PATHOLOGY OF THE LIVER, GALLBLADDER, AND PANCREAS

Subjects for the theoretical exam

1. Acute liver failure
2. Chronic hepatitis
3. Alcoholic liver disease
4. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (Metabolic dysfunction-Associated Steatotic Liver Disease - MASLD)
5. Liver cirrhosis
6. Focal nodular hyperplasia of the liver
7. Liver cell adenoma
8. Hepatocellular carcinoma
9. Cholangiocarcinoma
10. Metastatic tumors of the liver
11. Acute cholecystitis
12. Chronic cholecystitis
13. Carcinoma of the gallbladder
14. Cystic fibrosis
15. Acute necrotizing and hemorrhagic pancreatitis
16. Chronic pancreatitis
17. Pancreas pseudocysts
18. Pathology of diabetes mellitus
19. Pancreatic adenocarcinoma
20. General features of the neuroendocrine tumors of the pancreas

PATHOLOGY OF THE LIVER

PATTERNS OF HEPATIC INJURY

Liver responses *to injuries, regardless of cause*

1. Degeneration and intracellular accumulation

Swelling of hepatocytes

- *Moderate cell swelling: reversible*
- *Ballooning degeneration: irreversible*
- *Feathery degeneration: Diffuse, foamy appearance; in cholestatic liver injury*

Accumulation of substances: iron, copper, triglycerides → steatosis: macro/microvesicular

2. Necrosis and apoptosis

Features:

- *Ischemic coagulative necrosis: liver cells are poorly stained and "mummified"*
- *Apoptotic cell death: isolated hepatocytes. Cells are rounded, shrunken, intensely eosinophilic. Contain fragmented nuclei*
- *Lytic necrosis: hepatocytes osmotically swell and rupture*

Distribution

- *Zonal – most common:*
- *Centrilobular: immediately around the terminal hepatic vein: ischemic injury, drug and toxic reactions*
- *Pure midzonal and periportal necrosis are rare (i.e., periportal necrosis in eclampsia)*
- *Usually there is a variable mixture of hepatocellular death through the parenchyma*

Extension:

- *Focal or spotty necrosis (apoptosis): scattered cells within hepatic lobules. The fundamental lesion of acute viral hepatitis. Remnants of dead cells are rapidly removed by blood flow or by phagocytosis*
- *Interface hepatitis (formerly named piecemeal necrosis)*
  - *Death of hepatocytes at <u>the interface</u>:*
    - *Of parenchyma and the connective tissue of the portal zone*
    - *Of regenerative nodules and the fibrous septa in cirrhosis*
  - *It is almost certainly apoptosis rather necrosis. Accompanied by a variable degree of inflammation and fibrosis. Present in chronic and in acute hepatitis*
- *Bridging necrosis: Involve contiguous hepatocytes (groups of hepatocytes). May span adjacent lobules: portal-to-portal, portal-to-central, or central-to-central bridges. Present in more severe inflammatory injury*
- *Submassive necrosis*: necrosis of entire lobules*
- *Massive necrosis*: necrosis of most of the liver*

**: usually accompanied by hepatic failure*

3. Inflammation

***Hepatitis** = injury to the liver associated with an influx of acute or chronic inflammatory cells*
Pathogenesis of inflammation:
- *Toxic or ischemic hepatocyte necrosis elicits an inflammatory reaction*
- *Destruction of antigen-expressing liver cells by **cytotoxic lymphocytes** is a common mechanism of liver damage, especially during viral infection*

Location:
- *In the portal tracts: mild hepatitis*
- *Periportal parenchyma: moderate hepatitis*
- *Within the entire parenchyma: severe hepatitis*

Observations:
- *Macrophages (Kupffer cells and circulating monocytes) engulf the apoptotic cell fragments within a few hours*
- *Foreign bodies, organisms, and a variety of drugs may incite a granulomatous reaction*

4. Regeneration
!! All cells in the liver may regenerate (hepatocytes, endothelial, ductal)
- *Hepatocytes:*
  - *Have long life spans*
  - *Proliferate in response to tissue resection or cell death*
  - *Regeneration occurs in all but the most fulminant hepatic diseases*
  - *Histological signs of regeneration: mitoses, thickening of the hepatocyte cords, variable disorganization of the parenchymal structure*
- *Toxic injury and extensive hepatic necrosis stimulate the proliferation of progenitor cells (oval cells):*
  - *Located in the canal of Hering (bile ductule)*
  - *Double differentiation potential: hepatocytes, biliary epithelium*

5. Fibrosis
Observations:
- *Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver*
- *Unlike other responses, which are reversible, fibrosis is generally considered to be irreversible*
- *The key events involve:*
  - *Stellate cells (Ito cells)*
  - *Deposition of extracellular matrix*
  - *Alteration in parenchymal vasculature*

In the normal liver extracellular matrix may be produced by:
- *Perisinusoidal stellate cells*
- *Hepatocytes*
- *Sinusoidal endothelial cells*
- *Fibroblasts, myobfibroblasts → presence of collagen types I and III (portal tracts, around centrilobular venule), type IV (thin strands alongside hepatocytes in the space of Disse)*

Matrix production and degradation:
- *After injury, cytokines produced by inflammatory cells stimulate matrix producing cells*
- *Fibrosis develops after repeated and persistent injury that overcomes the degrading ability of matrix (degrading enzymes produced by fibroblasts, neutrophils and macrophages: interstitial collagenases, stromelysin, type IV collagenase-gelatinase)*
- *In the initial stages, fibrosis may develop around portal tracts or the terminal hepatic vein or may be deposited directly within the space of Disse*
- *With continuing fibrosis, the liver is subdivided into nodules of proliferating hepatocytes surrounded by scar tissue: cirrhosis*
- *<u>Acute liver injury</u> features regeneration, inflammation, and limited deposition of extracellular matrix*
- *If <u>hepatic injury persists</u> the liver regeneration fails, and matrix deposition is activated → **fibrosis***

HEPATIC FAILURE

This is the most severe clinical consequence of liver disease
Etiopathogenesis:
- *Sudden and massive hepatic destruction*
- *The end point of chronic liver diseases*
- *May be a liver decompensation by intercurrent diseases: gastrointestinal bleeding, systemic infection, electrolyte disturbances, severe stress: major surgery, heart failure*
- *It occurs when 80% to 90% of hepatic functional capacity is disappeared*

The morphologic alterations that cause liver failure:
Massive hepatic necrosis:
- *Most often drug- or toxin-induced: acetaminophen, halothane, antituberculosis drugs (rifampin, isoniazid), antidepressant monoamine oxidase inhibitors, industrial chemicals (carbon tetrachloride), mushroom poisoning (amanita phalloides)*
- *Infectious hepatitis: A, B (hepatitis C infection does not cause massive hepatic necrosis)*

Chronic liver disease: *the most common route to hepatic failure. The endpoint of chronic hepatitis ending in cirrhosis*
Hepatic dysfunction without overt necrosis: *Reye's syndrome, tetracycline toxicity, acute fatty liver of pregnancy*
Clinical features:

- *Jaundice, hypoalbuminemia → peripheral edema; hyperammonemia → cerebral dysfunction; fetor hepaticus*
- *Impaired estrogen metabolism → hyperestrogenemia → Plmar erythema (local vasodilatation), spider angiomas of the skin, hypogonadism and gynecomastia - in the male*
- *Failure of multiple organ systems: respiratory failure with pneumonia and sepsis, renal failure, coagulopathy → bleeding tendency - massive GI bleeding, petechial bleeding*

ACUTE LIVER FAILURE (ALF)

Definition: Acute liver disease associated with coagulopathy and encephalopathy that occurs within 8 (fulminant hepatic failure) to 26 (subfulminant hepatic failure) weeks after the initial hepatic injury, in the absence of pre-existing liver disease
Synonyms: fulminant hepatic failure, subfulminant hepatic failure
Etiology:

- United States: 50% acetaminophen; autoimmune hepatitis, other drugs, toxins, acute hepatitis A and B
- Asia: acute hepatitis B and E

Pathogenesis: massive hepatic necrosis induced, most frequently, by drugs or toxins

- Acetaminophen: hepatic insufficiency develops within a week after the onset of symptoms
- Hepatic viruses: hepatic insufficiency develops after a longer period of time
- The mechanism of hepatocellular necrosis: direct toxic injury (acetaminophen) or a combination of immune-mediated hepatocyte destruction and toxicity (eg infection with hepatotropic viruses)

Pathology: massive necrosis of the hepatic parenchyma with large necrotic zones surrounding islands of regenerative hepatocytes
Macroscopy:

- Liver: small, contracted → 500 g
- Wrinkled Glisson's capsule
- Soft consistency of the parenchyma, with areas of red, green or yellow discoloration

Microscopy:

- Necrosis: the entire lobule → only the periportal hepatocytes remain
- The convergence of the portal tracts
- Collapse of the reticulin network
- Weak inflammatory infiltrate within the lobule and the portal tracts
- Specific elements for etiology: CMV, herpes viruses
- Fibrosis and ductular proliferation: according to the etiology and duration of the aggression

INFECTIOUS DISORDERS OF THE LIVER

Generalities: dominate the clinical practice of hepatology. The most frequent inflammatory diseases of the liver, because the liver is almost inevitably involved in blood-borne infections: systemic, abdominal
Etiology: the foremost are viral. Other hepatic infections: miliary tuberculosis, malaria, staphylococcal bacteremia, salmonelloses, candida, amebiasis

Viral hepatitis

Definition: hepatic infection caused by a group of viruses having a particular affinity for the liver
Etiology:

- *Systemic viral infections that can involve the liver: Infectious mononucleosis (Epstein-Barr virus): may cause mild hepatitis during the acute phase. Cytomegalovirus: in the newborn or immunosuppressed patient. Yellow fever: a major and serious cause of hepatitis in tropical countries. Rubella, adenovirus, herpesvirus, enterovirus: infrequently, in children and immunosuppressed patients*
- *Hepatotropic viruses: cause overlapping patterns of disease*

Pathology of acute hepatitis

Macroscopy: *the liver is enlarged, reddened, greenish if cholestatic*
Microscopy:
Parenchymal changes:

- *Hepatocyte injury: swelling (ballooning degeneration); HCV: mild focal fatty change*
- *Hepatocyte necrosis: Isolated cells or clusters: cytolysis (necrosis) or apoptosis (shrinkage). Bridging necrosis (portal-portal, central-central, portal-central)*
- *Lobular disarray: loss of normal architecture (hepatocyte swelling, regeneration)*
- *Regenerative changes: hepatocyte proliferation*
- *Sinusoidal cell reactive changes: Accumulation of cellular debris in Kupffer cells (phagocytosis). Influx of mononuclear cells into sinusoids*
- *Cholestasis: canalicular bile plugs*

Portal tracts: *inflammation: predominantly mononuclear. Inflammatory spillover into adjacent parenchyma, with hepatocyte necrosis*

CHRONIC HEPATITIS

Definition: symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, with histologically documented inflammation and necrosis

Etiology:

- Most common: hepatitis viruses (HBV, HCV, HBV + HDV)
- Chronic alcoholism
- Wilson's disease
- A1-antitrypsin deficiency
- Drugs (e.g., isoniazid, α-methyldopa, methotrexate)
- Autoimmunity
- Metabolic disorders
- Etiology is the single most important indicator of likelihood to progress to cirrhosis!

Pathology of chronic hepatitis

1. Inflammation and hepatocyte necrosis

Portal inflammation:

- Characteristic for chronic hepatitis
- T cells (CD4 +) + plasma cells, macrophages
- Affects all the portal tracts
- More intense than in acute hepatitis

Interface hepatitis:

- Apoptosis and inflammation (periportal necrosis, piecemeal necrosis)
- T cells (suppressor/cytotoxic CD8 +); plasma cells, macrophages
- In relation to dead/dying hepatocytes

Lobular hepatitis and confluent necrosis:

- Inflammatory infiltrate with lymphocytes
- Necrosis:
  - Focal
  - Confluating: bridging necrosis, that links portal tract between them or portal tracts with the centrilobular vein, rarely centrilobular veins with centrilobular veins.
- !!! Bridging necrosis is the most important predictive factor for fibrosis

2. Fibrosis

- Advanced stages of the disease
- The stellate cells
- Collagen I, III, reticulin
- Initially portal fibrosis, then periportal fibrosis, and later bridging fibrosis: connects the portal tracts, portal tracts with centrilobular veins or centrolobular veins between them

3. Regeneration

- Thick (2-3 cells) hepatocyte cords

Particular features related to etiology:

HBV (hepatitis B virus):

- *"Ground-glass" cytoplasm:*
  - Histopathological hallmark of chronic HBV infection
  - Homogeneous glassy cytoplasm comparable to the window glass with a granular surface appearance
  - This feature is determined by the *presence, in the cytoplasm, of hepatitis B surface antigen (HBsAg)*
- *"Sanded" nuclei*
  - Spiky, finely granular, and eosinophilic nuclear inclusions
  - This feature is determined by the *presence, in the cytoplasm, of hepatitis B core antigen* (*HBcAg*)

HCV (hepatitis C virus):

- Bile duct epithelial cell proliferation
- Portal lymphoid aggregates (lymphoid follicles within portal tracts)
- Macrovesicular steatosis (related to type 3 genotype of the virus)

Grading and staging of chronic hepatitis

Grade of chronic hepatitis: refers to the **necroinflammatory activity** (the presence and the extent of **necrosis** and **inflammatory cells** (mainly lymphocytes)

The grade evaluates ***portal/periportal (interface)*** and ***lobular*** activity (necrosis + inflammation)

HAI (histologic activity index):

Minimal activity:

- Mild inflammatory infiltrate limited to the portal triads
- No or minimal lobular inflammation

Mild activity :

- Moderate portal inflammation
- Focal (mild) interface hepatitis
- Focal lobular necrosis or apoptosis

Moderate activity:

- Moderate/severe portal inflammation
- Moderate interface hepatitis
- Severe lobular focal cell damage

Severe activity:

- Severe portal inflammation
- Severe interface hepatitis
- Bridging lobular necrosis

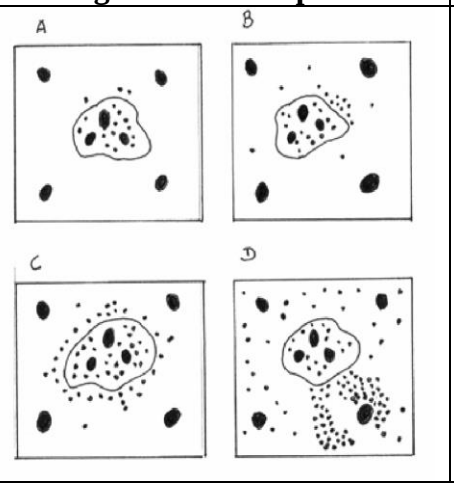
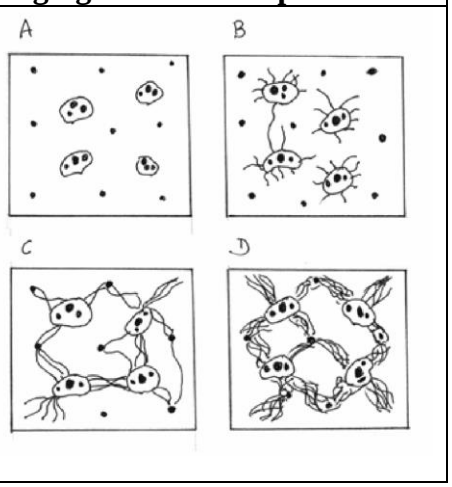
Stage of chronic hepatitis: evaluates the extent of **fibrosis**

Portal fibrosis: fibrous portal extension without septa formation

Periportal fibrosis: with rare septa formation (portal-portal, portal-centrilobular)

Septal (bridging) fibrosis: numerous septa (bridges) without cirrhosis

Cirrhosis: bridges of fibrosis surround completely regenerative nodules of hepatocytes

Grading of chronic hepatitis	**Staging of chronic hepatitis**
	

!!! *Grading and staging a chronic hepatitis are possible on liver biopsies, stained with hematoxylin-eosin and with special stains for fibrosis (Sirius red, Masson's trichrome). The final pathological diagnosis contains the* ***grade*** *and the* ***stage****; together, grade + stage give the* ***score*** *of the hepatitis (presented as numerals by different evaluation systems). Some of these systems, used for chronic hepatitis of viral etiology, are known under different names: Ludwig, Scheuer, Ishak, Knodell, Metavir. The Metavir system is designated only for chronic C virus hepatitis. Liver biopsy is helpful for diagnostic and follow-up purposes. Etiology cannot be established on histological bases (with few exceptions), the final diagnosis being elaborated by a combination of clinical laboratory and histopathological data.*

The clinical course of chronic viral hepatitis:

- *Unpredictable:*
  - *Spontaneous remission*
  - *May have indolent disease without progression for many years*
  - *Rapidly progressive disease and development of cirrhosis within a few years*
- *The major causes of death are:*
  - *Cirrhosis: liver failure and hepatic encephalopathy; massive hematemesis from esophageal varices*
  - *Hepatocellular carcinoma: long-standing HBV (particularly neonatal) or HCV infection*

AUTOIMMUNE HEPATITIS

Generalities:

- *Chronic hepatitis with histologic features that may be indistinguishable from those of chronic viral hepatitis*
- *May run an indolent or severe course*
- *Genetic susceptibility (HLA-B8, -B14, -DR-3, -DR-4)*

Suggestive for the diagnosis:

- *Female predominance (78%) - young and perimenopausal women*
- *Absence of viral serologic markers*
- *Elevated serum IgG and γ-globulin levels (>1.5 times normal)*
- *High serum titers of autoantibodies in 80% of cases: antinuclear (ANA); antismooth muscle (SMA); and/or antiliver/kidney microsomes (anti-LKM1) antibodies*
- *Negative antimitochondrial antibody (AMA)*
- *60% of patients have other forms of autoimmune disease: rheumatoid arthritis, thyroiditis, Sjögren's syndrome, ulcerative colitis*

Classification:

- *Type 1: the most common, with ANA and/or SMA serum markers*
- *Type 2: younger patients, antibodies to liver/kidney microsomes (anti-LKM1)*

Pathology: *the entire histological spectrum of chronic hepatitis*

- *Prominent inflammatory infiltrates of lymphocytes and* ***plasma cells***
- *Substantial liver destruction and scarring at the time of diagnosis*
- *Rarely may exhibit histologic destruction of bile ducts ("autoimmune cholangitis") – difficult distinction from primary biliary cirrhosis or primary sclerosing cholangitis*

Clinical presentation:

- *Similar to other forms of chronic hepatitis*
- *May progress to cirrhosis without clinical diagnosis*
- *Forms of disease:*
  - *Acute*
  - *Fulminant presentation with onset of hepatic encephalopathy within 8 weeks of onset*

Prognosis:

- *Untreated severe disease: death within 6 months of diagnosis*
- *Cirrhosis develops in at least 40% of survivors*
- *Patients with less severe disease fare better*
- *The disease is responsive to immunosuppressive therapy*
- *Liver transplantation is effective in patients with severe disease*

Drug- and toxin-induced liver disease

Pathogenesis:

- *Direct toxicity*
- *Hepatic conversion of a xenobiotic to an active toxin*
- *Immune mechanisms*

Hepatocellular damage	***Examples***
Microvesicular fatty change	*Tetracycline, salicylates, yellow phosphorus, ethanol*
Macrovesicular fatty change	*Ethanol, methotrexate, amiodarone*
Centrilobular necrosis	*Bromobenzene, ccl4, acetaminophen, halothane, rifampicin*
Diffuse or massive necrosis	*Halothane, isoniazid, acetaminophen, methyldopa, trinitrotoluene, amanita phalloides*
Hepatitis, acute and chronic	*Methyldopa, isoniazid, nitrofurantoin, phenytoin, oxyphenisatin*
Fibrosis-cirrhosis	*Ethanol, methotrexate, amiodarone, most drugs that cause chronic hepatitis*
Granuloma formation	*Sulfonamides, methyldopa, quinidine, phenylbutazone, hydralazine, allopurinol•*
Cholestasis (with or without hepatocellular injury)	*Chlorpromazine, anabolic steroids, erythromycin estolate, oral contraceptives, organic arsenicals*

ALCOHOLIC LIVER DISEASE

Generalities:

- Excessive alcohol (ethanol) consumption: the leading cause of liver disease in western countries
- 67% of the population 18 years of age or older drink alcohol
- Alcohol abuse: fifth-leading cause of death, many related to automobile accidents
- 40% of deaths from cirrhosis are attributed to alcohol-induced liver disease

Forms of alcoholic liver disease: hepatic steatosis, alcoholic hepatitis, cirrhosis

Pathology:

Hepatic steatosis (fatty liver) – see the first semester!!!

Alcoholic hepatitis:

Macroscopy:

- The liver is mottled red with bile-stained areas
- Normal or increased size
- Often with visible nodules and fibrosis - evolution to cirrhosis

Microscopy:

- *Hepatocyte swelling* (ballooning degeneration) and necrosis
- *Macrovesicular steatosis*
- Cholestasis in surviving hepatocytes
- Mild deposition of hemosiderin: hepatocytes, Kupffer cells
- *Mallory bodies*: cytoplasmic deposits of hyaline material, characteristic but not specific
- *Megamitochondria*: swollen mitochondria, seen as red globules in the cytoplasm; highly suggestive for chronic alcohol abuse
- *Neutrophilic* reaction: around degenerating hepatocytes and around hepatocytes with Mallory bodies
- Ly and Mph enter portal tracts and spill into the parenchyma
- Fibrosis: activation of sinusoidal stellate cells and portal tract fibroblasts
    - Most frequently *sinusoidal and perivenular fibrosis*
    - Occasionally, periportal fibrosis may predominate

Alcoholic cirrhosis:

- The final and irreversible form of alcoholic liver disease
- Usually evolves slowly and insidiously

Pathology:

Macroscopy:

- Initially: yellow-tan, fatty, and enlarged: over 2 kg
- Over years: brown, shrunken, nonfatty organ: less than 1 kg
- Cirrhosis may develop more rapidly in the setting of alcoholic hepatitis: 1 - 2 years
- Micronodular → mixed, micro and macronodular ("hobnail" appearance on the liver surface)

Microscopy:

- Initially:
    - Delicate fibrous septa extend through sinusoids from central to portal regions and from portal tract to portal tract
    - Regenerative activity: uniform "micronodules"
- With time:
    - The nodularity becomes more prominent: scattered larger nodules
    - Fibrous septa dissect and surround nodules → the liver becomes more fibrotic → it shrinks progressively, loses fat
    - Mixed micronodular and macronodular cirrhosis
    - Bile stasis, decreased number of Mallory bodies
- **!!!** End-stage alcoholic cirrhosis resembles, both macroscopically and microscopically, the cirrhosis developing from viral hepatitis and other causes

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) = Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic dysfunction-Associated Steatohepatitis (MASH)

Definition: nonalcoholic fatty liver disease (NAFLD) is a condition that resembles alcohol-induced liver disease but occurs in patients who are not heavy drinkers

Generalities:

- Men and women are equally affected
- There are strong associations with obesity, dyslipidemia, hyperinsulinemia and insulin resistance, and overt type 2 diabetes
- MASLD is a diagnosis of exclusion (especially of excessive alcohol intake)
- Spectrum of lesions: steatosis, steatohepatitis (**MASH**), cirrhosis

Microscopy: on liver biopsies

- *Macrovesicular steatosis:* there are no appreciable hepatic inflammation, hepatocyte death, or scarring (despite persistent elevation of serum liver enzymes)
- *Steatohepatitis:*
    - Steatosis
    - Multifocal parenchymal inflammation
    - Mallory hyaline
    - Hepatocyte death (both *ballooning* degeneration and apoptosis)
    - Sinusoidal fibrosis
- *Cirrhosis:* the result of years of subclinical progression of the inflammation and fibrosis

Clinical features:

- Asymptomatic
- Abnormalities only in biochemical laboratory tests

Evolution:

- MASLD accounts for up to 70% of the cases of chronic hepatitis of "unknown" cause
- 10 - 30% of patients with MASLD develop cirrhosis: common cause of "cryptogenic" cirrhosis
- Contributes to the progression of other liver diseases such as hepatitis C viral infection
- Unknown incidence of hepatocellular carcinoma in MASLD

LIVER CIRRHOSIS

Definition: end-stage of chronic liver disease, defined by three characteristics:

- Bridging fibrous septa: delicate bands or broad scars linking portal tracts with portal tracts or portal tracts with terminal hepatic veins
- Parenchymal nodules: proliferating hepatocytes encircled by fibrosis
- Disruption of the architecture of the entire liver

Pathology of liver cirrhosis:

- Basic modification: **nodules of regenerative hepatocytes** surrounded **by thick fibrous septa**
- *Classification:*
    - *Micronodular cirrhosis* (nodule diameter < 3 mm):
        - Thick, regular septa
        - Regenerative small nodules of uniform size
        - Involvement of every lobule
        - Often associated with the persistence of the injurious agent
    - *Macronodular cirrhosis* (≥ 3 mm → cm):
        - Nodules of variable size
        - Large areas of intact or regenerating parenchyma within each large nodule
    - Mixed *macronodular* and *micronodular cirrhosis:*
        - May result from regrowth in a previous micronodular cirrhosis
        - Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular, but there is a tendency for nodules to increase in size with time → macronodular

Macroscopy:

- The liver is contracted
- The size and weight are decreased (500-700 grams)
- Hard consistency
- The external surface and the margins are irregular due to the nodules and fibrosis
- The color of nodules may suggest the etiology:
    - Yellow – alcoholic, non-alcoholic cirrhosis
    - Tan/brown – hemochromatosis
    - Green – biliary cirrhosis

Microscopy:

- Regenerative nodules surrounded by fibrous septa (bridges)
- The nodules:
    - Normal architecture is distorted: no centrilobular vein or portal tracts within nodules
    - Hepatocytes:
        - Regenerative changes: mitoses, thick cell plates, binuclated cells, large, hyperchromatic nuclei
        - In early stages: features suggesting the etiology (Mallory bodies, fat, bile), **but** once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone
        - Sometimes nodules contain dysplastic cells or foci of hepatocellular carcinoma
    - Fibrous septa: may contain blood vessels, proliferated bile ducts, inflammatory cells

Clinical features

- All forms of cirrhosis may be clinically silent
- When symptomatic: nonspecific clinical manifestations
- The death may occur because:
    - Progressive liver failure
    - A complication related to portal hypertension (see the 1st semester)
    - The development of hepatocellular carcinoma

BILIARY CIRRHOSIS

Secondary biliary cirrhosis

Etiopathogenesis:

- *Prolonged obstruction of the extrahepatic biliary tree*
- *Most common causes:*
  - *In adults: extrahepatic cholelithiasis (gallstones), malignancies of the biliary tree or head of the pancreas, strictures resulting from previous surgical procedures*
  - *In children: biliary atresia, cystic fibrosis, choledochal cysts, paucity of bile duct syndromes*

Pathogenesis:

- *Cholestasis is the initial event*
- *Secondary inflammation resulting from biliary obstruction initiates periportal fibrosis*
- *Hepatic scarring and nodule formation → secondary biliary cirrhosis*
- *Subtotal obstruction promotes bacterial infection of the biliary tree (ascending cholangitis) → aggravates the inflammatory injury*

Pathology:

Macroscopy:

- *Yellow to green pigmentation*
- *Marked icteric discoloration of body tissues and fluids*
- *On cut surface: the liver is hard, finely granular (micronodular cirrhosis)*

Microscopy:

- *Coarse fibrous septa containing distended small and large bile ducts filled with inspissated bile*
- *Extensive proliferation of smaller bile ductules*
- *Edema at the interface between septa and the parenchyma*
- *Cholestatic features in the parenchyma: extensive feathery degeneration, bile lakes*

Primary biliary cholangitis

Definition: chronic, progressive, and often fatal cholestatic liver disease, characterized by:

- *Destruction of intrahepatic bile ducts*
- *Portal inflammation and scarring*
- *Eventual development of cirrhosis and liver failure*

Pathogenesis: nonsuppurative, autoimmune destruction of medium-sized intrahepatic bile ducts

Epidemiology: middle-aged women: peak- 40-50y (20-80); M:F=1:6

Clinical features:

- *Onset is insidious, usually presenting with pruritus*
- *Jaundice develops late in the course*
- *Hepatomegaly is typical*
- *Xanthomas and xanthelasmas (cholesterol retention)*
- *Hepatic decompensation after 2 or more decades*

Laboratory findings:

- *Serum alkaline phosphatase and cholesterol are almost always elevated*
- *Hyperbilirubinemia is a late development and usually signifies incipient hepatic decompensation*
- *Circulating "antimitochondrial antibodies"*

Pathology:

Macroscopy:

- *Weight is at first normal to increased (owing to inflammation)*
- *Ultimately, liver weight is slightly decreased as the disease progresses*
- *The capsule remains smooth and glistening until a fine granularity appears*
- *Later: well-developed, uniform micronodularity*

Microscopy:

- *Focal and variable disease, exhibiting different degrees of severity in different portions of the liver*
- *During the precirrhotic stage:*
  - *Portal tracts are infiltrated by a dense accumulation of inflammatory cells: Ly, **Pl**, Mph, Eo*
  - *Terminal and conducting bile ducts:*
    - *Are infiltrated by lymphocytes*
    - *May exhibit noncaseating granulomas*
    - *May undergo progressive destruction*
- *With time, the obstruction to intrahepatic bile flow leads to **progressive secondary hepatic damage**:*
  - *Ductular proliferation in portal tracts*
  - *Periportal inflammation and necrosis*
  - *Generalized cholestasis*
- *Over years to decades → portal tract scarring and bridging fibrosis lead to cirrhosis*

Primary sclerosing cholangitis

Definition: inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, with dilation of preserved segments

Epidemiology:

- *Commonly seen in association with inflammatory bowel disease, particularly chronic ulcerative colitis*
- *M:F= 2:1*
- *The third through fifth decades of life*

Pathogenesis:

- *Cause: unknown*
- *Key events: secretion of proinflammatory cytokines by activated hepatic macrophages followed by infiltration of T cells into the stroma immediately around bile*

Pathology:

Microscopy:

- *Fibrosing cholangitis of bile ducts: lymphocytic infiltrate, progressive atrophy of the bile duct epithelium, obbliteration of the lumen*
- *Concentric periductal fibrosis around affected ducts ("onion-skin fibrosis")*
- *Then disappearance of ducts → a solid, cordlike fibrous scar*
- *Ectatic bile duct segments between areas of progressive stricture*
- *End stage: biliary cirrhosis*

Clinical features:

- *Asymptomatic (elevation of serum alkaline phosphatase) or progressive fatigue, pruritus, jaundice*
- *Increased risk for cholangiocarcinoma*

NODULES AND TUMORS OF THE LIVER

Focal nodular hyperplasia (FNH)

Epidemiology:

- Common (second place after hemangioma)
- In young to middle-aged adults
- Female preponderance

Pathogenesis: may represent a hyperplastic response to arterial malformation or another vascular anomaly

Pathology:

Macroscopy:

- Well-demarcated but poorly encapsulated nodule
- Up to many centimeters in diameter
- Generally lighter than the surrounding liver, ± yellow
- Typically: a central gray-white, depressed stellate scar (fibrous septa):

Microscopy:

- The fibrous septa:
    - Radiate to the periphery
    - Contain:
        - Foci of intense lymphocytic infiltrates
        - Exuberant bile duct proliferation along septal margins
        - Large vessels: arteries with fibromuscular hyperplasia and narrowed lumen
- The parenchyma between the septa: normal hepatocytes with thickened plates (regeneration)

Clinical features: spontaneous mass lesion

BENIGN TUMORS

Liver cell adenoma

Definition: benign tumor of hepatocytes
Etiology: oral contraceptives, anabolic steroids
Pathogenesis: three large molecular subtypes, with a different relative risk of malignant transformation

- *HNF1-α inactivated hepatocellular adenomas:* women, oral contraceptives, tumor cells with steatosis, very low risk for malignant change
- *β-Catenin activated hepatocellular adenomas:* both sexes, anabolic steroids, high risk for malignant change
- *Inflammatory hepatocellular adenomas:* both sexes, NAFLD, low risk for malignant change

Pathology:
Macroscopy: single/multiple

- Position: anywhere in the liver parenchyma, but are often seen under the capsule
- Size: variable (up to 30 cm!)
- Color: different from surrounding liver
- Pale to yellow
- May be bile stained
- ± Hemorrhage, necrosis

Microscopy:

- Normal looking hepatocytes arranged in sheets and cords (do not form lobules)
- Bile deposition may be seen within and between the cells
- Significant vascular supply

Complications:

- Rupture with severe hemorrhage - especially during pregnancy
- Malignant change → hepatocelllular carcinoma

MALIGNANT TUMORS

Hepatocellular carcinoma (HCC)

Definition: malignant tumor of hepatocytes
Epidemiology:

- More than 85% of cases of HCC occur in countries with high rates of chronic HBV infection (Asia - Korea, Taiwan, Southeast China)
- M:F=1.5:1 (8:1 in endemic areas)
- Rarely before 40 years in nonendemic areas (usually after 60-65 years of age); decades 4-5 of life in endemic areas

Etiology:

- Viral infection (HBV, HCV)
- Chronic alcoholism
- Food contaminants (primarily aflatoxins)
- Tyrosinemia (rare, but 40% of patients develop HCC), hereditary hemochromatosis
- Chemicals

Pathology:
Macroscopy:

- Hepatomegaly
- Macroscopic forms of HCC:
    - Unifocal large mass: may be associated with smaller satellite nodules
    - Multifocal: widely distributed nodules of variable size
    - Diffusely infiltrative cancer, sometimes involving the entire liver (resembles cirrhosis)
- Color: paler than the surrounding liver, may have green areas (**tumor cells secrete bile**)

Microscopy:

- Tumor architecture:
    - Trabecular (like liver cell plates, but thicker)
    - Acinar
    - Pseudoglandular
- Tumor cells:
    - In well differentiated HCC:
        - Resembles normal hepatocytes
        - Secrete bile (useful for differential diagnosis with cholangiocarcinoma)
    - In poorly or undifferentiated HCC:
        - Cells are pleomorphic, with numerous anaplastic giant cells
        - May imitate a sarcoma
    - Malignant hepatocytes *may produce alpha-fetoprotein* (fetal protein produced by the yolk sac and the fetal liver): may be detected immunohistochemically in the cytoplasm or may be found in plasma of patients with HCC (useful in postsurgical monitoring of the patients)
    - *Immunohistochemistry:* tumor cells are positive for ***HepPar-1*** (useful for the diagnosis)

Evolution:

- Progressive enlargement of the tumor, impairing the hepatic function
- Spread:
    - HCC have a strong propensity for invasion blood vessels like solid cord of tumor cells growing into portal vein or inferior vena cava, extending into the right side of the heart
    - Lymph node metastases
    - Hematogenous metastases: to lungs and to other sites

Clinical features:

- Unspecific
- May be obscured by those of the background hepatitis or cirrhosis
- Upper abdominal pain, malaise, fatigue, weight loss, abdominal fullness, abdominal mass
- Jaundice, fever, and gastrointestinal or esophageal variceal bleeding are inconstant findings.

Laboratory findings:

- Elevated levels of ***serum α-fetoprotein*** (AFP) - <u>but</u> may be false-positive; not evident in small tumors
- Useful for after surgery monitoring of patients

Prognosis:

- Poor: patients survive less than 6 to 12 months
- Death usually occurs from: cachexia, gastrointestinal or esophageal variceal bleeding, liver failure with hepatic coma, rupture of the tumor with fatal hemorrhage

Fibrolamellar carcinoma*:* clinicopathologic variant of HCC

- M=F, young: 20 to 40 years of age, no association with HBV or cirrhosis
- Better prognosis

Pathology:

Macroscopy: large tumor, white-brown, with fibrous bands throughout and a central stellate scar

- Most cases involve left lobe, but may involve both lobes
- Variable bile staining, hemorrhage and necrosis

Microscopy: nests or cords of well differentiated eosinophilic cells in background of dense, acellular collagen bundles

Prognosis: better than the classic form

Cholangiocarcinoma

Definition: malignant tumor of the biliary tree (bile duct carcinoma)
Origin: bile ducts within and outside of the liver
Epidemiology: M:F=1:1
Risk factors:

- Primary sclerosing cholangitis
- Congenital fibropolycystic diseases of the biliary system, Caroli disease, choledochal cyst
- Previous exposure to thorotrast (formerly used in radiography of the biliary tract)
- Intrahepatic biliary lithiasis
- Biliary infection with *clonorchis sinensis*, *opistorchis viverrini* (parasites) – oriental countries
- No relationship with cirrhosis

Pathology:
Macroscopy:

- Solitary, 7-10 cm, multinodular ***or***
- Diffuse small nodules < 1 cm
- Gray-white and firm
- Often hepatomegaly and satellite nodules
- Rarely cirrhosis
- **Not** bile stained (bile may be seen in periphery): tumor cells do not produce bile (differential diagnosis with HCC)

Microscopy: moderate to well differentiated adenocarcinoma with glandular and tubular structures, mucin production, dense desmoplasia
Evolution:

- May directly invade the portal vein
- Hematogenous metastases: lungs, bones (vertebral bodies), adrenals, brain: are found at autopsy in about 50% of cases
- Lymph nodes metastases

Clinical features: asymptomatic until later stages
Prognosis: poor - death in 6 to 12 months from diagnosis

METASTATIC TUMORS OF THE LIVER

Generalities:

- Metastases are the most common neoplasms in an adult liver
- The liver is the second most common site for metastatic spread, after the lymph nodes
- Any cancer in any site may produce liver metastases
- Organs the most likely to cause liver metastases: eye, colon, stomach, pancreas, breast, lung

Macroscopy:

- Most commonly: multiple nodules
- Hepatomegaly: several kilograms
- May replace over 80% of hepatic parenchyma
- Most common located near the surface
- Central necrosis and umbilication: when viewed from the surface of the liver (metastatic nodules outgrow their blood supply)
- Sometimes a hyperemic zone at the periphery (angiogenesis)
- Usually have a smooth contour (differential diagnosis with primary tumors, which have irregular borders)

PATHOLOGY OF GALLBLADDER

CHOLECYSTITIS

Acute cholecystitis

Epidemiology: present in 5-10% of cholecystectomy specimens

Classification:

- Acute calculous cholecystitis: gallstone associated
- Acute acalculous cholecystitis: without gallstones

General pathologic features of acute cholecystitis:

There are no specific morphologic differences between acute acalculous and calculous cholecystitis, except the absence of macroscopic stones in the former

Macroscopy:

- The gallbladder is enlarged, distended, with congested blood vessels ("angry red color")
- Sometimes green-black discoloration, imparted by subserosal hemorrhages
- Fibrinous exudates on the serosal surface → may be suppurative in severe forms
- The wall:
  - Thickened: because of edema and hemorrhage
  - Green-black, necrotic, with small-to-large perforations: in gangrenous cholecystitis
- The lumen:
  - Cloudy or turbid bile that may contain large amounts of fibrin
  - Hemorrhagic or purulent bile
  - Blood clots
  - ± Stones
- Mucosa: ulcerations

Microscopy:

- Initially: edema, congestion, hemorrhage, fibrin deposition in and around the muscular layer
- Later: mucosal and mural necrosis with neutrophils
- Variable reactive epithelial changes resembling dysplasia
- Fresh thrombi within small veins

Chronic cholecystitis

Epidemiology:

- 95% are associated with cholelithiasis. 75% women, ages 40+

Pathogenesis:

- May be a sequel to repeated bouts of mild to severe acute cholecystitis
- In many instances, it develops in the apparent absence of antecedent attacks

Pathology:

Macroscopy:

- The morphologic changes in chronic cholecystitis are extremely variable and sometimes minimal
- The serosa: usually smooth and glistening, may be dulled by subserosal fibrosis
- Dense fibrous adhesions may remain as sequelae of preexistent acute inflammation
- On sectioning:
  - The wall:
    - Variably thickened: rarely to more than three times normal, may be less flexible than normal, has an opaque gray-white appearance (fibrosis)
  - The lumen contains clear, green-yellow, mucoid bile and usually stones
  - The mucosa is generally preserved

Microscopy:

- Variable chronic inflammatory infiltrate (lymphocytes, plasma cells, macrophages)
- Subepithelial and subserosal fibrosis
- Neutrophilic infiltrate if there is an acute episode

TUMORS OF THE GALLBLADDER

Gallbladder carcinoma

Generalities:

- The most common malignant tumor of extrahepatic biliary tract
- Slightly more common in women
- Most frequently in the seventh decade of life
- Most discovered at an unresectable stage
- Poor prognosis (1% 5-year survival rate)
- Risk factors: gallstones (they are present in 60% to 90% of cases); infectious agents (parasites)

Pathology:

Macroscopy:

- Infiltrating carcinoma:
    - More common
    - Appears as a poorly defined area of diffuse thickening and induration of the gallbladder wall
    - May cover several square centimeters or may involve the entire gallbladder
    - Deep ulceration can cause direct penetration of the gallbladder wall or fistula formation
    - Has a very firm consistency (it is scirrhous)
- Exophytic carcinoma:
    - Irregular, cauliflower mass
    - Grows into the lumen but at the same time invades the underlying wall
    - The luminal portion may be necrotic, hemorrhagic, and ulcerated
    - The most common sites of involvement are the fundus and the neck
    - 20% involve the lateral walls

Microscopy: adenocarcinoma

Evolution:

- Local invasion:
    - The liver: invasion is almost always present at the date of diagnosis
    - The cystic duct and adjacent bile ducts
- Metastases: perihepatic lymph nodes, peritoneum, liver, lungs

Clinical features:

- Asymptomatic or insidious
- May be found at the time of cholecystectomy for symptomatic gallstones.

PATHOLOGY OF THE PANCREAS

CYSTIC FIBROSIS (MUCOVISCIDOSIS)

Definition: disease of exocrine gland function that involves multiple organ systems and chiefly results in: chronic respiratory infections, pancreatic enzyme insufficiency, associated complications in untreated patients

Epidemiology:

- The most common lethal genetic disease in Caucasians: 1 in 3200 live births; 2% to 4% heterozygous carriers
- Uncommon among Asians and African Americans
- Autosomal recessive transmission
- Age of presentation: neonates
- Median age of survival is 36.9 years (higher in males than in females)

Pathogenesis:

- Abnormal function of an epithelial chloride channel protein encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene: on chromosome band 7q31.2
- Disorder in epithelial transport affecting fluid secretion in exocrine glands and the epithelial lining of the respiratory, gastrointestinal, and reproductive tracts
- Leads to abnormally viscid mucous secretions, which obstruct organ passages and results in:
    - Recurrent pulmonary infections leading to chronic lung disease
    - Pancreatic insufficiency, steatorrhea, malnutrition
    - Liver cirrhosis
    - Intestinal obstruction
    - Male infertility

Clinical manifestations may appear at any point in life from before birth to much later in childhood or even in adolescence

Pathology:

The pancreas:

- Involved in 85%-90% of patients with cystic fibrosis
- Initially: accumulations of mucus in the small ducts → dilation of the exocrine glands
- With time: ducts are totally plugged with viscid mucus → atrophy of the exocrine glands, progressive fibrosis
- Advanced stages: total atrophy of the exocrine pancreas → malabsorption, malnutrition, avitaminosis A, squamous cell metaplasia of the ductal epithelium

The lung:

- Involved in 90% -100% of patients surviving the neonatal period
- End-stage lung disease is the principal cause of death
- The bronchioles: distended with thick mucus (hyperplasia and hypertrophy of the mucus-secreting cells)
- Severe chronic bronchitis and bronchiectasis (superimposed infections)
- Lung abscesses: *Staphylococcus aureus, Hemophilus influenzae, Pseudomonas aeruginosa*
- Allergic bronchopulmonary aspergillosis

The liver:

- Bile canaliculi are plugged by mucinous material
- Ductular proliferation and portal inflammation
- Hepatic steatosis
- Over time → biliary cirrhosis

The salivary glands

- Frequently involved
- Like the pancreas:
    - Progressive dilation of ducts
    - Squamous metaplasia of the epithelium
    - Glandular atrophy followed by fibrosis

Small bowel:

- Thick viscid plugs of mucus in the small intestine of infants → sometimes cause meconium ileus (obstruction)

Testes:

- Azoospermia and infertility: 95% of the males who survive to adulthood
- Congenital bilateral absence of the vas deferens (CBAVD):
    - Common
    - May be the only feature suggesting an underlying CFTR mutation

Other findings:

- Recurrent sinonasal polyps: 25% of patients
- Children who present with this finding should be tested for abnormalities of sweat chloride!!!

PANCREATITIS

ACUTE PANCREATITIS (AP)

Defintion: group of reversible lesions characterized by inflammation of the pancreas ranging in severity from edema and fat necrosis to parenchymal necrosis with severe hemorrhage

Epidemiology: it is a common disease

Etiology:

- *Most common:* alcoholism, biliary tract disease (biliary litiasis)
- *Less common:*
  - Obstruction of the pancreatic duct system (periampullary tumors, parasites)
  - Medication
  - Infections: mumps, coxsackieviruses, Mycoplasma pneumoniae
  - Metabolic disorders: hypertriglyceridemia, hyperparathyroidism, hypercalcemic states
  - Acute ischemia: vascular thrombosis, embolism, vasculitis, shock
  - Trauma: blunt trauma, iatrogenic injury (surgery, endoscopic retrograde cholangiopancreatography - ERCP)
- *10% to 20% of patients:* no known etiology (genetic?)

Pathogenesis of acute pancreatitis:

- Autodigestion of the pancreatic substance by inappropriately activated pancreatic enzymes
- The main proenzymes involved in AP: trypsinogen, prophospholipase, proelastase
- The first activated is trypsinogen → trypsin → activates other proenzymes → autodigestion
  - Acinar necrosis (trypsin)
  - Fat necrosis (phospholipase)
  - Blood vessel injury (elastase)

!!! Activation of trypsinogen is an important triggering event in acute pancreatitis

- ***Acute interstitial pancreatitis:*** milder form of disease
  - Interstitial edema
  - Focal areas of fat necrosis: pancreatic, peripancreatic
- ***Acute necrotizing hemorrhagic pancreatitis:*** the most severe
  - Extensive parenchymal necrosis is accompanied by diffuse hemorrhage within the pancreas
  - Necrosis of pancreatic tissue: acinar and ductal tissues, the islets of Langerhans
  - Necrosis of blood vessels → hemorrhage

Macroscopy:

- Pancreas:
  - Enlarged
  - With areas of red-black hemorrhage and with foci of yellow-white, chalky fat necrosis
  - White-gray areas of acinar necrosis
- Fat necrosis may also be found in extrapancreatic fat deposits:
  - Omentum and the mesentery of the bowel
  - Outside the abdominal cavity: subcutis, mediastinum
- The peritoneal cavity contains a serous, slightly turbid, brown-tinged fluid, with globules of fat

Microscopy:

- Various features, from inflammation and edema to severe extensive necrosis and hemorrhage
- The basic alterations are:
  - Microvascular leakage causing edema
  - Necrosis of fat by lipolytic enzymes: stained blue with H&E stain because of calcium salts
  - Proteolytic destruction of pancreatic parenchyma: eosinophilic necrosis
  - Destruction of blood vessels with subsequent interstitial hemorrhage
  - Acute inflammatory reaction

Clinical features of acute pancreatitis:
- Abdominal pain: constant, intense, and is often referred to the upper back
- Full-blown acute pancreatitis is a medical emergency
- Systemic features: leukocytosis, hemolysis, disseminated intravascular coagulation, fluid sequestration, acute respiratory distress syndrome, and diffuse fat necrosis
- Peripheral vascular collapse and shock with acute renal tubular necrosis may occur

Laboratory findings:
- Marked elevation of serum amylase levels during the first 24 hours
- Rising serum lipase level within 72 to 96 hours
- Glycosuria
- Hypocalcemia

Evolution:
- Most patients recover fully
- 5% die: shock, acute respiratory distress syndrome, acute renal failure

Late complications:
- Sterile abscess
- Pseudocyst
- Infection of necrotic debris by Gram-negative organisms

CHRONIC PANCREATITIS (CP)

Definition: continuing chronic inflammatory process of the pancreas, characterized by irreversible morphological changes, which can lead to: chronic abdominal pain and/or impairment of exocrine and endocrine function of the pancreas

Pathogenesis:
- Repeated bouts of acute pancreatitis
- Irreversible impairment in pancreatic function

Etiology:
- Significant overlap in the causes of acute and chronic pancreatitis
- The most common cause of CP: long-term alcohol abuse (usually middle-aged males)
- Less common causes:
    - Chronic obstruction of the pancreatic duct (pseudocysts, calculi, trauma, neoplasms, pancreas divisum)
    - Tropical pancreatitis
    - Hereditary pancreatitis: germ line mutations in the PRSS1 or SPINK1 genes
    - Idiopathic chronic pancreatitis:

Pathology:

Macroscopy:
- The pancreas is hard
- Sometimes with extremely dilated ducts and visible calcified concretions

Microscopy: two morphological forms
- Calcifying chronic pancreatitis (95%)
- Obstructive chronic pancreatitis

General microscopic features in chronic pancreatitis:
- Parenchymal fibrosis
- Reduced number and size of acini (a constant feature)
- Islets of Langerhans: relatively spared initially, may fuse together (appear enlarged), with time disappear
- Variable dilation of the pancreatic ducts
- Chronic inflammatory infiltrate (lymphocytes, plasma cells) around lobules and ducts
- The interlobular and intralobular ducts: dilated, with protein plugs in the lumens ± calcifications
- The ductal epithelium: atrophic or hyperplastic ± squamous metaplasia

Autoimmune pancreatitis: is a distinct form of chronic pancreatitis characterized by a duct-centric mixed inflammatory cell infiltrate with many IgG4-secreting plasma cells.

Clinical features:
- Repeated attacks of moderately / severe abdominal pain
- Recurrent attacks of mild pain
- Persistent abdominal and back pain
- May be entirely silent until pancreatic insufficiency and diabetes mellitus develop
- *Recurrent attacks of jaundice*
- *Vague attacks of indigestion*
- *Attacks may be precipitated by alcohol abuse, overeating, use of opiates and other drugs that increase the tone of the sphincter of Oddi*

Prognosis: the long-term outlook is poor, with a 20-to-25-year mortality rate of 50%
Complications:
- Severe pancreatic exocrine insufficiency and chronic malabsorption
- Diabetes mellitus
- Pancreatic pseudocysts
- Pancreatic cancer (4% of those with hereditary forms of CP)

PANCREATIC PSEUDOCYSTS

Definition: localized collections of necrotic-hemorrhagic material rich in pancreatic enzymes
Epidemiology: account for approximately 75% of cysts in the pancreas
Etiology:
- After an episode of acute pancreatitis
- Chronic alcoholic pancreatitis
- Traumatic injury to the abdomen

Pathogenesis: are formed by the walling off of areas of peripancreatic hemorrhagic fat necrosis with fibrous tissue
Pathology:
Macroscopy:
- Usually solitary
- 2 to 30 cm in diameter
- Location:
    - Within the pancreas
    - Attached to the surface of the gland and involve peripancreatic tissues (most common)
    - Other:
        - The lesser omentum
        - In the retroperitoneum: between the stomach and transverse colon
        - Between the stomach and liver
        - Subdiaphragmatic
- On section: composed of central necrotic-hemorrhagic material rich in pancreatic enzymes

Microscopy:
- No epithelial lining (hence the prefix "pseudo"; *a real cyst has an epithelial lining*)
- A central area of necrosis and hemorrhage
- At the periphery: granulation tissue, fibrosis

Evolution:
- Resolves spontaneously
- May be secondarily infected
- Larger pseudocysts may compress or perforate into adjacent structures

PATHOLOGY OF DIABETES MELLITUS (DM) AND ITS LATE COMPLICATIONS

Pancreas:

- Pathologic findings in the pancreas are variable and not necessarily dramatic
- Lesions are inconstant and rarely of diagnostic value
- Distinctive changes are more commonly associated with type 1 diabetes
- *Type 1 DM:* one or more of the followings:
    - Reduction in the number and size of islets
        - Particularly with rapidly advancing disease
        - Most of the islets are small and inconspicuous, not easily detected
    - Insulitis: infiltration of the islets with T lymphocytes
        - May be seen at the time of clinical presentation
        - Uneven distribution
    - Electron microscopy: β-cell degranulation
- *Type 2 DM:* islets modifications:
    - Subtle reduction in cell mass
    - Amyloid replacement: deposition of pink, amorphous material
    - Fibrosis: in long-standing cases of type 2 diabetes.

Diabetic macrovascular disease (macroangiopathy):

- The hallmark of diabetic macrovascular disease is accelerated **atherosclerosis**:
    - Involves: aorta, large- and medium-sized arteries
    - Greater severity
    - Earlier age at onset
    - Effects:
        - Myocardial infarction - common cause of death in diabetics (M=F)
        - Gangrene of the lower extremities (about 100 times more common in diabetics)
        - Brain infarction
- **Hyaline arteriolosclerosis**:
    - Associated with hypertension
    - More prevalent and more severe in diabetics
    - ***Microscopy:*** amorphous, hyaline thickening of the arteriolar wall, narrowing of the lumen

Diabetic microangiopathy:

- Diffuse thickening of basement membranes (BM)
- Most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, renal medulla
- ***Microscopy:***
    - Concentric layers of hyaline material composed predominantly of type IV collagen
    - Despite thickened BM, diabetic capillaries are more leaky than normal to plasma proteins
- Effects of microangiopathy: diabetic nephropathy, retinopathy, some forms of neuropathy

Diabetic ocular complications:

- Retinopathy
- Cataract formation
- Glaucoma

Diabetic neuropathy:

- Central: linked to atherosclerosis
- Peripheral – linked to the microangiopathy

Diabetic nephropathy: see urinary pathology

EXOCRINE NEOPLASMS OF THE PANCREAS
PANCREATIC CARCINOMA

Infiltrating ductal adenocarcinoma = "pancreatic cancer"

Epidemiology:
- The fourth leading cause of cancer death in the United States (lung, colon, and breast)
- Disease in the elderly: 80% of cases occur between 60 and 80 years of age
- M>F
- More common in black people
- The most common type of pancreatic cancer

Precursors to pancreatic cancer: "pancreatic intraepithelial neoplasias" (PanINs)

Etiopathogenesis:
- Smoking: doubles the risk of pancreatic cancer
- Diet rich in fats
- Chronic pancreatitis
- Diabetes mellitus
- Familial clustering: inherited genetic syndromes that increase pancreatic cancer risk (HNPCC Lynch II, hereditary breast and ovarian cancer, hereditary pancreatitis, Peutz-Jeghers syndrome)

Pathology:

Location:
- Head: 60%
- Body: 15%
- Tail: 5%
- Diffuse: 20%

Macroscopy: hard, stellate, gray-white, poorly defined masses

Microscopy:
- Usually moderately to poorly differentiated adenocarcinoma
- Two features are characteristic:
    - Highly invasive (appear in early stages)
    - Desmoplasia: dense stromal fibrosis

Clinicopathologic correlations:

Carcinomas of the head of the pancreas obstruct the distal common bile duct → marked distention of the biliary tree in about 50% of patients, jaundice

Carcinomas of the body and tail: remain silent for some time; may be large and widely disseminated by the time they are discovered

Extension of pancreatic cancers (generally):
- Through the retroperitoneal space, entrapping adjacent nerves (perineural invasion is very characteristic)
- Invade: spleen, adrenals, vertebral column, transverse colon, stomach
- Lymph node metastases: peripancreatic, gastric, mesenteric, omental, portohepatic
- Distant metastases: liver, lungs, bones

Clinical features:
- Remain silent until invade other structures
- Pain is usually the first symptom (in this stage most cancers are beyond cure)
- Obstructive jaundice - carcinoma of the head of the pancreas
- Weight loss, anorexia, and generalized malaise and weakness: in advanced disease
- Migratory thrombophlebitis: Trousseau sign

Prognosis:
- Has one of the highest mortality rates of any cancer
- Fewer than 20% of pancreatic cancers are resectable at the time of diagnosis
- Median survival from diagnosis: 3 to 6 months; 5-year survival is less than 5%

TUMORS OF THE ENDOCRINE PANCREAS

NEUROENDOCRINE TUMORS (NET)

General features of NET:

- Also named "islet cell tumors"
- Are rare in comparison with tumors of the exocrine pancreas (2% of all pancreatic neoplasms)
- Most common in adults
- Can occur anywhere along the length of the pancreas, intrapancreatic or peripancreatic
- Resemble neuroendocrine tumors of the digestive tract
- Single or multiple (each tumor may be composed of a different cell type)
- May have a benign or malignant course
- Can be functional (elaborate pancreatic hormones) or nonfunctional

!!! It is difficult to predict the biologic behavior of a pancreatic endocrine neoplasm based on light microscopic criteria alone

Unequivocal criteria for malignancy:

- Metastases to regional lymph nodes or distant organs (including the liver)
- Vascular invasion
- Gross invasion of adjacent viscera

Other features suggestive of malignancy:

- *Infiltration beyond the tumor capsule into the pancreatic parenchyma*
- *High mitotic indexKi-67 labeling index*
- *Tumor necrosis*
- *Significant cellular atypia*
- *Size: tumors less than 2 cm in diameter tend to be indolent*
- *The functional status: i.e., 90% of insulinomas are benign*

The most common clinical syndromes associated with functional NETs:

- *Hyperinsulinism*
- *Hypergastrinemia and Zollinger-Ellison syndrome*
- *Multiple endocrine neoplasia*