ENDOCRINE and EXOCRINE PANCREAS

PA Fundamentals of Surgery

EMBRYOLOGY

- Pancreatic buds (dorsal/ventral) form in 12-15 mm fetus
- Islets appear in 54 mm fetus
- Endocrine/Exocrine cells
  - Neural crest (early theory)
  - Embryonic foregut endoderm (now generally accepted

Anatomy

- Transverse retroperitoneal organ 18 cm long
- Head, Neck, Body and Tail
- Duct anatomy dependent on fusion of buds to form main duct and GI drainage
- 90% main duct drains into ampulla
- 10% - Pancreas divisum – ducts not fused – main duct thru accessory duct (Santorini)

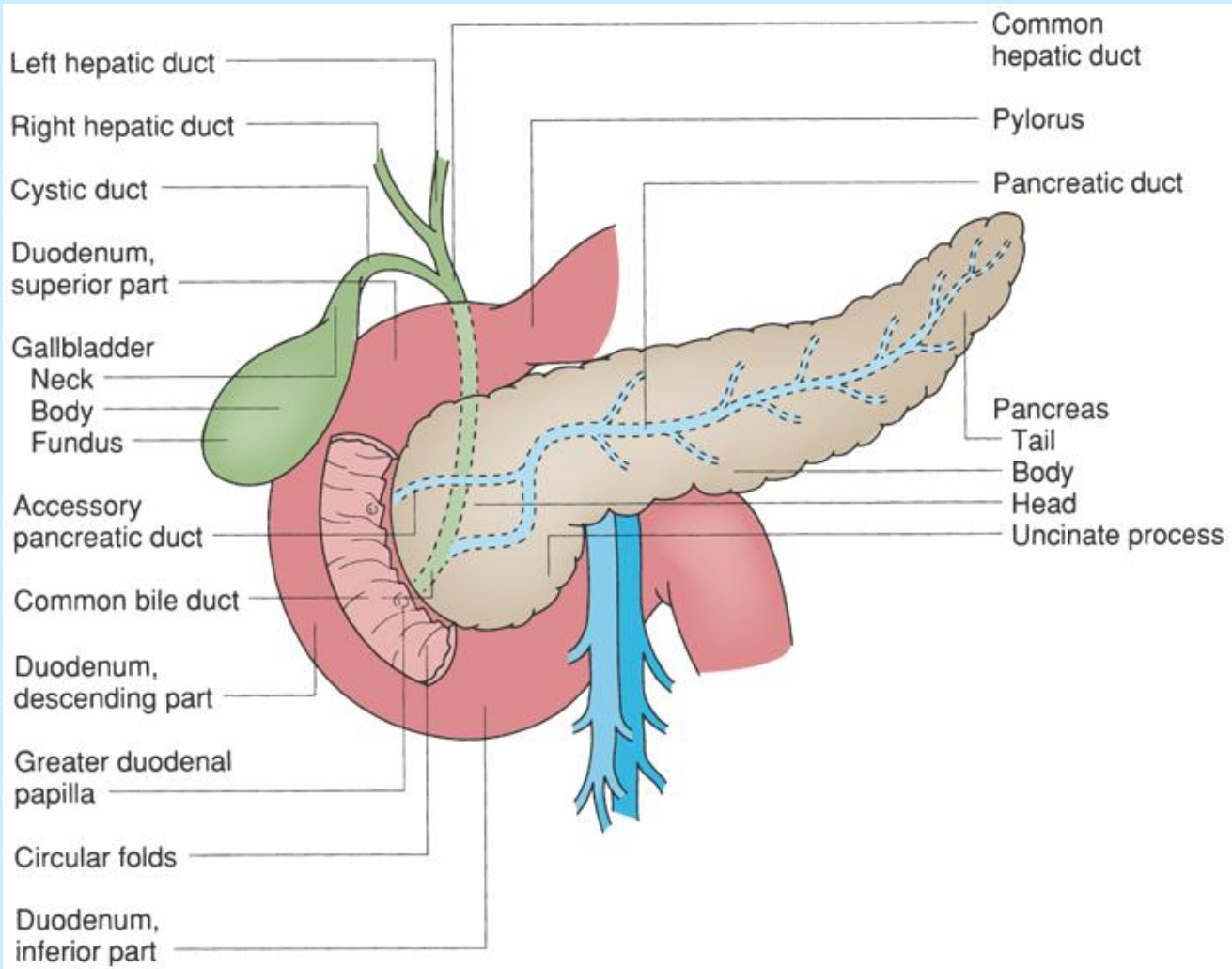


FIGURE 53.1 Relation of the pancreas to the duodenum and extrahepatic biliary system. (After Woodburne RT. *Essentials of human anatomy*. New York: Oxford University Press; 1973.)

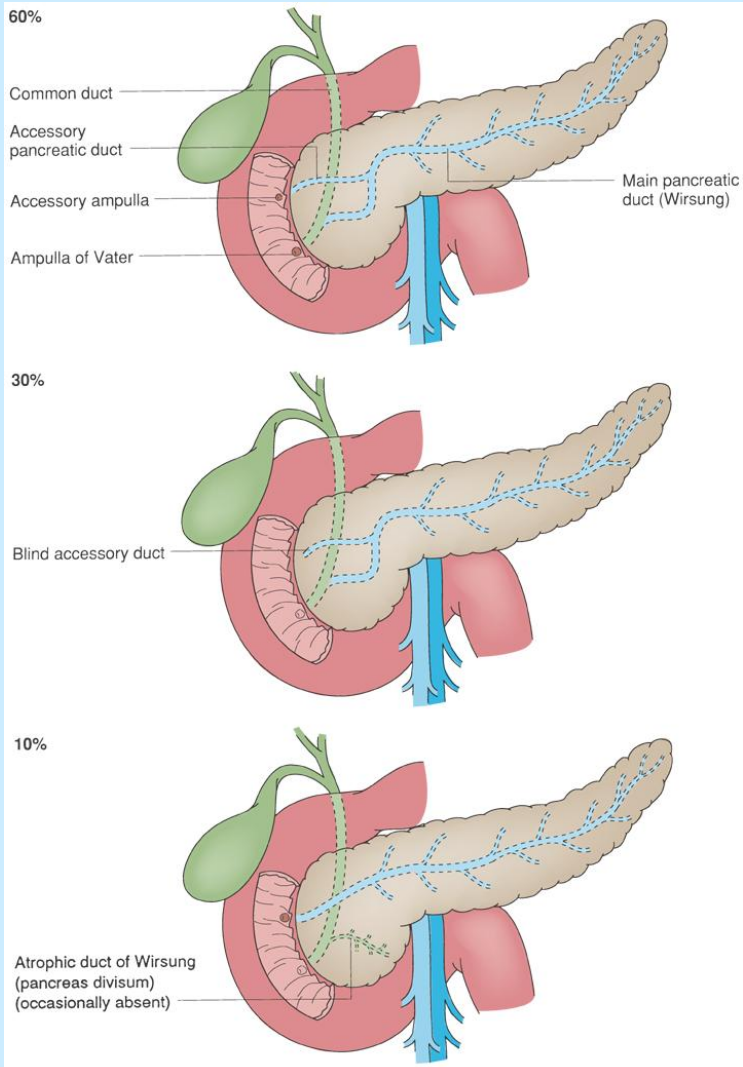


FIGURE 53.3 Anatomic configuration of the intrapancreatic ductal system. A lack of communication between the two ducts, which occurs in 10% of cases, is referred to as pancreas divisum. (After Silen W. Surgical anatomy of the pancreas. *Surg Clin North Am.* 1964;44:1253.)

Exocrine Function

- 1-2 liters alkaline fluid – elevated bicarb otherwise isotonic
- 20 enzymes or precursors
  - Amylase, lipase, trypsinogen, pepsinogen….
- Regulated by hormones
  - CCK
    - Peptides, AA and FFA
  - Secretin
    - Duodenal acid and CCK

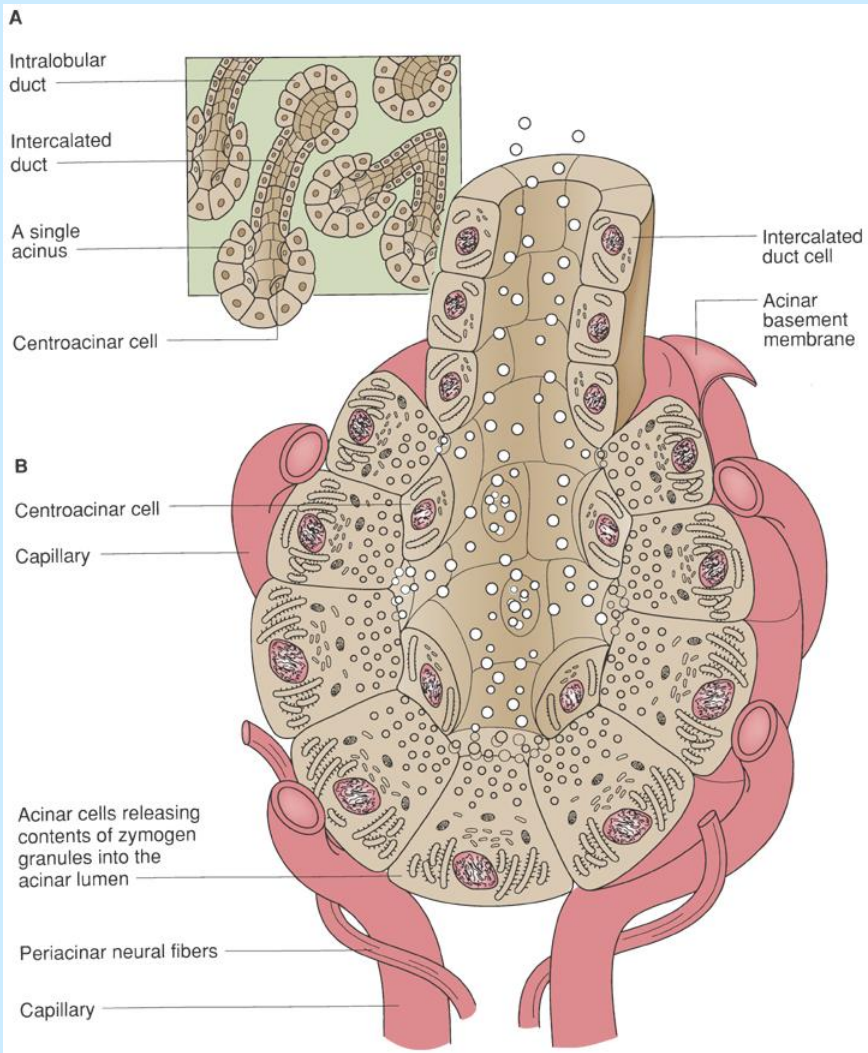


FIGURE 53.13 Histologic anatomy of the acinus. (*A*) Low-magnification view of a portion of the pancreas. (**B**) High-magnification view of a single acinus. (After Krstic RV. *Die Gewebes des Menschen und der Saugetiere*. Berlin: Springer-Verlag, 1978, with permission.)

ADULT PANCREAS

- Islet cells approx 2% of pancreatic mass (as opposed to 33% in mature fetus)
- 10^6 islets with 3000 cells/islet
- Four main cell types in islets
  - Alpha (periphery of islet)
  - Beta (center of islet)
  - Delta (periphery)
  - PP (periphery)
- Islets in:
  - Head/uncinate rich in PP cells, poor in Alpha cells
  - Body/tail rich in Alpha cells, poor in PP cells
  - Beta/Delta cells equally distributed

Physiology

INSULIN

- A and B side chains connected by disulfide bridge
- Joined by C-peptide in newly synthesized form (proinsulin)
- C-peptide cleaved in Beta cell, insulin stored in secretory granules
- Secreted insulin to portal system
  - ½ cleared by first pass through liver
- Incretins (stimulate insulin secretion): Glucose, Gastric Inhibitory Peptide, CCK
- Inhibitors: somatostatin, pancreastatin, amylin, leptin
- Function: increase glc trans into cells

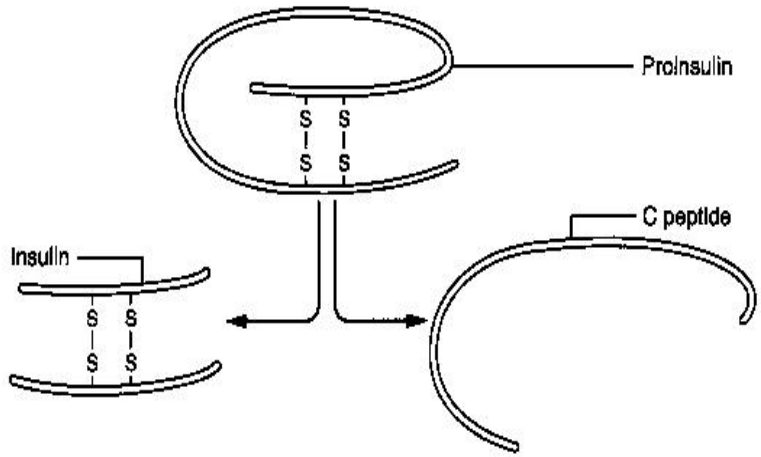


Figure 34–4. Diagram of insulin synthesis. Proinsulin, synthesized by the endoplasmic reticulum, is packaged within secretory granules of the B cell, where it is cleaved to insulin and C peptide. Equimolar amounts of insulin and C peptide are secreted to the bloodstream. (From Andersen DK, Brunicardi FC: Pancreatic anatomy and physiology. *In* Greenfield LJ, Mulholland MW, Oldham KT, et al [eds]: Surgery: Scientific Principles and Practice, 2nd ed. Philadelphia, Lippincott-Raven, 1997, p. 869.)

PHYSIOLOGY

Glucagon

- 29 amino acid peptide secreted by Alpha cells
- Function: promote hepatic glycogenolysis
- Secretagogues: low blood Glucose, sympathetic stimulation
- Inhibitors: high blood Glucose, Insulin, Somatostatin

PHYSIOLOGY

SOMATOSTATIN

- 14 amino acid peptide secreted by Delta cells
- Universal hormonal “off switch”
- Unknown whether hormone modulation via simple paracrine effect or via transport to other islet cells via islet portovenous system

PHYSIOLOGY

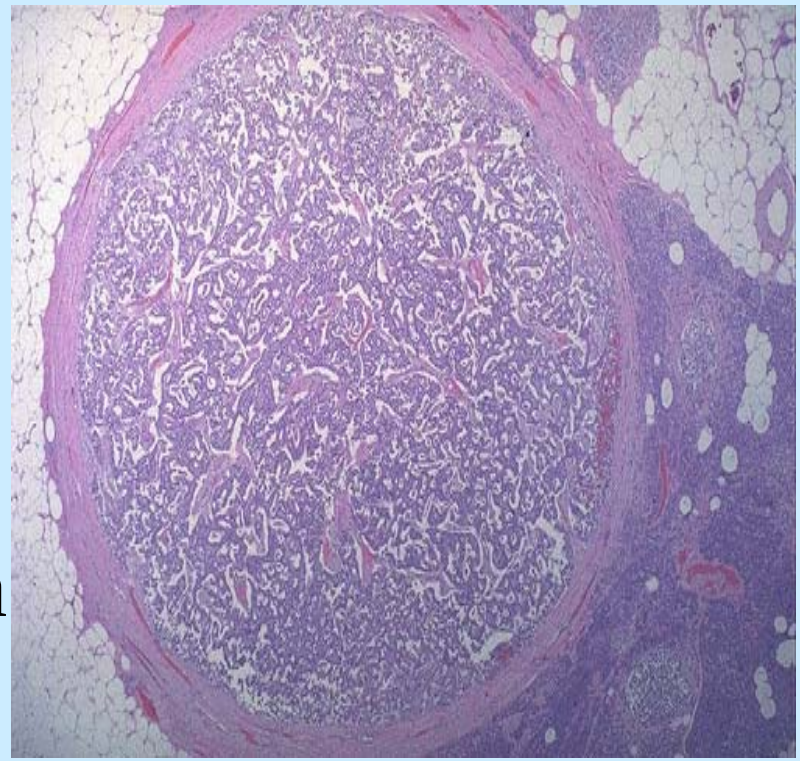
PANCREATIC POLYPEPTIDE

- 36 amino acid peptide secreted by PP cells (formerly known as F cells)
- Effects unknown
- Primarily seen as marker for other pancreatic endocrine tumors

PHYSIOLOGY

- VIP
  - Delta2 cells
  - Stimulates insulin, inhibits gastric secretions
  - Vasodilator/bronchodilator
- Amylin
  - Beta cells
  - Inhibits insulin secretion and uptake
- Pancreastatin
  - Part of chromogranin molecule found in envelope of secretory granules
  - Inhibits insulin secretion

Endocrine Neoplasms



- **<u>Insulinoma</u>**
- Arise from Beta cells
- Equally distributed throughout the pancreas
- 80% solitary and benign
- 15% malignant
- 5% associated with MEN-I, usually multiple

Endocrine Neoplasms (Insulinoma)

- Clinical Presentation - bizarre behaviour, memory lapse, unconsciousness, palpitations, nervousness, sweating, tachycardia
- Related to decreased cerebral glucose and activation of sympathetic nervous system

Endocrine Neoplasms (Insulinoma)

- *Whipple's Triad*
- 1) Hypoglycemic symptoms with fasting
- 2) Blood glucose below 50mg/dl during symptomatic episodes
- 3) Relief with glucose administration

Endocrine Neoplasms (Insulinoma)

- Fasting glucose - Patient fasted with blood samples q6hrs for glucose and insulin levels
- Ratio of insulin to glucose of > 0.3 is diagnostic
- Most are positive within 48hrs; test is carried out to 72hrs maximum
- Provocative testing: tolbutamide, leucine, arginine, calcium; diagnostic only 50% of the time

Endocrine Neoplasms (Insulinoma)

- **Treatment**
- Medical - frequent feedings with slowly absorbed carbohydrate, diazoxide (suppresses release of insulin), streptozocin if unresectable
- Surgical - enucleation, partial or distal pancreatectomy (up to 80%) if tumor is deep seated or cannot be localized, debulking if malignant

Endocrine Neoplasms (Insulinoma)

- **Pre - and intra-operative localization**
- CT scans - usually not seen as 40% < 1cm
- Selective angiography - 50% successful
- Percutaneous Transhepatic Venous Catheterization with sampling (hold diazoxide before testing)
- Intraoperative ultrasound

Endocrine Neoplasms

- **<u>Gastrinoma</u>**

- Most found in pancreas
- 60% non-beta islet cell carcinomas
- 25% solitary adenomas
- 10% microadenomas or hyperplasia
- 25% associated with MEN-I (usually multiple)
- Slow growing

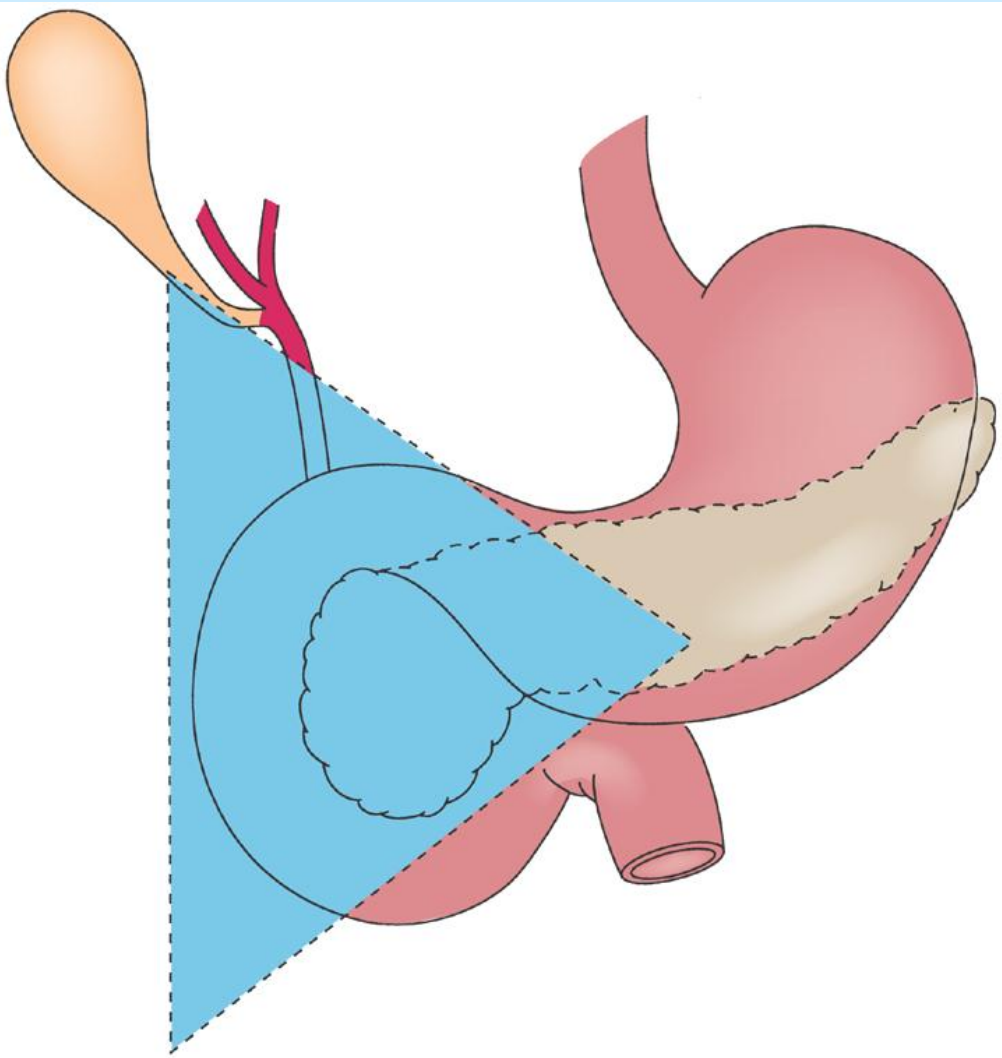


FIGURE 57.8 Most gastrinomas are found within the gastrinoma triangle. (After Stabile BE, Morrow DJ, Passaro E. The gastrinoma triangle: operative implications. *Am J Surg*. 1984;147:26, with permission.)

Endocrine Neoplasms (Gastrinoma)

- **<u>Clinical Manifestations</u>**

- Zollinger-Ellison syndrome: severe, refractory peptic ulcer disease and diarrhea
- 5% present with diarrhea alone
- Multiple ulcers or unusual locations (3rd and 4th portion of duodenum or proximal jejunum)
- Recurrent ulcers after surgical therapy

Endocrine Neoplasms (Gastrinoma)

- **<u>Diagnosis</u>**

- Fasting hypergastrinemia (>200pg/mL) with gastric acid hypersecretion (>15meq/h output with intact stomach or >5 after ulcer surgery)
- If gastrin 200-500pg/mL, a secretin provocative test is usually done

Endocrine Neoplasms (Gastrinoma)

- **Secretin test**

- 2 units/kg secretin given with a rise in gastrin of 200pg/mL within 15 mins or doubling of fasting gastrin is diagnostic

- **Other Diagnostic Tests**

- UGI, CT scan, angiography, portal venous sampling

Endocrine Neoplasms (Gastrinoma)

- **<u>Treatment</u>**

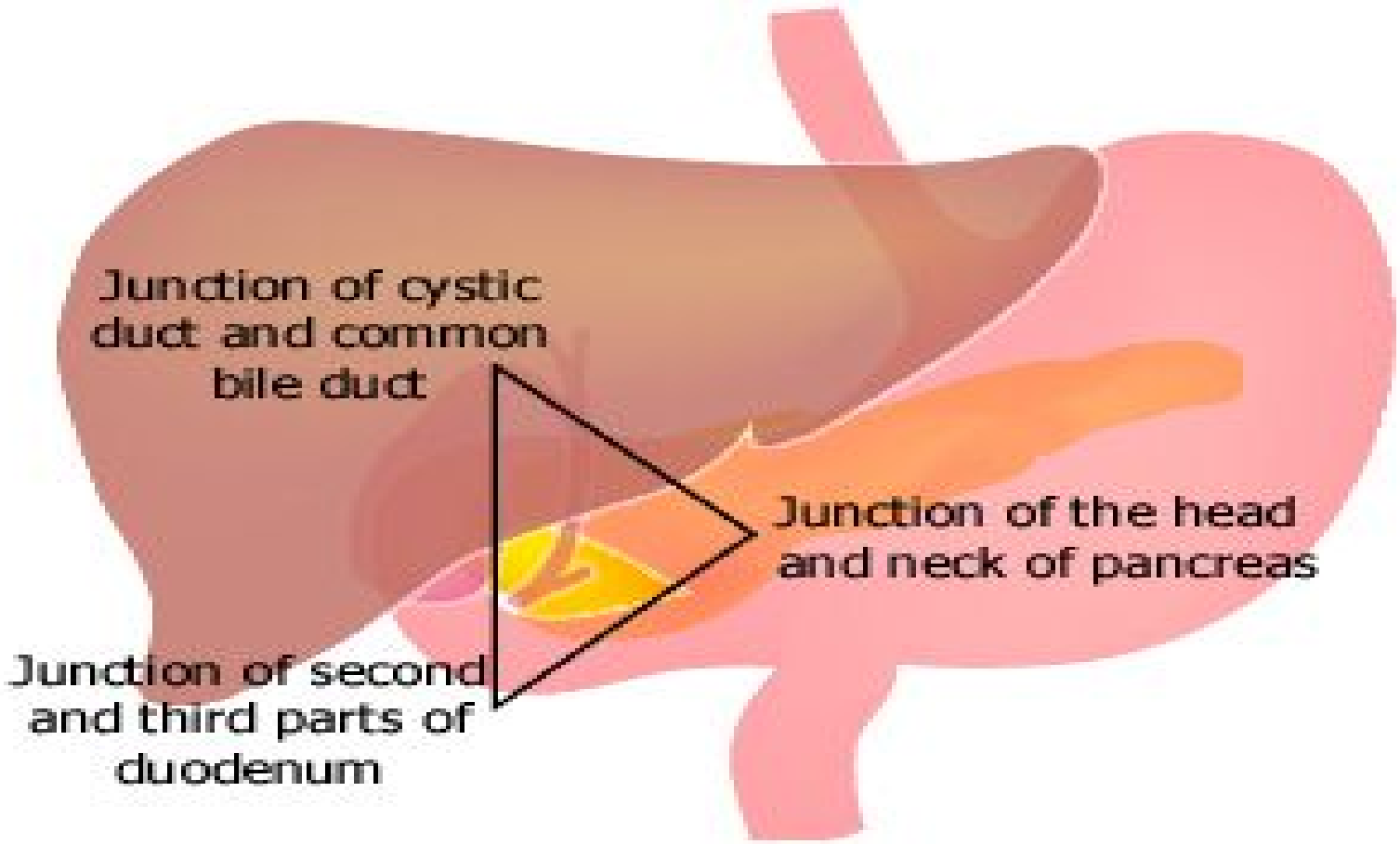
- **Medical**
- Omeprazole is the drug of choice; dose adjusted to keep basal output < 5meq/hr
- If malignancy, streptozocin and 5-FU with or without doxorubicin

Endocrine Neoplasms (Gastrinoma)

- **Surgical**
- If it is sporadic, then exploration is warranted.
- If associated with MEN, they are usually multiple and unable to be completely resected.
- Tumors can be enucleated

Endocrine Neoplasms (Gastrinoma)

- **Surgical (continued)**
- 90% found within the Gastrinoma Triangle
- Junction of cystic and common bile duct, junction of 2nd and 3rd portions of the duodenum, junction of the neck and body of the pancreas
- 1/3 are never found
- Total gastrectomy may be indicated if refractory to medical therapy or inability to totally resect the tumor


Junction of cystic duct and common bile duct
Junction of the head and neck of pancreas
Junction of second and third parts of duodenum

Endocrine Neoplasms

- **VIPoma (Verner-Morrison Syndrome, <u>WDHA Syndrome, Pancreatic Cholera)</u>**
- 80-90% of cases are associated with an intra-pancreatic tumor
- Extrapancreatic locations include the sympathetic chain and adrenal medulla
- 50% malignant and 75% of those have metastasized by diagnosis

Endocrine Neoplasms (VIPoma)

- **Clinical Manifestations**

- **W**atery **d**iarrhea high in potassium which results in **h**ypokalemia (2-3meq/L) and subsequent weakness
- 50% have gastric acid secretions, 50% do not (**a**chlorhydria)
- May have hypocalcemia secondary to PTH-like secretions
- Metabolic acidosis because of HCO^{3-} loss in the stool
- 15% with flushing (usually associated with diarrhea)
- Abnormal glucose tolerance due to altered insulin sensitivity

Endocrine Neoplasms (VIPoma)

- **<u>Diagnosis</u>**

- Elevated fasting VIP by radioimmunoassay
- PP and prostaglandin levels may be elevated with a normal VIP
- CT scan, angiography, transhepatic portal and splenic venous sampling

Endocrine Neoplasms (VIPoma)

- **Treatment**

- **Medical**
- Correction of dehydration and electrolyte imbalances
- Somatostatin trial preoperatively
- If metastatic or inoperable, streptozocin with or without 5-FU
- Symptomatic relief noted occasionally with high dose steroids or trifluoperazine

Endocrine Neoplasms (VIPoma)

- **Surgical**
- Tumor resection if located, otherwise explore sympathetic chain and adrenals.
- 80% pancreatectomy if unable to find the tumor
- Tumor debulking if metastatic
- **Prognosis:** if malignant, survival is ~1 yr; benign disease can be cured surgically

Endocrine Neoplasms

- **<u>Glucagonoma</u>**

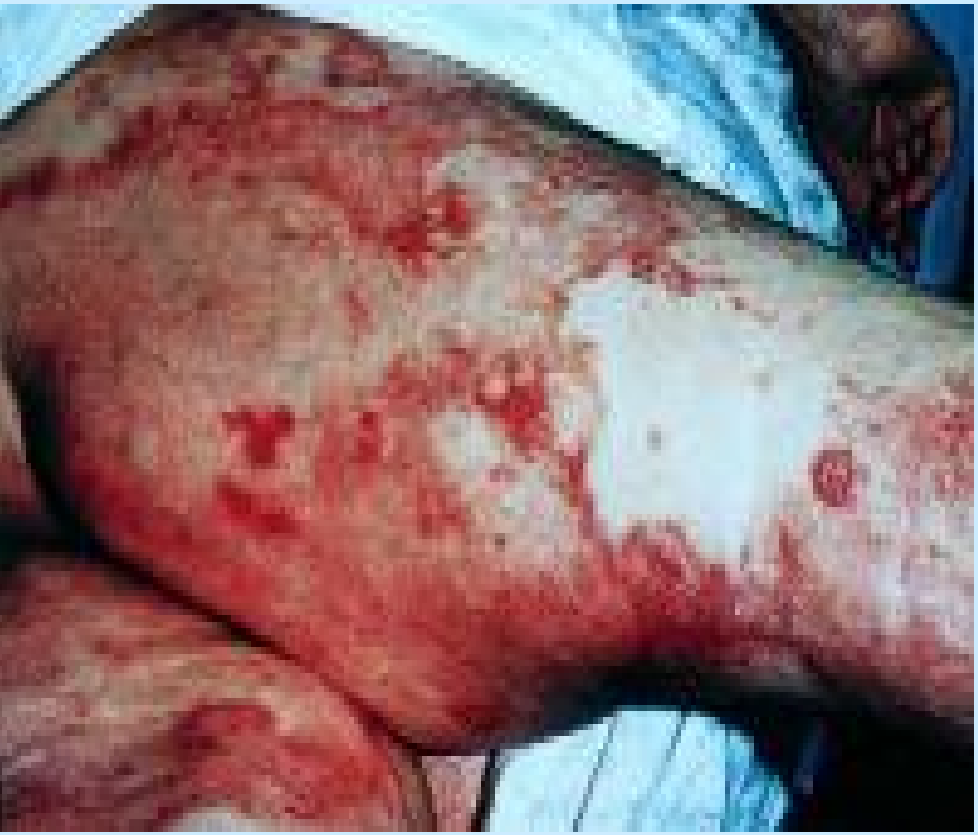
- Alpha-2 cell derivative
- More common in women
- Age 20-70
- 75% malignant, 25% benign
- Majority have metastasized by diagnosis

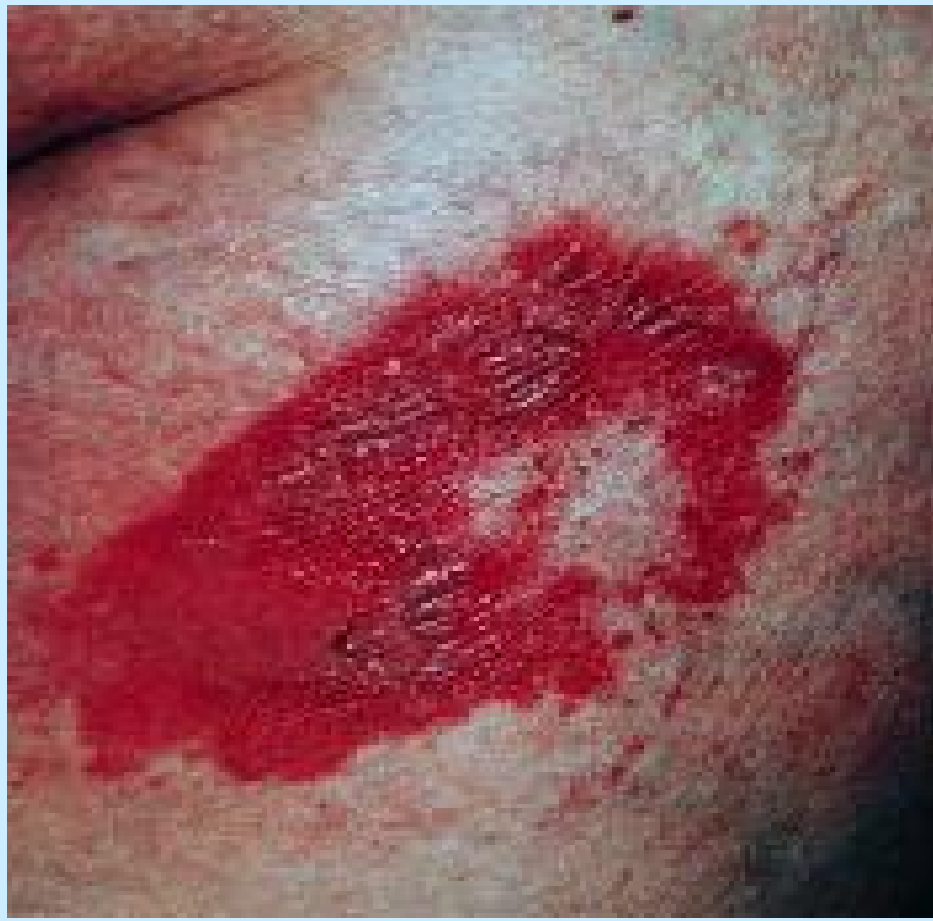
Endocrine Neoplasms (Glucagonoma)

- **Clinical Manifestations**

- Migratory necrolytic dermatitis usually on legs and perineum
- Weight loss, stomatitis, anemia, diabetes, hypoaminoacidemia, visual scotoma, increased tendency towards venous thrombosis and PE

Migratory Necrolytic Dermatitis





Endocrine Neoplasms (Glucagonoma)

- **Diagnosis**

- Elevated plasma glucagon levels
- CT scan and occasionally arteriography

- **Treatment**

- **Medical** – oral zinc for dermatitis, somatostatin; streptozocin and dacarbazine if malignant
- **Surgical** – excision of tumor or debulking of metastases

Endocrine Neoplasms

- **<u>Somatostatinoma</u>**

- Most located within pancreatic head
- Most malignant
- Most with metastases (primarily to liver) at diagnosis

Endocrine Neoplasms (Somatostatinoma)

- **Clinical Manifestations**

- Weight loss, mild diabetes mellitus, malabsorption and diarrhea, dilatation of the gallbladder with or without cholelithiasis

- **Diagnosis**

- Elevated serum somatostatin levels
- CT scan (mass in the head of the pancreas)

Endocrine Neoplasms (Somatostatinoma)

- **Treatment**

- **Surgery** occasionally indicated if disease is localized
- **Medical** therapy primarily consisting of streptozocin, dacarbazine, doxorubicin independently or in combination

Endocrine Neoplasms

- **Miscellaneous Tumors**

- PPomas, Calcitonin-secreting tumors, Carcinoid (5-hydroxytryptophan secreting) tumors
- Related to pancreatic islet role in Amine Precursor Uptake and Decarboxylation (APUD) system

Exocrine Tumors

- Adenocarcinoma – 30,000 cases/year; 30,000 deaths/year
- Age and Smoking risk factors
- Present as painless jaundice and weight loss
  - Couvoisier's sign
- Usually present late

Diagnosis

- Ultrasound
  - Dilated ducts
- CT
  - Pancreatic mass and nodes
  - Arterial anatomy
- MRCP
  - Ductal anatomy
- ERCP/EUS
  - Same

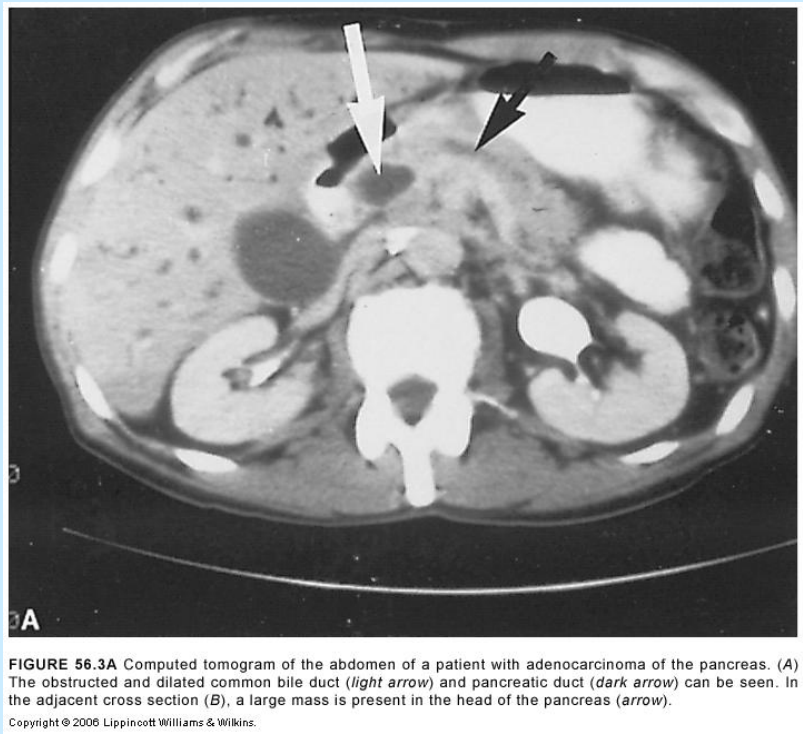


FIGURE 56.3A Computed tomogram of the abdomen of a patient with adenocarcinoma of the pancreas. (*A*) The obstructed and dilated common bile duct (*light arrow*) and pancreatic duct (*dark arrow*) can be seen. In the adjacent cross section (*B*), a large mass is present in the head of the pancreas (*arrow*).

Treatment

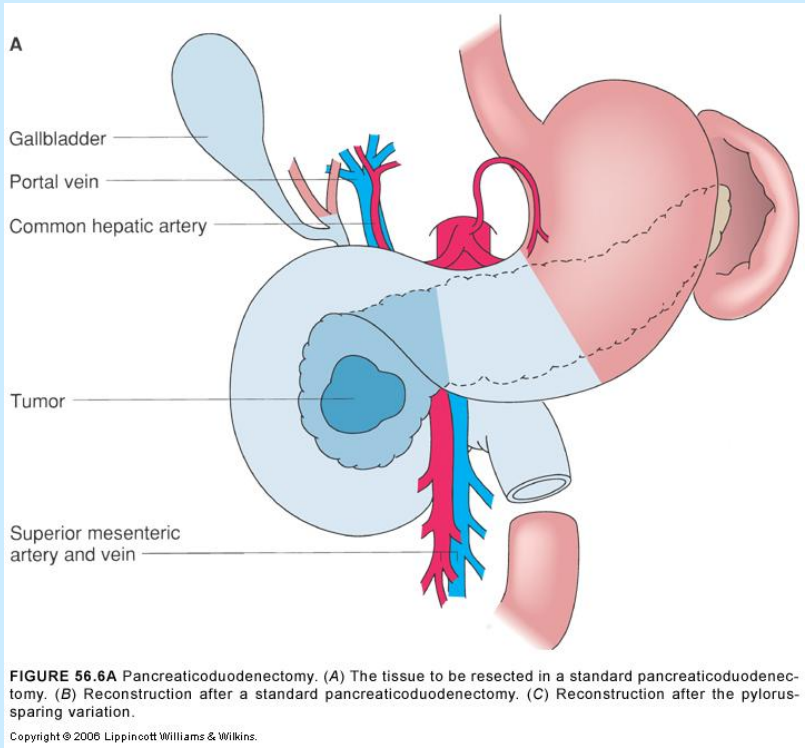


FIGURE 56.6A Pancreaticoduodenectomy. (*A*) The tissue to be resected in a standard pancreaticoduodenectomy. (*B*) Reconstruction after a standard pancreaticoduodenectomy. (*C*) Reconstruction after the pylorus-sparing variation.

- Exploration
- Pancreatico-duodenectomy
- Diversion/Palliation
- Surgery only chance for cure
- Most die from recurrence in less than one year

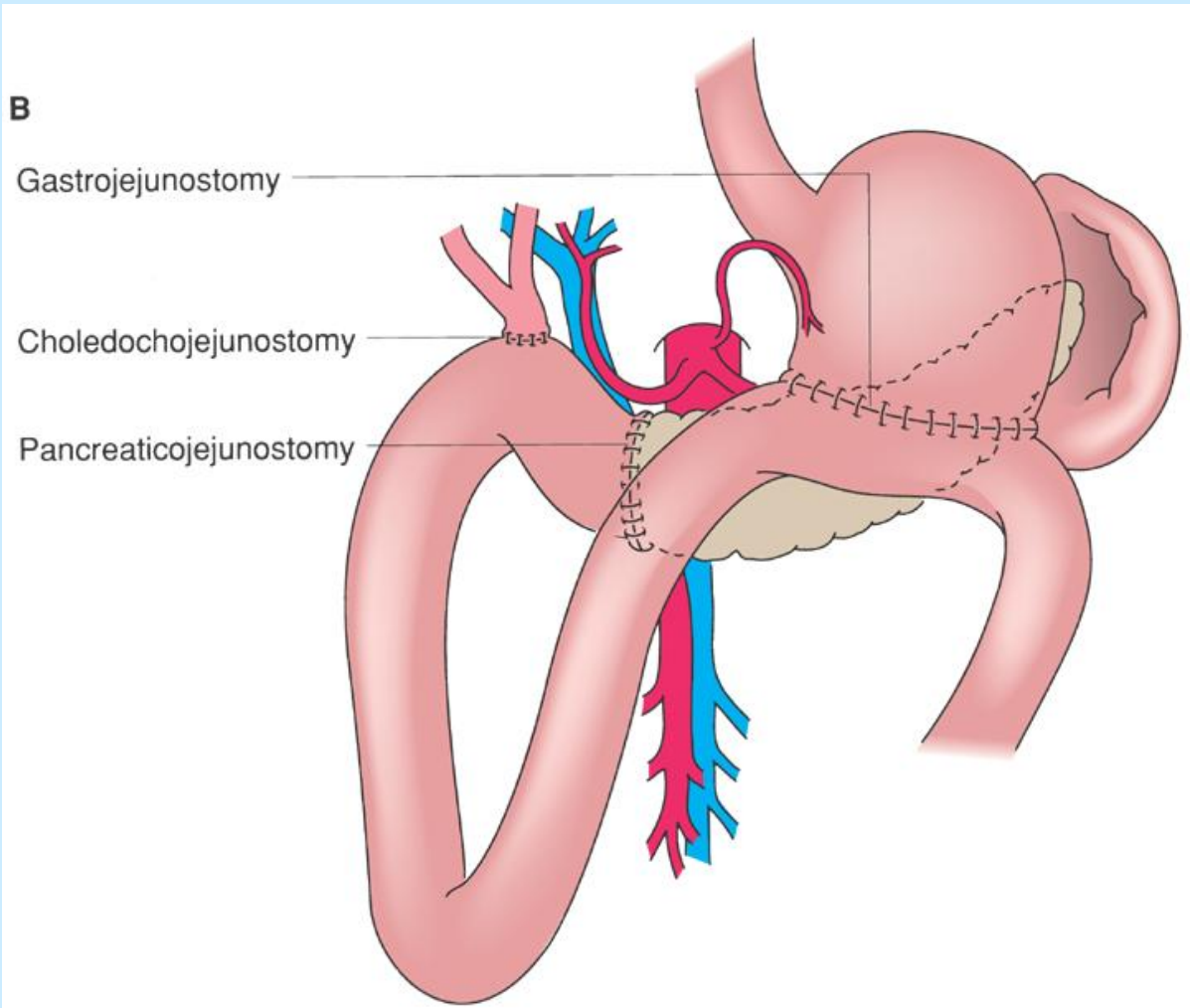


FIGURE 56.6B Pancreaticoduodenectomy. (*A*) The tissue to be resected in a standard pancreaticoduodenectomy. (*B*) Reconstruction after a standard pancreaticoduodenectomy. (*C*) Reconstruction after the pylorus-sparing variation.

Cystic Tumors

- Benign
  - Papillary
    - Young women, great prognosis with resection
  - Cystadenoma - resect
    - Mucinous – common, women . men
    - Serous
- Malignant
  - Cystadenocarcinoma – resect – good survival

Pancreatitis

- Acute
  - Single event
    - Majority - gallstones
- Acute relapsing
  - No damage
- Chronic relapsing
  - Damaging, but intervals without
- Chronic
  - Irreversible

Presentation and W/U

- Severe epigastric pain
  - Provoking events
- Upright and moving
- +/- Rebound, distension
  - Cullen's, Grey – Turner's
- Amylase, lipase, WBC
- U/S, CXR, CT abdomen and pelvis

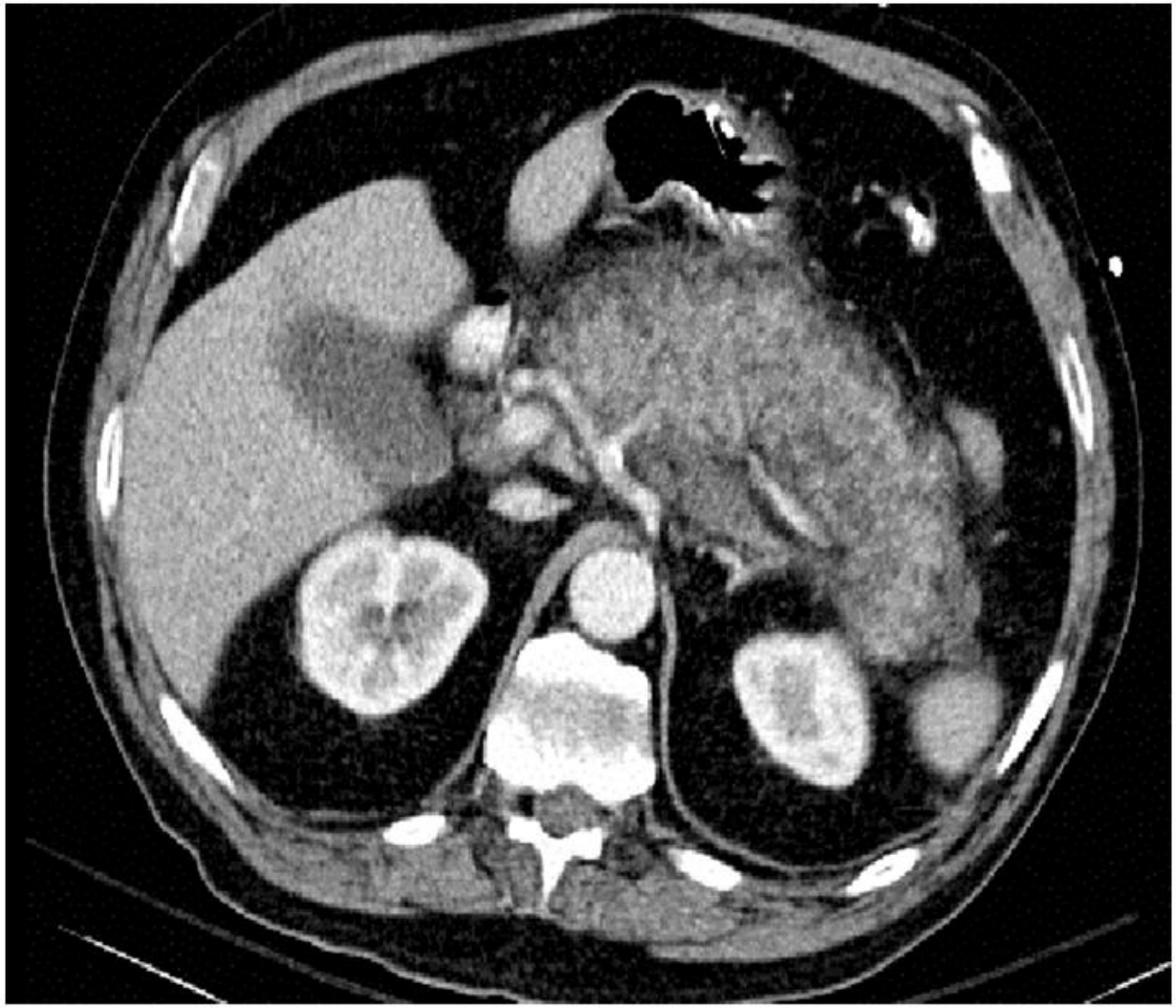


FIGURE 54.3 Computed tomography scan of acute interstitial pancreatitis.

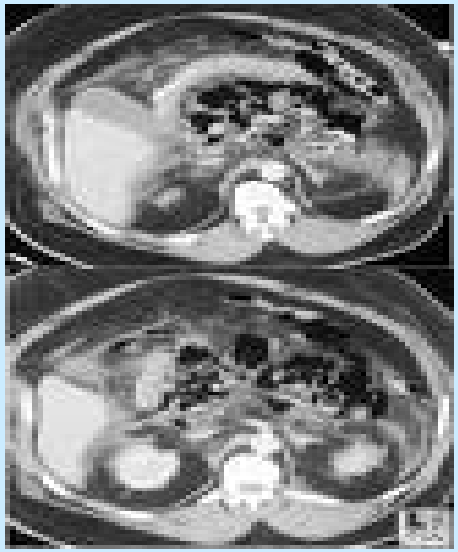
Ransons's Criteria

On Admission	Within 48 Hours
Age >55 years	Drop in hematocrit >10%
WBC >16,000/mm^3	Fluid deficit >6 L
Serum glucose>200 mg/dl	Serum calcium<8.0 mg/dl
Serum LDH>350 mg/dl	Hypoxemia (pO_2 <60 mm Hg)
Serum AST >250 IU/L	Rise in BUN >5 mg/dl
	Albumin <3.2 g/dl

Treatment

- Supportive
  - Analgesia and Fluids
- Causative
  - Biliary and abstinence
- Monitored
  - Complications and chronicity

Complications



- Critical Care issues
  - MSOF
- Pancreatic Necrosis
  - Serial CT
- Pancreatic abscess
  - Surgical Drainage
- Pseudocysts
  - > 6 weeks of symptoms

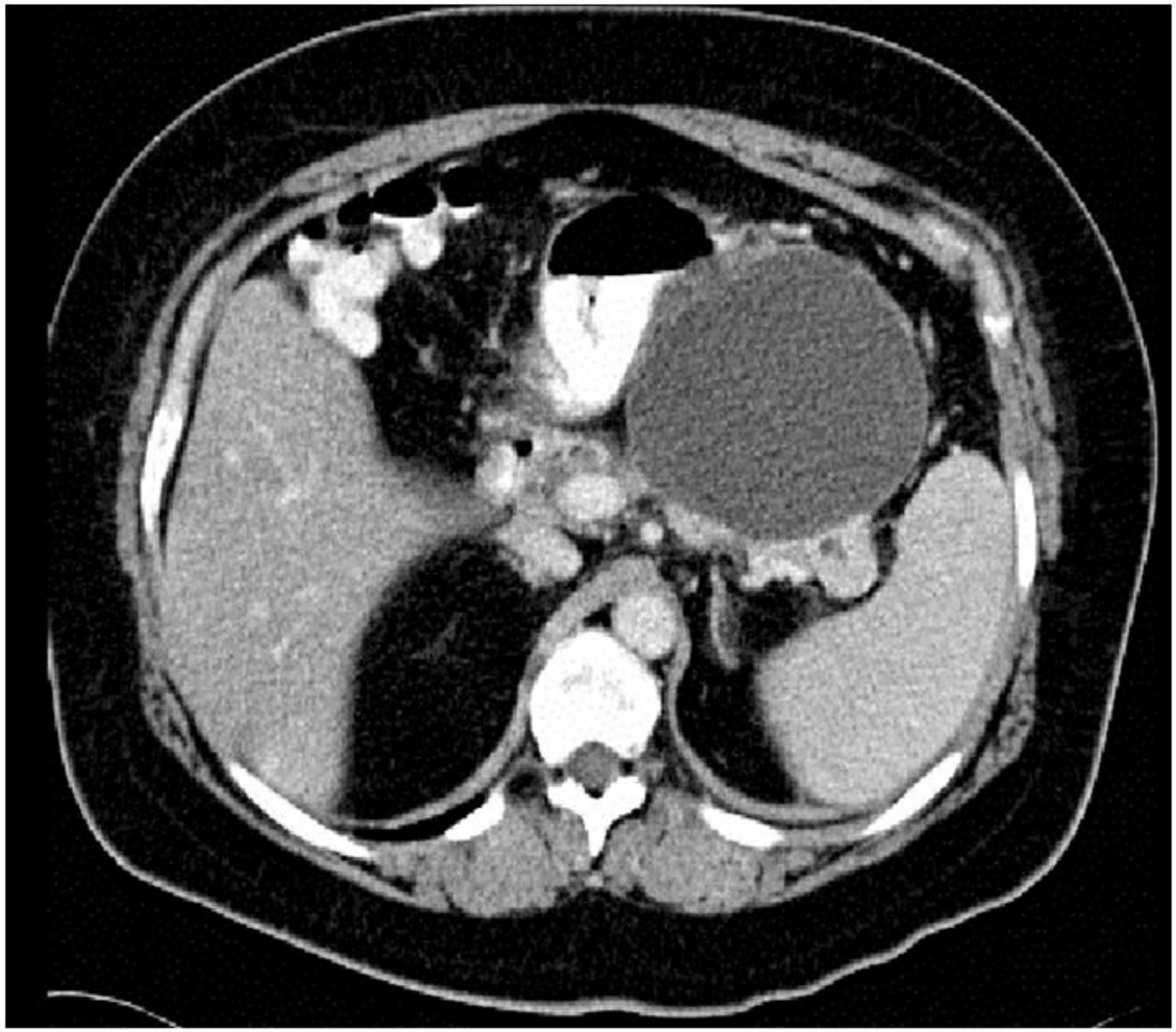


FIGURE 54.5 Computed tomography scan of pancreatic pseudocyst.

Pseudocyst treatment

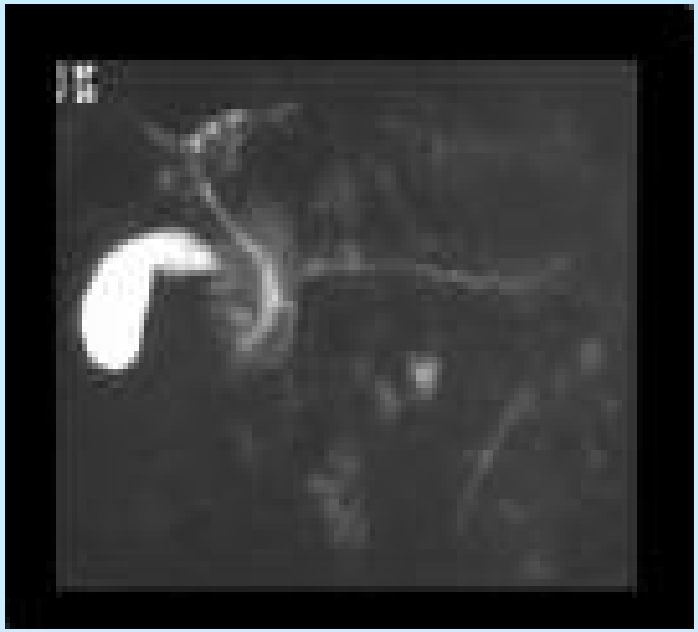
- Observation
- Internal Drainage
  - ERCP/sphnicterotomy
  - Cyst - ostomy
- External Drainage
- Complications of cysts
  - Infection and hemorrhage

Chronic Pancreatitis

- Usually alcohol abuse
- Chronic pain, endo- and exocrine gland dysfunction
- Treatment medical
- Surgery only for failure of medical management or obstruction

Evaluation

- ERCP/MRCP
- Outline ductal anatomy
- Stenosis
  - Ampullary
  - Single site
  - Chain of lakes



Treatment

- Drainage
  - Puestow – lateral pancreaticojejunostomy
- Adjunctive
  - Injection of celiac plexus
  - Splanchnesectomy
- Resection
  - Partial/Total
    - Outcomes Dismal – pain still there + diabetes worse