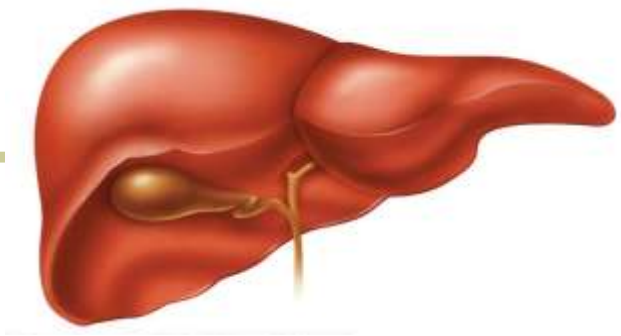
Drugs in Liver Disease



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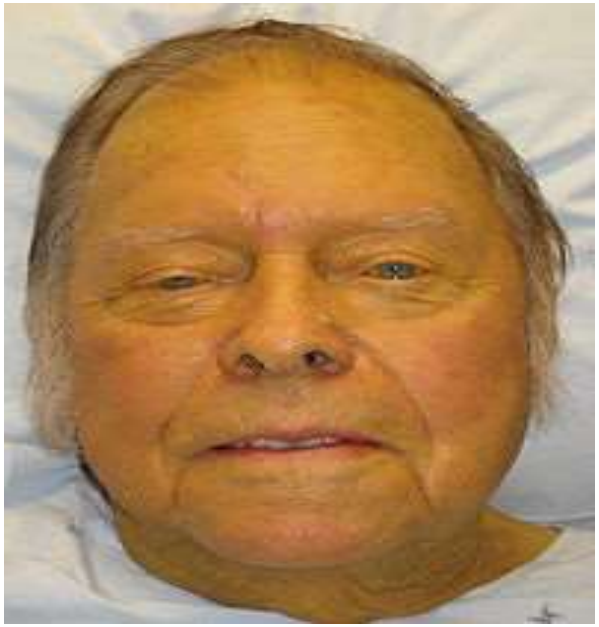
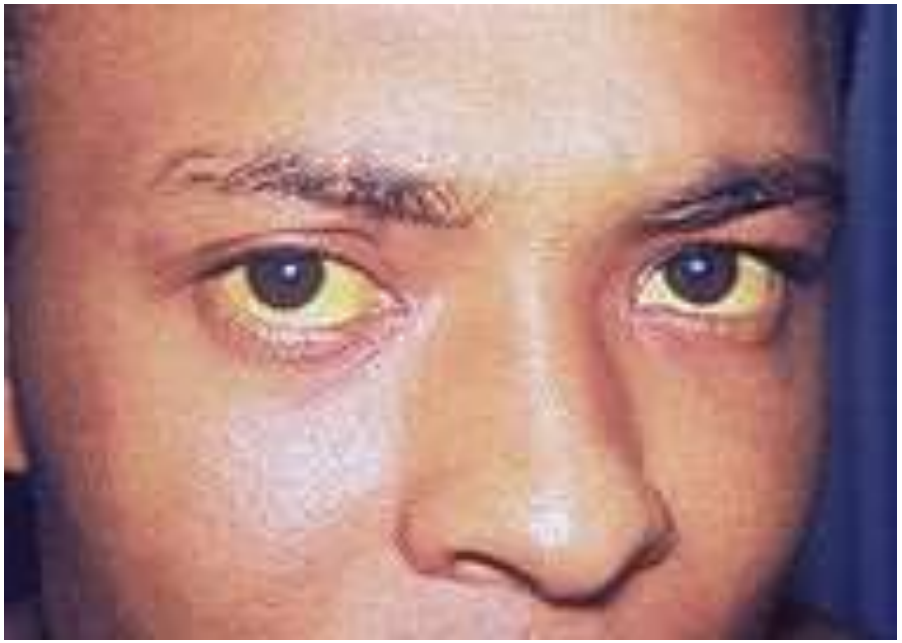
Liver

- Liver disease alters response to drugs
- Drugs may alter liver function
- **Drugs** used by patients with severe liver disease should be kept to **minimum**
- Main problems may occur in patients with:
  - Jaundice
  - Ascites
  - Evidence of encephalopathy

Jaundice in a man with hepatic failure



Jaundice in a man caused by hepatitis A



Jaundice also known as **icterus**, is a yellowish discoloration of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membrane caused by hyperbilirubinemia (increased levels of billirubin in the blood). This hyperbilirubinemia subsequently causes increased levels of billirubin in the extracellular fluids.

The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile

Liver

- Liver is the most important organ of **metabolism** of drugs
- **Metabolites** may be **inactive**, **active** or **toxic**
- Liver is exposed to drugs in **higher** concentration than other organs as most drugs are administered orally & have to pass through liver after absorption
- Liver is **susceptible** to injury
- Liver disease can produce abnormal drug handling & response

Effects of liver disease on drugs

1. **Pharmacodynamic alterations:**

- Patients with severe liver disease show abnormal response to drugs:
  - Increased effects of **anticoagulant drugs**
  - Increased response to drugs acting on **CNS**
  - Increased sodium retention following **NSAIDs**

1. Pharmacodynamic changes

Reduced clotting:

- **Reduced** hepatic **synthesis** of **clotting factors**
- As indicated by prolonged **prothrombin time**
- Increases sensitivity to **oral anticoagulants**:
  - Warfarin resulting in increased risk of **bleeding**

1. Pharmacodynamic changes

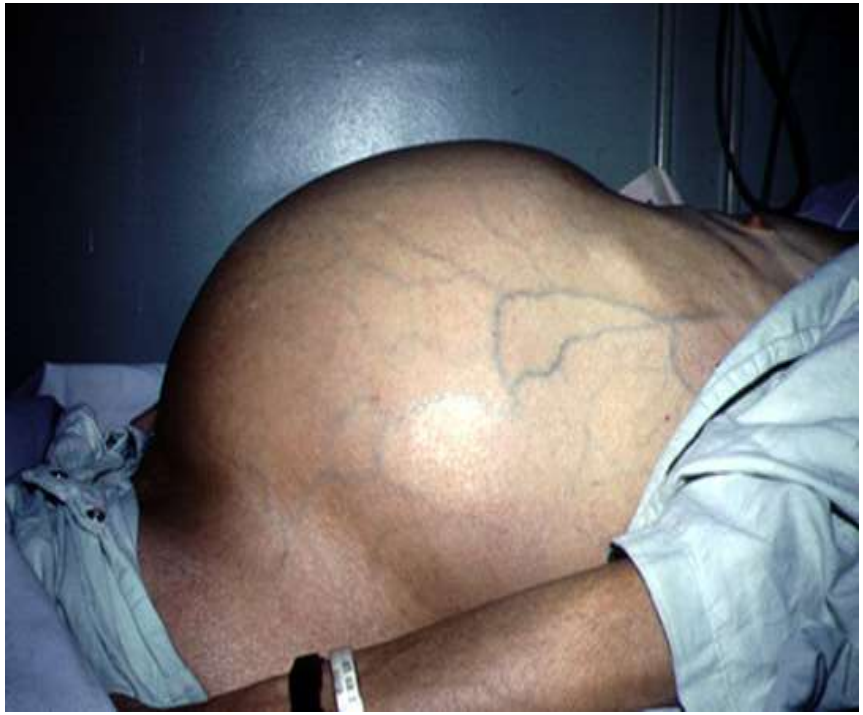
Hepatic encephalopathy

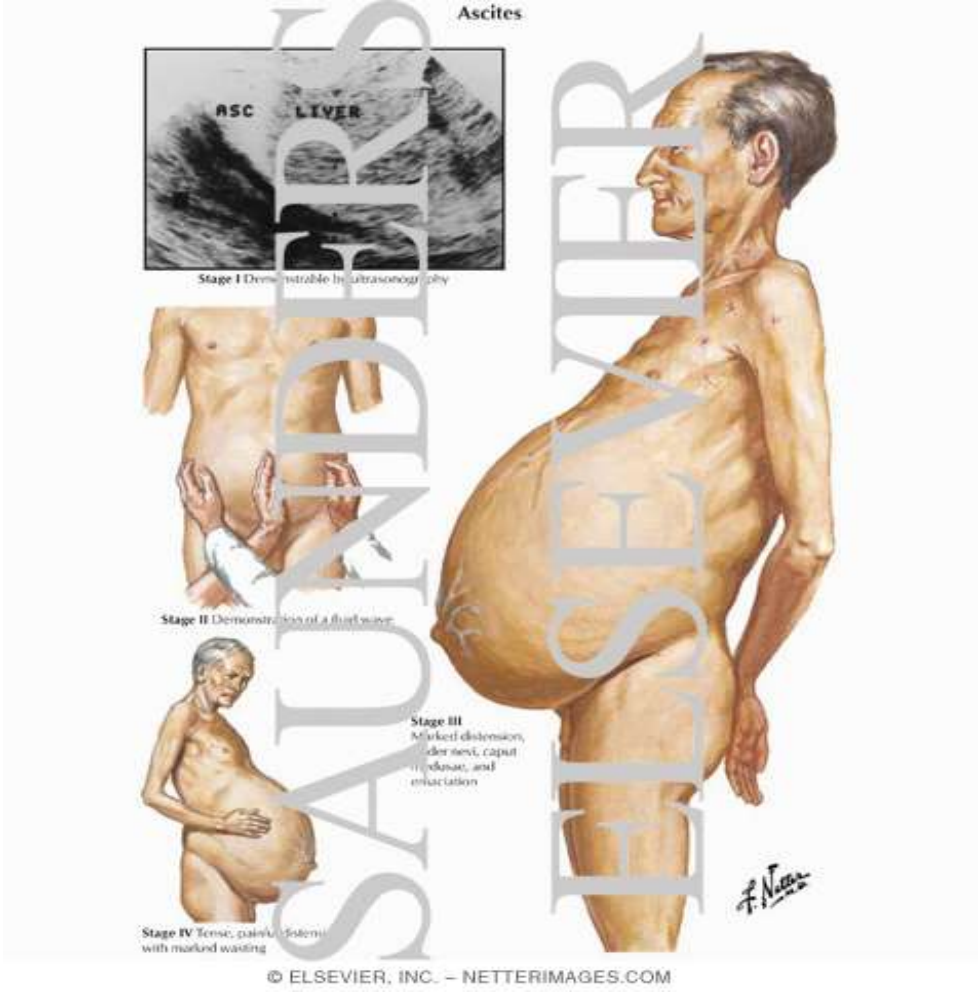
- In **severe** liver disease (e.g. cirrhosis, hepatitis) many drugs can **impair cerebral** function & may precipitate hepatic **encephalopathy** as:
  - Sedative-hynotics
  - Opioid analgesics
  - Hypokalemia producing diuretics (Thiazides)
  - Drugs causing constipation (Al Hydroxide)

1. Pharmacodynamic changes

Fluid overload

- **Oedema** and **ascites** (fluid in the peritoneal cavity) in chronic liver disease may be **exacerbated** by drugs that result in fluid retention as
  - **NSAIDs**, **corticosteroids**





Ascites (also known as **peritoneal cavity fluid**, **peritoneal fluid excess**, **hydroperitoneum**) is an accumulation of fluid in the peritoneal cavity. Although most commonly due to cirrhosis and severe liver disease, its presence can portend other significant medical problems.

2. Pharmacokinetic changes

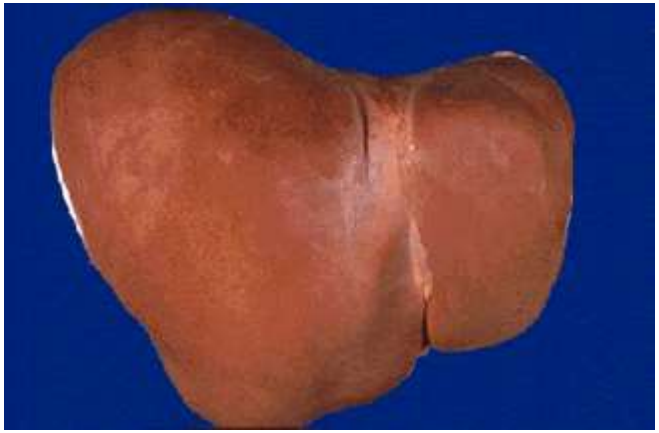
Impaired drug metabolism

- **Liver disease** may result in **impairment** of hepatic **metabolism** of drugs causing:
  - **Reduced clearance** of drugs & increased toxicity e.g. warfarin

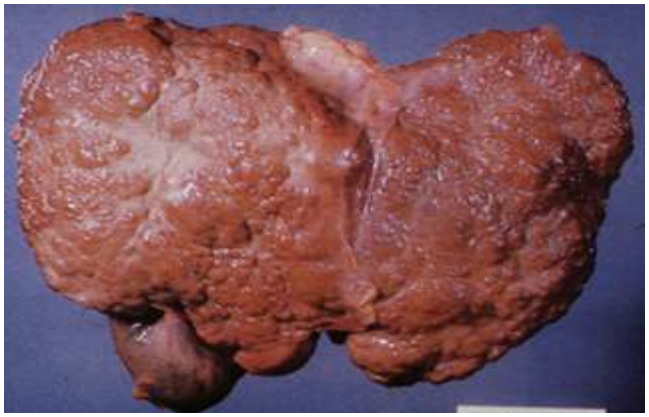
NB: Liver function tests (LFT) are poor guide to the capacity of the liver to metabolize drugs & relying on them alone is not sufficient to predict the extent of impairment of drug metabolism

e.g. Liver diseases

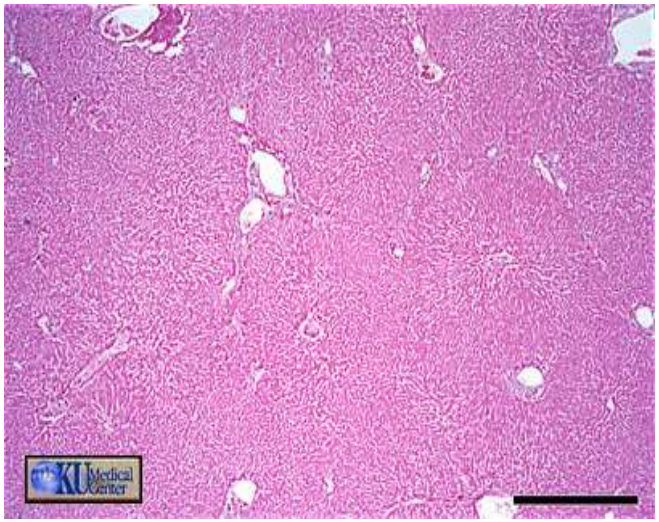
- **Hepatitis**, inflammation of the liver, caused mainly by various viruses but also by some poisons, autoimmunity or hereditary conditions.
- **Cirrhosis** is the formation of fibrous tissue in the liver, replacing dead liver cells. The death of the liver cells can for example be caused by viral hepatitis, alcoholism or contact with other liver-toxic chemicals.
- **Haemochromatosis**, a hereditary disease causing the accumulation of Fe in the body, eventually leading to liver damage.
- **Cancer** of the liver (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the GIT).
- **Wilson's disease**, a hereditary disease which causes the body to retain Cu.
- **Primary sclerosing cholangitis**, an inflammatory disease of the bile duct, likely autoimmune in nature.
- **Primary biliary cirrhosis**, autoimmune disease of small bile ducts.
- **Budd-Chiari syndrome**, obstruction of the hepatic vein.
- **Gilbert's syndrome**, a genetic disorder of bilirubin metabolism.
- **Glycogen storage disease type II**, the build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and nervous system.
- There are also many **pediatric liver disease**, including **biliary atresia**, **alpha-1 antitrypsin deficiency**, **alagille syndrome**, and **progressive familial intrahepatic cholestasis**, to name but a few.



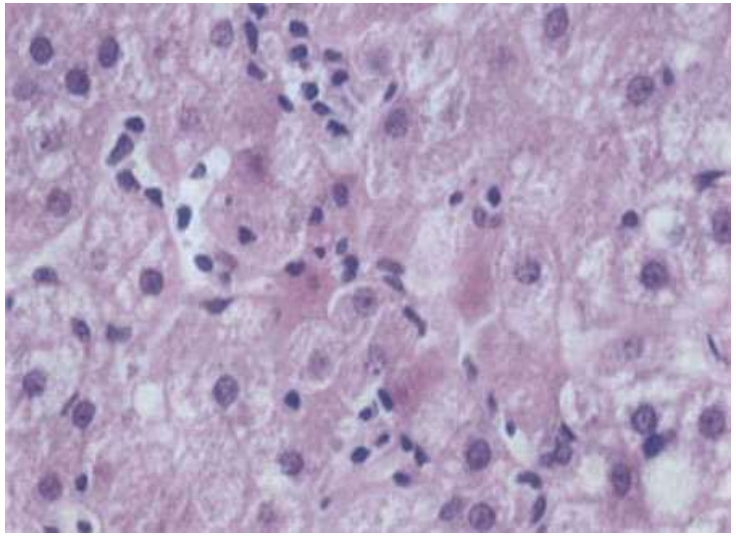
Healthy liver



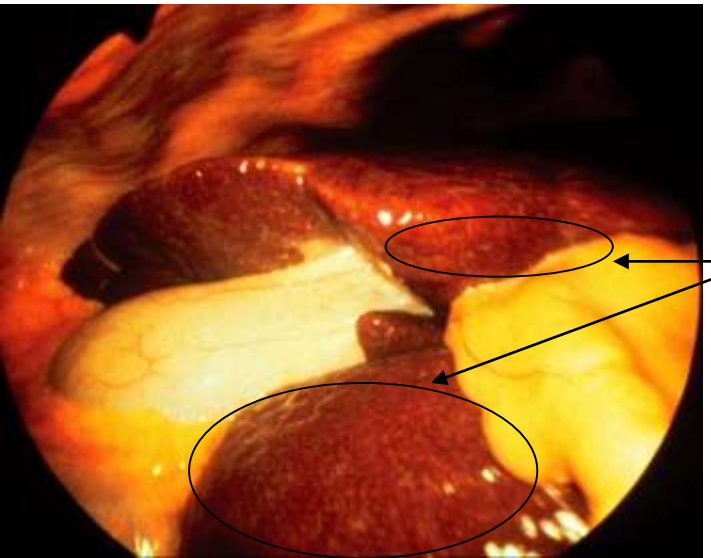
cirrhotic liver



Healthy liver

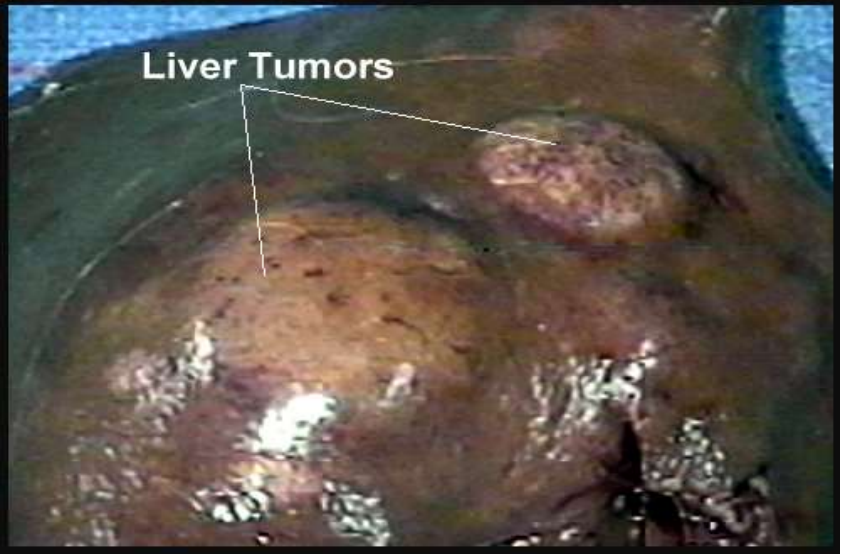


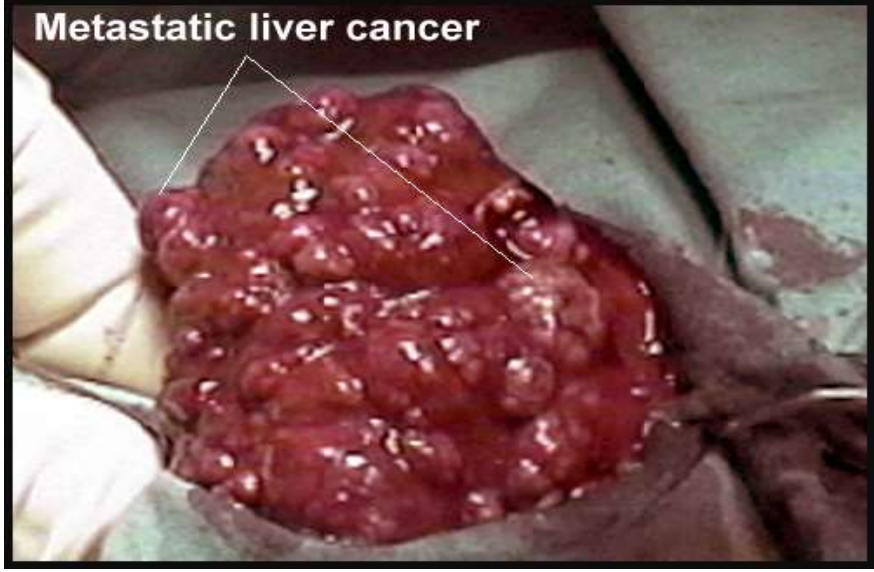
Liver infected by type C virus

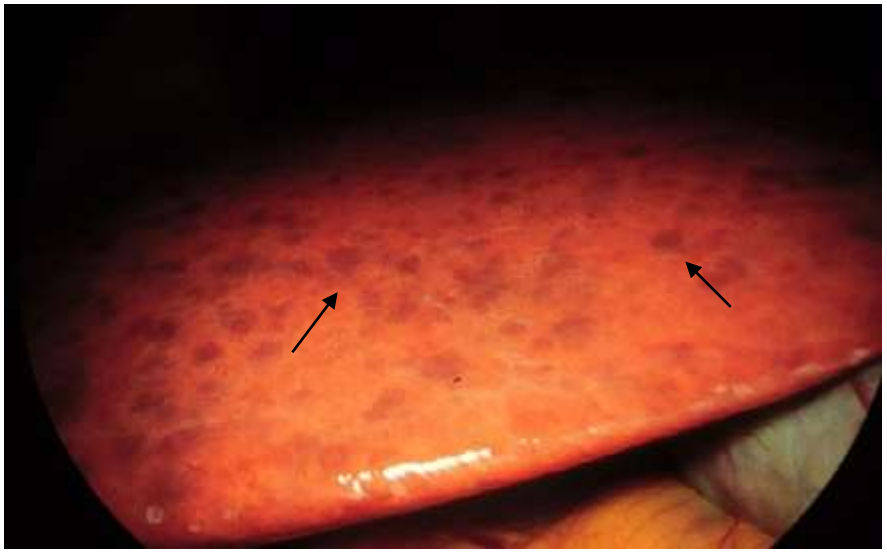


Hemochromatosis of liver

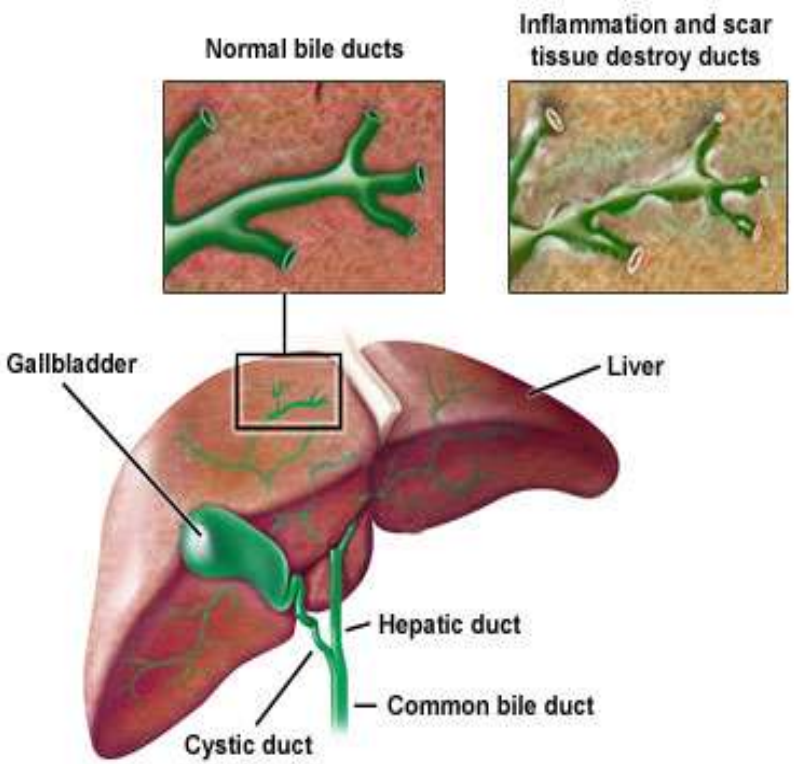
The dark reddish brown color of liver surface is characteristic in hemochromatosis. The liver surface of this case shows granular change, suggesting the presence of a fine nodular formation in liver histology





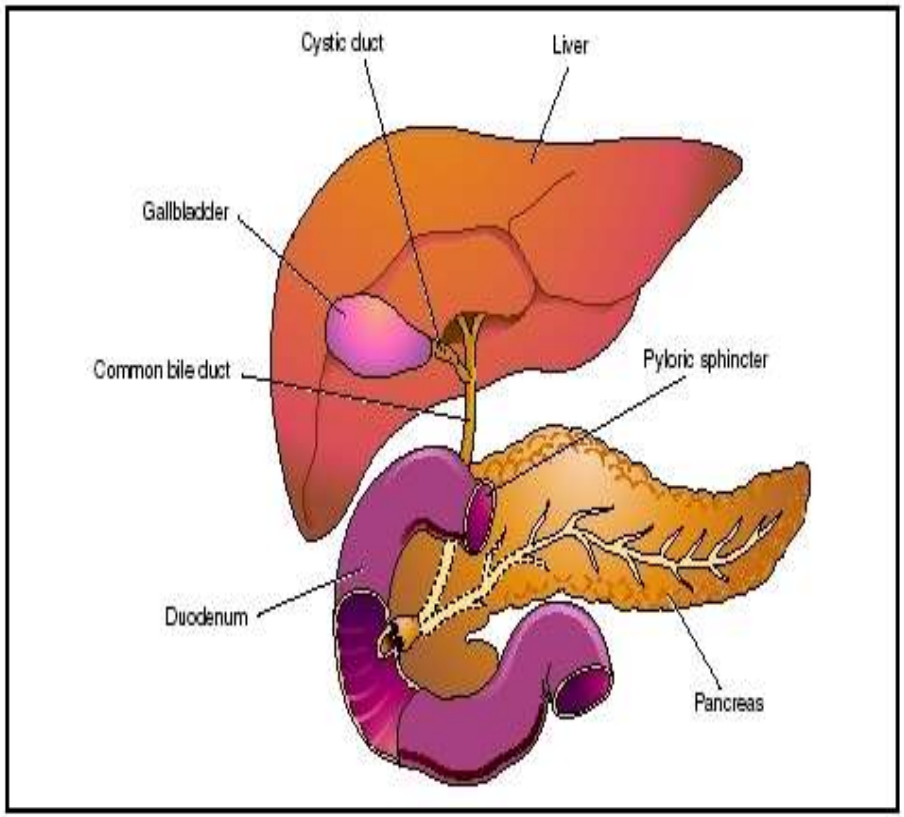


The liver in the non-cirrhotic stage of **Wilson's disease** is usually enlarged, and shows the characteristic spotty pigmentation. These spots are believed to be caused by Cu deposition in liver parenchyma.



Primary sclerosing cholangitis

Biliary Atresia - a serious disease of the very young infant. This disease results in inflammation and obstruction of the ducts which carry bile from the liver into the intestine**.**



2. Pharmacokinetic changes

Accumulation

- Some drugs as **Rifampicin & fusidic acid** excreted in bile unchanged
  - may **accumulate** in **obstructive jaundice** causing toxicity

3. Alterations in liver blood flow & metabolism

- Reduced blood flow in liver disease leads to:
  - **Reduced** drug **delivery** to liver cells
- Drugs with **high** first pass metabolism:
  - **Removal** of drugs will be **less**
  - **Increased** systemic **bioavailability**
  - Doses should be smaller
  - Therefore initial & maintenance **doses** of such drugs should be **smaller** e.g. opioid analgesics

4. Alteration in drug-protein binding

Hypoproteinaemia (Hypoalbuminaemia) result in:

- Reduced **protein**-bound fraction
- Increased **free fraction**
- Leading to increased:
  - Drug **effects** & increased **toxicity**
  - For **highly protein-bound**: more than 90% (phenytoin, warfarin, prednisolone)

Drug prescription in liver disease

- **In mild** liver disease & stable liver: prescribing is **safe**
- Prescription should be very **careful** in patients with **severe** liver disease and:
  - Impaired hepatic synthesis (as hypoalbuminaemia & reduced clotting factor)
  - Hepatic encephalopathy
  - Fluid retention
  - Renal impairment
  - Drugs with high protein binding, low therapeutic index and CNS depressants

Drug prescription in liver disease

- For drugs with significant liver metabolism, a good approach is:
  - To **reduce** dose to **25-50 %**
  - Monitor response carefully

  - **Examples:**

Drug prescription in liver disease

- **CNS depressants**: **avoid** or used **cautiously**
- **Opioids**: can precipitate hepatic **encephalopathy** in patients with liver disease and if required postoperatively the dose is reduced by 50%
- **Codeine** causes constipation & can precipitate **encephalopathy**
- **NSAID**: precipitate **fluid retention** & **GIT bleeding**
- **CVS** drugs: lipid-soluble β-blockers **avoided**

Drug prescription in liver disease

- **Na containing antacids**: **fluid retention**
- **Al antacids**: cause constipation & may precipitate **encephalopathy**.
- **Oral contraceptive pills (OCP):** may exacerbate **cholestatic** liver disease & jaundice

Hepatotoxic drugs

- **Hepatotoxicity** is either:
  - **Dose-related** or
  - **Idiosyncratic**
- Drugs causing dose-related toxicity may do so at **lower** doses than in those with normal liver
- Drugs producing idiosyncratic reactions do so more frequently in patients with liver disease
- So these drugs **should be avoided** or **used** very **carefully**

Drug-induced liver damage

Type A (Augmented):

- Liver damage is **dose-dependent**
- E.g.
- Centrilobular necrosis: **paracetamol** toxicity
- Liver failure: high doses **tetracycline**
- Hepatocellular necrosis: salicylates

Drug-induced liver damage

Type B (Bizarre; idiosyncratic):

- Occurs with **therapeutic doses** due to production of hepatotoxic **reactive metabolites** or due to **immunological reaction** against liver cell antigens. May include:
- Acute hepatocellular necrosis: **halothane**
- Cholestasis: **erythromycin**, **chlorpromazine**, **glibenclamide**

Drug-induced liver damage

Type C (Continued use):

- Benign liver tumour: **OCP** (>5 yrs)
- Chronic active hepatitis: **methyldopa** & **INH**
- Hepatic cirrhosis: **methotrexate** in psoriasis