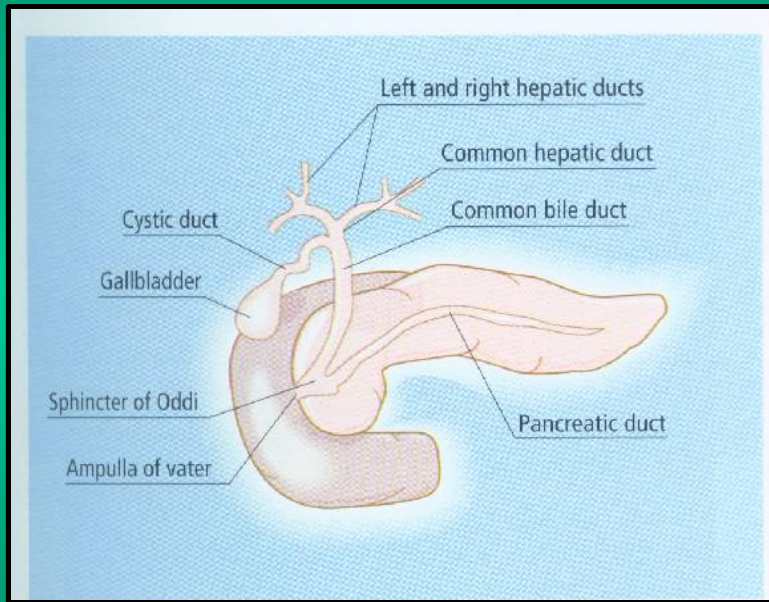


NORMAL ANATOMY OF BILIARY TREE



The normal **gallbladder** is a thin-walled sac with A 50-ml capacity. Located under the right lobe of the liver in the gallbladder fossa, it consists of fundus, body and neck. The gallbladder is connected (via the **cystic duct**) to the **common hepatic duct** to form the **common bile duct**. The bile duct continues for 7 to 9 cm, passing through the pancreas into the duodenal wall, where it usually *joins the pancreatic duct* to form a **common chanel** before emptying into the duodenum at the ampulla of Vater; or the ducts enter the duodenum separately.

HISTOLOGY OF BILIARY TREE

THE GALLBLADDER

- b) an inner mucosa (columnar epithelial lining and lamina propria)
- c) a muscular layer
- d) a perimuscular layer of loose connective tissue
- e) a covering of peritoneum (serosa), except in hepatic bed

BILE DUCT

-mucosa – a single layer of tall columnar epithelium connects with

subepithelial mucous glands.

-a supportive framework of connective tissue with rare smooth muscle

fibers.



DISORDERS OF THE BILIARY TRACT

DISORDERS OF THE GALLBLADDER

- cholelithiasis (gallstones)
- cholecystitis

DISORDERES OF EXTRAHEPATIC BILE DUCTS

- choledocholithiasis and ascending cholangitis
- biliary atresia

TUMORS

- carcinoma of the gallbladder

- extremely common
- >95% is cholelithiasis (gallstones) and/or cholecystitis (gallbladder inflammation)
- annual cost of managing is 6 billion dollars (represent 1% of the US health care budget)

CHOLELITHIASIS (GALLSTONES)

FREQUENCY

- afflict **10%** of adult populations in northern hemisphere Western countries (Latin American)
 - over *20 million* patients are estimated to *have* gallstones
 - about *1 million new* patients annually are found to have gallstones, of whom two thirds undergo surgery
 - overall surgical mortality is very low, but approximately *1000 patients die* per year from gallstone disease or complications of surgery
- a significant health burden

DIAGNOSIS

- ultrasonography (it detects virtually all stones greater than 3 mm in diameter)
- 10%-20% of gallstones are radiopaque (mixed cholesterol, black pigmented stones)

CHOLELITHIASIS (GALLSTONES) (pathogenesis)

Bile is a carrier fluid for elimination of excess cholesterol and bilirubin from the body.

CHOLESTEROL STONES (85%)

-cholesterol is water insoluble and is rendered water soluble by aggregation with bile salts and lecithins cosecreted into bile.

-when cholesterol concentrations exceed the solubilizing capacity of the bile, cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals

-Three conditions necessary for formation of cholesterol stones:

1) bile must be **supersaturated** with cholesterol

(failure of the liver to provide enough bile salts and lecithin; increased hepatic synthesis of cholesterol)

2) initial **nucleation** step, around a calcium crystal nidus

3) cholesterol crystals must remain in the gallbladder **long enough** to agglomerate into stones

PIGMENTED STONES (15%)

-is based on the presence in the biliary tree of **unconjugated bilirubin** (poorly soluble in water) and precipitation of calcium bilirubin salts.

-formation of unconjugated bilirubin in biliary tree promotes:

- infection with E. Coli, Ascaris lumbricoides, or the liver fluke Opisthorchis sinensis
- chronic hemolytic conditions

CHOLELITHIASIS (GALLSTONES) (risk factors)

Table 16-10. RISK FACTORS FOR GALLSTONES

Cholesterol Stones

Demography: Northern Europe, North and South America, Native Americans, Mexican Americans

Advancing age

Female sex hormones

Female gender

Oral contraceptives

Pregnancy

Obesity

Rapid weight reduction

Gallbladder stasis

Inborn disorders of bile acid metabolism

Hyperlipidemia syndromes

Pigment Stones

Demography: Asian more than Western, rural more than urban

Chronic hemolytic syndromes

Biliary infection

Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency

However, 80% of patients with gallstones have **no identifying risk factors** other than age and gender

CHOLELITHIASIS (GALLSTONES) (morphology)

CHOLESTEROL STONES

- arise in the gallbladder
- pure** cholesterol stones - **pale yellow**
(RADIOLUCENT)
- mixed** (increased proportion of calcium carbonate, phosphates, and billirubin)
gray-white to black discoloration
(RADIOPAQUE)
- ovoid and firm
- single or multiple (faceted surfaces)

PIGMENT STONES

- arise anywhere in the biliary tree
- black** pigment stones - in sterile gallbladder, are small, multiple, and crumble easily.
- contain calcium salts of unconjugated billirubin and lesser amounts of other calcium salts, mucin glycoproteins and cholesterol. (RADIOPAQUE-75%)
- brown** - in infected intrahepatic or extrahepatic ducts, single or few in number
- soft with a greasy soap like consistency owing to the presence of retained fatty acid salts released by the action of bacterial phospholipases on biliary lecithins. (RADIOLUCENT)

CHOLELITHIASIS (GALLSTONES) (clinical features)

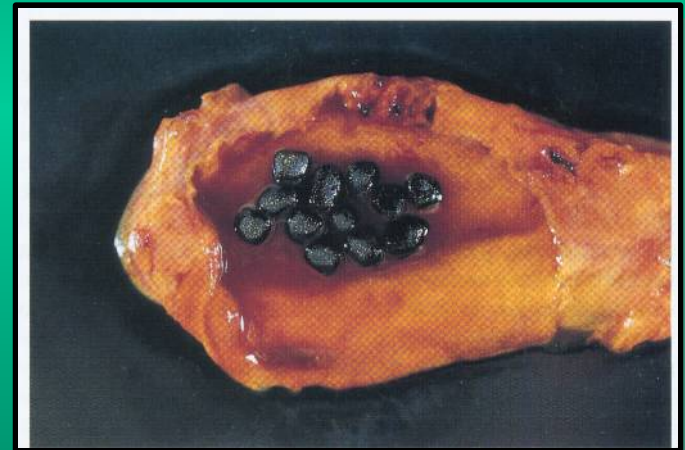
- 70%-80% patients remain asymptomatic through life
- convert to symptomatic ones at the rate of 1% to 3% per year and the risk diminished with time
- symptom: spasmodic “colicky” pain, owing to obstruction of bile ducts by passing stones. Gallbladder obstruction per se generates right upper abdominal pain.
- more severe complications:
 - gallbladder inflammation (cholecystitis), empyema, perforation, fistulas, biliary tree inflammation (cholangitis)
 - obstructive cholestasis or pancreatitis
 - erosion of a gallstone into a adjacent bowel (gallstone ileus)
 - clear mucinous secretions in an obstructed gallbladder (mucocele)

CHOLELITHIASIS (GALLSTONES) (clinical features)



CHOLESTEROL GALLSTONES

Fragmentation of several gallstones revealing the interiors that are pigmented because of entrapped bile pigments.



PIGMENTED GALLSTONES

Several faceted black gallstones from a patient with a mechanical mitral valve prosthesis, leading to chronic intravascular hemolysis

ACUTE CHOLECYSTITIS

- almost always is a consequence of cholelithiasis;
 - occurs as a complications of other serious illness or trauma (few cases)

PATHOGENESIS

- acute **calculous** cholecystitis: 90%-95%

act

-initiated by **gallstone impaction** in the gallbladder neck or the cyst duct. The **bile** becomes increasingly concentrated and as a **chemical irritant**. The obstruction leads to increased **intraluminal pressure**, vascular compromise, necrosis, and often, secondary bacterial invasion.

- acute **acalculous** cholecystitis: 5%-10%

one or more different mechanisms (e.g., ischemia, bacterial infection) in a variety of conditions (diabetes mellitus, shock, arteritis, sepsis, trauma, burns and AIDS)

CLINICAL FEATURES

- women (1,5 times more likely), 60 years
- right upper quadrant pain** (when the patient take a deep breath - Murphy's sign)
- nausea, vomiting, fever, slight jaundice**
- ↑ serum bilirubin

ACUTE CHOLECYSTITIS

PATHOLOGY

Macroscopic examination: enlarged, tense gallbladder, bright red to blotchy green-black with a serosal covering of fibrin.

Lumen is filled with a turbid bile that may contain fibrin, hemorrhage and frank pus.

Empyema of the gallbladder - (pure pus in lumen)

Gangrenous gallbladder - green-black necrotic walls in 90% -stones are present

Microscopically: acute inflammation + vascular congestion and edema. Mucosal erosion deeper ulceration and foci of necrosis may occur

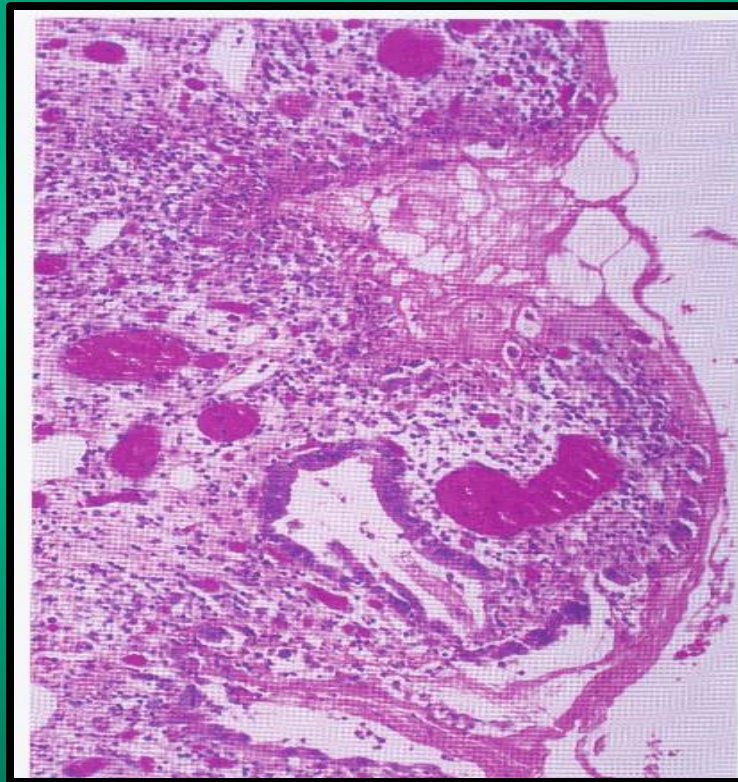
CLINICAL COURSE

-usually resolves (when a stone falls back into the gallbladder or when the pressure forces the stone past the obstruction in the duct) but may become chronic

THERAPY

-cholecystectomy

ACUTE CHOLECYSTITIS



The mucosa is congested, edematous, and infiltrated with neutrophils. The surface epithelium has focally undergone necrosis, and the luminal side of the gallbladder is covered with fibrin.

ACUTE CHOLECYSTITIS

COMPLICATIONS

inflammation progresses ⇒ mural blood vessels may become thrombosed ⇒ GANGRENE
⇒PERFORATION
(mortality rates 30%)

CHRONIC CHOLECYSTITIS

- may arise from repeated bouts of symptomatic acute cholecystitis or it develops without any history of acute attacks
- is almost always associated with gallstones, do not seem to play a direct role in the initiation of inflammation
- patient population and symptoms are the same as for the acute form.

MORPHOLOGY

Macroscopic findings: gallbladder may be contracted (from fibrosis)

normal in size or

enlarged (from obstruction)

mucosa generally is preserved but may be atrophied

stones are frequent

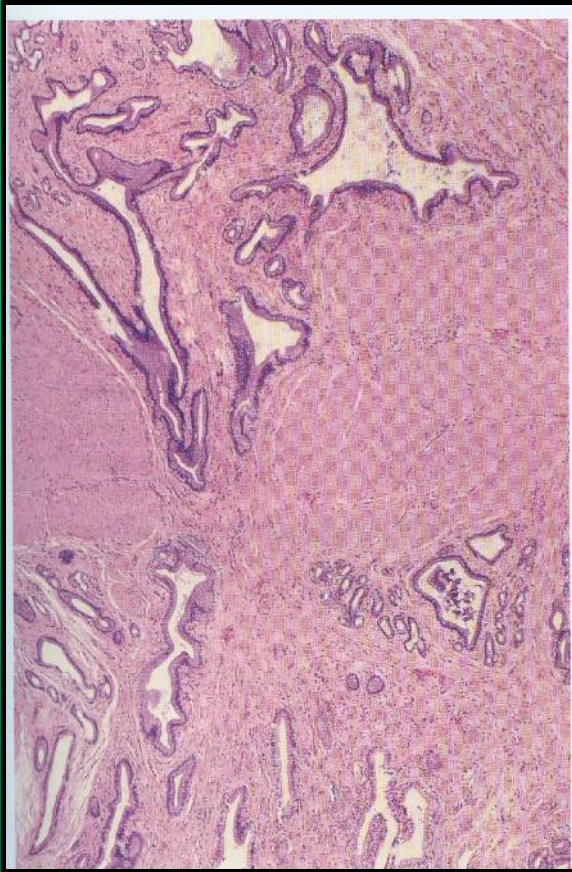
Microscopically: mononuclear inflammation + fibrosis

histiocytic inflammation - *Xanthogranulomatous cholecystitis*

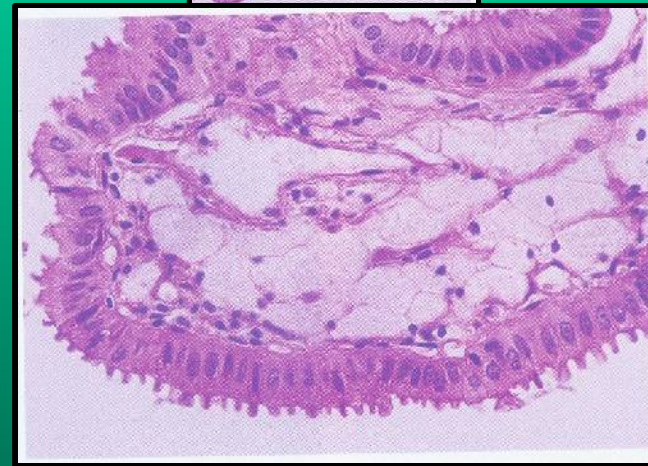
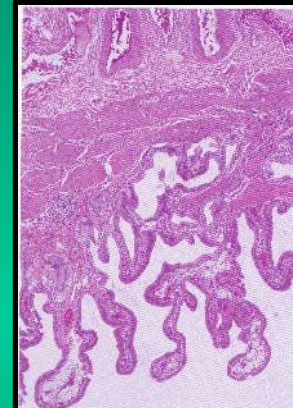
mucosal outpouchings through the wall -*Rokitansky-Ashoff sinuses*

mural dystrophic calcification -*porcelain gallbladder*

CHRONIC CHOLECYSTITIS



The epithelium of glands forms **Rokitansky-Aschoff sinuses** that extend into the thickened muscle layer.



Cholesterolosis: the lamina propria of the gallbladder mucosa contains lipid-laden macrophages.

DISORDERS OF EXTRAHEPATIC BILE DUCTS

1. BILIARY ATRESIA

2. CHOLEDOCHOLITHIASIS AND ASCENDING CHOLANGITIS

BILIARY ATRESIA

- is complete obstruction of bile flow owing to destruction or absence of all part of the extrahepatic ducts (between major hepatic or common bile ducts and duodenum), resulting in persistent conjugated hyperbilirubinemia
- occurs in 1 in 10,000 live births

PATHOGENESIS

- intact biliary tree at birth, progressive inflammatory destruction following birth
- cause is unknown (viruses and maternal alcohol use are suggested)

MORPHOLOGY

- inflammation and fibrosing stricture of both extrahepatic and with progression of disease, intrahepatic biliary tree
- Liver shows features of bile duct obstruction: bile ductular proliferation, portal tract edema and fibrosis progressing to cirrhosis within 3-6 month

CLINICAL FEATURE

- neonatal cholestasis in an infant with normal birth weight and postnatal weight gain
- persistent conjugated (direct) hyperbilirubinemia (only a few weeks after birth)

TREATMENT

- untreated, death occurs within 2 years of life
- surgery, usually Kasai procedure (portoenterostomy) should be performed by 10-12 weeks of life.
- hepatic transplantation (5 year survival rate >75%)

CHOLEDOCHOLITHIASIS AND ASCENDING CHOLANGITIS

CHOLEDOCHOLITHIASIS- the presence of stones within the biliary tree

Western nations: cholesterol stones derived from the gallbladder

Asia: pigmented stones, usually primary in the ducts

clinical features : pain, jaundice, fever

course and complications: unrelieved obstruction ⇒ infection, liver abscess

to secondary biliary cirrhosis

recurrent attacks of obstruction ⇒ fibrosis, stricture and

stenosis of the sphincter Oddi and cause

acute or relapsing pancreatitis

CHOLANGITIS-bacterial infection of the bile ducts

causes: usually arises in the setting of choledocholithiasis

uncommon causes- indwelling stents or catheters, tumors, acute

pancreatitis, benign strictures

ascending bacteria (E. coli, Klebsiella, other coliforms) entering the biliary

tract through the sphincter of Oddi

TUMORS OF BILIARY TREE

TUMORS OF THE GALLBLADDER

1. Benign tumors

- a) Nonneoplastic tumors: -cholesterol polyps
-inflammatory, lymphoid, hyperplastic polyps
- b) True benign epithelial neoplasms: adenomas

2. Malignant tumors

- a) Carcinoma

TUMORS OF THE BILE DUCTS

1. Benign tumors

- a) granular cell tumor, fibroma, leiomyoma
- b) adenomas

2. Malignant

- a) Carcinoma

CARCINOMA OF THE GALLBLADDER

- fifth** most common cancer of the digestive tract
- slightly more common in **women**
- most often in **seventh decade**
- gallstones coexist in 60% to 90% of patient in Western nations
- pyogenic and parasitic diseases in Asian populations

MORPHOLOGY:

Two patterns of growth: (1) infiltrating (diffuse thickening and induration of gallbladder)
(2) fungating (growth into the lumen as an irregular, cauliflower-like mass)

Histologic type: **adenocarcinoma** (patterns of papillary and/or infiltrating architecture, moderately to poorly differentiated to undifferentiated)

squamous, adenosquamous, carcinoid, mesenchymal

Patterns of spread: local invasion of liver,
extension to cystic duct and portohepatic lymph nodes
spreading of peritoneum, viscera, lungs

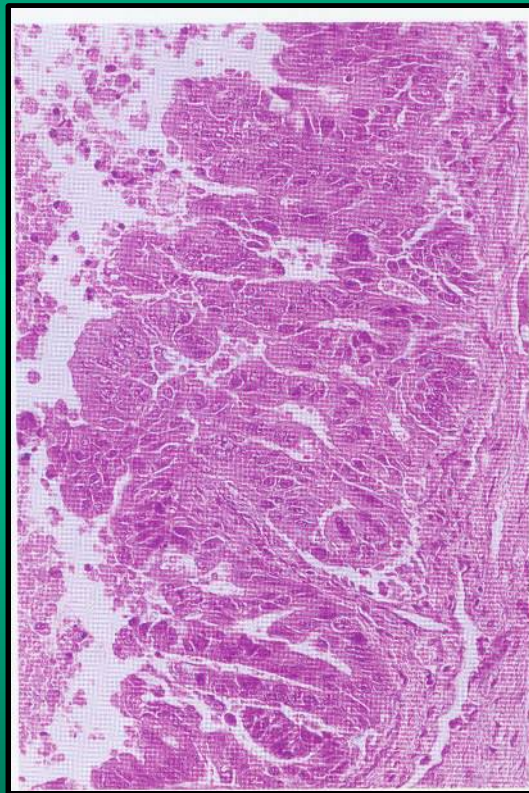
Usually unresectable when discovered

CLINICAL FEATURES:

Symptoms: insidious and indistinguishable from those caused by cholelithiasis

Prognosis: poor

CARCINOMA OF THE GALLBLADDER



Adenocarcinoma of the gallbladder

CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS

- uncommon malignancies
- increased risk in patients with choledochal cysts, ulcerative colitis, chronic biliary infection with *Opisthorchis sinensis* and *Giardia lamblia*

MORPHOLOGY

- adenocarcinomas (uncommon squamous cell carcinoma. adenosquamous ca.)
- Klatskin tumors**: tumors arising at the confluence of the right and left hepatic bile duct
- slow growth, sclerosin behavior and infrequency of distant metastasis

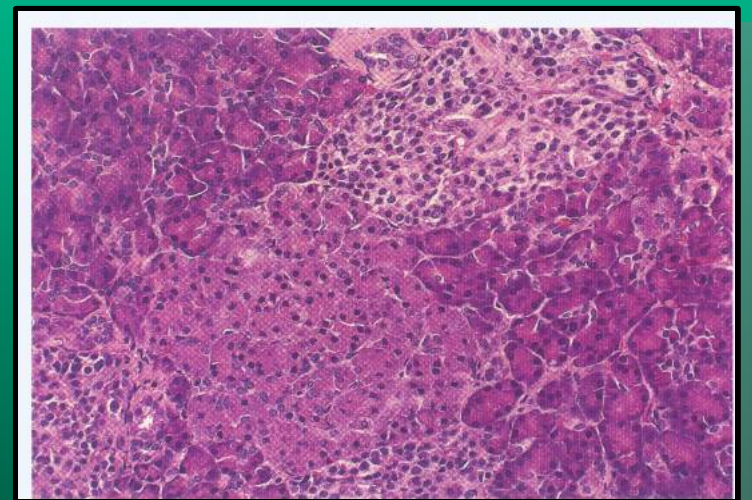
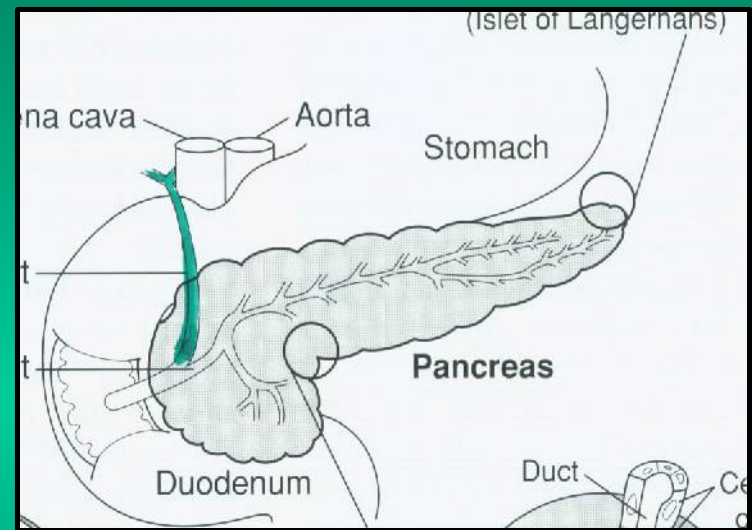
CLINICAL FEATURES

- symptoms similar to those of cholelithiasis
- most have invaded adjacent structures at the time of diagnosis
- prognosis is only fair

PANCREAS

(normal anatomy and histology)

- mixed exocrine-endocrine gland
- connected to the duodenum
- located in the retroperitoneal space of the upper abdomen
- The **exocrine** pancreas forms more than 90% and secretes 1,5-3 l/day fluid rich in proteases, lipase and amylase, necessary for digestion of food.
- the exocrine cells are arranged into acini, composed of trapezoid shaped cells (granular cytoplasm and basally located nuclei).
- The remaining 10% is **endocrine**, consisting of the islets of Langerhans, scattered throughout the pancreas (tail).
- several types of endocrine cells: β cells (70%) produce insulin; α cells –glucagon and variety of other cells secrete somatostatin, vasoactive intestinal polypeptide (VIP) and other hormones.
- immunohistochemistry is used to distinguish various endocrine cells.



DISORDERS OF EXOCRINE PANCREAS

-relatively uncommon, but can be life-threatening!

-**acute pancreatitis** may be subclinical or may produce a calamitous acute abdomen leading to death within a few days

-**chronic pancreatitis** is a cause of less severe abdominal pain, which, along with the attendant malabsorption, can be disabling

-**carcinoma** is a silent disease that comes to attention usually only after it is advanced and beyond ready cure.

CONGENITAL DISORDERS

1. Ectopic pancreatic tissue

- usually is asymptomatic
- most frequently sites: stomach and duodenum (jejunum, Meckel's diverticulum..)

2. Annular pancreas

- the pancreatic head encircles the duodenum with attendant risk of obstruction
- cause duodenal stenosis in infants with vomiting and failure to thrive

3. Pancreas divisum

- persistence of the two separate pancreatic ducts
- predisposes to recurrent pancreatitis

4. Cystic fibrosis

- autosomal recessive systemic disorder affects all exocrine gland
- a biochemical disorder of exocrine secretions causes the viscid secretions to be impacted in the exocrine ducts
- 80% have a pancreatic exocrine insufficiency manifested by steatorrhea and malabsorption
- diabetes mellitus due to pancreatic endocrine insufficiency may also be found

ACUTE PANCREATITIS

definition and morphology

-sudden onset that leads to intrapancreatic **activation of the proenzymes** and autodigestion of the gland and adjacent tissues

-presenting with abdominal pain associated with raised levels of pancreatic enzymes (amylase and lipase) in blood and urine.

-Four basic alterations caused by released activated pancreatic enzymes:

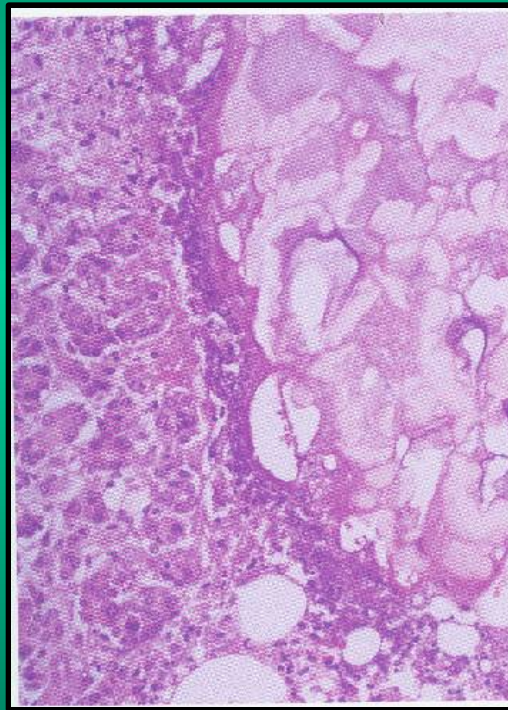
1. Proteolytic **destruction** of pancreatic substance
2. Necrosis of blood vessels with subsequent interstitial **hemorrhage**
3. **Necrosis of fat** by lipases
4. An associated acute **inflammatory** reaction

(the extent and predominance of each of these alterations depend on the duration and severity of the process)

-**pancreatic pseudocyst** is a common sequela of acute pancreatitis

(liquefied areas of necrotic pancreatic tissue are walled off by fibrous tissue to form a cystic space, which does not contain an epithelial lining)

ACUTE PANCREATITIS (pathohystology)



NECROSIS OF PANCREATIS ACINI AND ADJACENT FAT TISSUE: fat necrosis; vacuolated fat cells are transformed to shadowy outlines of cell membranes fill with pink, granular, opaque precipitate. The liberated glycerol is reabsorbed and the released fatty acid combine with calcium to form insoluble salts that precipitate in situ. These deposits are stain basophylic in routinely stained histological section.

ACUTE PANCREATITIS (gross appearance)



GROSS APPEARANCE OF THE MOST SEVERE FORM OF ACUTE PANCREATITIS: areas of blue-black hemorrhage interspersed with areas of gray-white necrotic softening, sprinkled with foci of yellow-white, chalky fat necrosis.

ACUTE PANCREATITIS (pathogenesis and etiology)

-two major pathways may lead to intrapancreatic activation of digestive enzymes, with subsequent pancreatic “autodigestion”

Pancreatic duct obstruction-reflux model

-the reflux of bile and duodenal contents into the pancreas secondary to ampullary obstruction

(80%)

-**gallstones**

-**alcoholism** (secretion of a protein rich pancreatic fluid predisposing to inspissation of calcified protein plugs)

The acinar cell injury model

-direct acinar cell damage may result from variety of insults, including viruses, toxins, ischaemia and trauma

Mechanism of activation of proenzymes and their escape from the zymogen granule ?

ACUTE PANCREATITIS

(clinical features)

1. Signs and symptoms

a) abdominal (epigastric) pain with radiation to the back

dif. dg. of acute abdomen:-perforated peptic ulcer

-acute cholecystitis

-infarction of the bowel

b) shock

7. Laboratory data

a) ↑ serum level of amylase

rises within the first 12 hours and then often falls to normal within 48-72 hours

dif. dg. of ↑ amylase : -perforated peptic ulcer

(but lesser degree) -carcinoma of the pancreas

-intestinal obstruction

-peritonitis

-any disease that impinge the pancreas

b) ↑ serum level of lipase

and remain elevated 7-10 days

c) hypocalcemia

Mortality rate is high (20%-40%)

death caused by: -shock, sec.abdominal sepsis or ARDS

CHRONIC PANCREATITIS

-repeated bouts of pancreatic inflammation, with continued loss of pancreatic parenchyma and replacement by fibrous tissue.

II) Etiology and pathogenesis

1. Chronic ethanol abuse

(forming the ductal plugs that may enlarge to form laminar aggregates containing calcium carbonate precipitate. They exacerbating small duct obstruction and atrophy of the draining pancreatic lobule)

2. Biliary tract disease

3. Hypercalcemia, hyperlipidemia, pancreas divisum

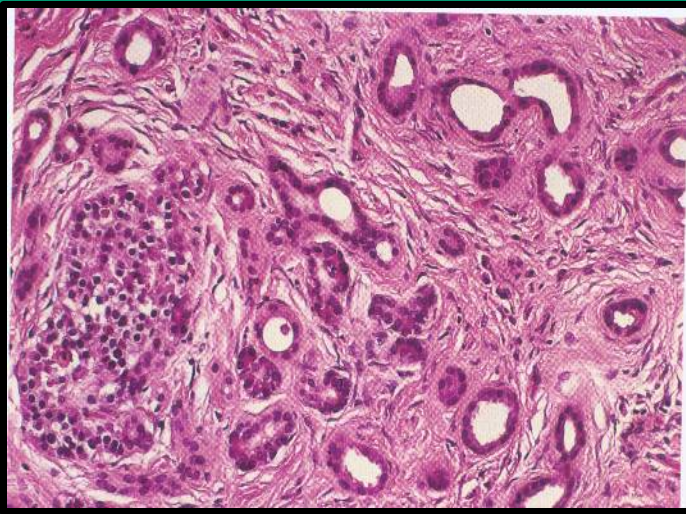
4. Hereditary predisposition

(mutation in the cystic fibrosis transmembrane conductance regulator gene /CFTR/ - reduce the solubility of secreted proteins and thus give rise to thickened and viscous secretions that tend to obstruct the ducts)

XIV) Clinical features

1. Pain (repeated attacks of moderately severe abd. pain, persistent abdominal and back pain)
2. Fat and protein malabsorption (at least 90% of pancreatic secretory capacity is lost)
3. Diabetes mellitus

CHRONIC PANCREATITIS



MORPHOLOGY: -extensive atrophy of the exocrine glands with sparing the of the islets.

A chronic inflammatory infiltrate around lobules and ducts and variable obstruction of pancreatic ducts by protein plugs.

GROSSLY the gland is hard, sometimes with

dilateted ducts and visible calcified concretions. Internal or external pseudocysts may also be found

COMPLICATIONS:

1. Pancreatic pseudocysts (encapsulated collections of fluid with a high concentration of pancreatic enzymes)
2. Retention cysts (occur when the main duct or the its larger branches has become occluded)
3. Bile duct strictures

CARCINOMA OF THE PANCREAS

- arising from the ductal epithelium
- the fifth leading cause of death from cancer in USA
- ↑ incidence in smokers
- show multiple mutations in cancer-associated genes

(in 90% of cases mutation: - in the K-RAS

- in the tumor suppressor gene CDKN2A (p16)

“MOLECULAR FINGERPRINT” of pancreatic cancers)

Clinical features and diagnosis

- symptoms don not develop until the tumor is well advanced
- tumor localized to the head present earlier (**obstructive jaundice**) than tumors of the body and tail (**weight loss, pain, Trousseau sign** (migratory thrombophlebitis) **massive metastasis to the liver**)
- ↑ serum levels of CEA and CA19-9 antigen (no prove to be specific for pancreatic cancer)
- imaging technics (ultrasonography and CT) with parcutaneous biopsy ↑

CARCINOMA OF THE PANCREAS (morphology)

Microscopically: -**adenocarcinoma** (more or less differentiated glandular pattern, mucus or non-mucus secreting)

Perineural or intraneural invasion are common.

-60%-70% -head

5%-10% - body

10%-15% -tail

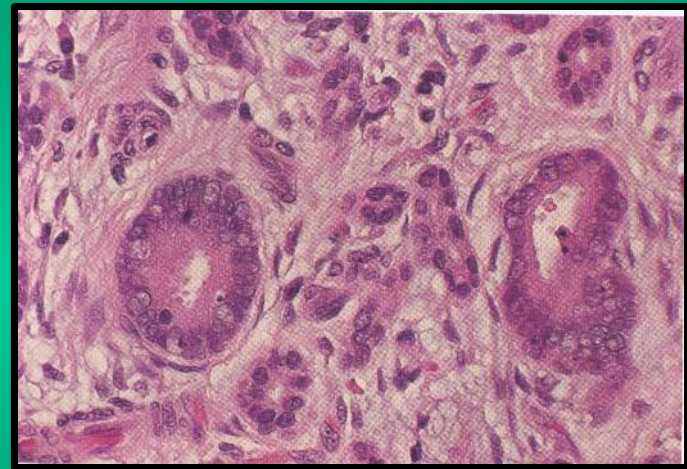
20%-diffusely

-Rare histologic variants:

adenosquamous ca.

anaplastic ca with giant cell formation

acinar cell carcinoma



Prognosis: 5-year survival rate > 5%

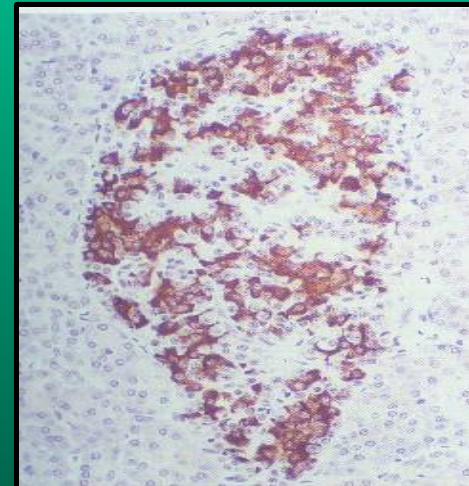
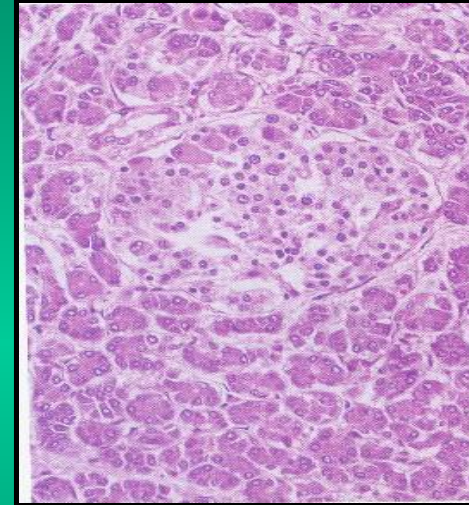
ENDOCRINE PANCREAS

- consist of **1 million of islets** of Langerhans
each islet contain about **1000 endocrine cells**

differentiated by their staining property
ultrastructural morphology of granules
their hormone content

- four most common cell types:
 - β cells (70%) synthesize insulin
 - α cells (5-20%) glucagon
 - δ cells (5-10%) somatostatin
 - PP cells (1.2%)

- Various endocrine cells can be distinguish
by immunohistochemistry using specific antibodies to in sulin, glucagon, and other hormones



DIABETES MELLITUS

- a chronic disorder of carbohydrate, fat and protein metabolism
- a relative or absolute deficiency in insulin secretory response



impaired glucose use



hyperglycemia

Clasification and incidence

Type I

(insulin-dependent diabetes mellitus /IDDM/
juvenile-onset diabetes

- 5-10% of all cases of diabetes
- two subgroups

-1A caused by autoimmune
destruction

-1B no evidence of autoimmunity

Type II

(non-insulin-dependent diabetes mellitus /NIDDM/
adult-onset diabetes

- 80%

- although the two major types of diabetes have different pathogenic mechanisms and methabolic characteristics, the long-term complications (vessels, kidneys, eyes and nerves) in both types are the same!
- the prevalence of DM varies widely around the world
- affects 13 million people in the USA; annualy mortality rate of about 35,000 (7th cause of death in USA)

DIABETES MELLITUS

(pathogenesis of Type I DM)

Interlocking mechanisms:

- **Genetic susceptibility** to altered immune regulation, related to HLA class II inheritance
- **Autoimmunity** to islet β -cells with lymphocytic “insulinitis”
 - 10% coincidence of Graves' disease, Addison 's disease, thyroiditis and pernicious anemia
- **Environmental factors.** viruses, chemical toxins
 - (postulated scenario: mild environmental β -cell injury, followed by autoimmune reaction against altered β -cells in persons with HLA-linked susceptibility)

DIABETES MELLITUS

(pathogenesis of Type II DM)

- the more common type, but much less is known - multifactorial
- metabolic defects: deranged insulin secretion,
 - insulin resistance of peripheral tissues
- Genetic predisposition:** not linked to HLA locus, appears to result from a collection of multiple genetic defects.
- Insulin deficiency:** cause of deficiency is unclear
 - loss of glucose transporters in β -cells
 - amylin accumulate around β -cells
- Insulin resistance:** -a major factor in type II DM
 - also seen in pregnancy and obesity
 - is based on a decrease in peripheral insulin receptors and postreceptor signalling

DIABETES MELLITUS

(pathogenesis of metabolic derangement)

- insulin is a major anabolic hormone
- deranged insulin function affects glucose, fat and protein metabolism
- counter-regulatory hormones (e.g. growth hormone, epinephrine) are secreted unopposed
- peripheral tissue cannot accumulate glucose
- excess glycosuria induces osmotic diuresis and **polyuria** with profound loss of water and electrolytes. Intense thirst (**polydipsia**) develops, with increased appetite (**polyphagia**), completing the classic diabetic triad.

-DIABETIC KETOACIDOSIS

occurs exclusively in **type I DM** due to severe ↓ **insulin deficiency** and ↑ ↑ ↑ **glucagon** excessive release of ↑ ↑ ↑ **free fatty acids** from adipose tissue hepatic oxidation generates **ketone bodies** (butyric acid and acetoacetic acid) ketonemia and ketonuria, with dehydration, generate life-threatening systemic metabolic ketoacidosis.

-NONKETOTIC HYPEROSMOLAR COMA

can develop in **type II DM** in the setting of severe dehydration (from sustained hyperglycemic **diuresis**) and an **inability to drink water**

COMPLICATIONS OF DIABETES

1. Susceptibility to **infections**, including tuberculosis, pneumonia, pyelonephritis and mucocutaneous candidiasis
2. Peripheral and autonomic **neuropathy**, manifesting as sensory loss, impotence, postural hypotension, constipation and diarrhea
3. **Vascular disorders** (chiefly from microangiopathy in type I and from arteriosclerosis in type II) including:
 - a) **retinopathy** (the most common cause of blindness in the US)
 - b) renal disease, notably glomerulosclerosis
 - c) atherosclerosis, causing coronary artery disease, stroke and gangrene of the lower extremities as well as nephropathy

PATHOGENESIS OF COMPLICATIONS

1. NONENZYMATIC GLYCOSYLATION

- Glucose chemically attaches to amino groups of proteins
- with glycosilation of collagens and other long-lived proteins, irreversible **advanced glycosylation end products (AGE)** accumulate over the lifetime of the blood vessel walls
- AGEs have a number of chemical and biologic properties that are potentially pathogenic:
 - a) AGE causes a cross-links between polypeptides and **may trap** nonglycosylated plasma and interstitial proteins (accelerating atherogenesis, affect the structure and function of capillaries)
 - b) AGE **binds to receptors** on many cells (endothelium, monocytes, macrophages, lymphocytes and mesangial cells) and inducing a variety of (undesired) biologic activities
- the measurement of glycosilated hemoglobin (HbA_{1c}) levels in blood (a useful adjunct in the management of DM)

2. INTRACELLULAR HYPERGLYCEMIA WITH DISTURBANCES IN POLYOL PATHWAYS

- some tissue (nerve, lens, kidney, blood vessels) that do not require insulin, develop **increased intracellular glucose**, which is metabolised to sorbitol and thence fructose. The osmotic load leads to influx of water and osmotic cell injury

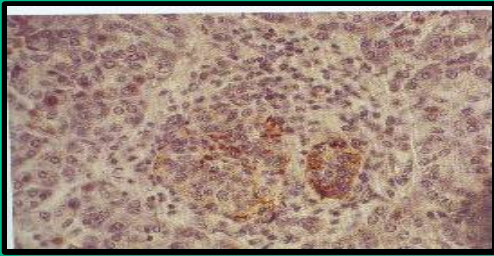
MORPHOLOGY OF DIABETES AND ITS LATE COMPLICATIONS

- Important morphologic changes in diabetes are related to its many late systemic complications, because they are the major causes of morbidity and mortality
- extreme variability of late complications among patients:
 - in the time of onset
 - their severity
 - the organs involved
- with tight control of diabetes the onset may be delayed
- in most patients, after 10-15 years morphologic changes are likely to be found
 - in arteries (atherosclerosis)
 - the basement membrane of
 - small vessels (angiopathy)
 - kidneys (diabetic nephropathy)
 - retina (retinopathy)
 - nerves (neuropathy)
 - and other tissue

MORPHOLOGY OF DIABETES IN **PANCREAS (islet changes)**

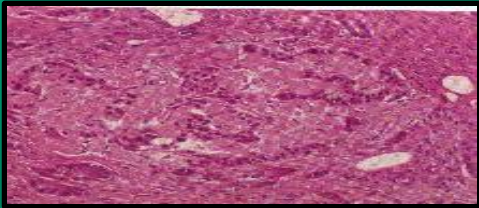
-Islet changes are inconstant and rarely of diagnostic value

- reduction in the number and size of the islet (type I)
- leukocytic infiltration of the islets (insulinitis) (type IA)



∇β-cell degranulation (by electron microscopy; type IA)

- amyloid replacement of islets (type II)



- ↑ in the number and size of islets (in nondiabetic newborns with diabetic mother)

MORPHOLOGY OF DIABETES IN VASCULAR SYSTEM

1. ATHEROSCLEROSIS –accelerated and severe

- (indistinguishable from atherosclerosis in nondiabetic patients)
- coronary, cerebral, mesenteric, renal and femoral
- myocardial infarction –most common cause of death in diabetics
- gangrene of the lower extremities –100 times more common in diabetics

2. HYALINE ARTERIOLOSCLEROSIS

- more prevalent and more severe in diabetic patients

3. DIABETIC MICROANGIOPATHY (diffuse thickening of basement membranes)

- capillaries of the skin, skeletal muscles, retinas, glomeruli, renal medullae and
- nonvascular structure: renal tubules, Bowman's capsule, peripheral nerves and placenta
- capillaries are more leaky to plasma proteins
- underlies the development of diabetic nephropathy and neuropathy

MORPHOLOGY OF DIABETES IN KIDNEYS (diabetic nephropathy)

- most severely damaged organ in diabetics
- renal failure is second cause of death

3. GLOMERULAR LESIONS

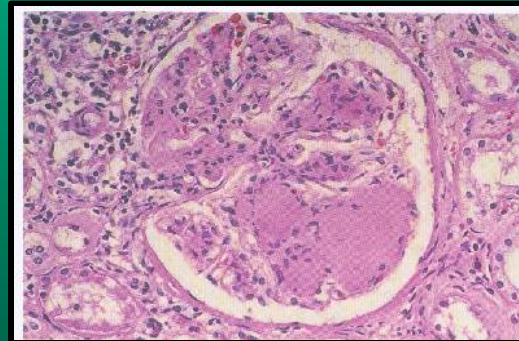
a) CAPILLARY BASEMENT MEMBRANE (B.M.) THICKENING (detected by electron microscopy)

b) DIFFUSE GLOMERULOSCLEROSIS

- ↑ mesangial matrix, mesangial cell proliferation, thickening of B.M.
- found in >10 years duration of disease
- manifest the nephrotic syndrome (proteinuria, hypoalbuminemia, edema)

c) NODULAR GLOMERULOSCLEROSIS (Kimmelstiel-Wilson lesions)

- ball- like deposits of a laminated matrix, within the mesangial core of the lobule
- occurs irregularly throughout the kidney
- deposits are PAS positive



-advanced glomerulosclerosis ⇒ tubular ischemia and interstitial fibrosis ⇒renal

MORPHOLOGY OF DIABETES IN KIDNEYS (diabetic nephropathy)

2. RENAL VASCULAR LESIONS

- a) atherosclerosis (part of the systemic involvement of blood vessels but in the kidney they are the most frequently and most severely affected)
- b) hyaline arteriosclerosis
 - affects not only the afferent but also the efferent arteriole

3. PYELONEPHRITIS

- more common and more severe in diabetic patients
- necrotizing papillitis –more prevalent in diabetics

MORPHOLOGY OF DIABETES IN EYES (diabetic ocular complications)

1. RETINOPATHY

a) NONPROLIFERATIVE RETINOPATHY

hemorrhages (intraretinal or preretinal)

retinal exudates

microaneurysms

venous dilatations

edema

microangiopathy (thickening of the retinal capillaries)

b) PROLIFERATIVE RETINOPATHY

process of neovascularisation and fibrosis

rupture of the newly formed capillaries



vitreous hemorrhage



organisation



retinal detachment

19. CATARACT FORMATION

3. GLAUCOMA

MORPHOLOGY OF DIABETES IN NERVOUS SYSTEM (diabetic neuropathy)

- a symmetric peripheral neuropathy affecting motor and sensory nerves of the lower extremities
- Schwann cell injury, myelin degeneration, axonal damage
- autonomic neuropathy may lead to sexual impotence and bowel and bladder dysfunction
- focal neurologic impairment (diabetic mononeuropathy) most likely due to microangiopathy

CLINICAL FEATURES OF DIABETES MELLITUS

TYPE I

- begins by age 20 years
- polyuria, polydipsia, polyphagia
- ketoacidosis, ↓ insulin, ↑ glucose
- metabolic derangements and insulin need are directly related to physiologic stress

TYPE II

- usually older than age 40 years
- polydipsia, polyuria
(often but not necessarily) obesity
- metabolic derangements are mild and controllable

COMPLICATIONS OF BOTH TYPES

ATHEROSCLEROTIC EVENTS:

- myocardial infarction
- cerebrovascular accidents
- gangrene of the lower extremity
- renal insufficiency

DIABETIC MICROANGIOPATHY:

- blindness
- peripheral neuropathy

↑ SUSCEPTIBILITY TO INFECTION

ISLET CELL TUMORS

- rare compared with tumors of exocrine pancreas
- in the substance of the pancreas or may arise in the peripancreatic tissues
- have a propensity to elaborate pancreatic hormones (insulinoma, but pancreas give rise to gastrinoma although normal islets of Langerhans do not contain gastrin secreting G-cells)
- may be functioning or nonfunctioning
- may be benign or malignant
 - considered benign: circumscribed or encapsulated and no metastases
 - borderline lesions: infiltrative borders, mitoses, or vascular invasion
 - islet cell carcinoma: metastases to nodes or liver
- classified on the basis of their cellular composition and secretory activity
- resemble in appearance to carcinoid tumors
- all endocrine pancreatic tumors have the same histological features and are indistinguishable from one another
- final designation for each tumor depends on the immunohistochemical demonstration of the predominant secretory product

β -CELL TUMORS (INSULINOMA)

- most common islet cell tumor
- may elaborate sufficient insulin to cause hypoglycemia (s Glc < 50 mg/dl - symptomatic attacks)
- symptoms: confusion, stupor, loss of consciousness
- attacks promptly relieved by glucose feeding or infusion

MORPHOLOGY

-pale to red-brown nodules located anywhere in the pancreas

(70% solitary adenomas, 10% multiple adenomas)

(10% metastasizing carcinomas; the remainder are diffuse islet hyperplasia in ectopic pancreatic tissue)

HISTOLOGICALLY

-look remarkably like giant islets, with preservation of the regular cords of normally oriented cells. Not even the malignant lesions present much evidence of anaplasia.

IMMUNOCYTOCHEMICALY

insulin can be located in the tumor cells

ELECTRON MICROSCOPE

round granules that contain polygonal or rectangular dense crystals separated from the enclosing membrane by a distinct halo.

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

- marked **hypersecretion of gastrin**
- its origin in **gastrin-producing tumors** - arise in the duodenum and peripancreatic tissue as in pancreas
- **peptic ulceration** in 90% to 95% patients (duodenal to gastric ulcer ratio is 6:1)

MORPHOLOGY

- gastrin producing tumors are histologically bland and rarely exhibit marked anaplasia
- ulcers (duodenal, gastric, jejunal) intractability to usual therapies

- 60% are malignant
- most common in the pancreas, but 10%-15% arise in duodenum