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 channel 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 bad

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

DISORDERS 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, or whom two thirds undergo surgery
  - overall surgical mortality is very low, but approximately 1,000 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)
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
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 bilirubin) 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 bilirubin 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)
- 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 **calculosis** cholecystitis: 90%-95%
  - initiated by gallstone impaction in the gallbladder neck or the cyst duct. The bile becomes increasingly concentrated and act 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
- $\uparrow$ serum bilirubin
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
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*
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.
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 peristant 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 patients 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, mesenchimal

*Patterns of spread:* local invasion of liver,

   extension to cystic duct and portahepatic 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 sinesis 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
-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 basaly located nuclei).

- The remaining 10% is **endocrine**, consisting of the islets of Langerhans, scattered throughout the pancreas (tail).
-several types of endocrine cells: $\beta$ cells (70%) produce insulin; $\alpha$ cells – glucagon and variety of other cells secrete somatostatin, vasoactive intestinal polypeptide (VIP) and other hormones.
- immunohistochemistry is used to distinguish various endocrine cells.
- 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.
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. Proteolitic destruction of pancreatic supstance
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 pancreatis tissue are walled off by fibrous tissue to form a cystic space, which does not contain an epithelial lining)
NECROSIS OF PANCREATEIS 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 basophilic in routinely stained histological section.
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”

- 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)

- 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
      
      \[ \text{dif. dg. of acute abdomen: - perforated peptic ulcer} \]
      \[ \text{- acute cholecystitis} \]
      \[ \text{- infarction of the bowel} \]
   b) shock

7. Laboratory data
   a) ↑ serum level of amylase
      
      \[ \text{rises within the first 12 hours and then often falls to normal within 48-72 hours} \]
      \[ \text{dif. dg. of ↑ amylase: - perforated peptic ulcer} \]
      \[ \text{(but lesser degree) - carcinoma of the pancreas} \]
      \[ \text{- intestinal obstruction} \]
      \[ \text{- peritonitis} \]
      \[ \text{- any disease that impinge the pancreas} \]
   b) ↑ serum level of lipase
      
      \[ \text{and remain elevated 7-10 days} \]
   c) hipocalcemia

Mortality rate is high (20%-40%)

\[ \text{death caused by: - shock, sec. abdominal sepsis or ARDS} \]
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 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 dilated 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 its larger branches have 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 do 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 percutaneous 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
  - λ cells (5-10%) somatostatin
  - PP cells (1.2%)

• Various endocrine cells can be distinguish by
  immunohistochemistry using specific antibodies to insulin, 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

Classification 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
- although the two major types of diabetes have different pathogenic mechanisms and metabolic characteristics, the long-term complications (vessels, kidneys, eyes and nerves) in both types are the same!

Type II

(non-insulin-dependent diabetes mellitus /NIDDM/
 adult-onset diabetes
• 80%

-the prevalence of DM varies widely around the world

-affects 13 million people in the USA; annually mortality rate of about 35,000 (7th cause of death in USA)
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-regularory 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 electrolites. 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
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
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 menny 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
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 (insulitis) (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 ARTERIOLOMCSCLEROSIS**
   - more prevalent and more severe in diabetic patients

3. **DIABETIC MYCROANGIOPATHY** (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 failure
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 arteriolosclerosis
      - 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
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
<table>
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<th>TYPE I</th>
<th>TYPE II</th>
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| - begins by age 20 years  
- polyuria, polydipsia, polyphagia  
- ketoacidosis, ↓ insulin, ↑ glucose  
- metabolic derangements and insulin need are directly related to physiologic stress | - 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 indisistinguishable 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 MICROSKOPE**
- round granules that contain polygonal or rectangular dense crystals separated from the enclosing membrane by a distinct halo.
- 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