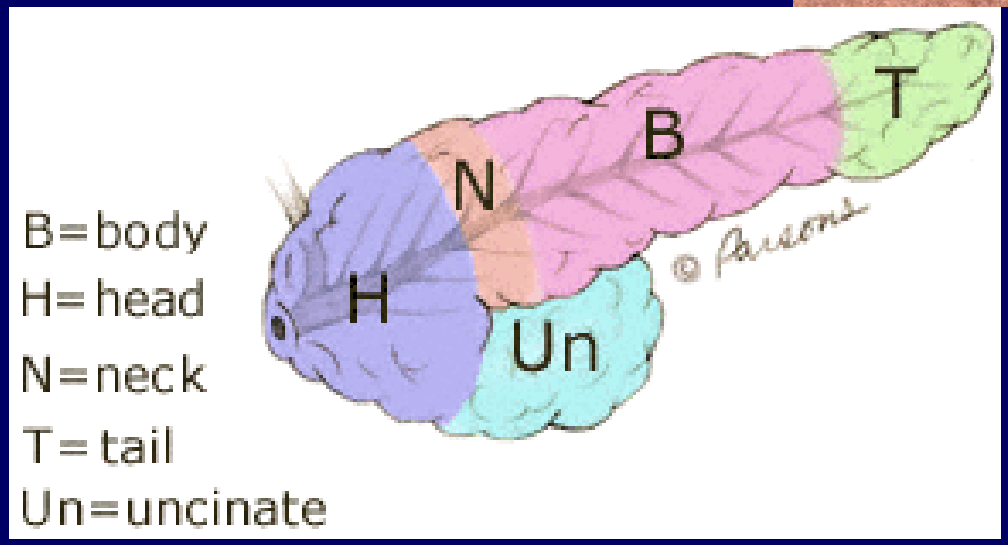
Margin most likely
To be positive is the
Uncinate margin -
Retroperitoneal/mesenteric
Margin along the right
Lateral border of the SMA
And should be inked.

Margin evaluation: (Black posterior)
Bile duct (Yellow anterior)
Pancreatic distal
Posterior/Retroperitoneal
Uncinate

Tumor size:
Measure Gross

Submit 2 complete cross sections.





Definition of Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** *In situ* carcinoma
- **T1** Tumor limited to the pancreas, 2 cm or less in greatest dimension
- **T2** Tumor limited to the pancreas, more than 2 cm in greatest dimension
- **T3** Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues
- **T4** Tumor is not resectable and extends directly into any of the following: stomach, spleen, colon, adjacent large vessels

Pancreatic Cancer Prognosis

- 2 yr survival – 28%
- 5 yr survival – 3-12%

- Mean survival in untreated patients 3 mo.
- Mean survival after radical resection 10-20 mo

- (Less than 20% of patients are surgical candidates).

Pancreas Cancer Genetics

5-10% of cases are familial, some with defined genetic syndromes

Hereditary Pancreatitis: germline mutations in trypsinogen gene on 7q35 with 40% lifetime risk of developing pancreatic cancer.

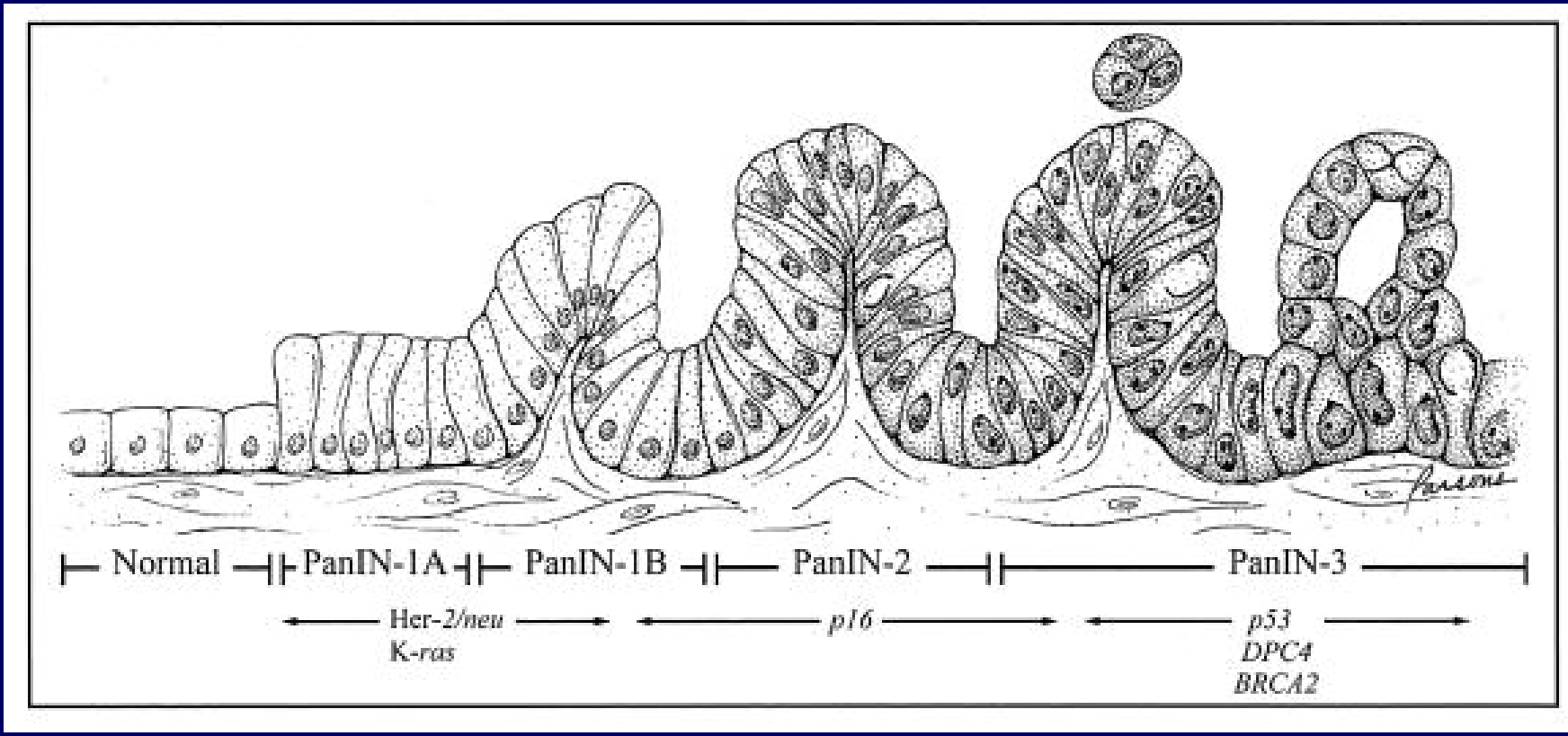
Pancreatic cancers described in BRCA2 mutations in familial breast cancer kindreds.

Associated with germline p16 mutations, and HNPCC.

Role of oncogenes: KRAS-90%, p16-95%, p53-75%

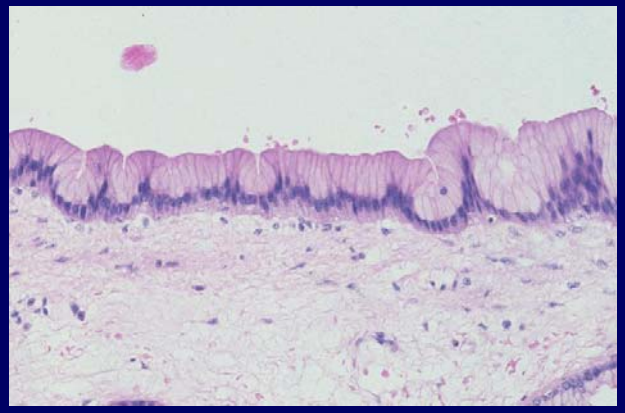
In-situ progression to Cancer

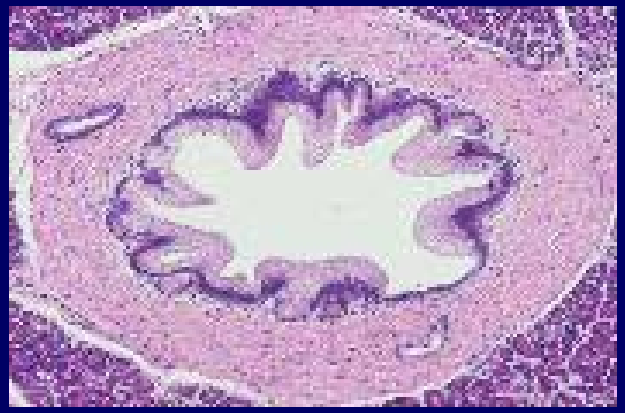
Takaori and Hruban *Pancreas* 2004 28:256-262.

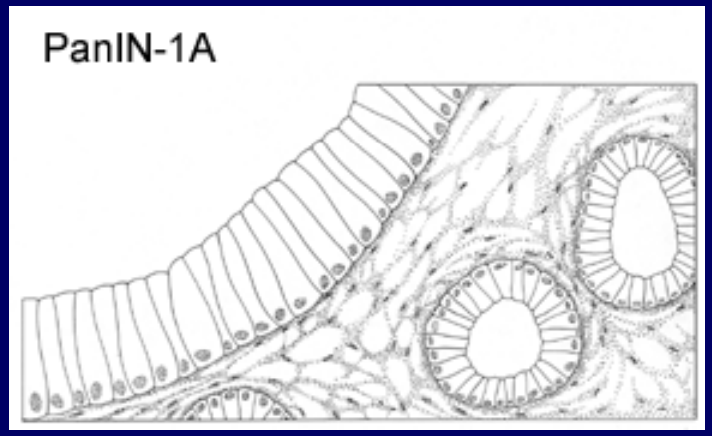


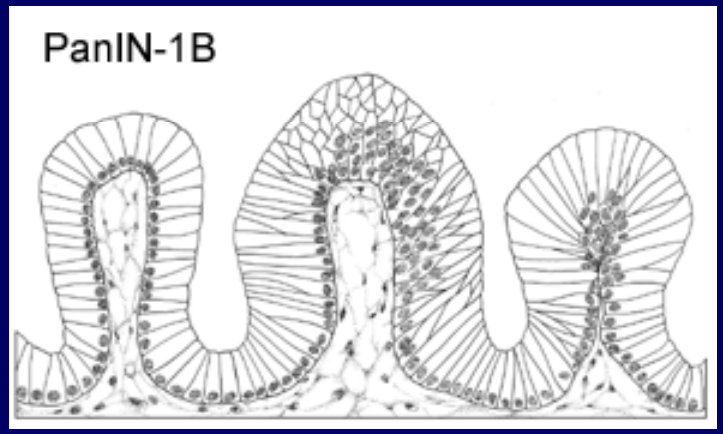
Pan IN (Pancreatic Intraepithelial Neoplasia)

PanIN-1A-flat epithelium; basal nuclei, abundant supranuclear cytoplasm
PanIN-1B – papillary, micropapillary architecture; cytology same as 1A.



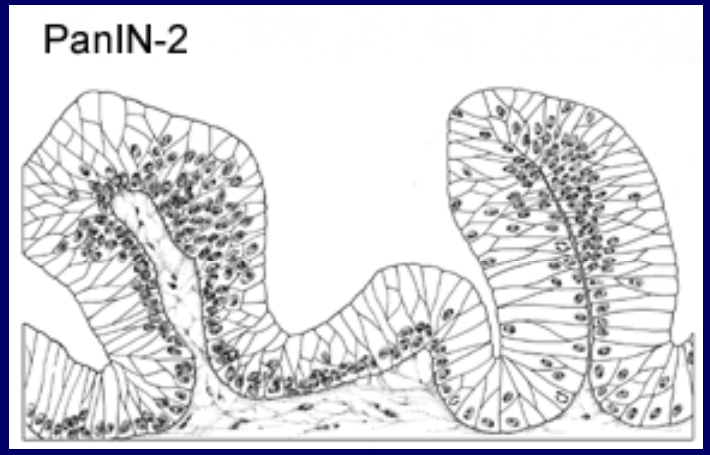


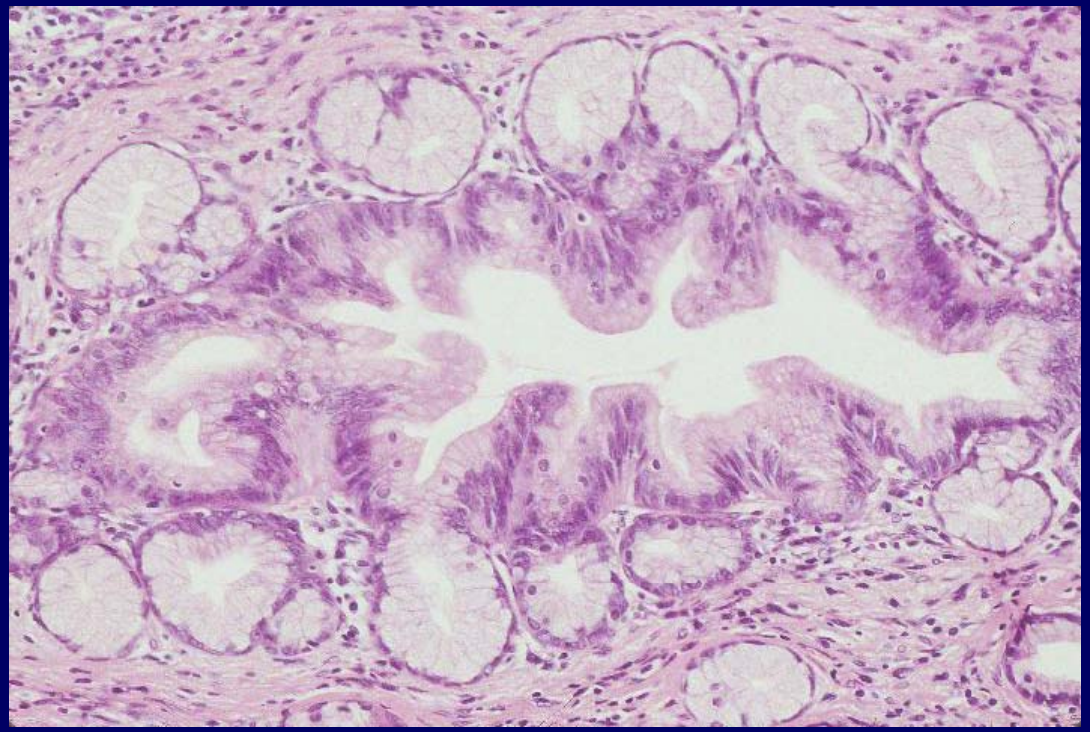




Pan IN-2 (Pancreatic Intraepithelial Neoplasia "Moderate Dysplasia")

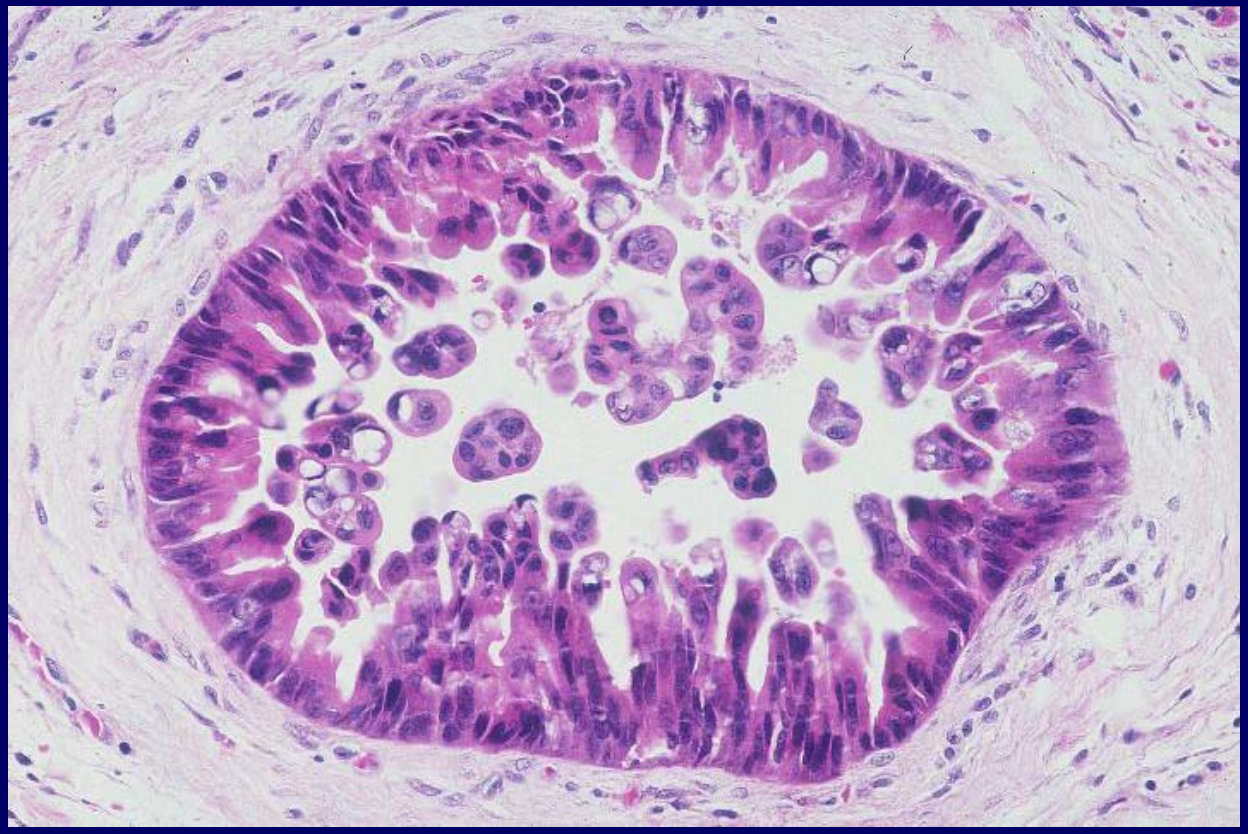
PanIN-2- flat or papillary, micropapillary; some nuclear abnormalities (some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromasia – but less than PanIN-3)





Pan IN (Pancreatic Intraepithelial Neoplasia)

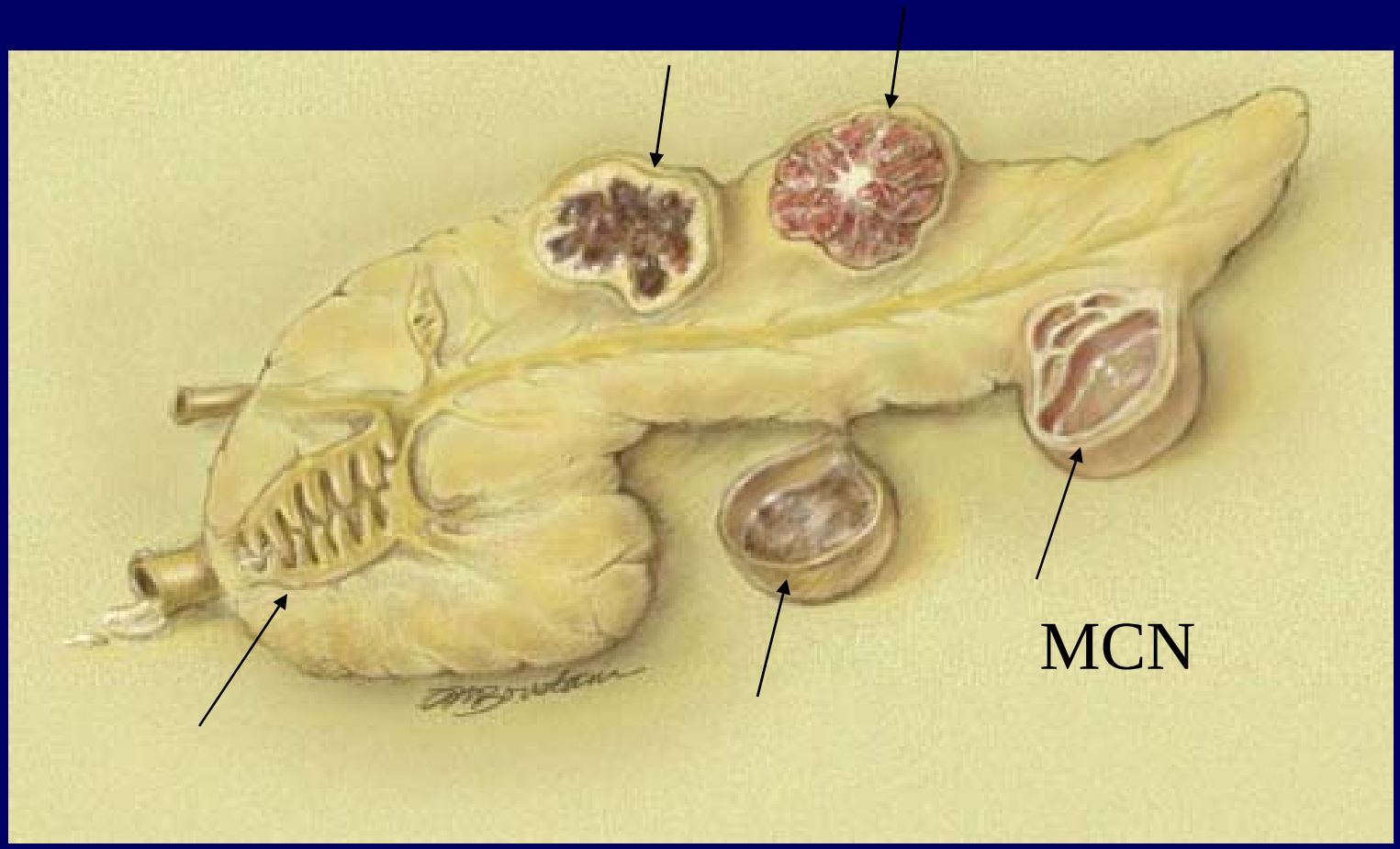
PanIN3 – cribriform, papillary, micropapillary (rarely flat)
(marked loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromasia, abnormal mitoses)



Pancreatic Cystic Lesions

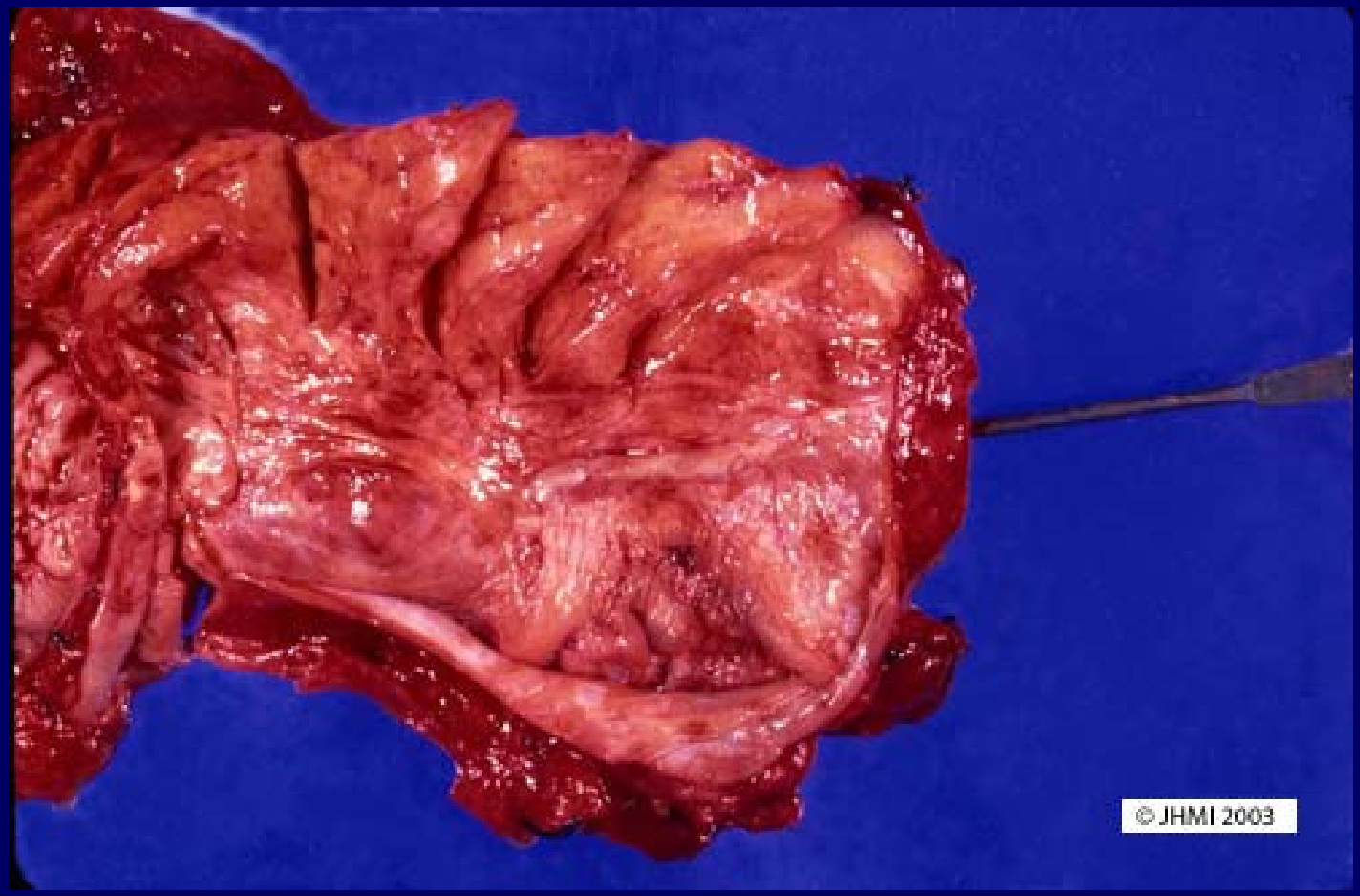
- **Mucinous cystic neoplasm** (benign, borderline or malignant)
- **Intraductal papillary mucinous neoplasm** (benign, borderline or malignant)
- **Serous cystadenoma** (benign)
- **Pseudocyst** (benign – NOT a NEOPLASM)

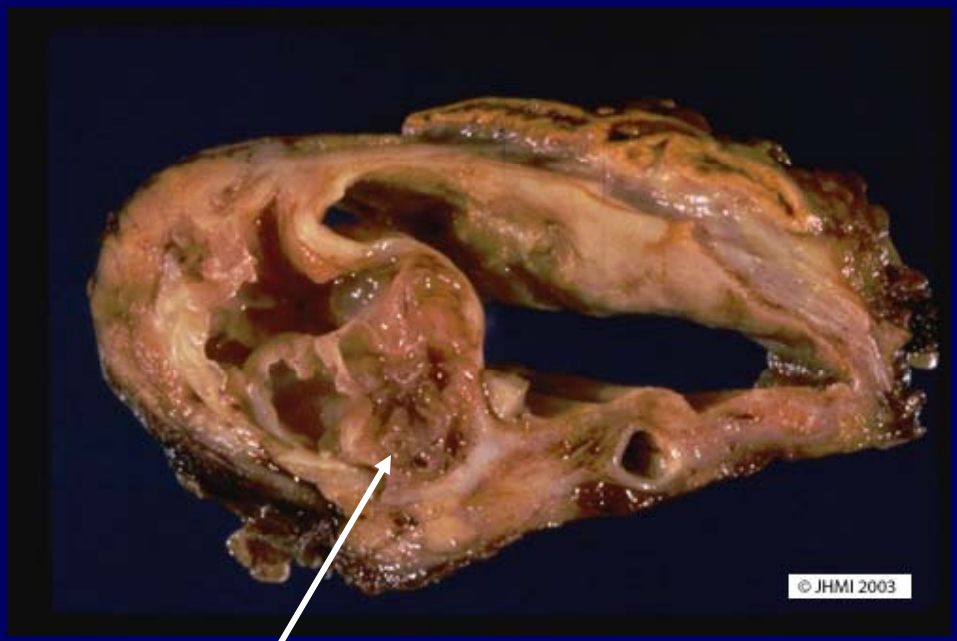
PANCREATIC CYSTIC LESIONS



Mucinous cystic Neoplasm

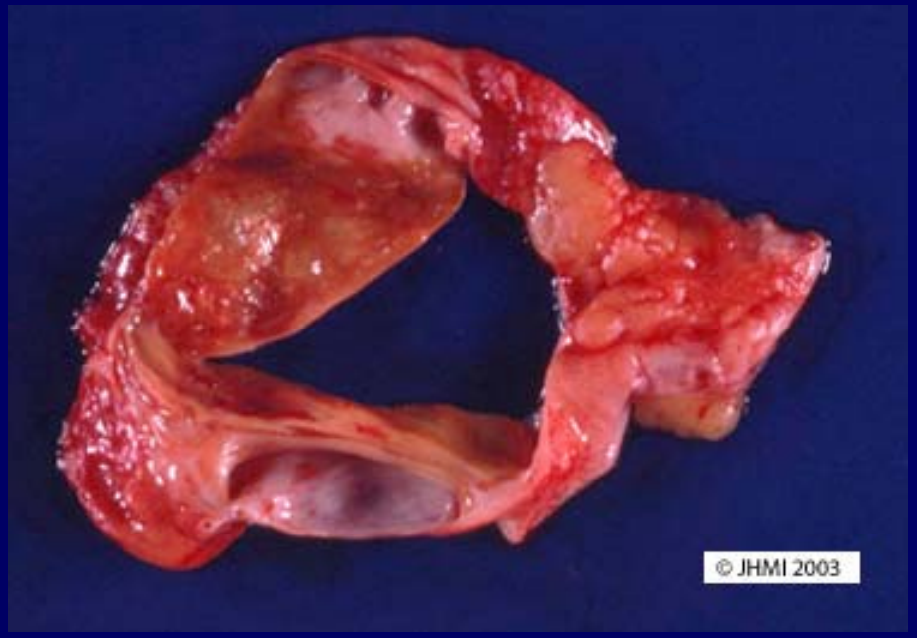
NOT connected with pancreatic ducts!



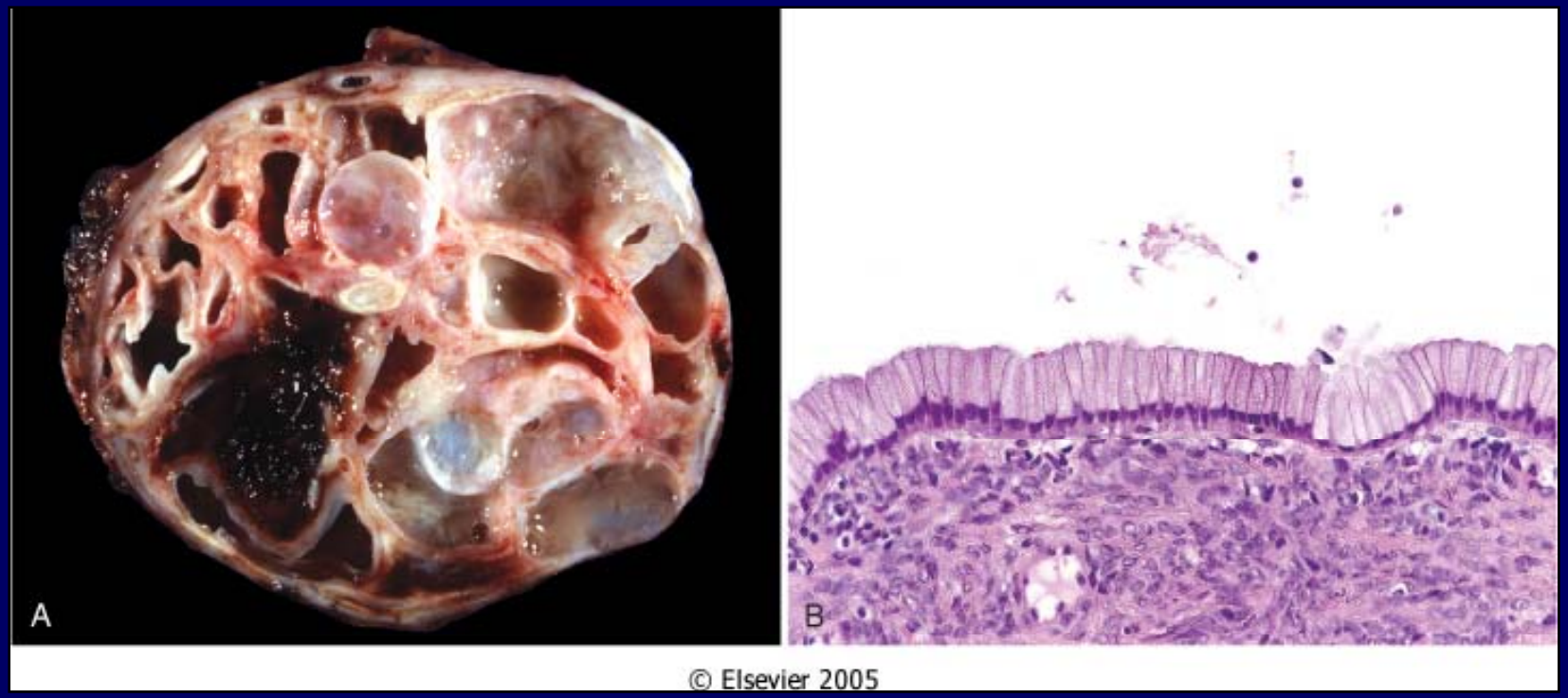


Mucinous cystadenocarcinoma

Mucinous cystadenoma



Mucinous cystic neoplasm



Mucinous epithelium; "ovarian type stroma"

Clinical spectrum: benign to malignant

Mucinous Cystic Neoplasms
MCNs

Mainly Females (mean age 45)

Abdominal Pain or Mass

Sample extensively to rule out invasive component

Classification:
- Mucinous cystadenoma (minimal atypia)
- Borderline MCN (moderate atypia, papillary architecture)
- MCN with CIS (high grade cytology, cribriform architecture)
- Invasive CA (destructive stromal invasion, usual ductal CA)

Gross: large (mean 10cm); Body/Tail; Multilocular, unilocular rare
NO communication with pancreatic duct.

Micro: Columnar mucin cells; intestinal or gastric foveolar type.
Ovarian stroma (ER+, PR+, inhibin+)

DD: IPMN (Head/communicate with ducts/ no ovarian stroma)
Pancreatic Pseudocyst (MCN lining can be denuded)

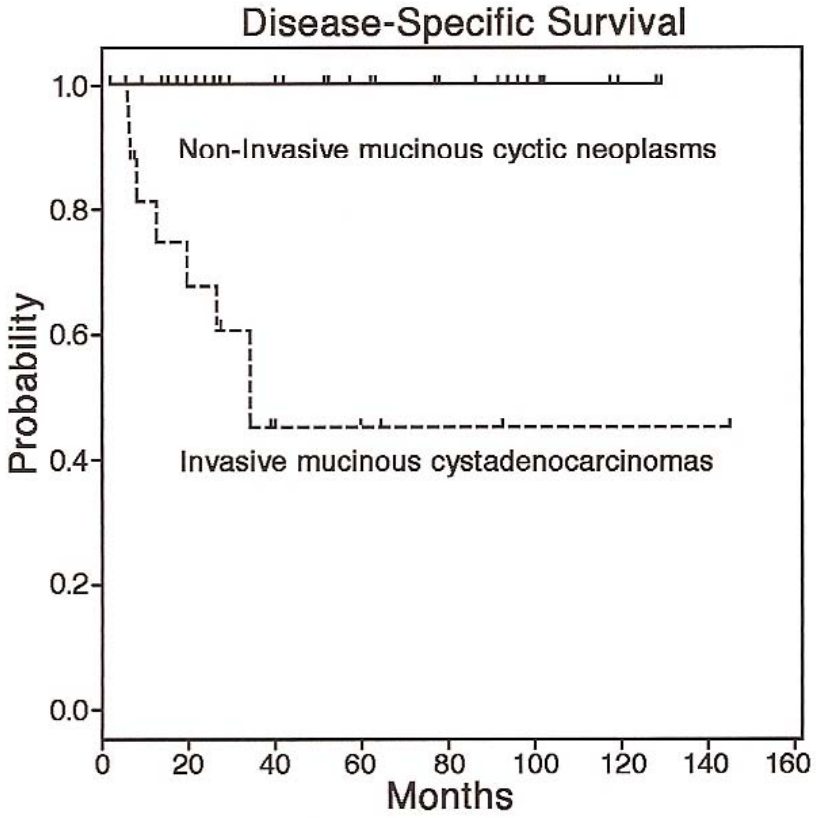
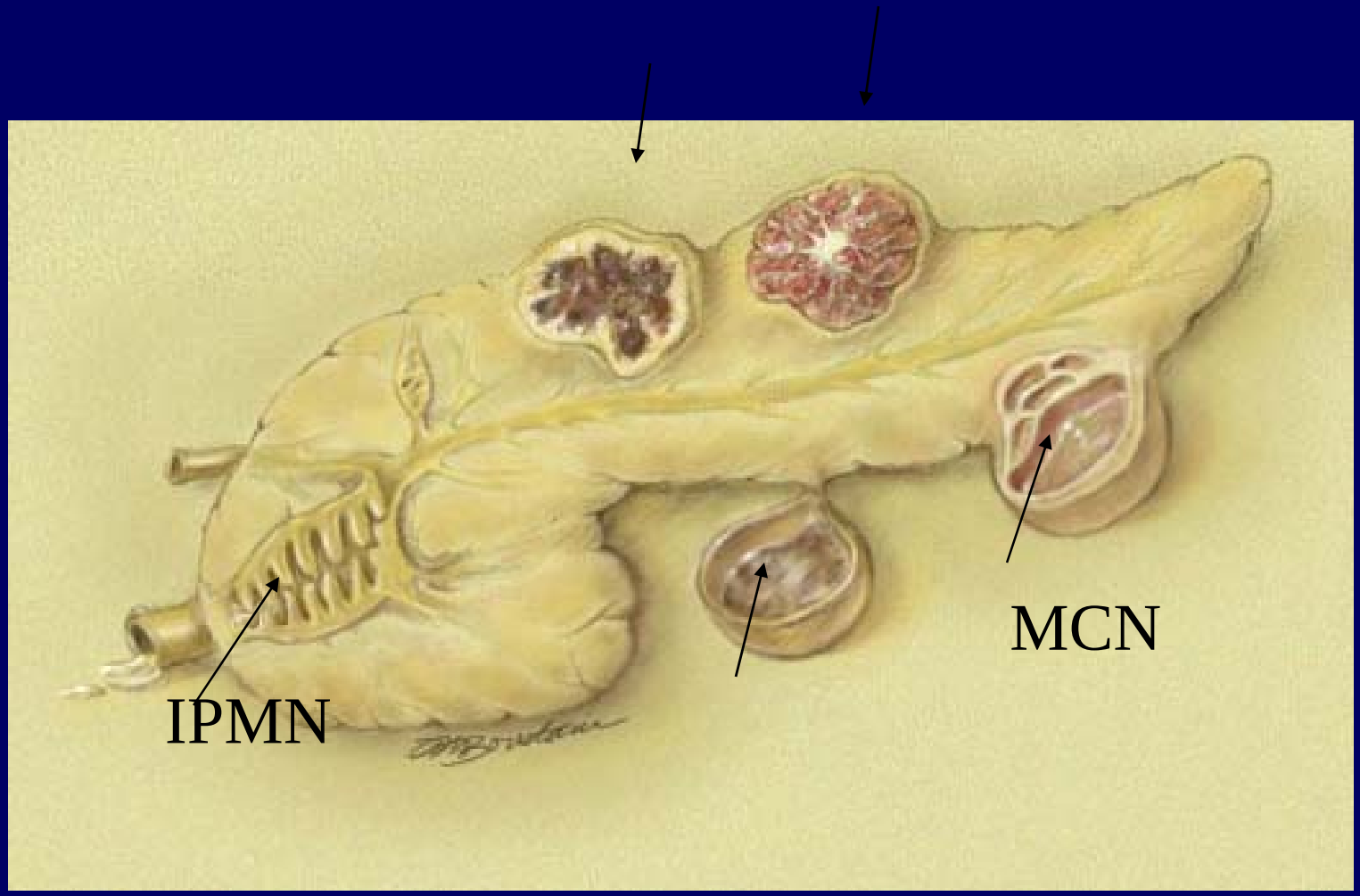


Figure 5-33

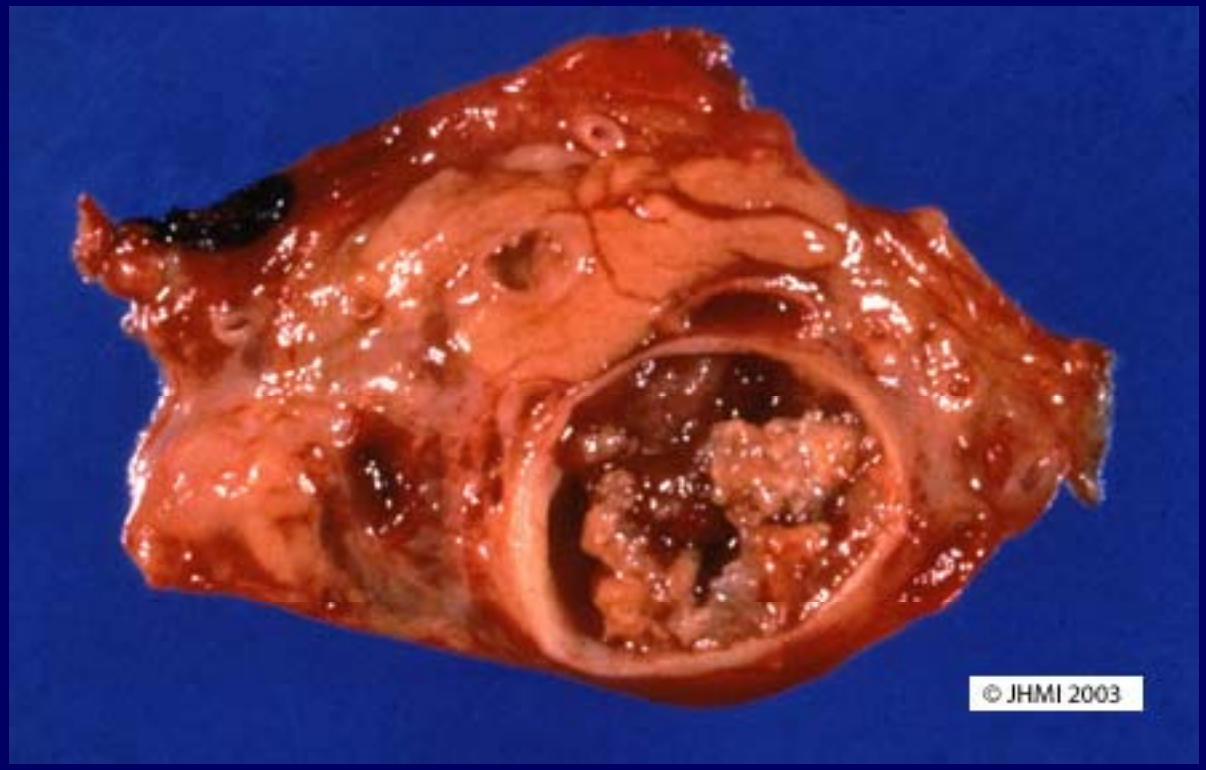
DISEASE-SPECIFIC SURVIVAL AFTER SURGICAL RESECTION

The presence or absence of an associated invasive carcinoma is the best predictor of survival following surgical resection of a mucinous cystic neoplasm. (Fig. 5 from Wilentz RE, Albores-Saavedra J, Zahurak M, et al. Pathologic examination accurately predicts prognosis in mucinous cystic neoplasms of the pancreas. Am J Surg Pathol 1999; 23:1324.)

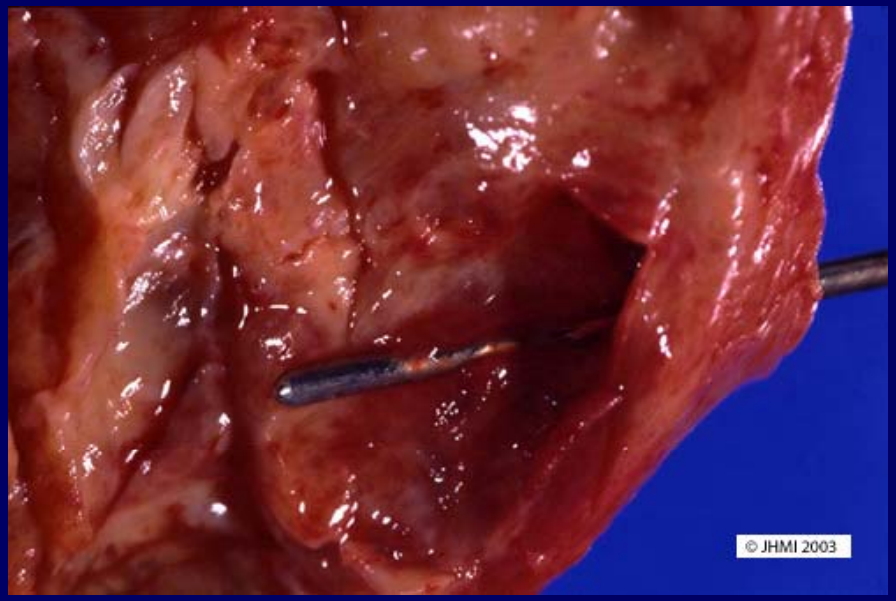
PANCREATIC CYSTIC LESIONS



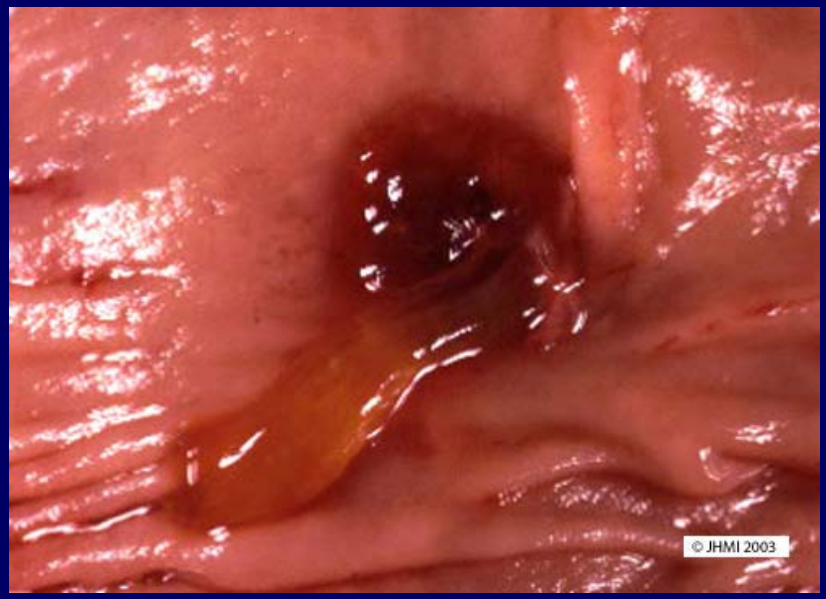
Intraductal Papillary Mucinous Neoplasm (IPMN)



IPMNs (Intraductal Papillary Mucinous Neoplasms)

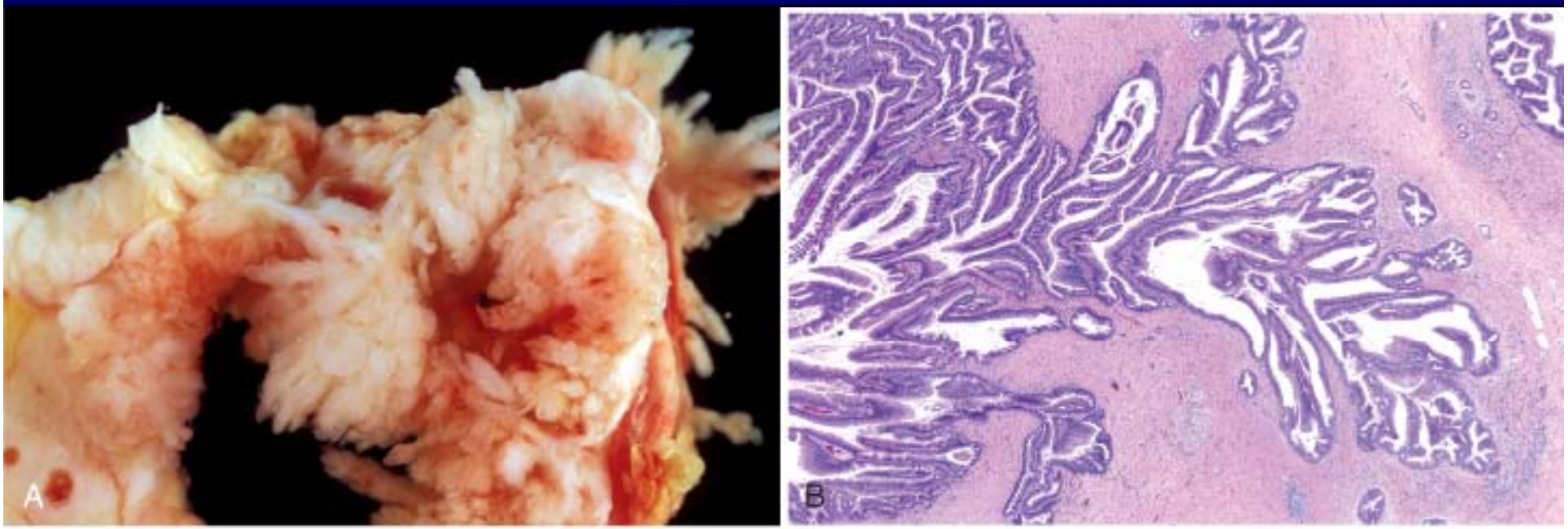


Communicates with duct



Mucin oozes out of ampullae

Intraductal papillary mucinous neoplasm (IPMN)



Associated with the pancreatic duct

Clinical spectrum: benign to malignant

Intraductal Papillary Mucinous Neoplasm (IPMN)

- IPMT (first named in 1995)
- Radiologic or grossly visible lesion (>1cm)
- Contiguous or multicentric with cytologic atypia
- Head of pancreas; More common in male >60 y.
- Invasive tumors associated with 30% of IPMNs (often colloid type – more indolent clinical behavior than usual invasive ductal-NOS.)
- Resection often with frozen sections, since most lesions are contiguous.
- Grade (Benign, Borderline, Intraductal CA);
- DD: Mucinous cystic neoplasms, PanIN (resembles small IPMN)

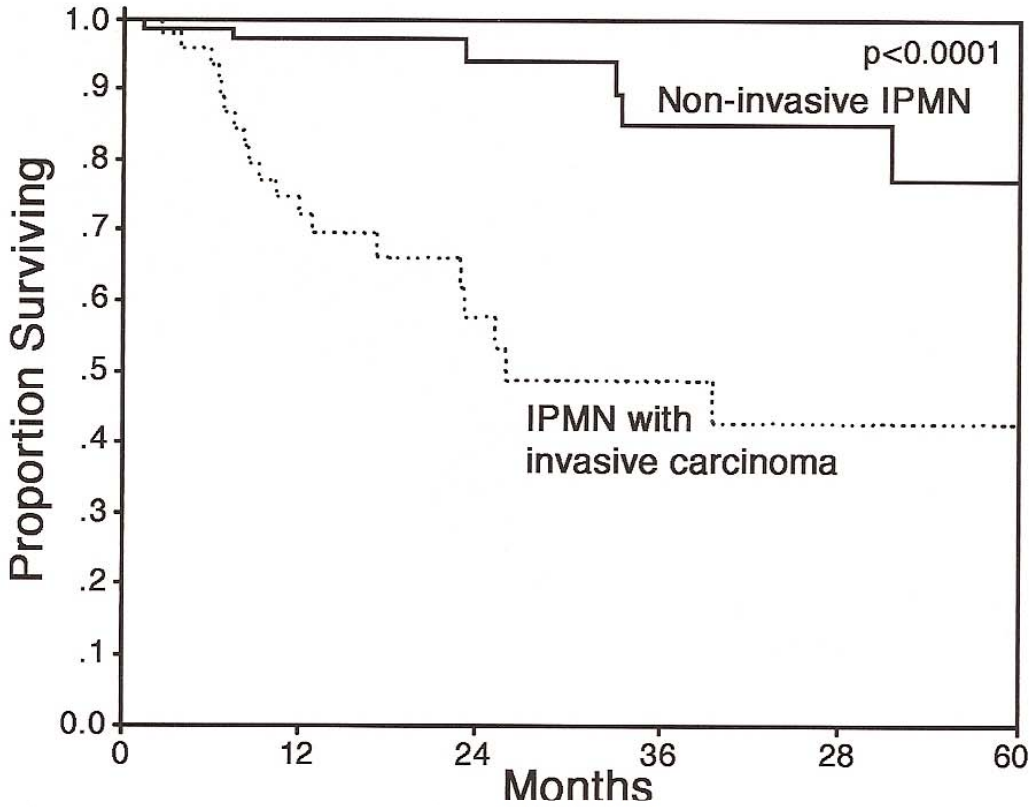
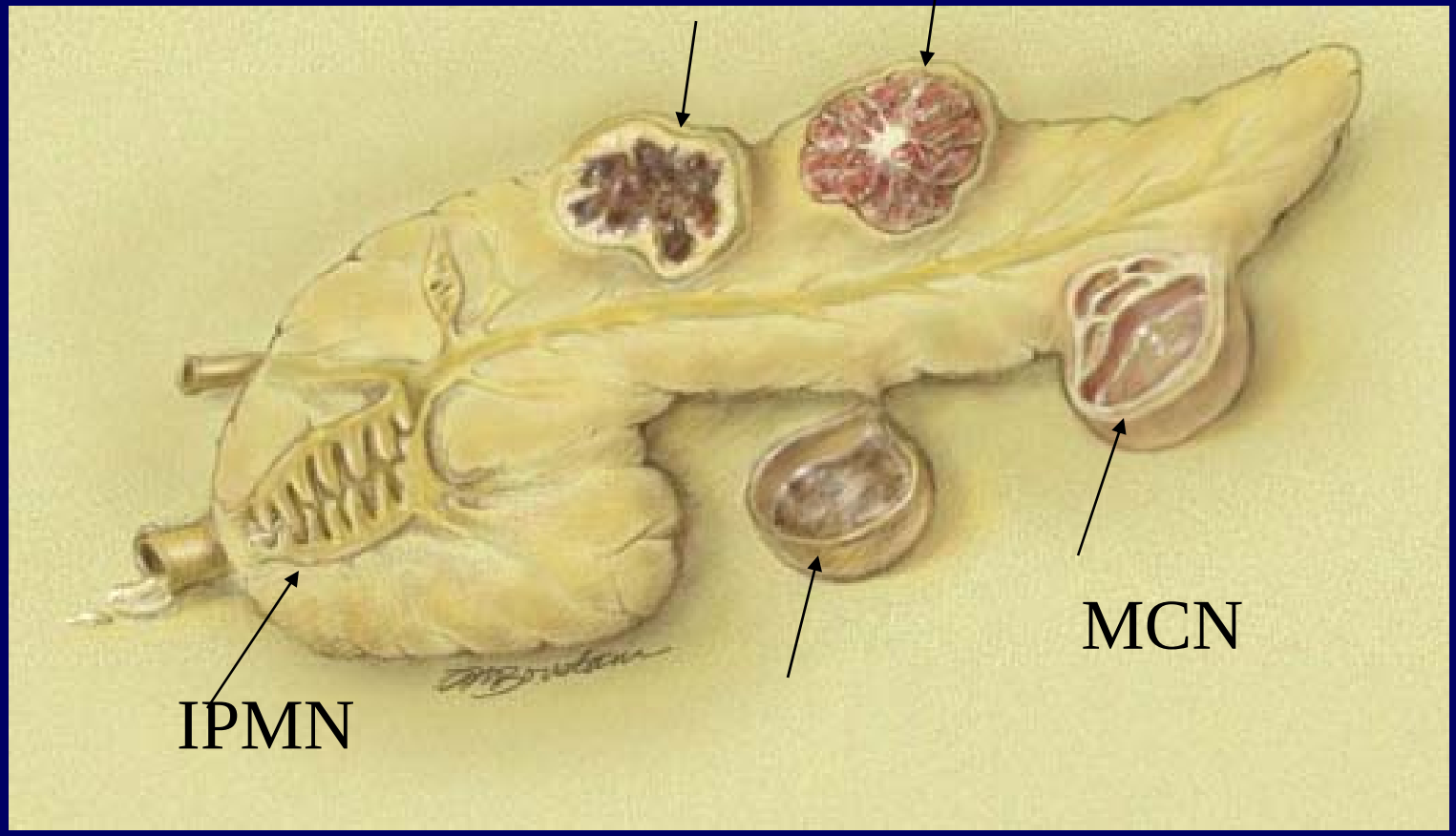


Figure 6-38

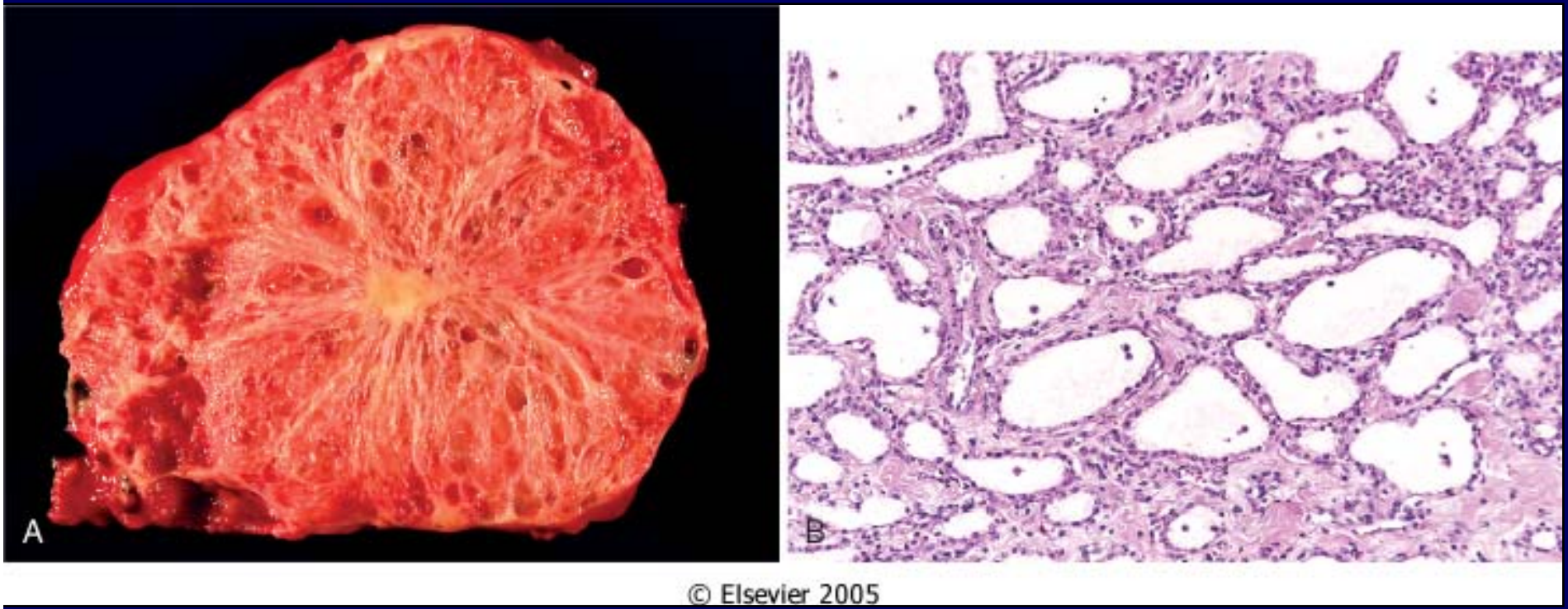
INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Kaplan-Meier actuarial survival curves compare patients with surgically resected noninvasive and invasive IPMNs. (Fig. 5 from Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg 2004;239:793.)

PANCREATIC CYSTIC LESIONS



Pancreatic serous cystadenoma

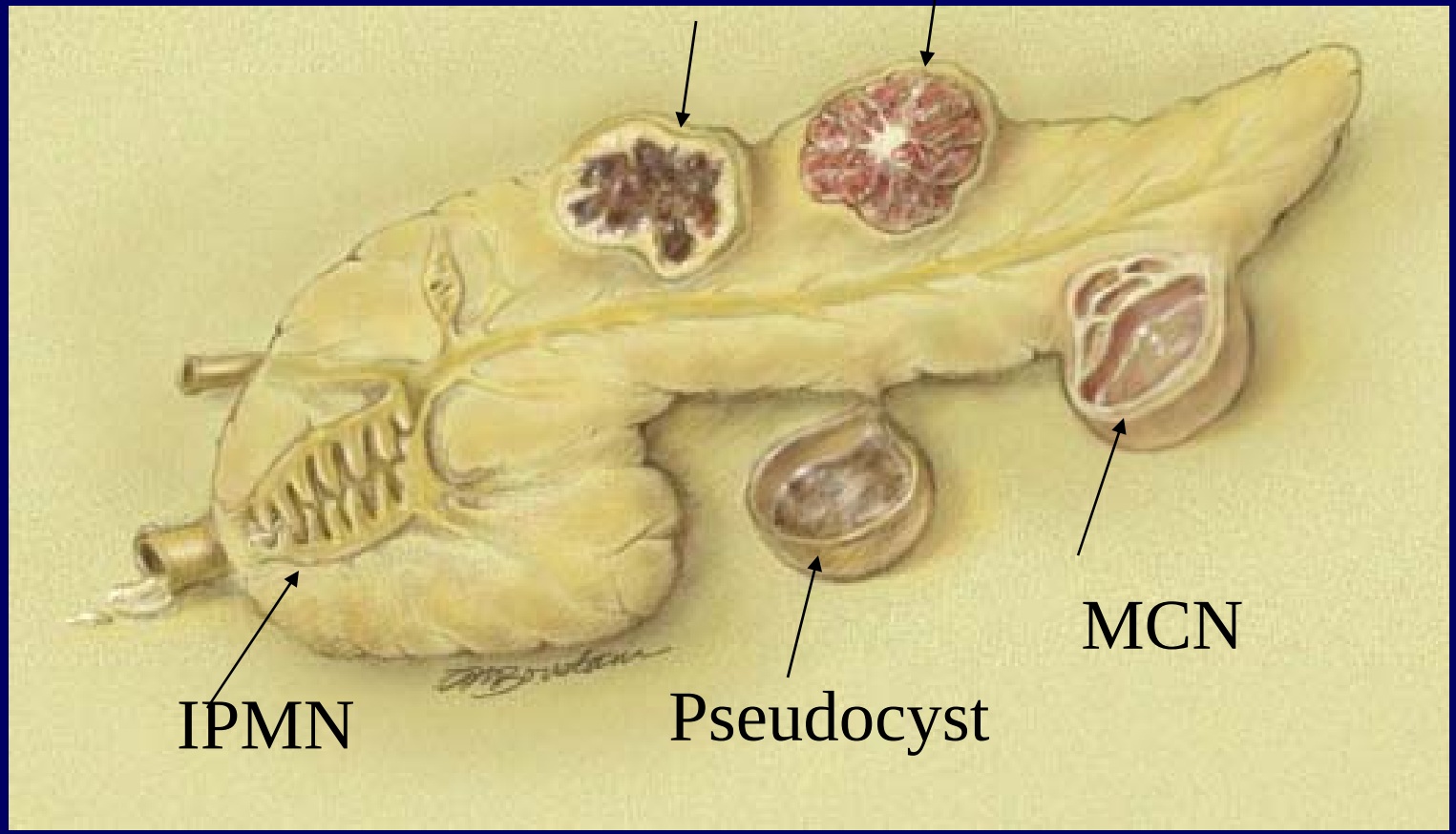


BENIGN

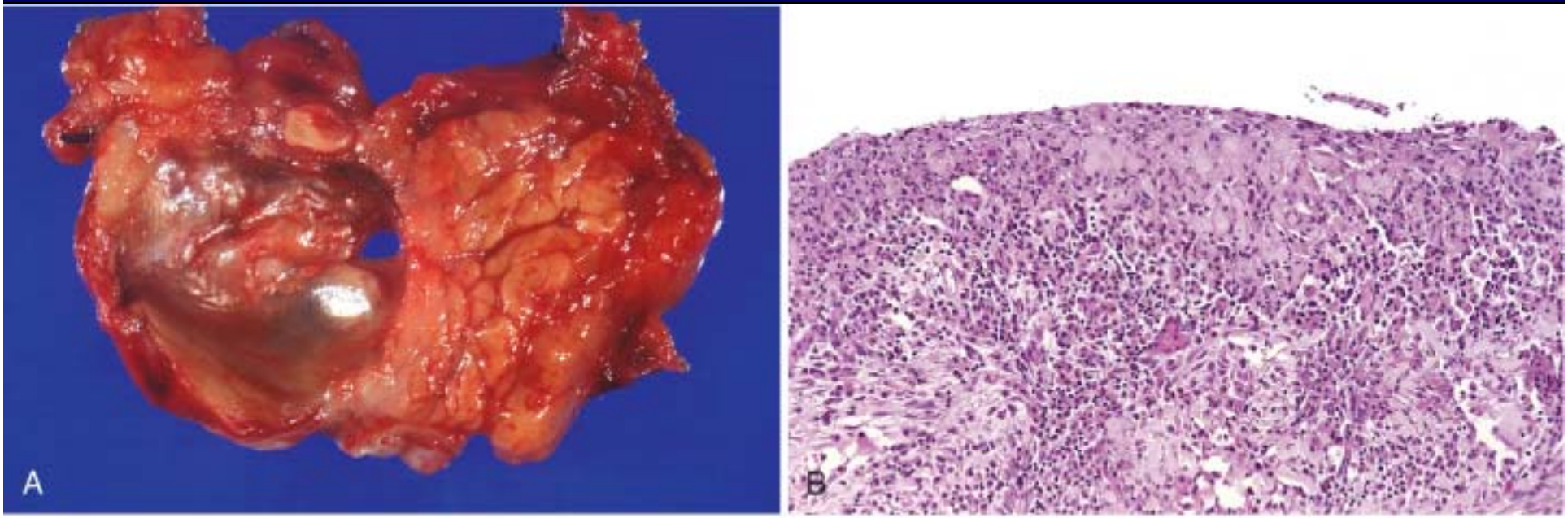
Serous Cystadenoma

- Aka microcystic adenoma, glycogen rich adenoma
- F/M =7/1; mean age 66y
- Association with von Hippel Lindau syndrome
- Symptoms: none, local pain, obstruction if in head
- Clinical behavior: benign
- Gross: mean 11 cm; multiloculated mass, cysts filled with clear fluid; spongy; often central scar.
- Micro: small cystic spaces lined with cuboidal cells with clear cytoplasm (glycogen rich); round nuclei; some cases papillary.

PANCREATIC CYSTIC LESIONS



Pancreatic Pseudocyst



NOT NEOPLASTIC - RESULT OF ACUTE PANCREATITIS

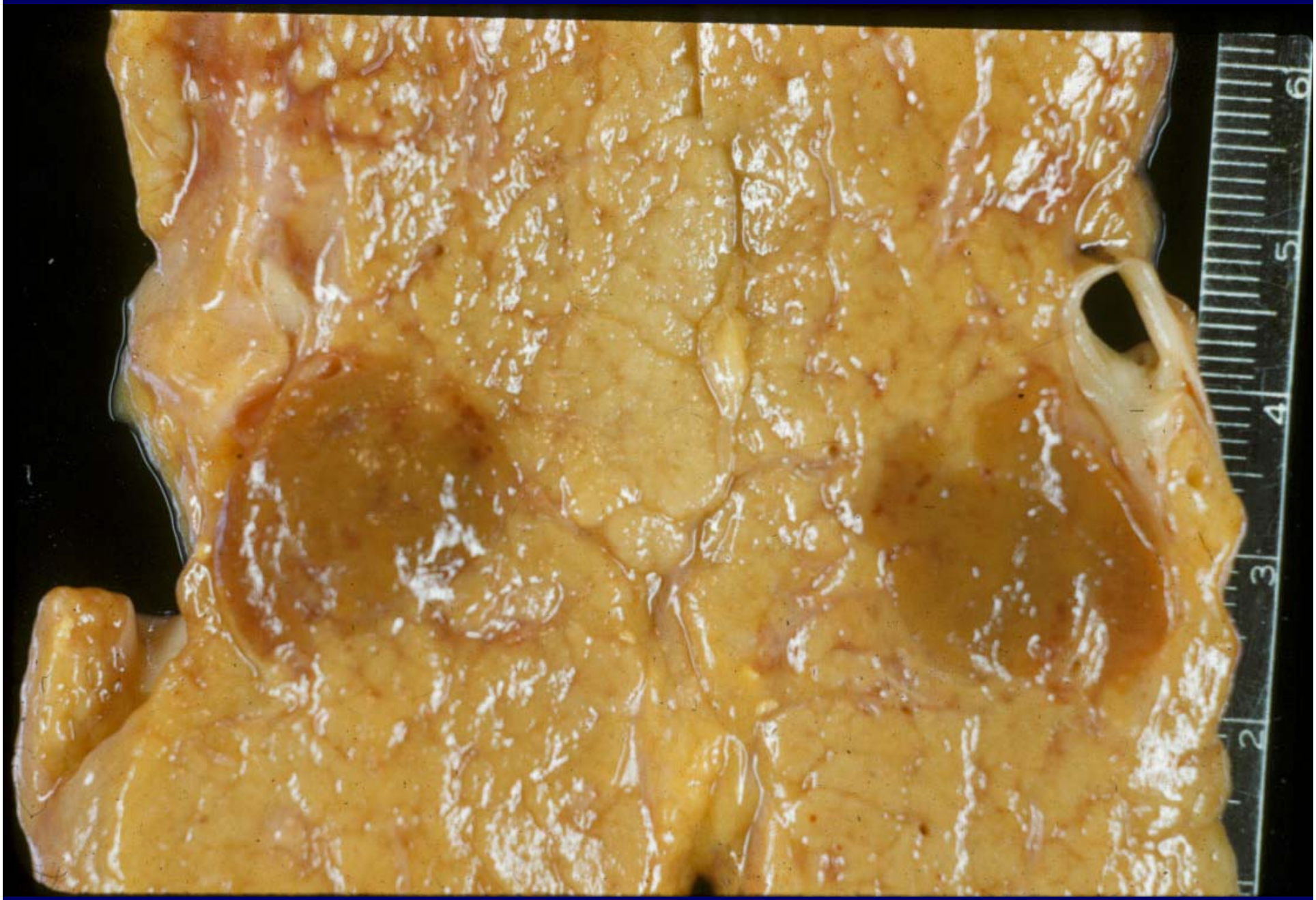
Pseudocyst

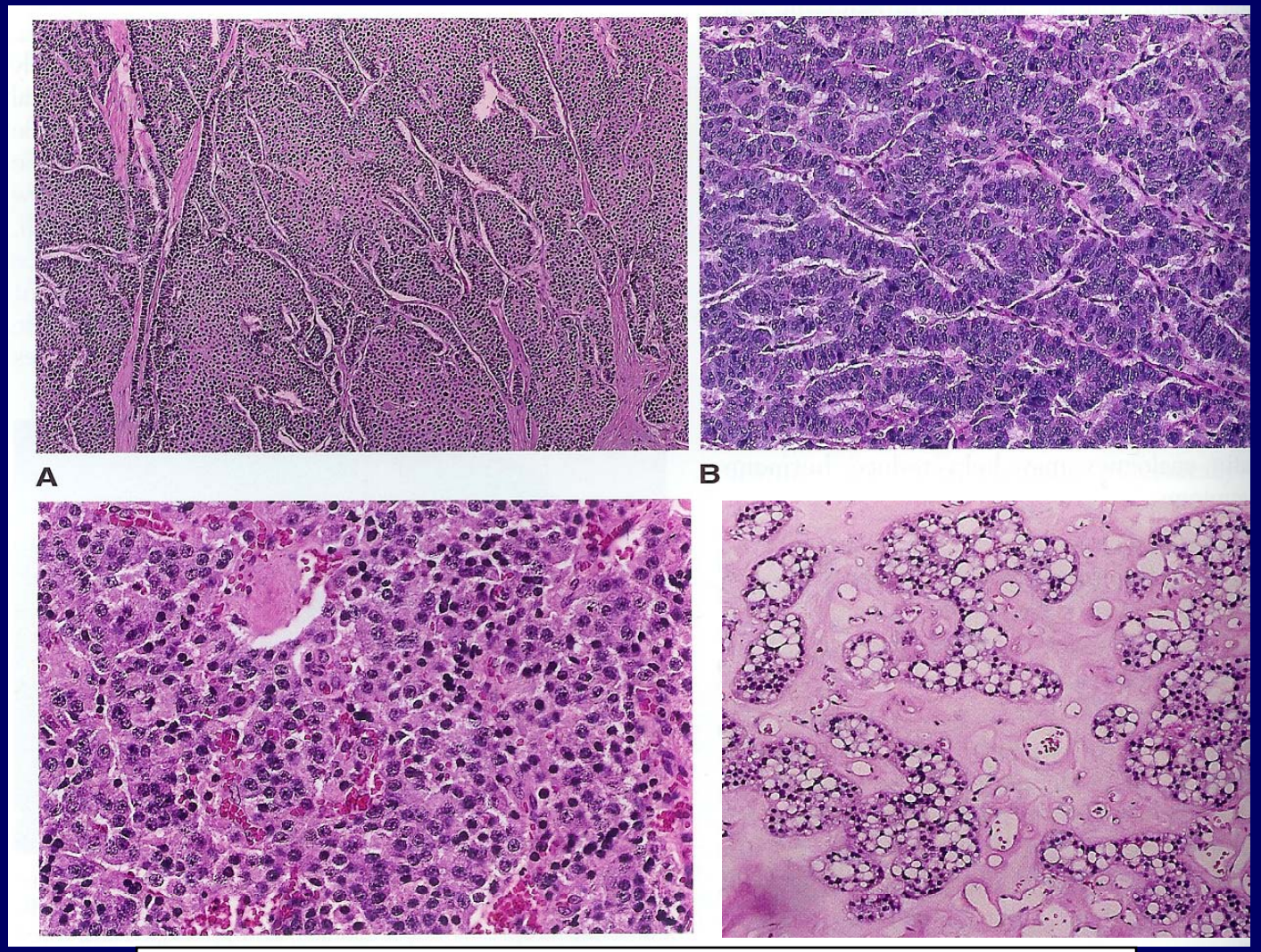
- Localized collections of pancreatic secretions that follow pancreatitis, trauma, ductal calculi.
- Symptoms: Painful, Hemorrhage, Infection, Perforation
- Treatment: excise small pseudocysts in body/tail; drain cysts in head.

- Gross: 85% solitary, usually unilocular in/near pancreas; thick irregular wall, ragged inner surface.
- Micro: No epithelial lining, fluid has high amylase
- Cyst arises from drainage of pancreatic secretions from damaged ducts into interstitial tissue; wall consists of fibrous tissue/granulation tissue.

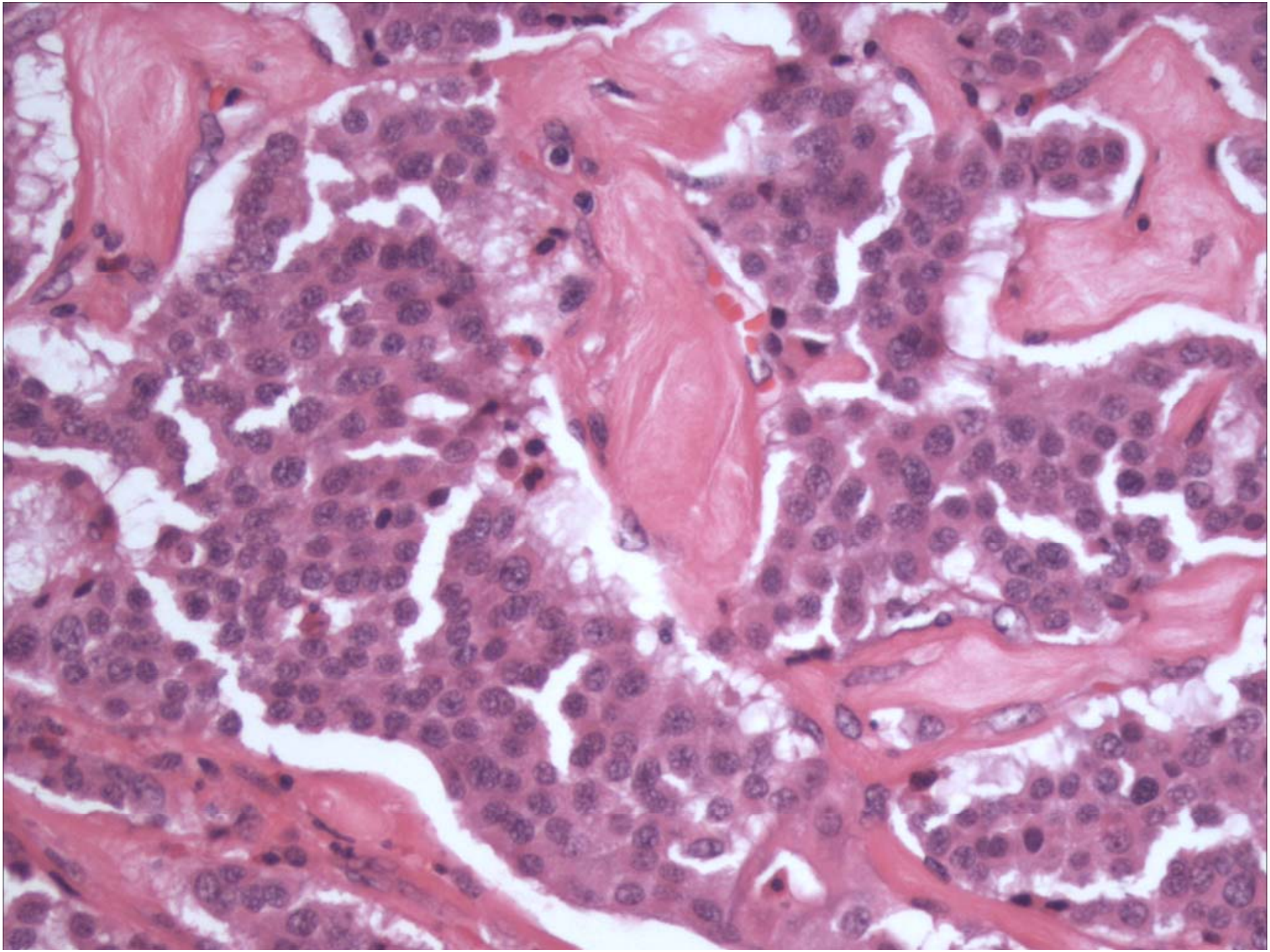
Pancreatic Endocrine Neoplasms

- 5% of pancreatic neoplasms
- “Islet cell Tumors” – inaccurate; arise from pluripotential ductal cells that differentiate along neuroendocrine lines.
- All have malignant potential except microadenomas (<5mm); No definite criteria to distinguish between benign and malignant (except for mets)





Pancreatic Endocrine Tumors



Pancreatic Endocrine Neoplasms Microscopic

Nests of uniform polygonal cells

Delicate vasculature

Salt and Pepper (stippled) chromatin.

Often (no necrosis, low mitotic activity)

Immunostains do not correlate with secretion.

(Other than chromogranin and synaptophysin; **specific stains: glucagon, insulin, PP, VIP, ACTH, somatostatin not really useful**.)

Pancreatic Endocrine Neoplasms

Functional - recognizable syndrome; detect hormone in serum.

- Insulinoma (most common); hypoglycemia; 10% malignant
  - 10% assoc with MEN1
- Gastrinoma; duodenal ulcers; 75% malignant
  - 25% assoc with MEN1

Nonfunctional - no syndrome; normal serum hormone levels (except Pancreatic Polypeptide).

- Incidental; Obstructive Sx- head of pancreas; 50 – 90% malignant.

Pancreatic Endocrine Neoplasms

- Usually occur in body/tail
- Hypervascular, circumscribed
- Highlighted with Octreotide Scan (somatostatin receptors)
- Usually slow growing, mets to LNs, liver, bone (recommend resection of mets)

Pancreatic Endocrine Neoplasms

Classification:

Neuroendocrine neoplasm, well differentiated

- Low grade: 0-1 mit/50HPF; no necrosis
- Intermediate grade: > or = 2mit/50 HPF; +/- necrosis

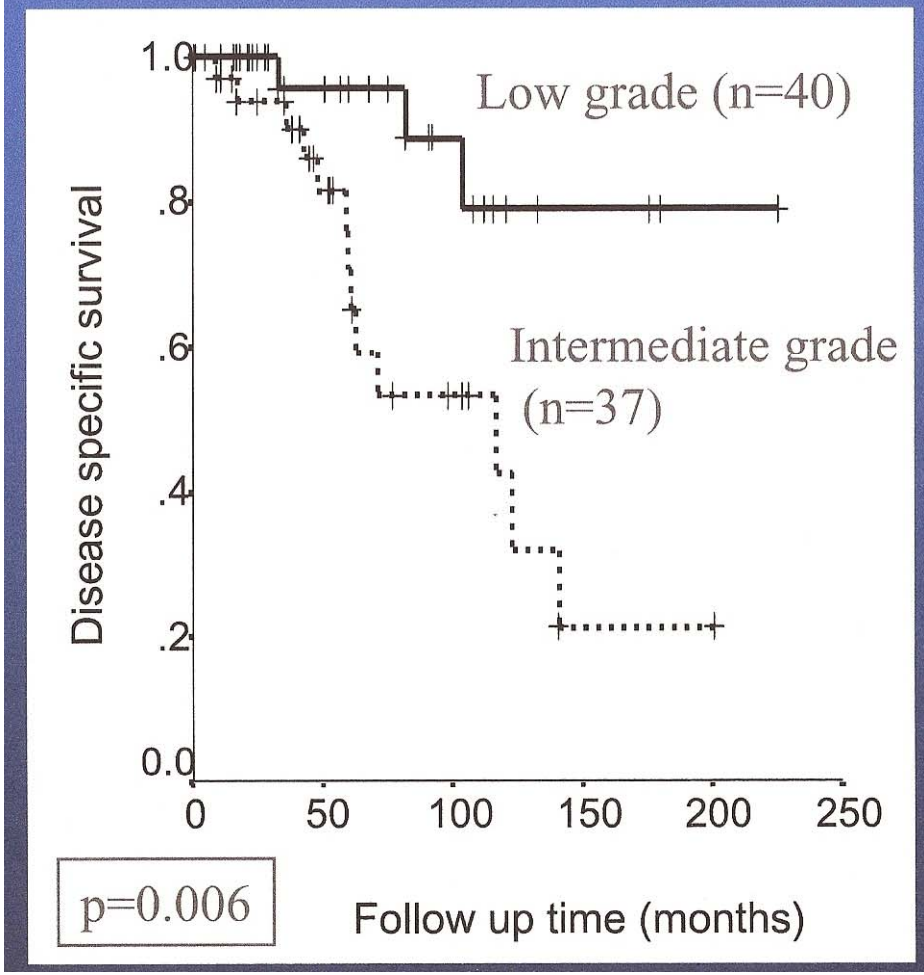
Reference: Hochwald et al. J Clin Oncol 2002; 20: 2633-42

Neuroendocrine carcinoma, high grade

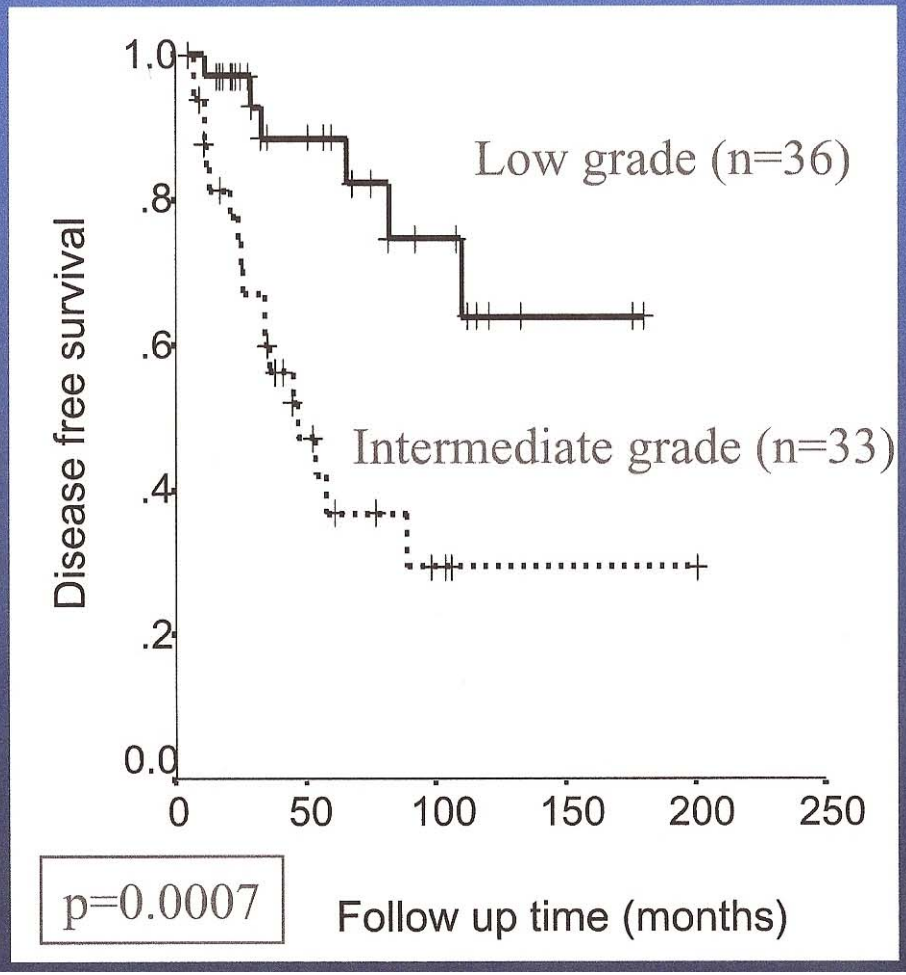
- Small cell carcinoma / large cell neuroendocrine
- High grade: >10mit/10 HPF; widespread necrosis

Survival in Pancreatic Endocrine Neoplasms

Disease Specific Survival



Disease Free Survival



- Questions or Comments…
- Please email me..
  - her2007@columbia.edu
  - (all feedback welcome… negative or positive.. your imput will help improve lectures for the next year of medical students…)