Objectives

- to appreciate the pathophysiology of syndromes of aberrant function in liver disease in terms of hepatocyte dysfunction, portal-to-systemic shunting or both
- to describe the pathology of common diseases causing
  - acute hepatitis and fulminant hepatic failure
  - chronic hepatitis and cirrhosis
  - cholestasis
- to describe the pathology of focal or extrinsic diseases with variable manifestations in the liver
- to distinguish the pathology of space-occupying lesions in the liver
- to describe the pathology of common diseases of the pancreas

Outline

I. Pathophysiology of liver injury and repair

a. **Liver anatomy and microarchitecture**
b. **Evaluation of liver disease:** *Liver panel*
c. **Mechanisms of liver injury and repair:** *Hepatocyte and parenchymal response, scar formation and regression, inflammation and immunity*
d. **Liver failure:** *Acute, chronic (associated with cirrhosis and portal hypertension) and acute on chronic*

II. Liver diseases

a. **Infectious:** *Viral hepatitis, bacterial, parasitic and helminthic*
b. **Autoimmune hepatitis (AIH)**
c. **Drug and toxin-induced liver injury (DILI):** *Drugs, Alcoholic liver disease (ALD)*
d. **Metabolic disease:** *Non-alcoholic fatty liver disease (NAFLD), haemochromatosis, Wilson disease, a1-antitrypsin deficiency*
e. **Circulatory disorders:** *Hepatic vein outflow obstruction (HVOO), passive congestion etc.*

III. Cholestatic / biliary diseases

a. **Definitions and pathophysiology of jaundice**
b. **Large bile duct obstruction**
c. **Primary hepatolithiasis**
d. **Neonatal cholestasis:** *Biliary atresia, neonatal hepatitis*
e. **Autoimmune cholangiopathies:** *Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)*
f. **Structural anomalies of the biliary tree:** *Choledochal cyst, fibropolycystic disease*

IV. Neoplasms of liver and biliary tract

a. **Non-neoplastic:** *Focal nodular hyperplasia (FNH)*
b. **Neoplastic (benign):** *Cavernous haemangioma, Hepatocellular adenoma*
c. **Neoplastic (malignant):** *Hepatocellular carcinoma (HCC), Hepatoblastoma, Cholangiocarcinoma, Metastases*

V. Gallbladder

a. **Cholelithiasis (gallstones):** *Cholesterol vs pigment stones*
b. **Cholecystitis:** *Acute cholecystitis, chronic cholecystitis*
c. **Gallbladder carcinoma**

VI. Pancreas

a. **Normal anatomy and function**
b. **Congenital anomalies:** *Pancreas divisum, Annular pancreas etc.*
c. **Pancreatitis:** *Acute pancreatitis, chronic pancreatitis*
d. **Masses (non-neoplastic):** *Pseudocysts, congenital cysts*
e. **Masses (neoplastic):** *Cystic epithelial neoplasms, Ductal adenocarcinoma, Neuroendocrine neoplasms*

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 9th ed.
Odze R, Goldblum J. *Odze and Goldblum Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas.* 3rd ed.

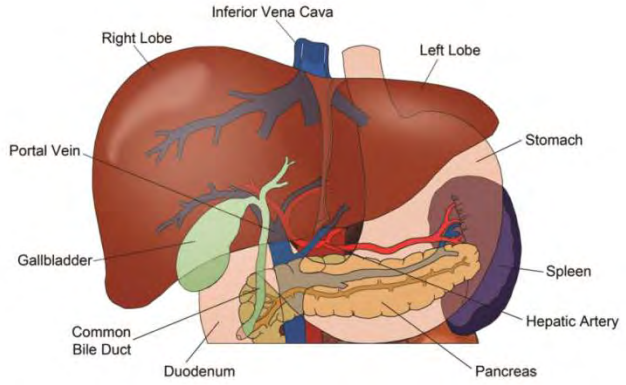
Image credits

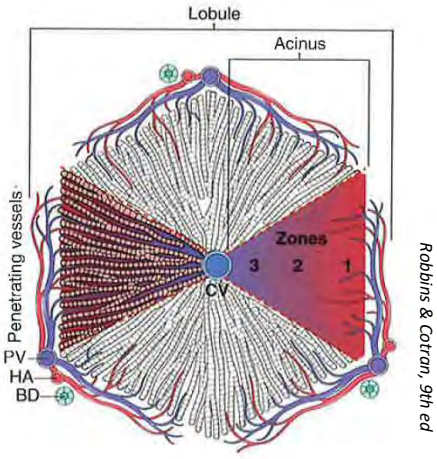
Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 9th ed.
Prof Aileen Wee, Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. PATHOPHYSIOLOGY OF LIVER INJURY AND REPAIR

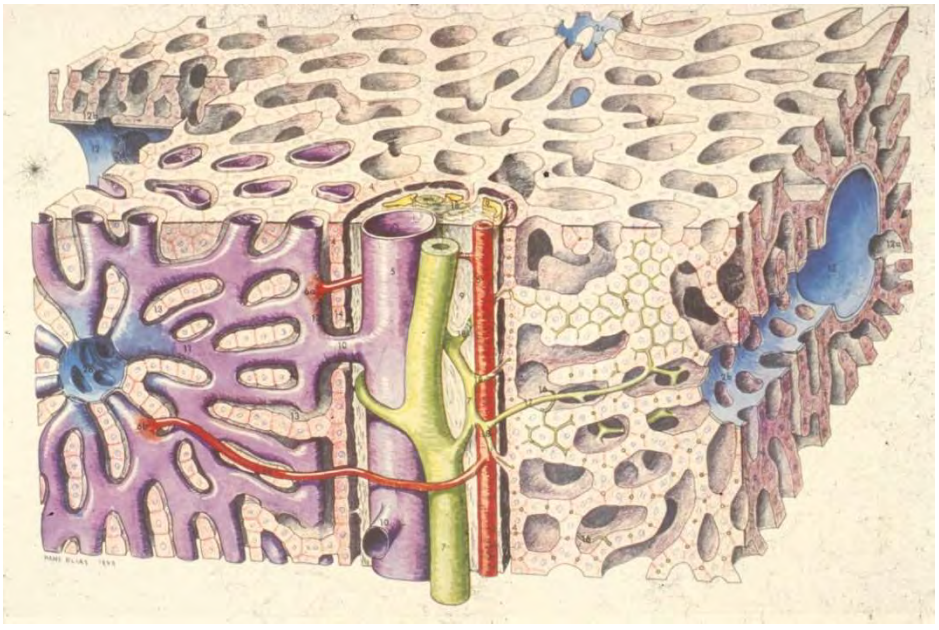
Liver anatomy and microarchitecture





Robbins & Cotran, 9th ed

- Major metabolic organ, 1400-1600 grams
- Highly vascular with dual blood supply (portal vein: 60-70%, hepatic artery: 30-40%). In comparison, the biliary tract is solely supplied by the hepatic artery
- **Anatomical** (3 lobes) versus **Functional** division (8 independent segments)
- 3 major components: Hepatocytes, vasculature and biliary tract, organized into hepatic **lobules** (lobular model: oriented around the central vein) or **acini** (acinar model: based on blood flow)
    - **Portal tract**: Portal vein (PV), hepatic artery (HA) and interlobular bile duct (BD)
    - **Central vein**
    - **Hepatocytes** arranged in liver cell plates, bathed on either side by a mixture of portal venous and hepatic arterial blood in **sinusoids**, which are fenestrated
    - **Kupffer cells** in sinusoids and **hepatic stellate cells (HSCs)** in space of Disse between endothelial cells of sinusoids and hepatocytes
    - **Bile canaliculi** between hepatocytes → **canal of Hering** → **bile ductule** → **bile duct**



Evaluation of liver disease

- The liver panel evaluates parameters of normal liver **function** as well as hepatocyte **integrity**
- It helps to give an indication of the degree of liver damage (inflammation / scarring), and is a surrogate of the functional capacity of the liver
- However, as the liver has enormous functional reserve, mild liver damage may be clinically masked. Therefore, by the time of clinical presentation, most liver diseases are already chronic

Test category	Serum measurement	Tests
Hepatocyte integrity	Cytosolic hepatocellular enzymes^	Serum aspartate aminotransferase (AST) Serum alanine aminotransferase (ALT) Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances normally secreted in bile^	Serum bilirubin – Total, unconjugated (indirect) and conjugated (direct) Urine bilirubin Serum bile acids
	Plasma membrane enzyme (from damage to bile canaliculus)^	Serum alkaline phosphatase (ALP) Serum γ-glutamyl transpeptidase (GGT)
Hepatocyte synthetic function	Proteins secreted into the blood	Serum albumin* Coagulation factors: prothrombin (PT) and partial thromboplastin (PTT) times (fibrinogen, prothrombin, factors V, VII, IX, X)
Hepatocyte metabolism		Serum ammonia^ Aminopyrine breath test (hepatic demethylation)*

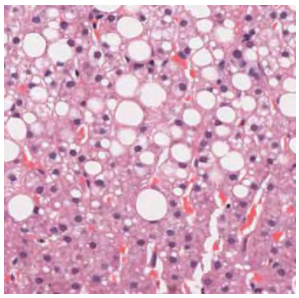
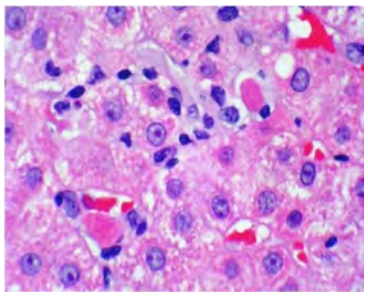
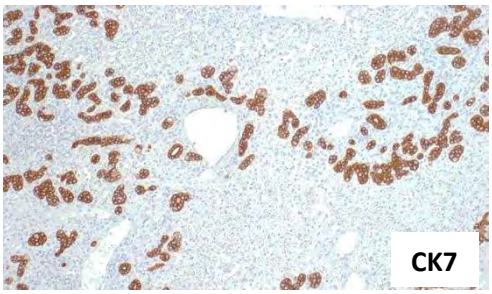
Liver test	Normal range
Total Bilirubin	5 - 30 µmol/L
- Conjugated	0 - 5 µmol/L
- Unconjug	5 - 25 µmol/L
Albumin	38 - 48 g/L
AST	10 - 50 U/L
ALT	10 - 70 U/L
ALP	40 - 130 U/L
LDH	250 - 580 U/L
GGT	15 - 90 U/L

^ increased in liver disease
* decreased in liver disease

Mechanisms of liver injury and repair

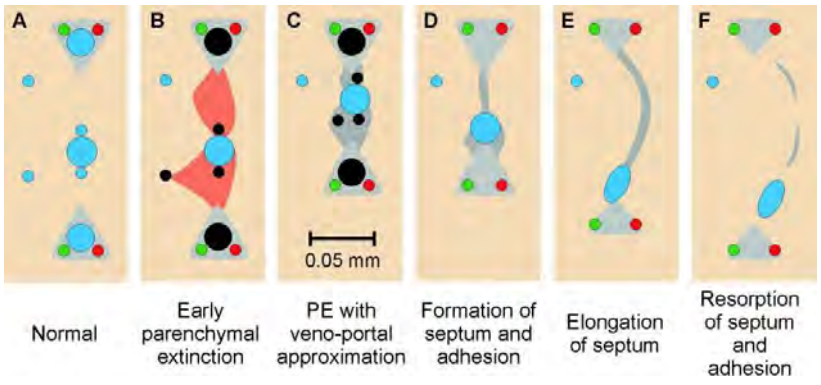
I. Hepatocyte and parenchymal responses

Degenerative but potentially reversible changes	Cellular swelling (**ballooning degeneration**) **Steatosis** (accumulation of fat) **Cholestasis** (accumulation of bilirubin)
Irreversible injury and cell death	**Necrosis**: usually in ischaemic / hypoxic injury, resulting in cellular swelling and rupture, which are then phagocytosed by macrophages **Apoptosis**: Caspase cascades activated, resulting in cellular shrinkage and eosinophilia (acidophil bodies) **Spotty necrosis → Confluent necrosis (zonal → bridging → submassive → massive hepatic necrosis)**
Regeneration	Primary mechanism: **Mitotic replication** of hepatocytes If extensive injury: Activation of primary **stem cell** niche (canals of Hering) Eventually, hepatocytes reach replicative senescence and there is stem cell activation (seen as 'ductular reaction')

II. Scar formation and regression

MacSween's Pathology of the Liver, 6th ed

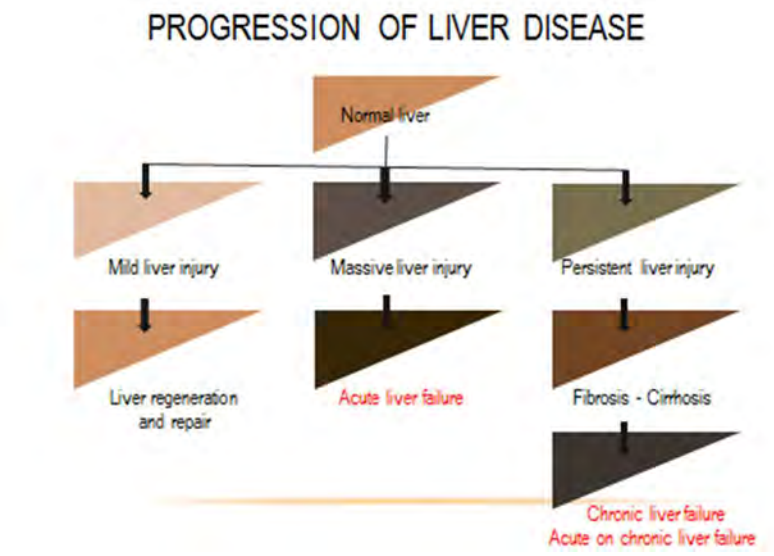


- Zones of parenchymal loss transform into dense **fibrous septa** through a combination of (i) the **collapse of underlying reticulin** and (ii) **activation of HSCs** in response to inflammatory cytokines from chronic inflammation, cytokine and chemokines from Kupffer cells (e.g. PDGF, TNF), endothelial cells, hepatocytes, bile duct epithelial cells, disruption of the extracellular matrix and direct stimulation by toxins
- When quiescent, HSCs are lipid (vitamin A) storage cells. When activated, they are converted into **highly fibrogenic contractile myofibroblasts**
- Scar deposition often begins in the space of Disse, manifest as **pericellular / perisinusoidal fibrosis**
- Other contributors to scar deposition include portal fibroblasts and ductular reaction (by activation and recruitment of fibrogenic cells, and via epithelial-mesenchymal transition)
- Fibrous septa encircle surviving regenerating hepatocytes in late stages of chronic liver disease (**bridging fibrosis**), giving rise to diffuse scarring (**cirrhosis**)
- If the chronic injury is interrupted, **scar formation can be reversed (regression)** as stellate cell activation ceases, scars condense and are resorbed by **matrix metalloproteinases** produced by hepatocytes (**extracellular matrix remodeling**)
- Therefore, in any chronic liver disease, there is actually a **mixture of both fibrotic progression (matrix deposition) and regression (matrix resorption)**. The balance is influenced by the severity and persistence of the underlying disease

III. Inflammation and immunity

- Liver injury and repair involves both innate and adaptive immune systems
- Adaptive immunity is especially important in viral hepatitis, whereby antigen-specific and CD8+ T cells are involved in eradication of Hepatitis B and C via elimination of infected hepatocytes
- Cytokines released by the various inflammatory cells are involved in recruitment of inflammatory cells, hepatocyte injury, vascular disturbances, promotion of scarring, hepatocyte replication

Liver failure



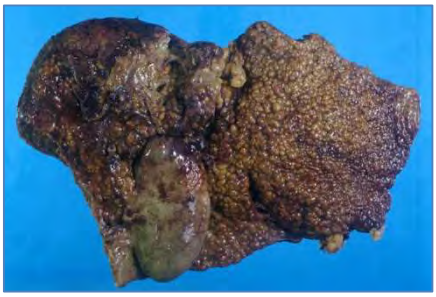
- The most severe clinical consequence of liver disease is **liver failure**, where there is loss of 80-90% of the hepatic functional capacity. Without liver transplantation, the mortality rate is ~80%
- Liver failure has several manifestations:
    - **Cholestasis**: impaired bile secretion (bilirubin and other solutes in bile)
    - **Coagulopathy**: impaired synthesis of Vit K-dependent and -independent clotting factors, and reduced removal of activated coagulation factors leading to disseminated intravascular coagulation
    - **Hepatic encephalopathy**: decreased ammonia metabolism causes impaired neuronal function and cerebral oedema
    - **Portal hypertension**: more often seen in chronic than acute liver failure; results in **ascites**, **portosystemic venous shunts**, **congestive splenomegaly** and **hepatic encephalopathy**
    - **Hepatorenal syndrome**: renal failure that occurs in individuals with liver failure without intrinsic morphologic or functional causes for kidney dysfunction
    - **Hepatopulmonary syndrome**: intrapulmonary vascular dilatations in chronic liver disease result in V/Q mismatch and right to left shunting, manifesting as hypoxia
    - **Portopulmonary hypertension**: pulmonary arterial hypertension arising in chronic liver disease and portal hypertension, manifesting as dyspnea on exertion and finger clubbing
- **Most common terminal events**: hepatic encephalopathy, bleeding from oesophageal varices, bacterial infections / sepsis (resulting from gut bacterial translocation and Kupffer cell dysfunction), hepatocellular carcinoma (in chronic liver disease)

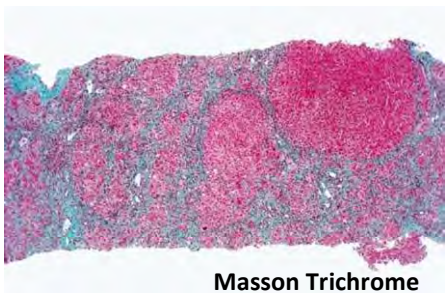
Acute liver failure: sudden and massive hepatic destruction

- Acute liver illness associated with encephalopathy and coagulopathy that occurs within 26 weeks of the initial liver injury, **in the absence of pre-existing liver disease**
- Causes: Drugs / toxins (faster time course), acute Hepatitis A/B/E, autoimmune hepatitis
- Histology: **Massive hepatic necrosis;** (Diffuse injury without obvious cell death)

Chronic liver failure: follows years of insidious progressive liver injury

- Causes: Chronic Hep B and C, NAFLD, alcoholic liver disease, cryptogenic
- Histology: **Cirrhosis -**
  Diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular (often portosystemic) shunting





Masson Trichrome

- Caveats:
  - Not all end-stage chronic liver disease is cirrhotic e.g. primary biliary cholangitis
  - Not all cirrhosis leads to chronic liver failure (Child-Pugh clinical classification A-C)
  - Regression of cirrhosis is now considered possible (no longer 'end-stage')
- 40% of cirrhotics are asymptomatic until most advanced stages; when symptomatic, the features are often non-specific e.g. anorexia, weight loss, weakness or symptoms / signs of liver failure in advanced disease
- **Portal hypertension**: increased resistance to portal blood flow, due to prehepatic, intrahepatic or posthepatic causes.

  Pathophysiology in cirrhosis involves:

  1. Resistance to portal flow at sinusoids: caused by contraction of vascular smooth muscle and myofibroblasts, disruption of blood flow by scarring and formation of parenchymal nodules, and sinusoidal remodeling and arterial-portal anastomosis / intrahepatic shunts
  2. Increase in portal flow due to a hyperdynamic circulation, which results from arterial vasodilatation primarily in the splanchnic circulation

Signs and symptoms of chronic liver disease

- Cholestasis
  - Jaundice → pruritus
  - Scleral icterus
- Hyperoestrogenemia
  - Palmar erythema
  - Spider angiomas
  - Hypogonadism
  - Gynaecomastia
- Coagulopathy → easy bruising
- Portal hypertension
  - Ascites
  - Portosystemic venous shunts: caput medusae, anorectal varices
  - Splenomegaly
  - Hepatic encephalopathy: asterixis 'hepatic flap'

Causes of portal hypertension

Prehepatic	Portal vein: Obstructive thrombosis or narrowing Massive splenomegaly with increased splenic vein blood flow
Intrahepatic	Cirrhosis (any cause) Non-cirrhotic portal hypertension e.g. Nodular regenerative hyperplasia Diffuse infiltrative processes e.g. granulomatous inflammation, amyloid, malignancy
Posthepatic	Hepatic vein outflow obstruction Heart problems: right heart failure, constrictive pericarditis

- **Ascites**: accumulation of excess fluid in the peritoneal cavity (500 ml is clinically detectable)
    - 85% of cases are caused by cirrhosis
    - If long-standing, peritoneal fluid can seep through trans-diaphragmatic lymphatics, resulting in hydrothorax (R>L).
    - Pathogenesis involves (i) **sinusoidal hypertension** which drives fluid into the space of Disse (due to Starling's forces and facilitated by hypoalbuminemia) which is removed by hepatic lymphatics, (ii) **percolation of hepatic lymph into the peritoneal cavity** as the thoracic duct capacity is exceeded, and (iii) **splanchnic vasodilation**, thereby reducing arterial blood pressure and the effective circulatory volume. This triggers the activation of the renin-angiotensin system and anti-diuretic hormone secretion, causing sodium and water retention and increased perfusion pressure of the interstitial capillaries with subsequent extravasation of fluid into the abdominal cavity
- **Portosystemic shunts**: portal hypertension causes reversal of flow from portal to systemic circulation by dilatation of collateral vessels and development of new vessels wherever the systemic and portal circulation share common capillary beds – rectum, oesophago-gastric junction, retroperitoneum and falciform ligament / periumbilical and abdominal wall.
- **Congestive splenomegaly**: may manifest as haematologic abnormalities in hypersplenism
- **Hepatic encephalopathy**: spectrum of disturbances in consciousness ranging from subtle behavioural abnormalities to confusion, stupor, coma and death

Acute on chronic liver failure: (1) An **unrelated** acute injury supervenes on a well-compensated late-stage chronic disease, or (2) the **chronic disease itself has a flare of activity** that leads directly to liver failure.

- Causes: Intrahepatic (e.g. chronic Hep B patients superinfected with Hep D, ascending cholangitis in a PSC patient, development of malignancy or liver metastases) or Systemic (e.g. sepsis and causes of hypotension)

II. LIVER DISEASES

Insult	Primary liver disease	Secondary / Systemic
Metabolic	Nonalcoholic fatty liver disease (NAFLD)	Amyloidosis
Toxic	Alcoholic liver disease (ALD)	Drug-induced liver injury (DILI)
Infectious	Viral hepatitis	Extrahepatic/systemic infections, e.g. viruses, bacteria, fungi
Immune-mediated	Autoimmune hepatitis (AIH) Primary biliary cholangitis (PBC) Primary sclerosing cholangitis (PSC)	Systemic lupus erythematosus (SLE)
Obstructive	Small intrahepatic biliary disorders (congenital, acquired)	Extrahepatic obstructive lesions
Vascular	Veno-occlusive disease (VOD) / sinusoidal obstruction syndrome (SOS)	Heart failure
Neoplastic	Hepatocellular carcinoma (HCC)	Metastatic cancer

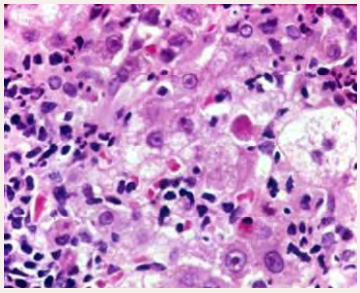
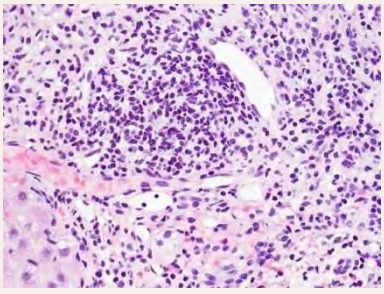
*The term 'hepatitis' refers liver injury in general, not necessarily infection by Hepatitis viruses A-E

Infectious liver diseases

Viral hepatitis

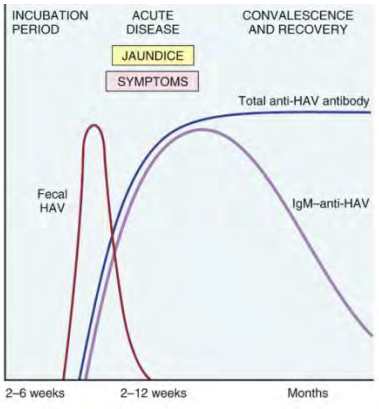
- Includes **hepatotropic viruses** (viruses that have a specific affinity for the liver – Hep A, B, C, D and E) and **non-hepatotropic viruses** (often systemic infections with multiorgan involvement - EBV, CMV)
- Clinicopathologic syndromes of viral hepatitis:
    - **Acute infection**
        - **Asymptomatic** with recovery (serologic evidence only)
        - **Symptomatic** with recovery (4 phases): incubation period → symptomatic preicteric → symptomatic icteric → convalescence
        - **Acute liver failure** with submassive/massive hepatic necrosis
    - All hepatotropic viruses can cause acute asymptomatic or symptomatic infection
    - Fulminant hepatitis usually with HAV, HBV or HDV; HEV in pregnant women
    - **Chronic hepatitis, with or without progression to cirrhosis**
        - Definition: **Symptomatic, biochemical or serologic evidence** of continuing or relapsing hepatic disease **for more than 6 months**
        - Causes: Usually HCV (or HBV); HAV and HEV do not cause chronic hepatitis unless immunocompromised host
        - **Carrier state**: An individual who harbours and can transmit an organism, but has **no** manifest symptoms i.e. they carry one of the viruses, and either have no liver disease or have non-progressive liver damage, free of symptoms and disability. These individuals are reservoirs for infection. The carrier rate is largely dictated by the age at infection: highest perinatally and lowest in adulthood.

  - HBV 'healthy carrier': HBsAg+, HBeAg- but anti-HBe+, low/undetectable HBV DNA, AST/ALT normal, liver biopsy no significant inflammation. However, this is probably not a stable state – re-activation may occur e.g. co-infection, changes in immunity
  - HCV: does not exist as infected individuals usually progress to chronic hepatitis
- As the clinical and histopathologic picture of **acute and chronic hepatitis** shows similarities amongst the various viruses as well as with non-viral causes of liver injury (autoimmune hepatitis, drug/toxin-induced hepatitis), serologic and molecular studies are essential for diagnosis and subtyping

Acute viral hepatitis ≤ 1 month	**Chronic viral hepatitis** > 6 months
Lobular hepatitis	**Portal hepatitis**
▪ Lobular disarray ▪ Hepatocyte degeneration (hydropic swelling) ▪ Apoptosis, spotty necrosis with hepatocyte dropout to confluent necrosis (perivenular, bridging) ▪ Lymphoplasmacytic infiltrate ▪ Kupffer cell hypertrophy ▪ Cholestasis +/-	▪ Lymphoplasmacytic portal infiltration ▪ Portal and periportal (interface) hepatitis to bridging hepatic necrosis ▪ Fibrosis to cirrhosis; regression may occur ○ Hep B: ground-glass hepatocytes ○ Hep C: lymphoid aggregates/follicles, fatty change, bile duct injury
	
It is **the pattern of injury** that is different between the two time-courses, not the nature of the inflammatory cell infiltrate (both are mononuclear, mainly T cells)	

Hepatitis A

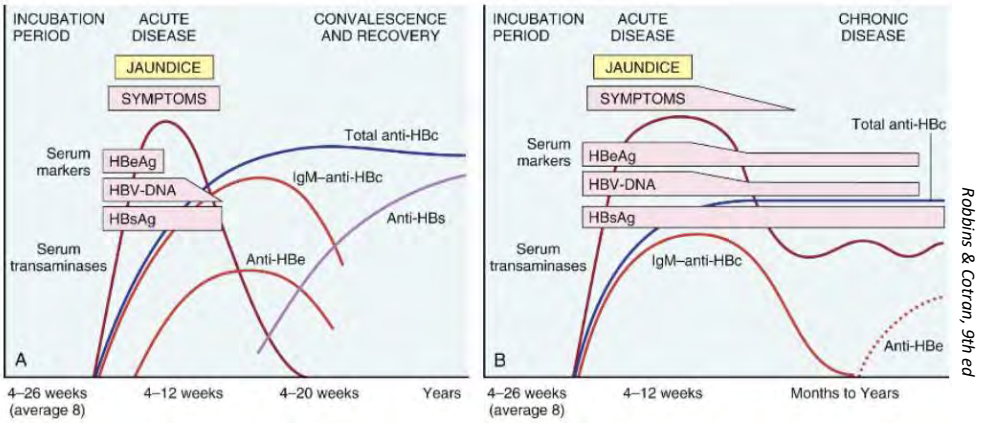
- Benign **self-limited disease** which is often mild or asymptomatic
  - **Does not** cause chronic hepatitis or carrier state
  - Only uncommonly causes acute hepatic failure
- 2-6 weeks incubation period; transient viraemia
- Fecal-oral transmission
  - Endemic in countries with poor hygiene / sanitation
  - Outbreaks in close quarters
  - Sporadic infections via consumption of raw shellfish
- IgG anti-HAV persists for years ~ lifelong immunity



Robbins & Cotran, 9th ed

Hepatitis B

- Can cause acute hepatitis (25%), acute hepatic failure (<1%), chronic hepatitis (5-10%) +/- cirrhosis or carrier state. **65% of acute infections are subclinical with subsequent recovery**.
- **Risk factor for hepatocellular carcinoma** even in the absence of cirrhosis (HBx protein)
- HBV generally does not cause direct hepatocyte injury; injury is caused by CD8+ cytotoxic T cells attacking infected cells
- 2-26 weeks incubation period
- Enormous global health problem. Mode of transmission varies with geographic areas
    - High prevalence: Vertical transmission
    - Intermediate prevalence: Horizontal transmission esp. early childhood
    - Low prevalence: Sexual and IVDA
- Vaccination induces protective anti-HBs response in 95% of infants, children and adolescents

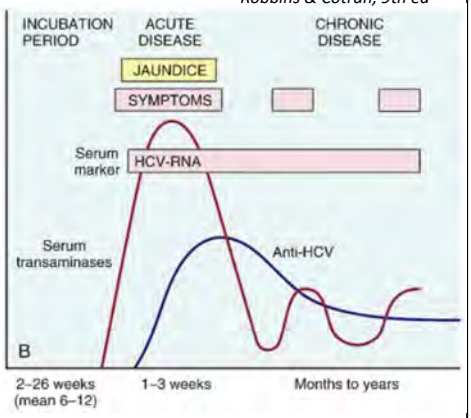


Acute infection with resolution | *Progression to chronic infection*

Hepatitis C

- Acute infection is generally asymptomatic; in contrast to HBV, **persistent infection and chronic hepatitis occurs in The majority (80-90%) of infected individuals,** and is a major cause of liver disease worldwide
- 4-26 weeks incubation period
- Modes of transmission: IVDA, sexual, needle-stick injury, vertical. 1/3 of infected individuals have no identifiable risk factors
- **HCV is inherently genomically unstable** (many quasispecies and antigenic variability), and has multiple strategies to evade host anti-viral immunity. Repeated bouts of hepatic damage therefore occur, leading to persistent infection / chronic hepatitis and cirrhosis (20%)

Robbins & Cotran, 9th ed



Progression to chronic infection

- As such, elevated titers of anti-HCV IgG occurring after an active infection do not confer effective immunity. As circulating HCV RNA often persists despite the presence of antibodies, **HCV RNA testing** in chronic hepatitis must be performed to assess viral replication and confirm diagnosis of HCV infection
- This also means that there is no effective vaccine, although a cure [direct-acting antiviral (DAAs)] is now available to achieve sustained virologic response (undetectable HCV RNA in blood 24 weeks after of treatment).
- Close association with metabolic syndrome (esp. HCV genotype 3) – insulin resistance and NAFLD

Hepatitis D

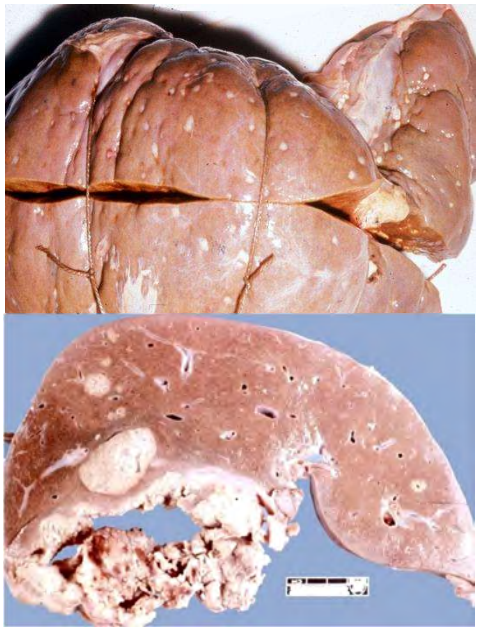
- Prevalence highest in Amazon basin, Middle East, Mediterranean and central Africa
- **Dependent for its life cycle on HBV** – vaccination for HBV prevents HDV infection
    - **Co-infection**: follows exposure to serum containing both HDV and HBV, resulting in acute hepatitis indistinguishable from acute hepatitis B. Self-limited, and usually followed by clearance of both viruses
    - **Superinfection:** occurs when a chronic HBV carrier is exposed to a new inoculum of HDV, presenting as severe acute hepatitis in a previous unrecognised HBV carrier or exacerbation of preexisting chronic Hep B infection. Chronic HDV infection occurs in almost all such patients. The disease can progress to cirrhosis +/- HCC
- Mode of transmission: blood-borne (IVDA, blood transfusions)
- IgM anti-HDV antibody is the most reliable indicator of recent HDV exposure

Hepatitis E

- Usually self-limited but has a high mortality rate in pregnant women (~20%). Chronic infection occurs only in immunosuppressed patients (HIV / transplant)
- 4-5 weeks incubation period
- Fecal-oral transmission
    - Zoonotic disease with animal reservoirs: monkeys, cats, pigs, dogs
    - Epidemics have been reported
    - Sporadic infection esp. in India (>> HAV)
- HEV RNA and virions can be detected by PCR in stool and serum
- IgM replaced by persistent IgG anti-HEV when symptoms start resolving in 2-4 weeks

Bacterial, parasitic and helminthic infections

- There are different routes of bacterial infection, including ascending infection from the biliary tree (**ascending cholangitis**), **direct spread from adjacent infected tissues** or **haematogenous spread (hepatic artery or portal vein)**.
- This can present as mass lesions (**abscesses**) or diffuse non-specific changes (**mild hepatic inflammation and varying hepatocellular cholestasis**)
- Fungi and mycobacteria can also infect the liver in disseminated disease, causing **granulomatous inflammation**
- Parasitic and helminthic infections also frequently involve the liver worldwide
    - Liver flukes (*Fasciola hepatica, Opisthorchis sp.* and *Clonorchis sinensis*) are strongly associated with development of cholangiocarcinoma
    - Echinococcal infections cause hydatid cysts
    - Amoebiasis can cause abscesses

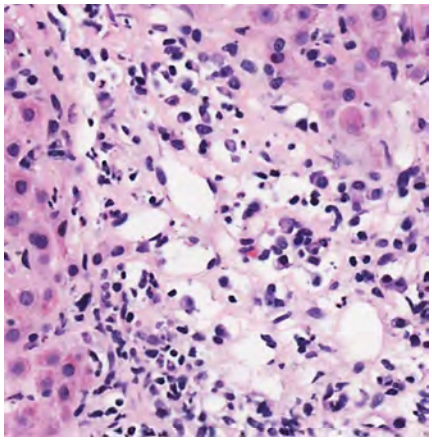


Autoimmune hepatitis

- **Chronic progressive disease** that commonly presents acutely (40%) and can have fulminant presentation within 8 weeks of disease onset. Scarring then rapidly follows, with at least 40% of survivors progressing to cirrhosis. The time course can also be more indolent, eventually presenting as burned-out cirrhosis
- Shares features of autoimmune diseases in general, including a **genetic predisposition** (HLA-association), **association with other AI diseases** (can overlap with other autoimmune liver diseases e.g. PBC/PSC), **presence of autoantibodies** (ANA, SMA, anti-SLA/LP, AMA, anti-LKM1) and **therapeutic response to immunosuppression** (80% of patients undergo remission)
- May be triggered by viral infections or drugs
- Female (78%) >> male
- There are two types, based on the pattern of circulating antibodies: **Type I** - Middle-aged to older; ANA, SMA vs **Type II** - Young; anti-LKM1

Simplified diagnostic criteria for AIH

- Presence of autoantibodies
- Elevated IgG
- Liver histology
  - *Typical*: 1. **Interface hepatitis** with **lymphoplasmacytic** predominance 2. **Emperipolesis** 3. **Hepatic rosette** formation
  - *Compatible with*: Chronic hepatitis (lymphocyte predominant) without typical features
  - *Atypical*: Histologic features of other diagnoses
- Absence of other conditions e.g. viral hepatitis



Drug and toxin-induced liver injury (DILI)

- The liver is the major drug metabolising and detoxifying organ in the body. Injury may therefore result from **direct toxicity**, through **hepatic conversion of xenobiotic to an active toxin** or through **immune-mediated mechanisms** (e.g. drug acts as a hapten)
- Diagnosis of DILI is made on the basis of a **temporal association** of liver damage with drug/toxin exposure, **recovery (usually) upon removal** of inciting agent and **exclusion of other potential causes**
- It can manifest as a variety of histologic patterns: cholestatatic, hepatocellular, steatosis, combination etc., and therefore **should always be included in the differential diagnosis of any form of liver disease.** A thorough clinical history is thus very important, as it can be caused by traditional medicines / herbal remedies, dietary supplements, topical applications, environmental exposure.
- www.livertox.nih
- **Reactions may be mild to very serious**, including acute liver failure or chronic liver disease. The most common hepatotoxin causing **acute** liver failure (in US) is **acetaminophen**, while the most common hepatotoxin causing **chronic** liver disease is **alcohol**
- Classification of drug toxic reactions:

- **Predictable (intrinsic)**: most people affected, dose-dependent
- **Unpredictable (idiosyncratic)**: rare, depends on host idiosyncrasies, independent of dose
- Both classes of injury may be immediate or take weeks to months to develop

Alcoholic liver disease

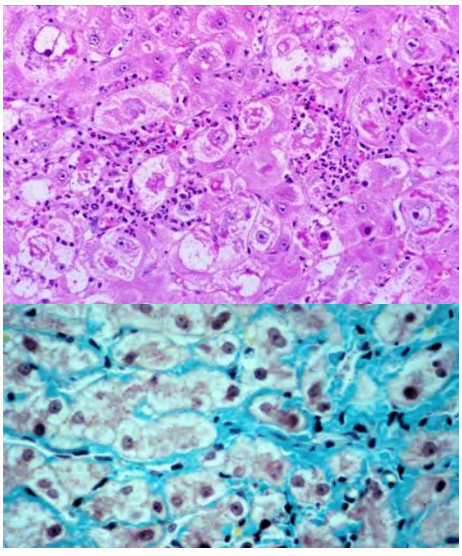
- Chronic disorder that can give rise to **steatosis**, **alcoholic (steato-)hepatitis**, progressive **steatofibrosis** and possibly cirrhosis with marked vascular derangements. These three disease forms are inter-related, can develop independently and do not necessarily follow a linear progression
- Excessive alcohol consumption is the leading cause of liver disease in most Western countries, although only 10-15% of alcoholics develop cirrhosis
- The development and severity of the disease depends on several factors:
  - Dosage and duration: ≥ 80g/day ethanol (~6 beers) generates significant risk for severe hepatic injury; especially over a duration of 10-20 years
  - Gender: Females are more susceptible to hepatic injury
  - Ethnic and genetic differences e.g. in detoxifying enzymes
  - Comorbid conditions e.g. concomitant liver pathologies like viral hepatitis
- Alcohol results in multiple pathologic effects:
  - **Steatosis**: ↑NADH leads to shunting of normal substrates towards lipid biosynthesis; ↓export of lipoproteins; ↑peripheral catabolism of fat
  - **Dysfunction of mitochondrial and cellular membranes**: acetaldehyde induces lipid peroxidation and acetaldehyde-protein adduct formation
  - **Hypoxia and oxidative stress**: CYP450 produces reactive oxygen species (ROS) and is also induced and enhances conversion of other drugs to toxic metabolites; impaired hepatic metabolism of methionine ↓glutathione levels
  - **↑ Inflammatory responses**: release of bacterial endotoxin from the gut into portal circulation
  - **↓ Hepatic sinusoidal perfusion**: release of endothelins stimulated, causing vasoconstriction and stellate cell contraction

Laboratory findings

- Serum AST↑↑>ALT (2:1 ratio)
- ↑ bilirubin, ↑ALP
- ↑WBC (neutrophils)

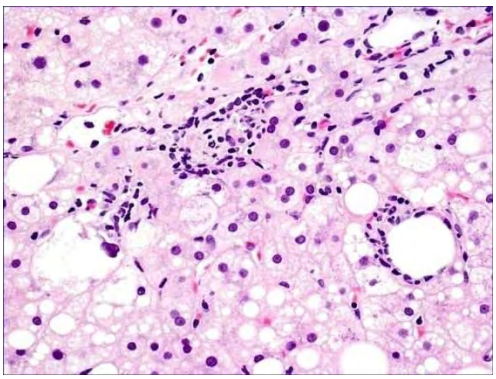
Histologic findings

- Centrilobular fatty change (reversible with abstention)
- Hepatocyte swelling (ballooning degeneration) and necrosis
- Mallory-Denk bodies
- Neutrophilic reaction
- Pericellular/perisinusoidal fibrosis ("Chicken-wire fence" pattern)
- Cirrhosis (micronodular)



Metabolic diseases

Non-alcoholic fatty liver disease (NAFLD)



- Spectrum of disorders that have in common the presence of hepatic steatosis in individuals who do not consume alcohol or do so in very small quantities (< 20g/wk)
    - **Steatosis**
    - **Steatohepatitis**: when there are histologic features of hepatocyte injury
- Now the most common cause of chronic liver disease in US, associated with **metabolic syndrome**
- 2-hit model of pathogenesis:
    - **Insulin resistance** leading to dysfunctional lipid metabolism and increased production of inflammatory cytokines
    - **Oxidative injury** resulting in liver cell necrosis as fat laden cells are highly sensitive to lipid peroxidation products
- NAFLD contributes to progression of other liver diseases e.g. viral hepatitis, and also increases the risk of hepatocellular carcinoma (HCC), often in the absence of significant scarring. However, because of the association with metabolic syndrome, cardiovascular disease is a frequent cause of death

Laboratory findings

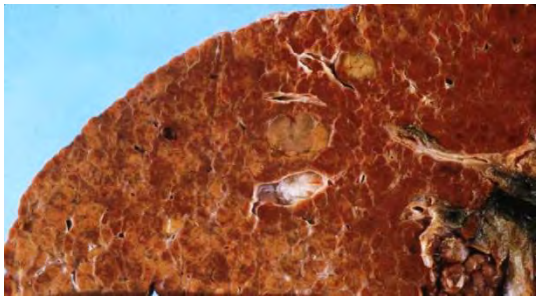
- ↑Serum AST and ALT (often asymptomatic)

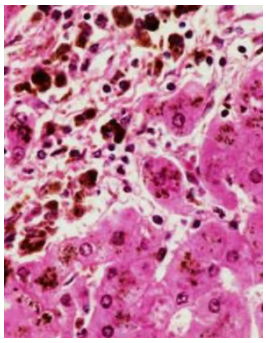
Histologic findings

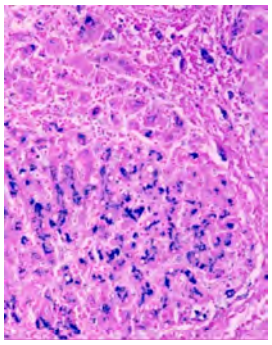
- Pathologic steatosis: > 5% of hepatocytes
- Histologic features similar to alcoholic hepatitis
- Fat may not be apparent in advanced fibrosis ('burned out' NAFLD) → cryptogenic cirrhosis

Haemochromatosis

- Caused by **excessive iron absorption**, deposited in parenchymal organs e.g. liver, pancreas, heart, joints, endocrine organs, skin; manifests usually after 20 g of stored Fe accumulates (normal = 2-6 g)
- Two types:
    - **Hereditary haemochromatosis** (HH) – genetic mutations e.g. in *HFE* which regulates hepcidin synthesis
    - **Secondary haemochromatosis** (secondary iron overload i.e. **haemosiderosis**)
- The total body content of iron is tightly regulated by intestinal **absorption** because there is no regulated iron excretion. Abnormal regulation of iron absorption occurs in HH
- Excessive Fe is directly toxic to tissues, but cell injury is still reversible if not fatally injured – removal of excess iron with therapy therefore promotes recovery of tissue function, although the risk of HCC is not fully removed. Inflammation is usually absent and fibrosis develops slowly
- M>F (protected by menstrual bleeding)
- Slow and progressive in hereditary forms → 4-5th decade
- Treatment: Regular phlebotomy, iron chelation therapy, liver transplant







Death from cirrhosis, HCC or cardiac disease

Diagnostic tests

- Screening: serum Fe, ferritin
- Liver biopsy and hepatic tissue iron content measurement
- Genetic testing

Pathologic findings

Liver:

- Early: slightly larger, dense and chocolate brown
- Later: shrunken, dark brown-black, micronodular cirrhosis
- **Fe deposits in (periportal) hepatocytes, Kupffer cells, bile duct epithelium**
- 200x ↑ risk of HCC!!

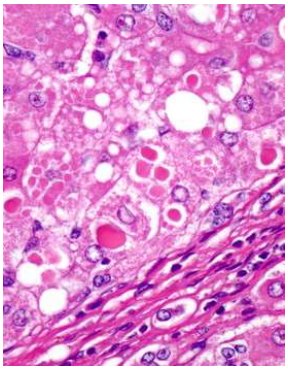
Pancreas: Intensely pigmented, diffuse interstitial fibrosis, +/- atrophy → diabetes mellitus
Heart: Cardiomegaly, brown, delicate fibrosis → cardiac dysfunction
Skin: Slate-grey pigmentation (esp. sun-exposed areas)
Joints: Acute synovitis, pseudogout
Testes: Small and atrophic → hypogonadism

Wilson disease

- **Autosomal recessive** disorder caused by ***ATP7B* gene mutation** (chr 13), resulting in **impaired copper excretion into bile and failure to incorporate copper into caeruloplasmin for secretion** into blood. Toxic levels of copper thus accumulate in many tissues and organs
- Manifests at 6-40 years old
- **Diagnostic tests**: (1) ↓ serum caeruloplasmin (2) ↑ urinary copper excretion (3) ↑ hepatic copper content (> 250ug/g in dry weight). Serum Cu levels have no diagnostic value as their levels depend on the stage of the disease
- **Clinicopathologic findings**:
  Liver: Variable – **steatosis / steatohepatitis**, acute fulminant hepatitis, chronic hepatitis, cirrhosis
  Brain: Atrophy and cavitation of basal ganglia, resulting in movement disorders e.g. tremors, dystonia ~Parkinsonism. Psychiatric symptoms also may be present
  Eyes: Kayser-Fleischer rings
  Blood: Haemolytic anaemia
- Treatment: D-penicillamine (copper chelation therapy), zinc-based therapy (block Cu uptake in gut), liver transplant

α1-antitrypsin deficiency

- **Autosomal recessive disorder of protein folding** resulting in impaired secretion and **very low serum α1AT**. α1AT is important in inhibition of proteases, particularly those released from neutrophils
- Wild-type genotype: PiMM; most common clinically significant mutation: PiZ (chr 14)



- **Clinicopathologic findings**:
  Lungs: pulmonary emphysema
- **Liver**: accumulation of misfolded protein manifests as **DPAS+ cytoplasmic globular inclusions** mainly in periportal hepatocytes. It can present as neonatal hepatitis +/- cholestasis and fibrosis, chronic hepatitis, cirrhosis, and HCC (2-3% of PiZZ adults). Liver disease presents early; α1AT deficiency is thus the most commonly diagnosed inherited hepatic disorder in infants and children
  Skin: necrotizing panniculitis
- Treatment: liver transplant, avoid smoking

Circulatory disorders

Impaired blood inflow

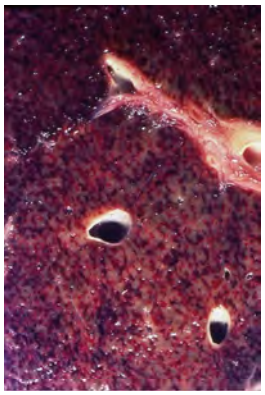
- **Hepatic artery compromise:** liver infarcts are rare due to dual blood supply to liver
- **Portal vein obstruction and thrombosis (intra- or extra-hepatic):** Usually has similar manifestations as portal hypertension (except ascites as the block is presinusoidal). Obstruction can occur by thrombosis (bland, infected, tumour), parasites (Schistosoma eggs), fibrosis (obliterative portal venopathy)

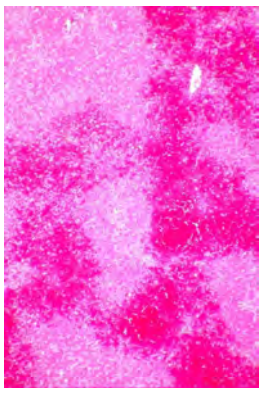
Impaired intrahepatic blood flow: usually **cirrhosis** or **sinusoidal occlusion** e.g. sickle cell disease, DIC

Hepatic vein outflow obstruction

- **Hepatic vein thrombosis:** obstruction of at least 2 major hepatic veins produces liver enlargement, pain and ascites (**Budd-Chiari syndrome**). Associated with myeloproliferative disorders, inherited disorders of coagulation, antiphospholipid syndrome, coagulopathies e.g. OCP, pregnancy, and intra-abdominal cancer especially HCC
- **Sinusoidal obstructive syndrome (SOS)** [veno-occlusive disease]**:** arises from toxic injury to sinusoidal endothelium – sloughed endothelium obstructs blood flow. Initially described in alkaloid-containing bush tea, post-chemotherapy or post stem cell transplan t

Passive congestion and centrilobular necrosis: hepatic manifestation of systemic circulatory compromise (cardiac decompensation)

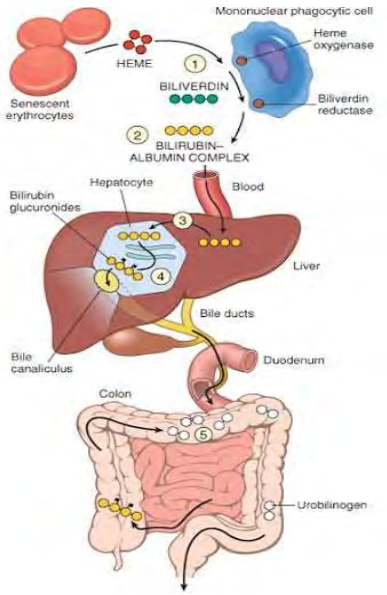




- **Right-sided heart failure:** passive congestion of centrilobular sinusoids with subsequent hepatocyte atrophy
- **Left-sided heart failure:** ischaemic coagulative necrosis of centrilobular hepatocytes
- Combination of hypoperfusion and retrograde congestion act synergistically to cause **centrilobular haemorrhage necrosis –** gross appearance of 'nutmeg liver'
- If chronic, **cardiac sclerosis** can develop (centrilobular fibrosis +/- bridging fibrous septa)

III. CHOLESTATIC / BILIARY DISEASES

- **Bile** = bilirubin and other non-water soluble waste products + bile salts (conjugated bile acids that have detergent action to help in fat emulsification)
- **Cholestasis**: systemic retention of bilirubin and other solutes eliminated in bile, caused by impaired bile formation and bile flow
- Tissue deposition of bilirubin:
    - **Jaundice**: yellow discolouration of skin (evident when se. Bil is more than 2-2.5 mg/dL)
    - **Icterus**: yellow discolouration of sclera
- Other symptoms / complications: pruritus, skin xanthomas, intestinal malabsorption / vit ADEK deficiencies



Robbins & Cotran, 9th ed

Pathophysiology of jaundice:

- Occurs when there is disturbance of equilibrium between bilirubin production and clearance
- Hyperbilirubinaemia can be predominantly **unconjugated** or **conjugated**
    - **Unconjugated** bilirubin: water-insoluble and tightly bound to albumin; cannot be excreted in urine even with high blood levels. Unbound unconjugated bilirubin in plasma can diffuse into tissues e.g. kernicterus in infants
    - **Conjugated**: water-soluble, non-toxic; can be excreted in urine ('tea-coloured')
- Causes of jaundice can also be classified as **pre-hepatic, intra-hepatic** or **post-hepatic**
    - **Pre-hepatic**: excess production of bilirubin e.g. haemolysis, ineffective erythropoiesis
    - **Hepatic**: due to reduced hepatic uptake e.g. drugs, impaired bilirubin conjugation e.g. physiologic / neonatal jaundice, genetic deficiency, diffuse hepatocellular disease, or impaired bile flow e.g. autoimmune cholangiopathies
    - **Post-hepatic**: impaired bile flow / large duct obstruction

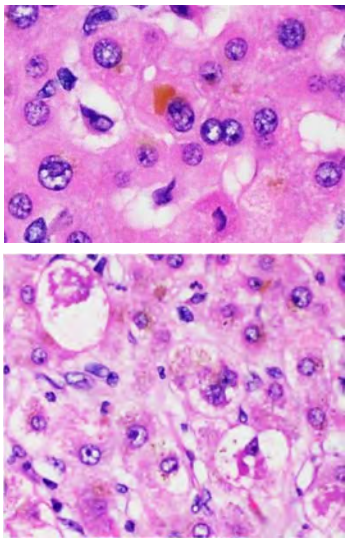
Localisation of the problem helps in determining treatment options and is important to distinguish as surgery can help relieve extrahepatic biliary obtruction but not intrahepatic cholestasis.

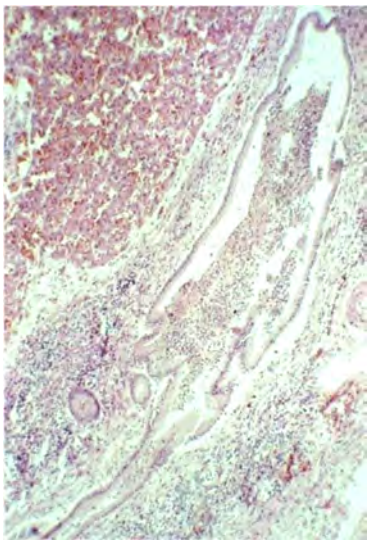
<u>Large bile duct obstruction</u>

- **Causes**: Mostly commonly extrahepatic cholelithiasis (gallstones), followed by malignancies of biliary tree / head of pancreas and post-surgical / inflammatory bile duct strictures. Less commonly, porta hepatis lymphadenopathy or, mostly in children, bile duct malformations / loss e.g. choledochal cysts, biliary atresia
- In acute obstruction, the effects are still reversible with correction of the obstruction. However, with subtotal / intermittent obstruction, there is increasing risk of **ascending cholangitis**, which can lead to intrahepatic cholangitic abscesses / sepsis (due to gut-associated bacteria). Prolonged obstruction can lead to **biliary cirrhosis**
- Superimposed ascending cholangitis can trigger acute on chronic liver failure

Histologic findings

- **Acute biliary obstruction**: Bile duct tortuosity, ductular reaction associated with neutrophils, portal tract stromal oedema
- **Ascending cholangitis**: neutrophils infiltrate the bile duct epithelium and lumen
- **Chronic biliary obstruction**: periportal fibrosis → biliary cirrhosis
    - Feathery degeneration of periportal hepatocytes with Mallory-Denk bodies
    - Bile infarcts





Primary hepatolithiasis

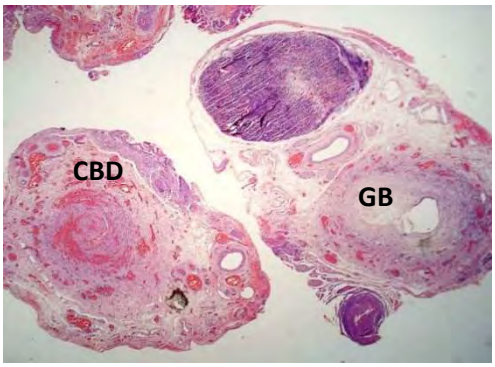
- Disorder of intrahepatic gallstone formation that leads to repeated bouts of ascending cholangitis, progressive inflammatory destruction / collapse and scarring of hepatic parenchyma ('**recurrent pyogenic cholangitis**')
- Predisposes to Biliary Intraepithelial Neoplasia (BilIN) and cholangiocarcinoma

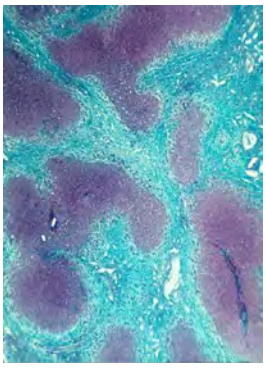
Neonatal cholestasis

- **Prolonged conjugated hyperbilirubinaemia** in the neonate (beyond 14-21 days after birth)
- Major causes:
    - Cholangiopathies: **Extrahepatic biliary atresia**
        - Complete or partial obstruction of the lumen of the extrahepatic biliary tree **within the first 3 months** of life. The obstruction may also extend to involve intrahepatic ducts, in which case surgical correction is insufficient and transplantation is usually required
        - Accounts for ~1/3 of neonatal cholestasis cases and is the single most frequent cause of death from liver disease in early childhood (death within 2 years of birth without surgical intervention)
        - 2 theories on pathogenesis are based on the presumed timing of luminal obliteration: (1) **Fetal form** (20%), whereby there is aberrant intrauterine development of the extrahepatic biliary tree, a/w other anomalies e.g. situs inversus, CHD, and (2) **Perinatal form**, in which the presumed normal biliary tree is destroyed after birth, possibly due to viral infection or autoimmune cause
        - Presents with jaundice, pale acholic stools, tea-coloured urine
    - **Neonatal hepatitis**: collective term referring to a variety of inherited and acquired disorders, including toxins (drugs, parenteral nutrition), metabolic causes (e.g. Tyrosinaemia), infections (CMV, bacterial sepsis) and idiopathic (~10-15%)

Pathologic findings of BA

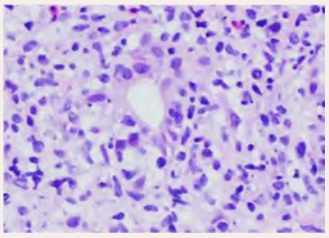
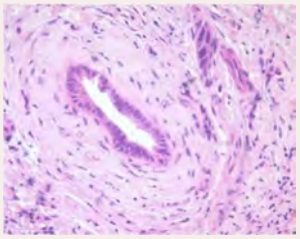
- **Hepatic ducts / CBD**: Progressive inflammation and fibrosing stricture
- **Gallbladder**: Atretic
- **Liver**: Features of large duct obstruction (cholestasis +/- biliary cirrhosis); if involvement of intrahepatic ducts → paucity of intrahepatic small bile ducts





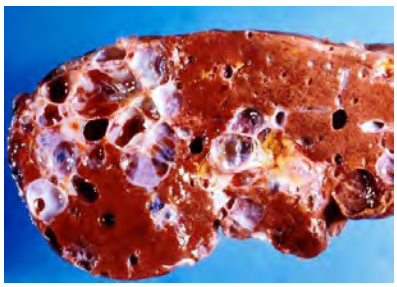
Autoimmune cholangiopathies

- Autoimmune disorders of intrahepatic bile ducts with progressive bile duct destruction

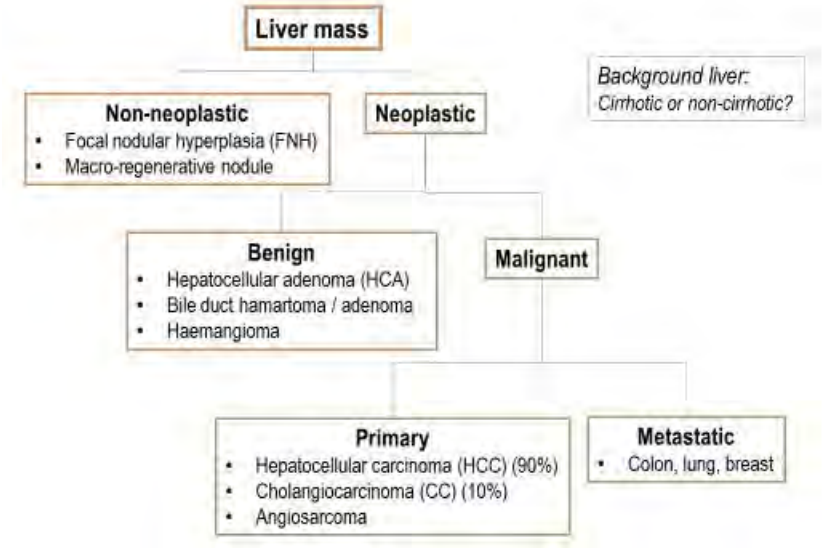
	Primary biliary cholangitis (PBC)	Primary sclerosing cholangitis (PSC)
Demographic	50F	30M
Associations	Sjogren syndrome, thyroid disease	Inflammatory bowel disease (UC) in 70% of patients
Serology	AMA+, ANA+ ANCA+ (40%)	AMA, ANA usually negative P-ANCA+ (60%)
Radiology	Non-specific	Strictures and beading of large bile ducts Pruning of small bile ducts
Histology	Florid duct lesions Loss of small / medium bile ducts	Inflammatory destruction of extrahepatic and large intrahepatic ducts Fibrotic obliteration of small / medium ducts
		20% lifetime risk of developing cholangiocarcinoma 

Structural anomalies of the biliary tree

- **Choledochal cyst**: Congenital dilatation of biliary tree (usually common bile duct) that predispose to stones, stenosis, strictures, pancreatitis and risk of bile duct cancer
- **Fibropolycystic disease**: Heterogeneous group of lesions in which the primary abnormalities are congenital malformations of the biliary tree (ductal plate malformations), including small bile duct hamartomas, biliary cysts (in isolation: Caroli disease; in association with congenital hepatic fibrosis: Caroli syndrome) and congenital hepatic fibrosis. It is often seen in association with AR polycystic renal disease, and also has an increased risk of cholangiocarcinoma

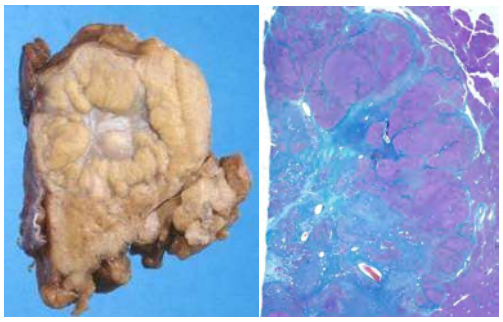


IV. NEOPLASMS OF LIVER AND BILIARY TRACT



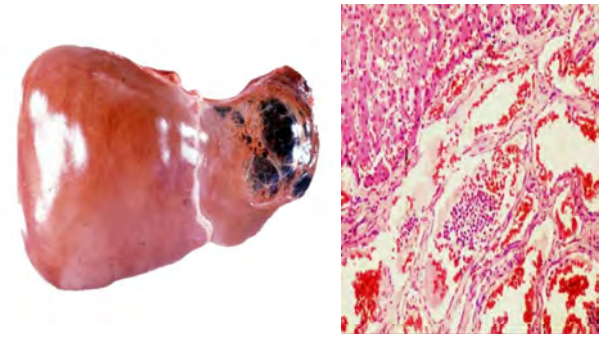
Metastases are more common than primary hepatic malignancies. The liver is the most common site of **metastatic cancers** from colon, lung and breast, while the main primary hepatic malignancies are **hepatocellular carcinoma** and **cholangiocarcinoma**

Non-neoplastic: Focal nodular hyperplasia



- Due to focal or diffuse alterations in hepatic blood supply (often obliteration of portal vein radicles and compensatory augmentation of arterial blood supply)
- Well-demarcated but poorly encapsulated pale nodule typically with central fibrous scar, which contains large misshapen arterial vessels with radiating fibrous septa and accompanying ductular reaction, separating hyperplastic hepatocytes. No normal bile ducts are seen.

Neoplastic – Benign: Cavernous haemangioma



- Most common benign liver tumour
- **Gross appearance**: Subcapsular, discrete, red-blue, soft
- **Microscopic findings**: Large vascular channels separated by thin fibrous connective tissue
- **Potential complications** include rupture (which can lead to intraperitoneal bleeding and surgical emergency) and thrombosis

Neoplastic – Benign: Hepatocellular adenoma

- Benign tumour arising from hepatocytes, that is often associated with use of oral contraceptives and anabolic steroids. It may present as an incidental finding, abdominal pain (from rapid growth or haemorrhagic necrosis) or intra-abdominal bleeding due to rupture

- There are at least 4 subtypes based on molecular analysis and associated clinicopathologic features, including their different relative risks of malignant transformation
  - **HNF1A-inactivated**: F, a/w MODY-3. ~0% risk of malignant transformation
  - **β-catenin activated**: M&F, a/w OCP and steroids. Highest risk of malignant transformation
  - **Inflammatory**: M&F, a/w NAFLD. 10% have concomitant β-cat activating mutations
  - **Unclassified**: subset are Sonic Hedgehog activated

Neoplastic – Malignant: Hepatocellular carcinoma (HCC)

- **Incidence varies according to risk factors**; more than 85% of cases occur in countries with high rates of chronic HBV infection e.g. China, Korea, Taiwan, whereby the patients tend to be younger and non-cirrhotic, although there is decreasing incidence with HBV vaccination. In contrast, the incidence of HCC is increasing in the West due to Hepatitis C epidemic. These patients tend to be older and cirrhotic. HCC affects more males than females, and is the 5th leading cause of death in males
- **Major aetiologic associations**: Viral infections (HBV, HCV), toxins (aflatoxin – mycotoxin by Aspergillus, alcohol), metabolic diseases (HH, a1AT >> Wilson) and NAFLD associated with metabolic syndrome. These causes can have synergistic effects on the development of HCC
- **Pathogenesis**: Hepatocarcinogenic mechanisms can be etiology-specific and non-specific mechanisms. No single universal sequence of molecular or genetic alterations leads to emergence of HCC, although there are 2 most common early mutational events: (1) **beta-catenin activation** (40%): tumours usually demonstrate genetic instability, unrelated to HBV (2) **p53 inactivation** (60%): strong association with aflatoxin. **Cirrhosis is not required for hepatocarcinogenesis**, as progression to cirrhosis and hepatocarcinogenesis take place in parallel over years to decades. However, **chronic liver disease is an important risk factor** in HCC development. Traditionally, this was thought to be due to cycles of cell death and regeneration in chronic inflammatory states increasing the risk of mutations in regenerating hepatocytes. However, recent research implicates the IL-6/JAK/STAT pathway (IL-6, an inflammatory cytokine, promotes hepatocyte proliferation by regulating the function of transcription factor HNF4a)
- **Precursor lesions**: HCA, large cell change / low grade dysplastic nodule, small cell change / high grade dysplastic nodule
- **Clinical presentation**: Asymptomatic, ill-defined upper abdominal pain, malaise, fatigue, weight loss, hepatomegaly, abdominal mass or fullness. Rarely: jaundice, fever, variceal bleeding
- **Screening and diagnostic tests**: Radiologic imaging is accepted for screening and diagnosis of HCC if the findings are characteristic and clinical presentation compatible (classic findings are seen on contrast-enhanced studies and are based on the increasing arterialization of tumours: arterial enhancement with portal venous washout). Serum alpha-fetoprotein (AFP) levels may be rising or elevated in 50% of patients with advanced HCC, but by itself is insensitive as a screening test

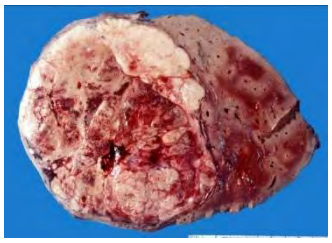
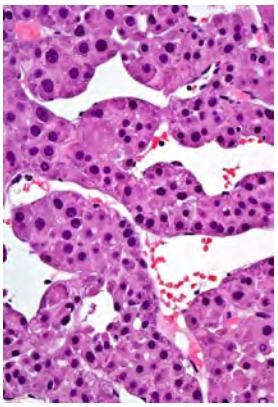
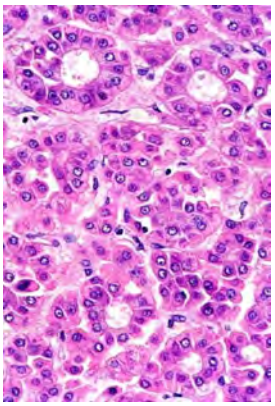
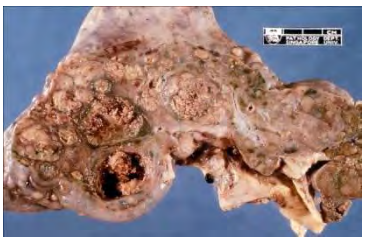
- **Natural course and treatment**: HCCs progressively enlarge until they rupture with haemorrhage, disturb hepatic function (variceal bleeding, liver failure / hepatic coma), or metastasize. Death may also result from cachexia. The 5-year survival is poor, with most patients dying within 2 years. Treatment may be (1) **Surgical**: resection or transplantation (2) **Non-surgical**: Locoregional ablation e.g. transarterial chemoembolization (TACE) or radioembolization (Y90), or radiofrequency ablation (RFA)
- **Prognostic factors**: Stage, Number and size of tumour nodules (tumour burden), vascular invasion, Histologic grade, Presence of cirrhosis, Serum AFP

Gross appearance

- **Unifocal**, **multifocal** or **diffusely infiltrative**
- Pale or variegated (depending on cytology – bile production, fatty change, stroma)
- Background: +/- cirrhosis
- Spread is usually **vascular** (which can result in intrahepatic metastases / satellite lesions), or portal vein / hepatic vein involvement. Lymph node involvement is less common

Microscopic findings

- Trabecular-sinusoidal, acinar / pseudoglandular, compact /solid and schirrhous growth patterns
- Polygonal cells with eosinophilic cytoplasm and central round nucleolus with distinct nucleolus. Degree of pleomorphism and bile production depends on grade of the tumour

Neoplastic – Malignant: Hepatoblastoma

- Rare (1-2 in 1 million births) but is most common liver tumour of early childhood (patients are usually < 3 years old). Can be associated with Beckwith-Wiedemann syndrome, as well as FAP. Molecular alterations involve the activation of WNT signaling pathway (beta-catenin mutations)
- 2 main histologic variants: **Epithelial type** (polygonal fetal or smaller embryonal cells, vaguely recapitulating liver development) and **Mixed epithelial and mesenchymal type** (primitive mesenchyme, osteoid, cartilage, striated muscle)
- Treatment: Surgical resection and chemotherapy; fatal if untreated

Neoplastic – Malignant: Cholangiocarcinoma

- Carcinoma of bile duct origin, which can arise both within and outside of the liver (**intrahepatic** – 10%, **perihilar / Klatskin tumours** – 50-60% and **extrahepatic** – 20-30%). It is the 2nd most common primary malignant hepatic tumour, after HCC
- **Risk factors**: Liver fluke infestation (*Opisthorchis*, *Clonorchis* sp. in Thailand, Laos), Primary sclerosing cholangitis, Hepatolithiasis, Fibropolycystic liver disease, and hepatic diseases (HBV, HCV, NAFLD)

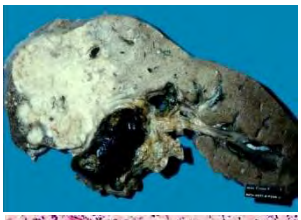
- **Pathogenesis**: Risk factors cause chronic inflammation and cholestasis which presumably promote somatic mutations or epigenetic alterations. However, there are also sporadic cases which are not associated with pre-existing conditions
- **Premalignant lesions**: Biliary intraepithelial neoplasia (BilIN) 1-3; intraductal papillary biliary neoplasia and mucinous cystic neoplasms
- **Clinical presentation**: Depends on tumour location; extrahepatic tumours tend to present earlier and smaller with biliary obstruction, cholangitis and RUQ pain while intrahepatic tumours are not usually detected till late, due to bile flow obstruction or as symptomatic liver mass
- **Prognosis**: Poor, with survival rates ~15% at 2 years after diagnosis for extrahepatic tumours, and 6 months median survival for intrahepatic CCA even after surgery

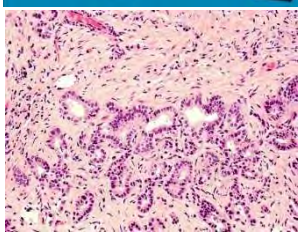
Gross appearance

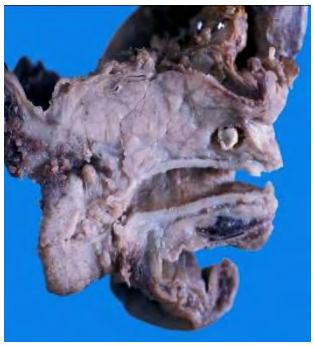
- **Intrahepatic:** Mass-forming, periductal or mixed. Sclerotic, pale, firm and irregular
- **Perihilar / Extrahepatic:** Stricture (firm gray nodules or diffusely infiltrative), intraluminal papillary / polypoid growth

Microscopic findings

- Adenocarcinoma, well to poorly differentiated
- Proclivity for lymphovascular and perineural spread → porta hepatis LN involvement







Neoplastic – Malignant: Metastases

- Far more common than primary hepatic neoplasms, often from primary malignancies of the colon, breast, lung or pancreas. Patients are usually asymptomatic or present with hepatomegaly. Liver function is usually normal unless the tumour causes bile duct obstruction
- **Gross pathology**: Hepatomegaly, solitary or usually multiple pale nodules in a non-cirrhotic liver. There may be subcapsular umbilication of nodules due to central tumour necrosis
- **Microscopic findings**: Depends on the primary tumour

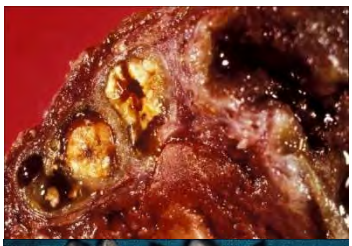
V. GALLBLADDER

Cholelithiasis (gallstones)

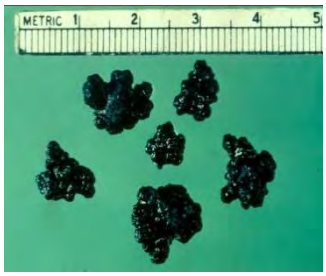
- Accounts for more than 95% of biliary tract disease; gallstones affect 10-20% of adult populations in developed countries. Majority of patients (80%) are **asymptomatic**; symptoms may include RUQ / epigastric pain - biliary 'colic' (actually non-intermittent), may be precipitated by a fatty meal (stone forced against the gallbladder outlet leading to increased pressure)
- **Complications**: acute cholecystitis, empyema, hydrops, perforation, fistulas, CBD obstruction [cholangitis (inflammation of the biliary tree), obstructive cholestasis and its associated sequelae],

pancreatitis, cholecysto-enteric fistula -> gallstone ileus (erode directly into adjacent loop of small bowel causing IO), increased risk of gallbladder carcinoma

- Two general classes of gallstones:
  1. **Cholesterol stones**: >50% crystalline cholesterol monohydrate, arise exclusively in gallbladder
     - **Pathogenesis**: Cholesterol is rendered soluble in bile by aggregation with water-soluble bile salts and water-insoluble lecithins, both of which act as detergents. When cholesterol concentrations exceed the solubilizing capacity of bile (**supersaturation**), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystal. There are **four contributing conditions**: (1) Supersaturation of bile with cholesterol (2) Hypomotility of gallbladder (3) Accelerated cholesterol crystal nucleation (4) Hypersecretion of mucus in gallbladder trapping nucleated crystals, leading to accretion of more cholesterol and appearance of macroscopic stones
     - **Risk factors**: Advancing age, Female sex hormones (F, OCP, pregnancy), Obesity and metabolic syndrome, Rapid weight reduction, Gallbladder stasis, Inborn disorders e.g. bile acid metabolism, Hyperlipidemia syndromes
     - **Appearance**: **Pure cholesterol stones** are radiolucent, yellow, round to oval with a finely granular hard surface showing a glistening radiating crystalline palisade on sectioning. radiolucent). If they are **mixed** with other substances e.g. calcium carbonate, phosphates, bilirubin, they will be radio-opaque, and often multiple with a grey-white to black, lamellated, round or faceted appearance



  2. **Pigment stones**: bilirubin calcium salts
     - **Pathogenesis**: Pigment stones are complex mixtures of insoluble calcium salts of unconjugated bilirubin with inorganic calcium salts, which are formed when there are increased levels of unconjugated bilirubin in bile. Unconjugated bilirubin may increase when infections of biliary tract leads to release of **microbial β-glucuronidases**, which hydrolyze bilirubin glucuronides, or in haemolytic anaemias whereby there is there is increase in secretion of conjugated bilirubin into the bile, where about 1% of **deconjugation** occurs and so there is a sufficiently large amount of deconjugated bilirubin left for stone formation
     - **Risk factors**: Chronic hemolytic anaemias, severe ileal dysfunction or bypass, and biliary tract infections (*E coli, Ascaris lumbricoides,* liver fluke *Clonorchis sinensis*)
     - **Appearance**: **Black stones** (sterile, gallbladder – oxidized polymers of calcium salts of unconjugated bilirubin) tend to be multiple, spiculated, molded. **Brown** stones (infected, intra or extrahepatic bile ducts – pure calcium salts of unconjugated bilirubin mixed with mucin glycoprotein, cholesterol, palmitate) are laminated, soft and greasy



Cholecystitis: inflammation of the gallbladder

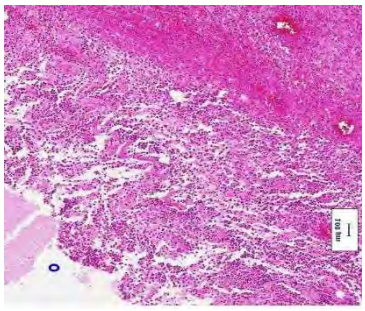
Acute cholecystitis

- Clinical presentation: Episode of acute progressive / constant biliary pain >6-24 hours with fever, anorexia, nausea, RUQ tenderness, leucocytosis. No jaundice – if present, suggests CBD obstruction
- Two types:
  Calculous (90%): primary complication of gallstones, which obstruct the neck or cystic duct causing chemical irritation and inflammation
    - Pathogenesis: Several mechanisms, including distension and increased intraluminal pressure compromising blood flow to mucosa (ischaemia), formation and release of inflammatory mediators by traumatized mucosa e.g. prostaglandins and mucosal phospholipases that hydrolyze luminal lecithins to toxic lysolecithins, and disruption of normal protective glycoprotein mucus layer, exposing the mucosal epithelium to direct detergent action of bile salts. Bacterial contamination may develop only later

  Acalculous (10%): severely ill patients e.g. sepsis with hypotension, trauma / burns, immunosuppressed, DM, infections
    - Due to mucosal ischaemia as the cystic artery is an end-artery, with further compromise of blood flow due to inflammation and oedema of the wall. Gallbladder stasis with increased bile viscosity forming biliary sludge and gallbladder mucus can also cause cystic duct obstruction in the absence of stones
- **Complications**: Gangrene (with perforation and peritonitis), empyema (filled with pus), acute 'emphysematous' cholecystitis (if infected by gas-forming organisms), pericholecystic and subdiaphragmatic abscesses, ascending cholangitis (+/- liver abscesses), septicemia

Gross appearance
- Enlarged, tense, edematous and congested with violaceous to green-black appearance
- Fibrinous to fibrinopurulent serosal exudates
- Mucosal ulceration
- +/- Stone(s)

Microscopic findings
- Acute inflammation: oedema, congestion, haemorrhage, neutrophils and necrosis

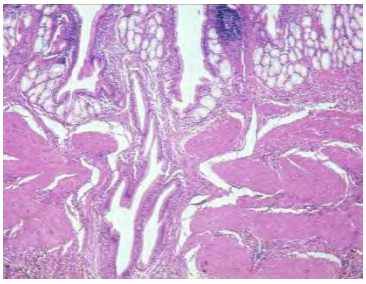


Chronic cholecystitis

- May be asymptomatic or vague abdominal symptoms, including episodic epigastric / RUQ pain ('biliary colic'). As it is associated with cholelithiasis in >90% of cases, the risk factors are similar
- **Pathogenesis**: Unclear; although it has been suggested as a sequel to repeated bouts of acute cholecystitis, it is often present in the apparent absence of antecedent attacks. Unlike acute calculous cholecystitis, obstruction of outflow is not a requisite. It is likely due to supersaturation of bile predisposing to both chronic inflammation and stone formation +/- bacterial superinfection
- **Complications**: Arise from the presence of gallstones e.g. cholecysto-enteric fistulas

Gross appearance
- Contracted with thickened wall, smooth mucosa +/- calculi

Microscopic findings
- Chronic inflammation
- Rokitansky-Aschoff (RA) sinuses
- Fibromuscular hypertrophy and subserosal fibrosis



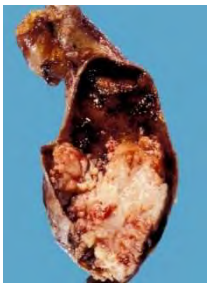
Hyalinizing cholecystitis: may have extensive dystrophic calcification within the wall ('porcelain GB'); a/w markedly increased risk of associated cancer
Xanthogranulomatous cholecystitis: triggered by rupture of RA sinuses followed by accumulation of foamy macrophages. Often massively thickened wall and can form a tumour-like aggregate
Hydrops: atrophic, chronically obstructed and often dilated GB containing only clear secretions

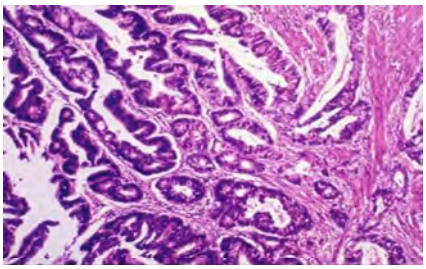
Gallbladder carcinoma

- Most common malignancy of the extrahepatic biliary tract; F:M = 2:1
- **Risk factor**: Gallstones (95%) (although only 1-2% of patients with gallstones develop ca); chronic bacterial and parasitic infections
- **Clinical presentation**: Often asymptomatic or insidious symptoms, similar to cholelithiasis
- **Prognosis**: **Directly invades** liver, stomach and duodenum or **metastasizes** to liver, regional lymph nodes or lungs. Prognosis is poor

Gross appearance
- Diffuse (70%) / infiltrating
- Polypoid (30%) / exophytic

Microscopic findings
- Usually Adenocarcinoma, resembling origin from pancreatic or bile ducts

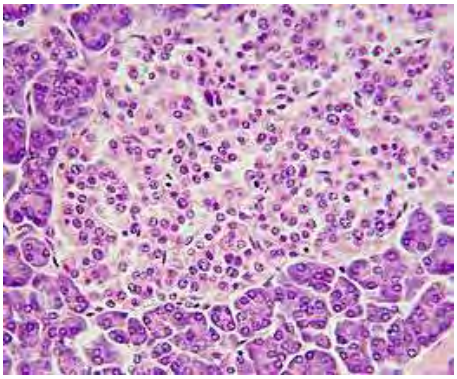




VI. PANCREAS

Normal anatomy and function

- Transversely oriented retroperitoneal organ from C-loop of duodenum to hilum of spleen
- Formed from fusion of dorsal and ventral outpouchings (primordia) of the foregut
    - **Dorsal primordium**: Body, tail, superior/anterior aspects of head and accessory duct of Santorini
    - **Ventral primordium**: Posterior/inferior aspects of head; drains through main pancreatic duct into papilla of Vater
- **Main pancreatic duct (of Wirsung)** joins the CBD just proximal to papilla of Vater
- **Accessory pancreatic duct (of Santorini)** drains into duodenum through separate minor papilla

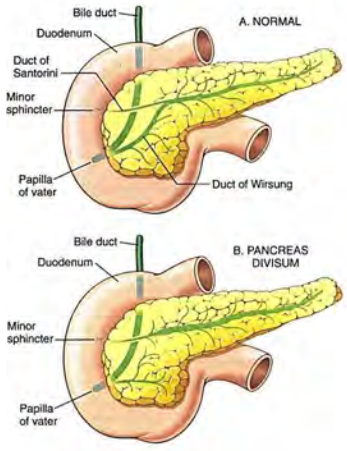


Exocrine component: Acinar cells (80-85%)
- Secretes enzymes for digestion
- Proenzymes (zymogens - trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase, kallikreinogen, prophospholipase A and B) carried by ductules and ducts to the duodenum, where they are activated by proteolytic cleavage

Endocrine component: Islets of Langerhans (1-2%)
- Secretes hormones: insulin, glucagon, somatostatin

Congenital anomalies

- **Pancreas divisum**: Most common, due to failure of fusion of fetal duct systems of dorsal and ventral pancreatic primordia, resulting in CBD and main pancreatic duct (of Wirsung) entering the duodenum separately, which has been postulated to predispose to chronic pancreatitis
- **Annular pancreas**: Band-like ring encircling duodenum (D2), which may result in stenosis / obstruction
- **Ectopic pancreas**: May be seen in stomach, duodenum, jejunum, Meckel diverticulum, ileum. Usually incidental, but can result in pain from localised inflammation or mucosal bleeding
- **Agenesis**: Homozygous germline mutations involving PDX1 gene



Robbins & Cotran, 9th ed

Pancreatitis

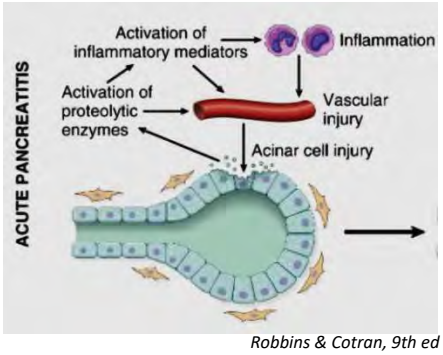
- Both acute and chronic pancreatitis are initiated by injuries that lead to autodigestion of the pancreas by its own enzymes, when the mechanisms that normally protect the pancreas from self-digestion are deranged or overwhelmed:
  - Most digestive enzymes are synthesized as **inactive proenzymes (zymogens),** which are packaged within secretory granules. Most of these proenzymes are **activated by trypsin**, which itself is activated by duodenal enteropeptidase (enterokinase) in the **small bowel** → intrapancreatic activation of proenzymes is minimal
  - Acinar and ductal cells also secrete **trypsin inhibitors**, including serine protease inhibitor SPINK1, which further limits intrapancreatic trypsin activity

Acute pancreatitis

- **Reversible** pancreatic parenchymal injury associated with inflammation. Relatively common
- **Causes:**
  - **Biliary tract disease (gallstones)** and **alcohol** (~80% of cases in Western countries)
  - Others: Metabolic causes (hyperlipoproteinemia, hypercalcemia), drugs, pancreatic duct obstruction (by periampullary neoplasms, choledochoceles, parasites, pancreas divisum), trauma or iatrogenic injury (ERCP, operative), inherited genetic defects often resulting in

increased / sustained trypsin activity (hereditary pancreatitis is characterised by recurrent attacks of severe acute pancreatitis often beginning in childhood and ultimately leading to chronic pancreatitis; Patients have a 40% lifetime risk of developing pancreatic cancer), ischaemic injury (shock, atherothromboembolism, vasculitis), and infections (mumps)

- **Pathogenesis:** Inappropriate release and activation of pancreatic enzymes, which destroy pancreatic tissue and elicit an acute inflammatory reaction. There are at least 3 major initiating events:
  1. **Duct obstruction**: Obstruction raises intrapancreatic ductal pressure, leading to accumulation of enzyme-rich fluid in the interstitium. Although most pancreatic enzymes are secreted as inactive zymogens, lipase is produced in active form and can cause local fat necrosis. The death of adipocytes is hypothesized to produce local 'danger' signals that stimulate release of proinflammatory cytokines and other mediators that initiate local inflammation and promote **development of interstitial oedema** through leaky microvasculature, further **compromising blood flow** and causing **ischaemic injury** to acinar cells
  2. **Acinar cell injury**: **Oxidative stress** may generate free radicals in acinar cells, leading to membrane lipid oxidation and activation of transcription factors to induce chemokine expression to attract mononuclear cells. This results in release of intracellular proenzymes and lysosomal hydrolases. **Increased calcium flux** also favours activation of trypsinogen by trypsin instead of autoinhibition
  3. **Defective intracellular transport**: **Inappropriate delivery of proenzymes** to the lysosomal compartment results in intracellular activation of proenzymes and release of activated enzymes
- Alcohol consumption may cause pancreatitis through all of these mechanisms: Duct obstruction results from a transient increase in contraction of the sphincter of Oddi as well as the secretion of protein-rich pancreatic fluid in chronic alcohol consumption that leads to deposition of inspissated protein plugs and obstruction of small pancreatic ducts. Alcohol also has direct toxic effects on acinar cells, resulting in oxidative stress. However, most drinkers never develop pancreatitis



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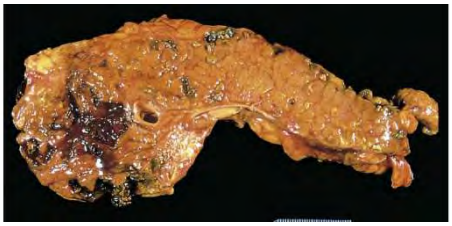
- **Clinical presentation:** Constant intense abdominal pain; may be referred to upper back or left shoulder. Associated with anorexia, nausea and vomiting
  - Severity is variable: Acute interstitial pancreatitis, acute necrotizing pancreatitis and haemorrhagic pancreatitis
  - **Full-blown acute pancreatitis is a medical emergency!** Systemic features in severe cases are due to release of toxic enzymes, cytokines and other mediators into the circulation, and explosive activation of a systemic inflammatory response (SIRS)
- **Complications**
  - **Local:** Sterile pancreatic abscess (40-60% can become infected), pancreatic pseudocyst
  - **Systemic:** Shock (due to SIRS), acute respiratory distress syndrome (ARDS), acute renal failure and disseminated intravascular coagulation (DIC) – multisystem organ failure

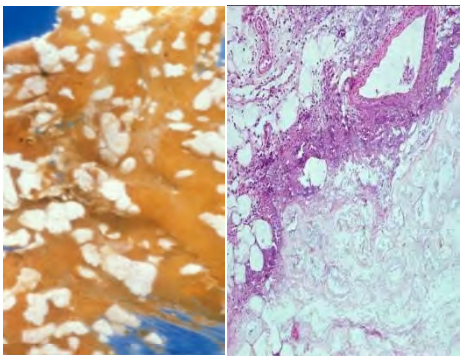
Laboratory findings

- ↑↑serum amylase (24 hrs) & lipase (72-96 hrs)
- Glycosuria (10%)
- Hypocalcemia (due to precipitation of calcium soaps in necrotic fat)
- Leukocytosis, DIC
- +/- jaundice if due to gallstones

Gross pathology and microscopic findings:

- Variable degrees of 1. microvascular leak and oedema, 2. fat necrosis, 3. acute inflammation, 4. destruction of pancreatic parenchyma, 5. destruction of blood vessels and interstitial haemorrhage
- Pancreas: Haemorrhage and necrosis
- Omental fat: Fat necrosis with saponification and neutrophilic response ("chicken broth" peritoneal fluid)

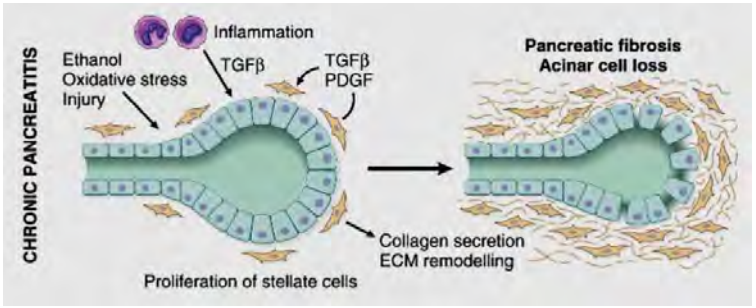




- **Management:** Supportive (most recover fully), monitor for complications and treat aetiology

Chronic pancreatitis

- Prolonged inflammation of the pancreas associated with **irreversible** destruction of exocrine parenchyma, fibrosis and in the late stages, destruction of endocrine parenchyma
- **Causes**: long-term alcohol abuse (most common; middle-aged males), long-standing obstruction of the pancreatic duct by calculi or neoplasms, autoimmune injury (**autoimmune pancreatitis** is a distinct form associated with IgG4+ plasma cells. Important to recognize because it responds to steroid therapy, and may also mimic pancreatic carcinoma) and hereditary pancreatitis (up to 25%)
- **Pathogenesis**: usually occurs after repeated episodes of acute pancreatitis. Fibrogenic factors tend to predominate in chronic pancreatitis vs acute pancreatitis e.g. TGF-ß, PDGF that induces the activation and proliferation of periacinar myofibroblasts (pancreatic stellate cells), resulting in collagen deposition and fibroblasts



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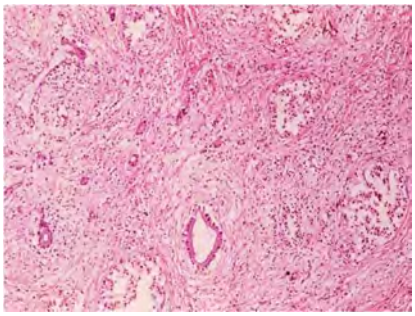
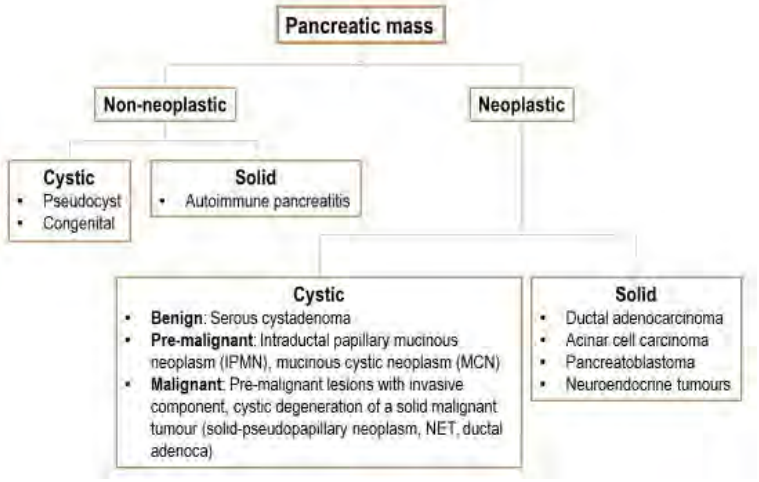
- **Clinical presentation:** Repeated attacks or persistent pain that may be precipitated by alcohol abuse, overeating, use of opiates or other drugs that increase the tone of sphincter of Oddi. Patients may also be asymptomatic until pancreatic insufficiency (intestinal malabsorption) and DM develop
- **Complications:** Chronic malabsorption from pancreatic exocrine insufficiency, Diabetes mellitus from endocrine insufficiency, severe chronic pain and pancreatic pseudocysts

Radiology: Pancreatic calcifications on US/CT scan
Microscopic findings:

- Fibrosis
- Acinar atrophy and dropout, with relative sparing of islets
- Variable dilatation of pancreatic ducts with protein plugs/ calcified concretions (esp if due to alcohol)
- AI: ductocentric inflammation, venulitis, ↑IgG4+ plasma cells
- Pseudocysts



Masses and Neoplasms



Non-neoplastic – Cystic: Pseudocyst

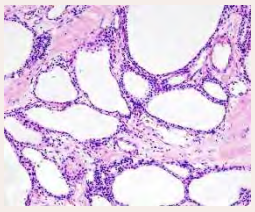
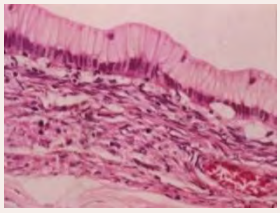
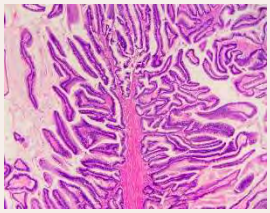
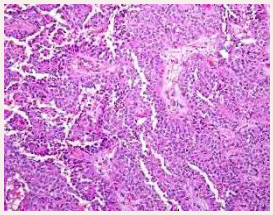
- 75% of all pancreatic cysts
- Usually solitary, localised collection of necrotic and haemorrhagic material rich in pancreatic enzymes and lack epithelial lining, often following a bout of acute pancreatitis (especially if superimposed on chronic pancreatitis), or traumatic injury.
- May spontaneously resolve, become secondarily infected or compress/perforate adjacent structures

Non-neoplastic – Cystic: Congenital

- Unilocular, thin-walled cysts containing serous fluid and lined by single layer of variably attenuated uniform cuboidal epithelium, believed to result from anomalous development of pancreatic ducts
- Sporadic vs inherited (e.g. ADPKD, VHL)

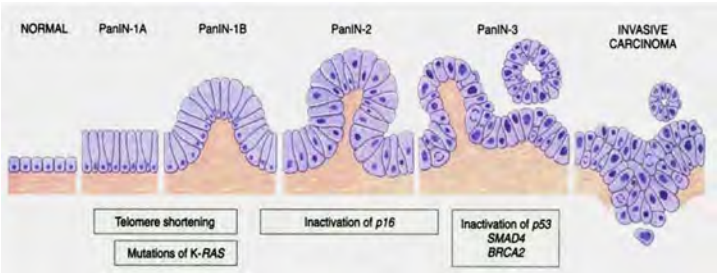
Neoplastic – Cystic epithelial neoplasms

Serous cystadenoma	Mucinous cystic neoplasm (MCN)	Intraductal papillary mucinous neoplasm (IPMN)	Solid-pseudopapillary neoplasm (SPN)
Benign	Pre-malignant	Pre-malignant	Malignant, low grade
Elderly, F>M	Middle-aged, F	Middle-elderly, M>F	Young, F>M

Tail of pancreas	Body/tail of pancreas - No connection with pancreatic duct	Head of pancreas - Connected to pancreatic duct	Body/tail of pancreas
Often multicystic, lined by glycogen-rich cuboidal cells	Columnar mucinous epithelium with "ovarian cortical-type" stroma	Intraductal papillae lined by columnar mucinous epithelium	Well-circumscribed, solid vascular nests with pseudopapillae
VHL inactivation	*KRAS* mutation	*KRAS*, *GNAS* mutations	*CTNNB1* mutation
			

Neoplastic – Solid: Ductal adenocarcinoma

- Very aggressive cancer usually affecting the elderly (60-80 yo); one of the highest mortality rates
- **Risk factors**: Smoking, high-fat diet, chronic pancreatitis, DM, genetic predisposition (*BRCA2*, *CDKN2A*)
- **Precursors**:
  - Premalignant neoplasms e.g. IPMN, MCN
  - Non-invasive small duct lesions – Pancreatic intraepithelial neoplasia (PanIN)
- **Pathogenesis**: Multiple genes are somatically mutated or epigenetically silenced. While there is a general temporal sequence, the accumulation of multiple mutations is more important than the specific order. Genes most frequently mutated or altered include *KRAS, CDKN2A, TP53* and *SMAD4.*



Model of progression from normal duct through PanINs to invasive carcinoma

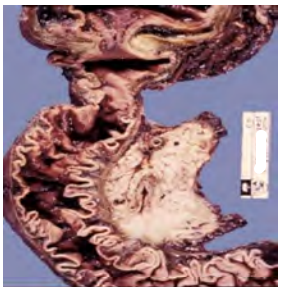
Robbins & Cotran, 9th ed

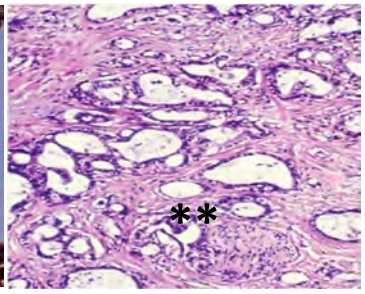
Gene	Chr	Protein	Category	Function
KRAS	12p	KRAS	Oncogene	GTP-binding protein involved in signaling pathways downstream of growth factor receptors with intrinsic tyrosine kinase activity for cell growth and survival e.g. MAPK
CDKN2A	9p	P16/INK4a ARF	Tumour-suppressor	Cyclin-dependent kinase inhibitor to cell cycle progression Augments function of p53
SMAD4	18q	SMAD4	Tumour-suppressor	Important in signal transduction from TGF-b family of cell surface receptors
TP53	17p	p53	Tumour-suppressor	Nuclear DNA-binding protein that responds to DNA damage by 1. arresting cell growth 2. inducing cell death 3. causing cellular senescence

- **Clinical presentation**: Asymptomatic or pain, obstructive jaundice (HOP lesions), systemic symptoms (i.e. LOW, LOA, lethargy especially in advanced disease) or GI bleeding (tumour erosion into adjacent structures). 10% of patients may have migratory thrombophlebitis (Trosseau sign) due to release of platelet-activating factors and procoagulants from the tumour or its necrotic products

Gross pathology:
- Locations: Head 60%, body 15%, tail 5%, entire gland 20%
- Large pale firm mass with infiltrative border

Microscopic findings:
- Adenocarcinoma with desmoplasia
- Perineural** and lymphatic involvement





Neoplastic – Solid: Pancreatic neuroendocrine tumours (PanNET) / Islet cell tumours

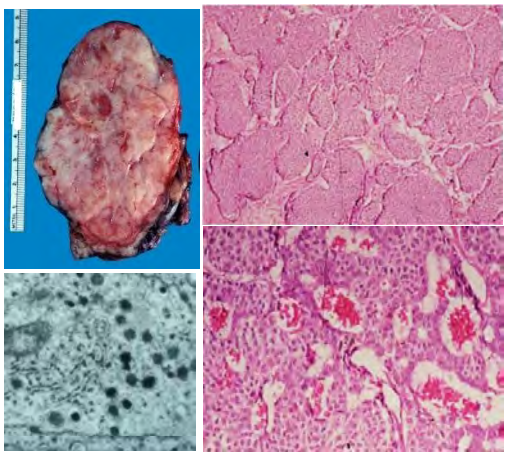
- Uncommon compared to pancreatic exocrine tumours
- These are **well-differentiated** pancreatic neuroendocrine neoplasms (PanNEN), as opposed to **poorly-differentiated** PanNEN which refers to **pancreatic neuroendocrine carcinomas** which resemble pulmonary small cell and large neuroendocrine carcinoma. However, **all PanNETs have malignant potential** even if they have a bland light microscopic appearance (unless <0.5 cm in size)
    - Prognostic factors: Size, mitotic rate, vascular invasion, extra-pancreatic invasion
- Traditionally, they can be divided into **functional** or **non-functional** categories, depending on the presence of an **associated clinical syndrome** (not just biochemical)

Cell type	Secretion and function	Neoplasm	Clinical syndrome
β-cells	Insulin *Regulates glucose utilization, reduces blood glucose*	Insulinoma (β-cell tumor) *Most common; usually benign behaviour*	WHIPPLE'S TRIAD: - Hypoglycemic episodes (blood sugar <50mg/dl) - CNS manifestations (confusion, stupor, loss of consciousness) related to fasting/exercise - Symptom relief with glucose administration
α-cells	Glucagon *Stimulates glycogenolysis, raise blood glucose*	Glucagonoma	Mild diabetes mellitus Necrolytic migratory skin erythema Anaemia
δ-cells	Somatostatin *Suppress insulin and glucagon release*	Somatostatinoma	Inhibitory actions on gallbladder contraction and secretion, insulin and pancreatic exocrine secretions, manifesting as Diabetes mellitus, Cholelithiasis, Steatorrhoea and Hypochlorhydria
PP cells	Pancreatic polypeptide *Stimulate gastric and intestinal secretions and intestinal motility*	PP-secreting endocrine tumour	Often asymptomatic, presents as mass lesions
D1 cells	Vasoactive intestinal polypeptide	VIPoma	WDHA SYNDROME: - Watery/secretory diarrhoea

	Glycogenolysis, hyperglycemia, GI fluid secretions		- Hypokalemia - Achlorhydria
Entero-chromaffin cells	Serotonin	Carcinoid tumour	CARCINOID SYNDROME: - Flushing - Diarrhoea - Bronchospasm - Heart valve lesions
Gastrin-producing cells	Gastrin *Secretion of gastric acid*	Gastrinoma	ZOLLINGER-ELLISON SYNDROME: • Gastric hypersecretion; hyperacidity • Intractable peptic ulceration • Diarrhoea

- **Pathogenesis**: Most PanNETs are **sporadic**. The molecular alterations are significantly different from ductal adenocarcinoma, with recurrent somatic alterations in 3 major genes or pathways:
  - ***MEN1*** (also causes familial MEN syndrome)
  - Loss of function mutations in tumour suppressor genes e.g. *PTEN*, *TSC2*, resulting in **activation of mTOR pathway**
  - **Inactivating mutations in *ATRX* and *DAXX*** genes which have multiple cellular functions, including telomere maintenance

- PanNETs that occur in **inherited syndromes** tend to be multiple and occur at a younger age. **Multiple endocrine neoplasia (MEN) syndrome** is a group of inherited diseases resulting in proliferative lesions (hyperplasia, adenomas and carcinomas) of multiple endocrine organs. PanNETs are seen in MENI syndrome, as well von Hippel Lindau syndrome and tuberous sclerosis.



Lesions	MEN I	MEN IIa	MEN IIb/III
Mutation	***MEN1***	***RET***	
Pituitary	++++	0	0
Medullary carcinoma (thyroid)	+	++++	++++
Parathyroid	++++	++	+
Adrenal cortex	++++	+	+
Pheochromocytoma	0	++++	++++
Pancreas	++++	0	0
Duodenum - gastrinomas	++++	0	0
Mucocutaneous neuromas	0	0	++++

Gross pathology:
- Solid pale mass

Microscopic findings:
- Small round cell tumors that are highly vascular
- Immunohistochemical stain for secretory products
- Electron microscopy: Neurosecretory granules in cytoplasm