United Kingdom Liver Pathology Group

Lecture for undergraduate medical students:

Medical liver diseases

1: Medical Liver Diseases

Aims

Cover curriculum

Lots of content

Follow Underwood chapter

Additional notes on PowerPoint slides

Medical liver diseases:

1. Jaundice
2. Acute and chronic hepatitis
   a) Viral
   b) Alcohol, obesity
   c) Drugs
   d) Inherited haemochromatosis,
      Wilson's
      Alpha-t antitrypsin deficiency
   e) Autoimmune
3. Cirrhosis
4. Hepatic failure

The lecture will concentrate on jaundice, hepatitis, cirrhosis, and follow the list of topics in the curriculurm.

1. Jaundice

- Visible when bilirubin >40umol/l
- Commonest sign of liver disease

- Pre-hepatic – too much bilirubin produced
  - Haemolytic anaemia

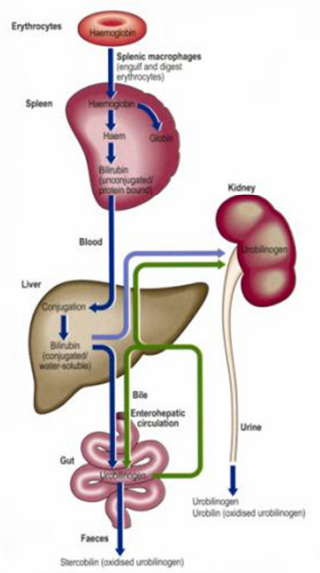
- Hepatic – too few functioning liver cells
  - Acute diffuse liver cell injury
  - End stage chronic liver disease
  - Inborn errors

- post hepatic – bile duct obstruction
  = stone, stricture, tumour – bile duct, pancreas

First visible in sclera (white of eye)

Classified according to where the abnormality is in the metabolism of bilirubin

1. Simplified pathways of bilirubin metabolism



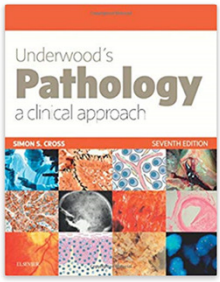
Bilirubin produced by red blood cell breakdown = unconjugated.

Metabolised in liver – conjugated and excreted in bile

Some bilirubin is re-absorbed from gut,
Enterohepatic circulation

Also bile salts

7th edition
2018



1.1 Jaundice

- Visible when bilirubin >40umol/l
- Commonest sign of liver disease

- Pre-hepatic – too much bilirubin produced
  - Haemolytic anaemia, (Gilbert's syndrome – enzyme deficiency)

  unconjugated – bound to albumin, insoluble, not excreted

  = patient notices yellow eyes/skin only

- Hepatic – too few functioning liver cells
  - Acute diffuse liver cell injury
  - End stage chronic liver disease
  - Inborn errors

  Mainly conjugated, Soluble

  = patient notices yellow eyes and dark urine

- post hepatic – bile duct obstruction, conjugated

  = stone, stricture, tumour – bile duct, pancreas

  conjugated – soluble, excreted, but can't get into gut

  = patient notices yellow eyes, pale stool and dark urine

The site of abnormality of the bilirubin excretion can be deduced from the clinical history of skin, urine, faeces colour

Liver function tests

Blood tests - Biochemistry:

Liver enzymes

- Leak from hepatocytes – ALT, AST,
  - Mild increase long time – chronic liver disease
  - Very high levels – severe acute liver disease
- Leak from bile ducts – Alk phos
  - Therefore high in obstructive jaundice and chronic biliary disease

Bilirubin – usually conjugated, dark urine

Albumin – low in chronic liver disease, long half life

Clotting factors – low in acute liver disease and liver failure
– short half life of clotting factors

'Liver function tests' = a set of biochemical tests that indicate

-damage to cells in the liver so that enzymes leak from cells (this is a 'damage' test rather than a 'function' test)

-Relative increase of Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) v. Alkaline phosphatase indicates whether injury is mainly to hepatocytes, bile duct cells or both

-Bilirubin, albumin, clotting factors – these are liver function tests – abnormalities because inadequate function of hepatocytes

-Raised conjugated bilirubin without extrahepatic duct obstruction indicates disease of hepatocytes or intrahepatic bile ducts

-Clotting factors and albumin are proteins manufactured by hepatocytes – so levels fall when insufficient liver synthetic function

-Albumin has a long half life, levels are low in chronic liver insufficiency (and also other causes = insufficient intake due to poor diet or malabsorption, or increased urinary excretion due to leaky glomeruli = nephrotic syndrome).

-Clotting factors – so blood takes longer to clot – measured by prothrombin time (PT) and INR (international normalised ratio – ratio of patient's clotting time to

normal control). The factors have a short half life so PT is prolonged after just a few days of severe liver injury. Poor clotting is also seen in patients with obstructive jaundice who can't absorb fat soluble vitamis – this is corrected by vitamin K.

Investigation of jaundice

- Ultrasound scan to check for dilated ducts in obstruction
- Only if no dilated ducts do a liver biopsy to find out the cause of jaundice
- Most (non-obstructive) cases are due to acute hepatitis:

1. Histopathological features in liver with obstructive jaundice

First sign:

- Bile in the liver parenchyma
  - (jaundice in the skin, patient is yellow)

Increasing with time:

- Portal tract expansion,
- Oedema
- Ductular reaction – proliferation of ductules around the edge of portal tracts
- Bile salts and copper can't get out
  - Accumulate in hepatocytes
  - (bile salts in skin – patient is itchy)

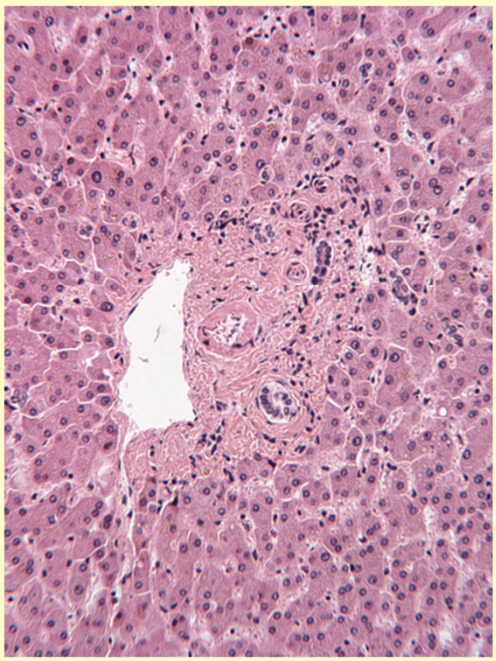
A patient with jaundice is first investigated with ultrasound scan (USS) to check for bile duct dilatation.

If ducts are not dilated, then liver biopsy may be performed to investigate the cause of jaundice.

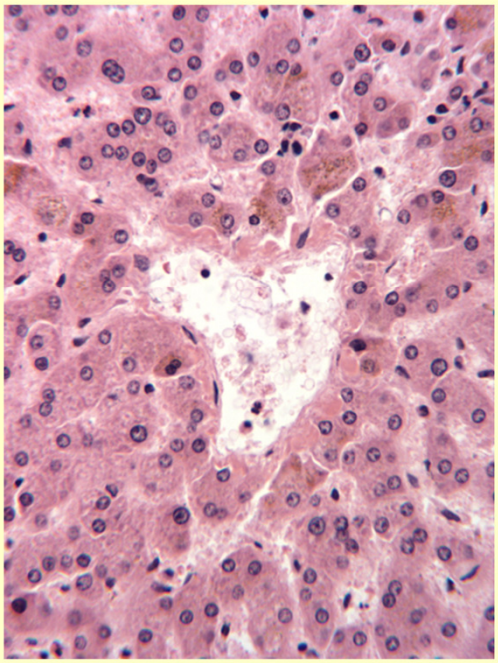
There are characteristic changes in the liver histology that indicate why there is jaundice – these can distinguish between obstruction to ducts (not always seen on ultrasound scan) and various patterns of liver cell injury.

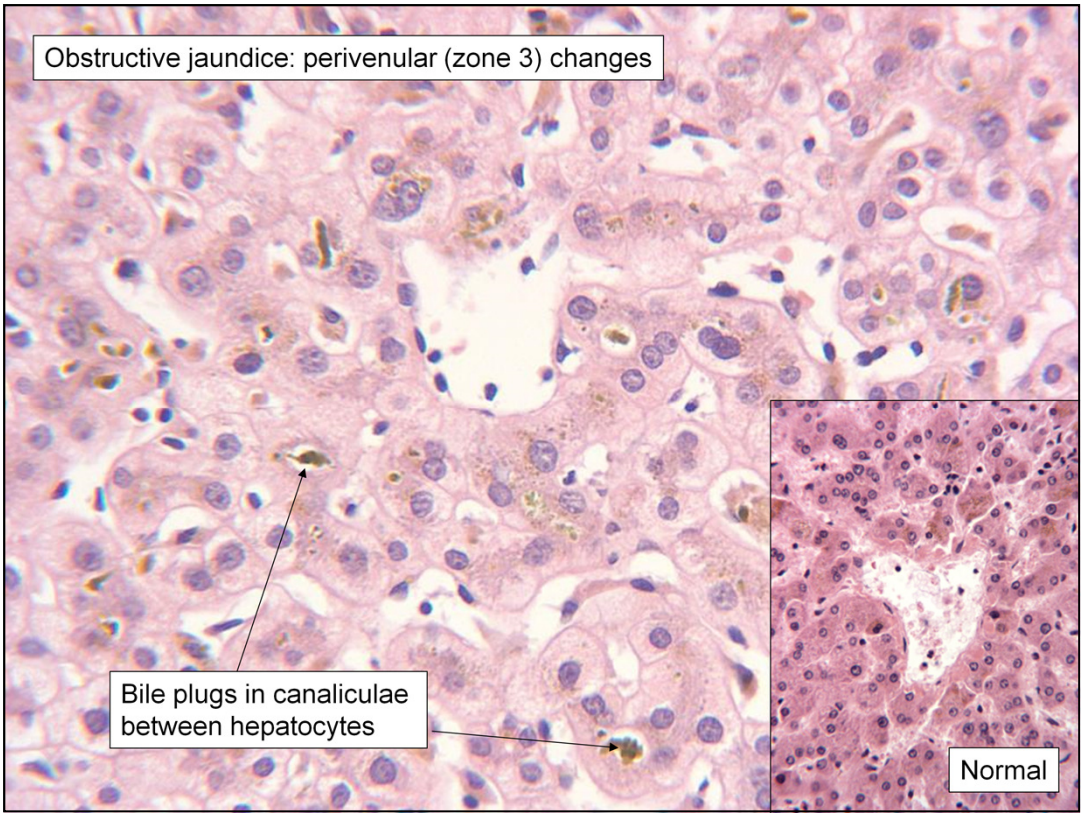
The features of bile duct obstruction gradually evolve over time. If unrelieved, the obstruction would eventually lead (over months/years) to severe chronic liver disease and cirrhosis.

Normal liver:
Portal tract

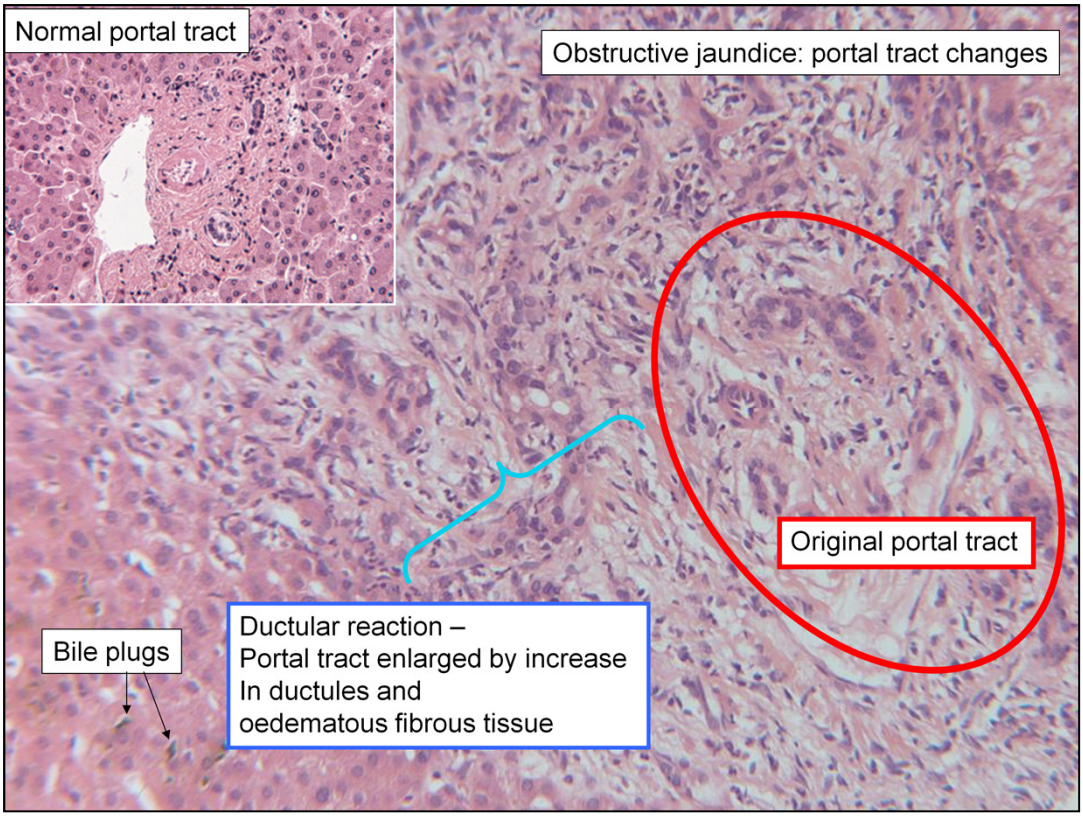


Normal liver:
Hepatic vein





Bile pigment is visible in the bile plugs which represent the bile that has been excreted by hepatocytes into intracellular canaliculi but because of low bile flow accumulates in the canaliculi where it can be seen. There is also swelling and irregularity of hepatocytes, and increased activity of macrophages (Kupffer cells) phagocytosing dead hepatocytes.



As time goes on, portal tracts get larger, initially due to swelling (oedema, tissue looks pale) then ductular reaction (increased number of small bile ducts around the periphery of the tracts) and some associated inflammatory cells including neutrophils. Over time, oedema reduces and fibrosis increases. These features combined together have a characteristic appearance (‘biliary Gestalt’).

2. Hepatitis

2. Acute and chronic hepatitis

a) Viral

b) Alcohol, obesity

c) Drugs

d) Inherited haemochromatosis,
Wilson's
Alpha-t antitrypsin deficiency

e) Autoimmune

2. Hepatitis

= inflammation in the liver – in broadest sense, any liver disease that is not neoplastic.

Pathology '-itis' implies inflammation of the liver

Clinically – liver enzymes raised, any cause

- Acute hepatitis – acute liver injury caused by something that goes away
- Chronic hepatitis – chronic liver disease caused by something that doesn't go away
  - balance of damage and attempts at repair

The word 'hepatitis' is used by clinicians and pathologists is rather different ways.

The actual liver inflammation can only be directly seen with a liver biopsy, (classical pain, swelling, etc. of inflammation doesn't apply)

'Hepatitis' is used by clinicians for illness with abnormal liver biochemical tests. Unless the liver disease is severe, symptoms are mild or non-existant.

Acute and Chronic refer to the time frame – acute hepatitis has a recent onset, and will resolve back to normal as long as the cause does not persist.

Chronic hepatitis has by definition been present for over 6 months, and results in ongoing liver cell injury and progressive structural liver damage of scarring and remodelling.

2.1 Causes of acute hepatitis and pathology

Clinical spectrum:

Asymptomatic, malaise, jaundice, coagulopathy, encephalopathy, death

Depends on how many hepatocytes are damaged at once, and how good the liver is at regenerating

Pathology - see cell death and inflammation and regeneration – next 3 slides

Causes – things that damage hepatocytes, short term:

- Inflammatory injury (hepatitis) –viral, drugs, autoimmune, unknown ('seronegative')
  – all have similar pathology spectrum
- toxic/metabolic injury - e.g. alcohol, drugs (paracetamol)

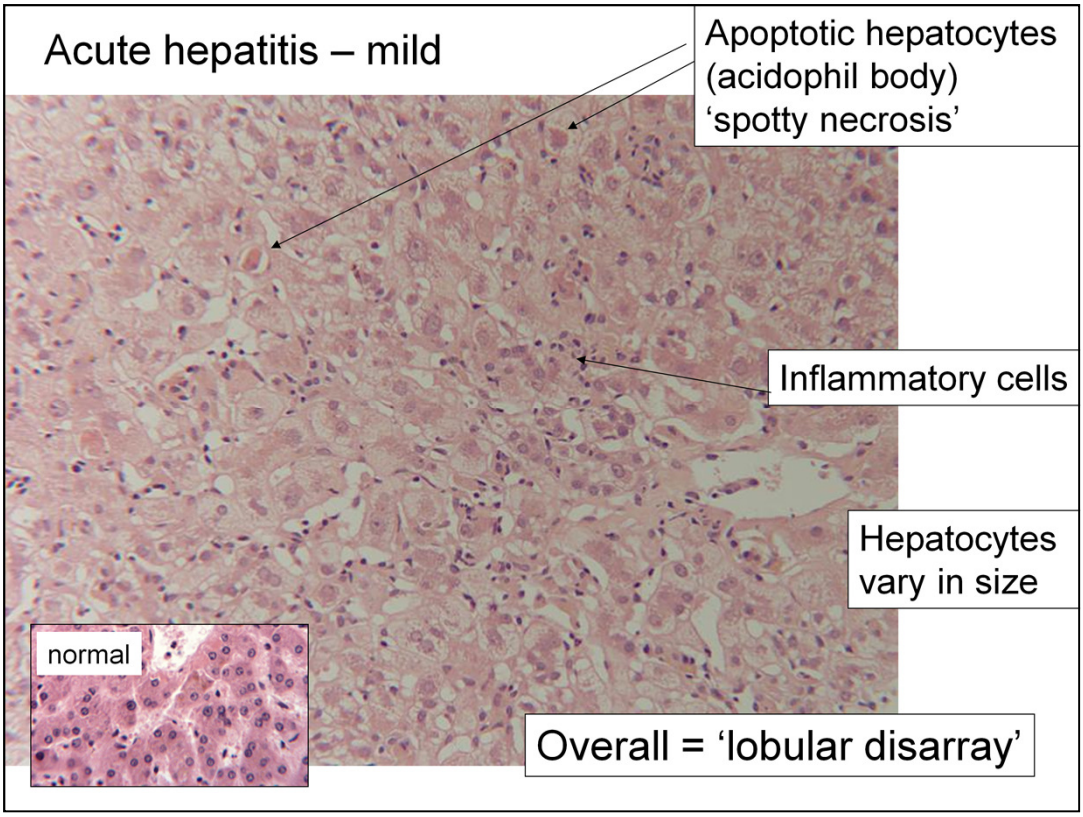
The clinical presentation of hepatitis is a consequence of the amount of hepatocytes that are injured/killed and how well the remaining ones can regenerate. At the rare severe end of the clinical spectrum, hepatocytes die faster than they can be replaced and result in rapidly progressing organ failure, and possibly death. Liver transplantation is necessary to save the life of a patient with severe acute liver failure = rapid progression from coagulopathy, encephalopathy (confusion, coma).

The clinical effects of acute hepatitis are due to the liver cell injury, independent of its cause.

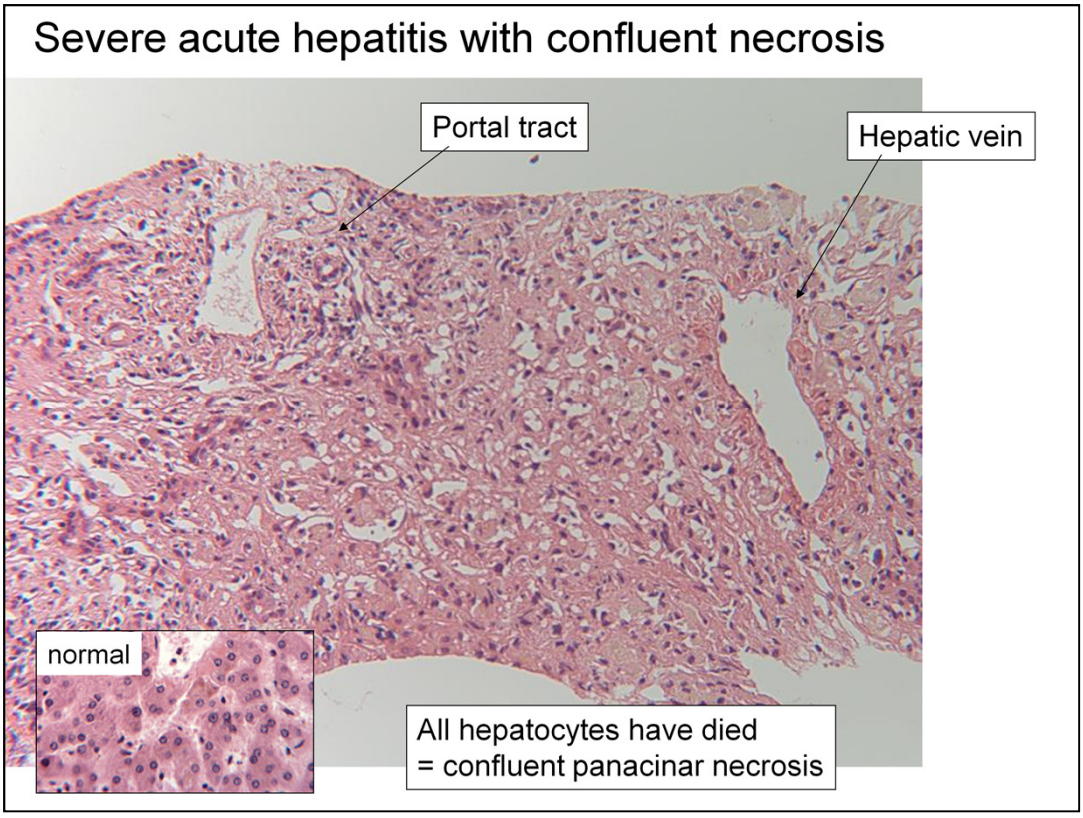
The commonest causes of severe liver cell injury in the UK are alcohol and paracetamol toxicity – cause known from the history.

Causes of severe inflammatory injury (acute hepatitis on biopsy) are viral (hepatitis A, B, E), drug induced liver injury (DILI) and autoimmune hepatitis.

The histology for these is very similar, and in many cases with severe acute hepatitis on histology no cause can be identified (= seronegative hepatitis)

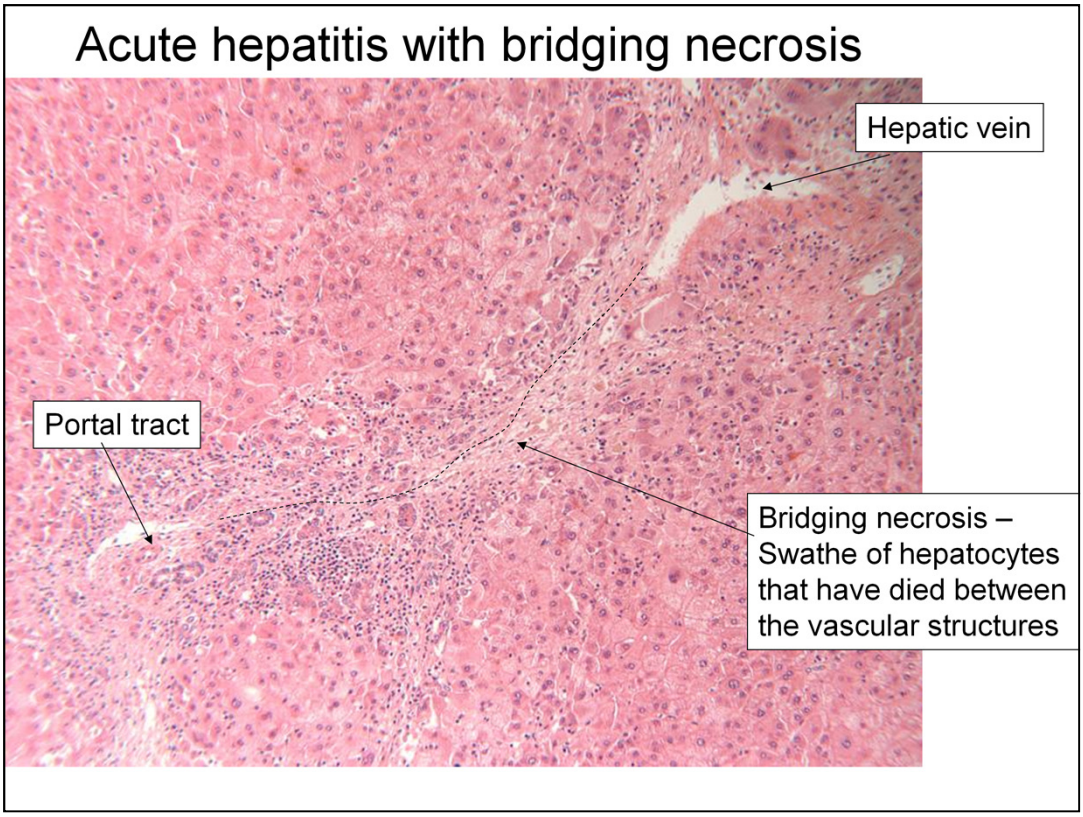


This is the liver biopsy appearance of a patient with acute hepatitis – the injury and death of individual hepatocytes results in a disordered appearance of the liver cell plates, known as 'lobular disarray'.



At the severe end of the spectrum of acute hepatitis, whole confluent areas of hepatocytes have died in some or all of the liver.

If this affects a high proportion of the liver, the patient will have severe liver failure with risk of death.



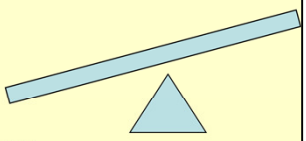
This is intermediate severity, where there is confluent necrosis of adjacent hepatocytes in a 'bridge' between a portal tract and hepatic vein.

In a patient transplanted for acute liver failure, all of the degrees of liver injury illustrated in the last 3 slides may be seen in different areas of the liver.

Causes of chronic hepatitis and pathology

Chronic hepatitis – chronic liver disease caused by something that doesn't go away

- balance of damage and attempts at repair



Causes:

- Immunological injury – virus, autoimmune, drugs
- Toxic/metabolic injury – fatty liver disease, alcohol, non-alcoholic fatty liver disease (NAFLD), drugs
- Genetic inborn errors – iron, copper, alpha1antitrypsin
- Biliary disease – autoimmune, duct obstruction, drugs,
- Vascular disease – clotting disorders, drugs

Clinically 'chronic hepatitis' is a persistence of abnormal liver tests for more than 6 months.

This is because the cause of the liver injury is not transient.

Continuing liver damage is combined with the body's attempts at regeneration of hepatocytes and repair – the wound healing response of angiogenesis and fibrosis.

The causes are in five groups, of which toxic/metabolic is by far the most common.

Liver biopsy can usually identify which of these five groups is the cause of chronic liver injury in an individual patient.

Pathology of chronic liver disease

Injury to liver cells, inflammation, formation of scar tissue and regeneration of hepatocytes
- *Non-specific features of injury*

Specific pathological features depend on the cause of injury

use of liver biopsy in diagnosis:
- To determine the cause of the damage
  - specific features, if present
- To assess the stage of disease
  - how much scarring,
  - spectrum from normal to cirrhosis

Many patients with chronic liver disease will have a liver biopsy for the purpose of diagnosis and staging.

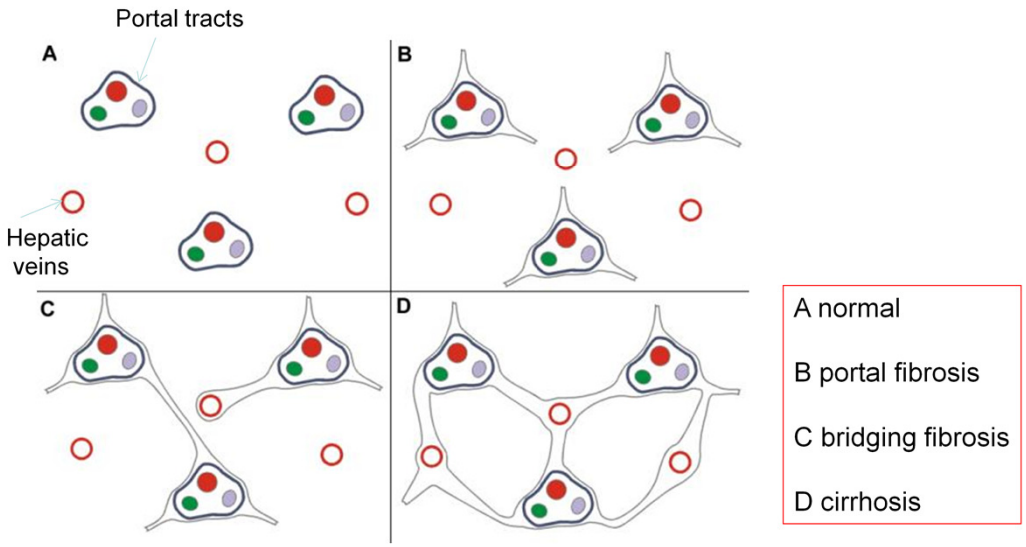
Diagnosis – liver histology in conjunction with the results of other investigations.

There may be more than one cause of liver injury - alcohol and metabolic syndrome are common.

The stage of chronic liver disease refers to the progression on a continuous spectrum from normal to cirrhosis – this is broadly similar for all chronic liver diseases.

Progression of chronic liver disease - stage

During any chronic liver disease,
scarring gradually increases and starts to link vascular structures (bridging)
eventually transforming the liver tissue into separate nodules – end stage = cirrhosis.



A cartoon version, showing how increasing fibrosis progressively remodels the liver. In 3d this is from a tree like structure (branches of portal tracts and hepatic veins seen in cross section in A) – these never normally join each other.

During chronic liver disease, remodelling results in bands of fibrosis that bridge between portal tracts and hepatic veins.

This progression happens in all causes of chronic liver disease, although the rate of progression is very variable (few months to several decades).

Gradually remodelling becomes complete, and hepatocytes form nodules surrounded by fibrous tissue (D). Portal blood entering the liver can flow through vessels in the fibrous tissue, and not percolate through sinusoids. The cirrhotic liver therefore is inefficient in its metabolic function, even though it may be of normal size or larger.

2a Viral hepatitides

Hepatotrophic viruses:

- A, B, C, - see table
- D = delta, only in people with B
- E waterborne, increasingly recognised in UK in last few years, zoonosis, pigs

Other viruses cause hepatitis, as part of systemic disease
EBV, CMV, HSV – usually immunocompromised host

Clinical features, pathology and complications – as for acute and chronic hepatitis

Hepatotrophic viruses specifically infect the hepatocytes causing liver disease, and are known as hepatitis A virus, hepatitis B virus etc.

Other viruses (Epstein Barr virus, Cytomegalovirus, Herpes simplex virus) can infect hepatocytes as well as other cells in the body and hepatitis is part of a systemic disease.

Characteristics of viral hepatitis

Characteristic	Hepatitis A	Hepatitis B	Hepatitis C
Type of virus	Picorna RNA	Hepadna DNA	Flavivirus RNA
Route	Faecal-oral	parenteral	parenteral
Acute jaundice	Common	Common	uncommon
Evolution to chronic hepatitis	Never	10% adults	>70%
Chronic infection worldwide	None	350 million	170 million
Treatment	None	YES + new ones	YES + new ones
Prophylaxis	Vaccine, Ig	Vaccine, Ig	none

This table compares the characteristics of the different hepatotrophic viruses.

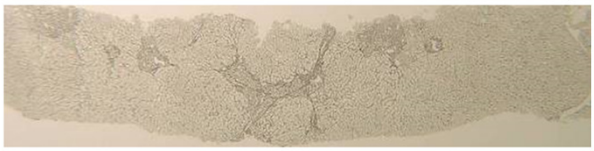
Hepatitis B and C are major causes of liver disease worldwide.

Hepatitis A does not cause chronic hepatitis.

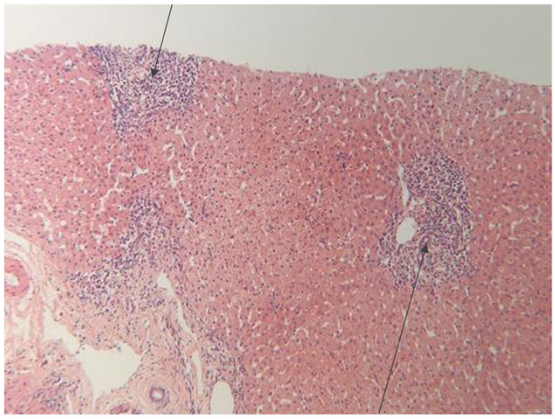
Pathology of chronic hepatitis - severity

Grade –
how much active injury?

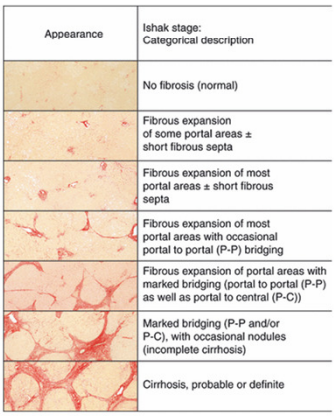
Stage – how much scarring and remodelling?



Portal tract inflammation
– more than parenchymal



interface hepatitis
- makes edges look fuzzy



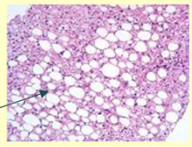
Liver biopsy is used to find out the severity of chronic viral hepatitis. This has two components

– the grade of disease is an estimation of how much inflammatory injury is currently going on – and can fluctuate over time.

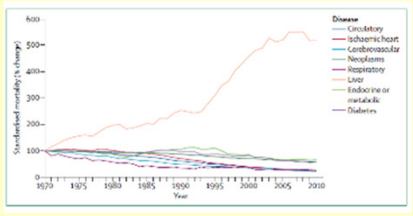
- the stage of disease is an estimation of the scarring, remodelling and nodular regeneration of the liver – how far has the disease progressed along a spectrum from normal to cirrhosis?

Use biopsy to decide how to treat chronic hepatitis B – not used now for hepatitis C unless there is uncertainty about the diagnosis

2b. Alcohol and the liver



Spectrum of
- Fatty change
- Alcoholic steatohepatitis
- Cirrhosis



Depends on dose and susceptibility

- **Death from liver disease have risen by a quarter in eight years due to alcohol and obesity, a report has warned.**

NHS national end of life care Intelligence Network March 2012

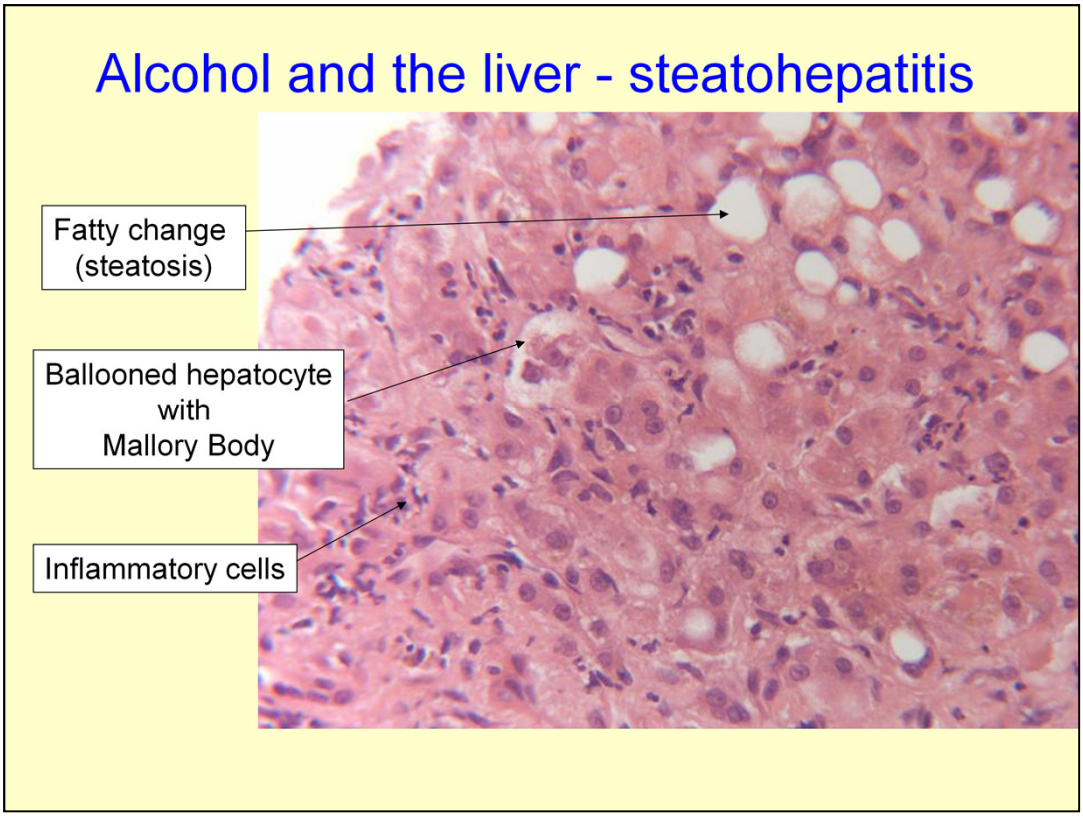
Alcohol is a major cause of liver disease.

It causes a characteristic range of liver pathology – fatty change, steatohepatitis, cirrhosis.

Many patients with metabolic syndrome (obesity, type 2 diabetes, etc) have a similar pathology of liver disease – called 'non-alcoholic fatty liver disease' NAFLD

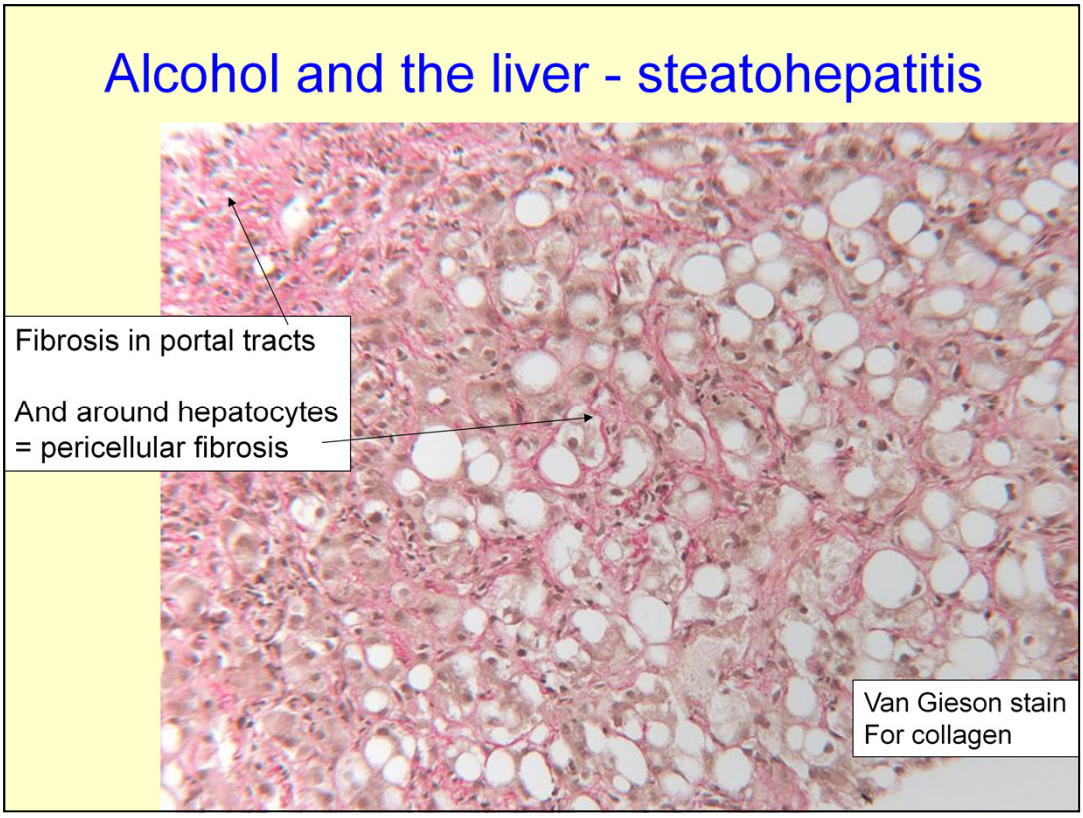
In fact, the combination of risk factors of alcohol and obesity is synnergistic.

These life style factors account for the big increase in deaths from liver disease.



A liver biopsy showing these severe features of steatohepatitis is very likely to be due to alcoholic liver disease – even if the patient has not volunteered the history.

Some patients with alcohol injury may just show fatty change – a reversible stage of liver injury that may or may not progress to steatohepatitis.



This liver biopsy has the collagen stained red.

In steatohepatitis the collagen surrounds liver cells like chicken wire.

This gradually increases as well as portal tract fibrosis.

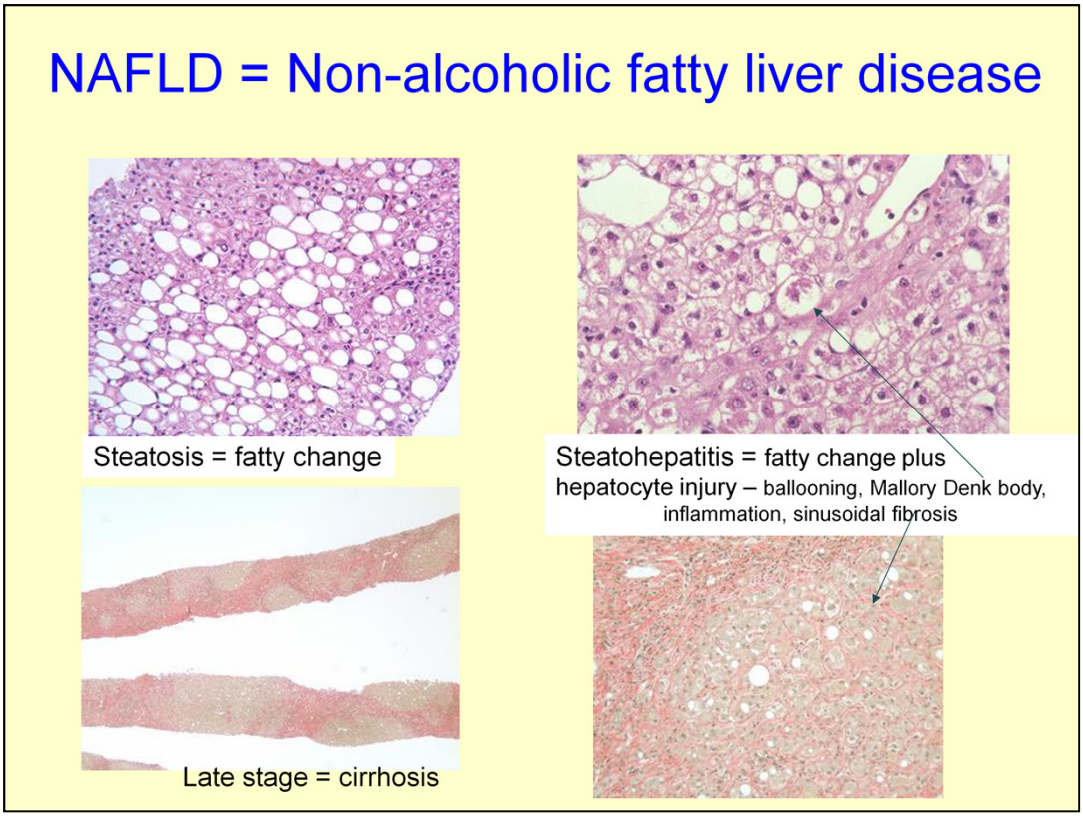
The cirrhosis from alcoholic liver disease is characteristically very fibrotic with small nodules of hepatocytes.

2b contd: obesity: NAFLD = Non-alcoholic fatty liver disease

- Same pathological spectrum as alcoholic liver disease
- Steatosis, steatohepatitis, cirrhosis, HCC

- Associated with Metabolic syndrome – obesity, type 2 diabetes, hyperlipidaemia, also some drugs
- Now recognised to be the commonest cause of liver disease
- Treatment – address the causes of metabolic syndrome

- Big public health issue –
  - 2016: NICE guidelines on NAFLD and cirrhosis
  - Manage patients in primary care whenever possible.



NAFLD is the liver counterpart to metabolic syndrome. Insulin resistance results from excess of calorie intake over the body's demands. Fat is stored in the body in various compartments including the liver - this depends on genetic factors. If stored in the liver, this is seen as fatty liver or steatosis.

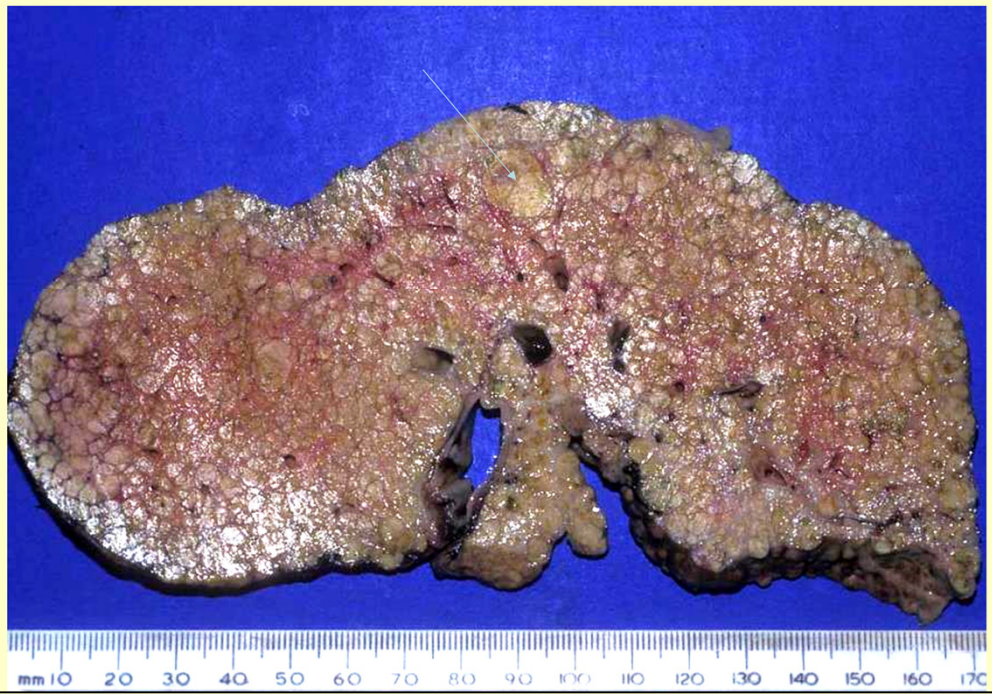
Long term, as a result of continuing excess caolories, plus other factors, some people with steatosis develop steatohepatitis. This is liver cell injury, inflammation and fibrosis due to liver cell stress, when the liver cell mitochondria start to be injured by the oxidative stress of too much energy transfer.

This evolves slowly and is reversible in the early stages – but if continuous for years results in cirrhosis.

The cirrhosis is eventually 'cryptogenic' because the microscopic features of fatty liver disease eventually disappear as the liver is completely re-modelled.

There is a risk of hepatocellular carcinoma developing, as in any cause of cirrhosis.

Cirrhotic liver with hepatocellular carcinoma



Cirrhosis – the late stage of chronic liver disease looks more or less the same macroscopically whatever the underlying cause of disease. The liver is diffusely altered to result in nodules of parenchyma surrounded by fibrous scar tissue. Most hepatocellular carcinoma (arrow) develop in cirrhotic liver, although some cases occur in normal liver or early stage chronic liver disease.

Patients with a diagnosis of cirrhosis are enrolled on surveillance for hepatocellular carcinoma, usually by ultrasound scan every 6 months.

2c. Hepato-toxic drugs

Iatrogenic: induced inadvertently

- by a doctor
- or by medical treatment
- or diagnostic procedures

= Drug Induced Liver Injury (DILI)

From the slide of causes of chronic liver disease – drugs can cause any pattern of liver injury.

2c. Classification of DILI

Hepatotoxicity

Intrinsic e.g. paracetamol
- every time, predictable

Idiosyncratic –
- rare, unpredictable
\+ metabolic
immunological

Clinical

Acute liver injury

- Hepatocellular
- Cholestatic
- Mixed

Clinico-pathological diagnosis

role of biopsy?

Raised liver enzymes:

– severe, persistant,

diagnostic uncertainty

- **Exclude other causes**
  - Alcohol, NAFLD
  - Acute presentation of underlying chronic liver disease
  - Autoimmune
  - Biliary
  - vascular

Drug induced liver injury is classified as intrinsic – anyone taking this drug is likely to get liver damage

Or idiosyncratic – depends on individual susceptibility. Rare and can be severe.

Recognising drug induced liver injury (DILI) is by a combination of clinical history, and histopathology to show the type of injury.

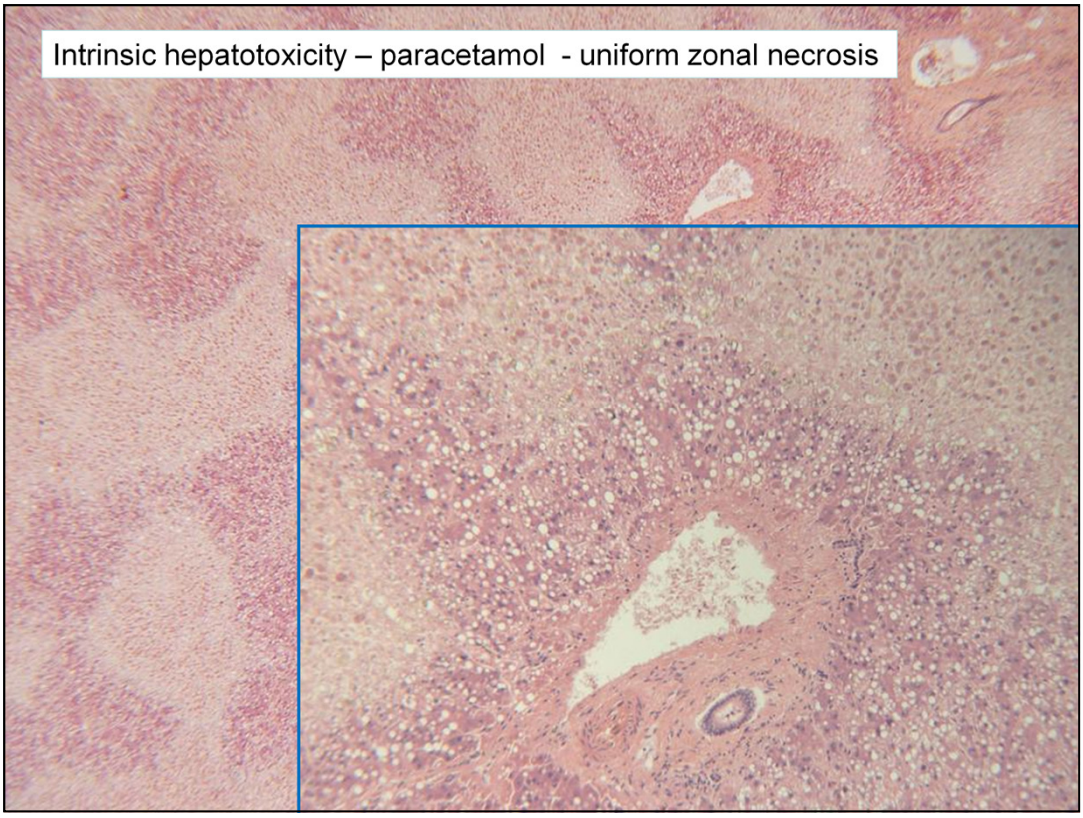
Jaundice is the commonest symptom of DILI.

The ratio of liver enzymes ALT:alk phos is used to classify the type of acute liver injury into hepatitic, cholestatic or mixed.

Hepatitic and mixed forms have a risk of severe disease and liver failure.

Patients should avoid using drugs that have caused injury in the past. Antibiotics are the commonest cause.

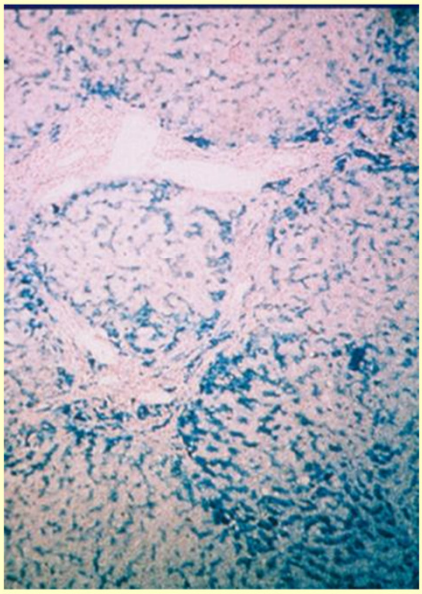
- Any drug can cause liver injury
- Same drug can cause different injury in different patients
- Time of onset variable
- Improves on stopping drug – so usually causes acute but not chronic liver disease - but not always



Paracetamol toxicity results in necrosis of a high proportion of hepatocytes in a predictable, zonal distribution, without any inflammation.

Hepatocytes around the portal tracts are spared and able to regenerate the liver back to normal if the toxicity is not too severe and the patient survives.

2d: inherited: Haemochromatosis



Perl's stain: blue = iron

- Inborn error of iron metabolism
  - 'bronzed diabetes'
- Iron accumulates in
  - Liver - cirrhosis
  - Pancreas - diabetes
  - Skin - pigmented
  - Joints – arthritis
  - heart - cardiomyopathy
- Rx venesection
  - to deplete iron stores to normal

There are three metabolic diseases in adults that can be diagnosed by specific changes on liver biopsy,

Haemochromatosis is a relatively common abnormality of the HFE gene, the C282Y is the usual severe genotype.

This leads to a failure of iron absorption regulation, and excess iron is stored in various organs – including liver, pancreas, skin, joints, heart.

Patients have high serum levels of transferrin, and high transferrin saturation.

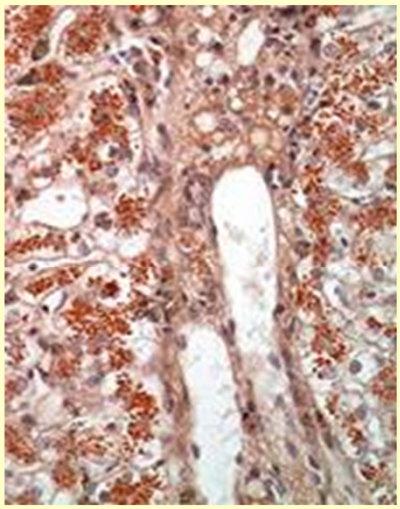
Large amounts of iron in hepatocytes cause liver injury and eventually cirrhosis and high risk of hepatocellular carcinoma.

Liver biopsies are routinely stained with the Perls' stain for iron, large amounts of iron prompt genetic investigations for haemochromatosis.

This is a disease that is easy to treat – frequent venesection, as for blood donors, to deplete the excess iron, which prevents the progression of liver disease.

Family members are screened using blood tests.

2d Inherited: Wilson disease



Rhodanine stain: copper = brown

- Inborn error of copper metabolism
- Copper accumulates in
  - liver – cirrhosis
  - Eyes – Kayser-Fleischer rings
  - Brain – ataxia, etc.
- Treatment to chelate copper and enhance its excretion

This is a much rarer genetic disease of copper metabolism. There is a wide range of alterations to the gene.

This results in too little caeruloplasmin – the copper transport protein in the blood. Copper accumulates in liver, eyes and brain.

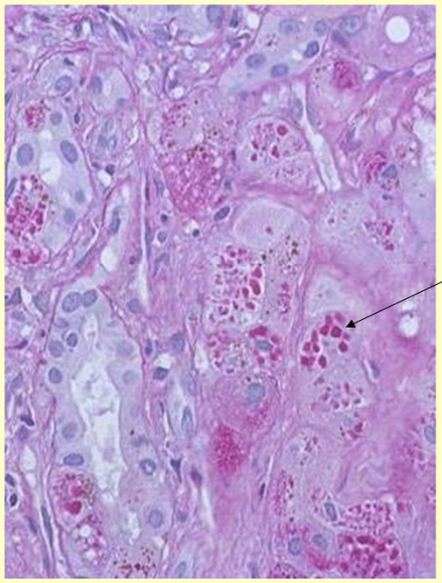
Patients have low serum copper, high urinary copper (24 hour urine collection) and high levels of copper in the liver tissue.

Copper deposited in the eye can be seen as a ring around the iris by slit lamp investigation (Kayser-Fleischer rings).

Some of the liver biopsy can be sent to measure the amount of copper in grams per dry weight of liver tissue.

Some patients present with acute liver failure and haemolysis. This is life threatening and an indication for super-urgent liver transplantation.

2d Inherited: Alpha 1 antitrypsin deficiency



PAS diastase stain

- Abnormal anti-protease which cannot be exported from hepatocyte
  - See PAS+ve globules in hepatocytes
- Accumulates in liver cells and injures them – cirrhosis
- Insufficient in blood, failure to inactivate neutrophil enzymes
  - emphysema

Alpha 1 antitrypsin is a protein made in the liver excreted into blood where it functions to neutralise proteolytic enzymes, particularly from active polymorphs.

This inborn error of metabolism results in abnormal structure of A1AT, which folds wrongly and can't be excreted from hepatocytes. There are many types, the commonest is PiZZ

The accumulated A1AT forms globules of glycoprotein that stain positive with PAS diastase stain.

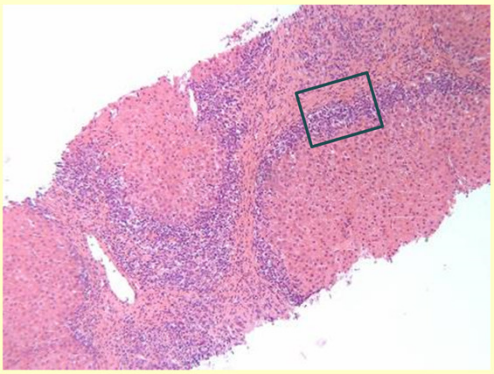
This damages liver cells, and may lead to fibrosis and cirrhosis – very variable, sometimes in childhood, sometimes in adulthood.

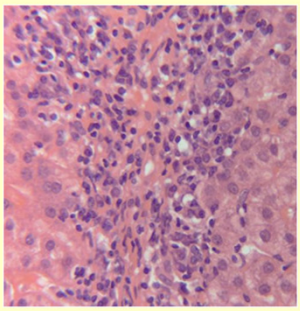
The low levels of A1AT in the serum make the patient susceptible to emphysema of the lung, especially if the patient also smokes.

2e. Autoimmune liver disease

Autoimmune hepatitis – diagnosis:

- Auto-antibodies (anti-nuclear, smooth muscle, etc.), raised IgG, ALT, other autoimmune diseases,
- Liver biopsy – plasma cells, interface hepatitis





Autoimmune liver diseases are chronic liver diseases due to disturbance of the immune system with recognition of 'self antigens' leading to chronic inflammation and destruction of hepatocytes (autoimmune hepatitis) or bile ducts (chronic biliary diseases).

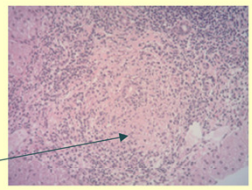
Autoimmune hepatitis is commoner in women, and can present as acute or chronic hepatitis. Diagnosis is based on autoantibodies, raised IgG and raised ALT. Liver biopsy is important for diagnosis, and characteristically shows prominent interface hepatitis with lots of plasma cells. Treatment is with immunosuppression with the aim of preventing progression of fibrosis to cirrhosis.

Some patients have an overlap of autoimmune hepatitis and an autoimmune biliary disease.

2e. Other autoimmune liver diseases – biliary diseases

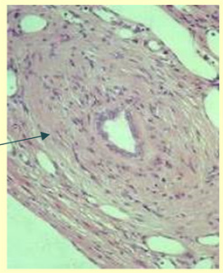
Primary biliary cholangitis (PBC, previously primary biliary cirrhosis)

- Anti-mitochondrial antibodies
- IgM, alkaline phosphatase,
- Bile duct granulomas at early stage,
- Then ductopenia and cirrhosis



Primary sclerosing cholangitis (PSC)

- Associated with ulcerative colitis, high alk phos
- 'pruned tree' on biliary imaging
- Periductal onion skin fibrosis
- then ductopenia and cirrhosis



Chronic biliary diseases – both of these result in gradual destruction of the intrahepatic bile ducts, leading to chronic cholestasis, itching, fatigue and eventually cirrhosis. They can be treated with urso-deoxycholic acid, a bile salt analogue, which delays disease progression.

Primary biliary cholangitis – commoner in women, diagnosed by anti-mitochondrial antibodies and raised alkaline phosphatase. Biopsy is not required for diagnosis, unless there is clinical uncertainty. Bile duct injury is characterised by granulomatous inflammation, leading to destruction of bile ducts. In 2016, the new name 'primary biliary cholangitis' was internationally agreed – at the request of patients – the previous name was 'primary biliary cirrhosis' but cirrhosis is only present at the end stage of the disease – and a diagnosis of cirrhosis carries a social stigma. The abbreviation 'PBC' is unchanged.

Primary sclerosing cholangitis – commoner in men, most patients (90%) also have ulcerative colitis. About 5% patients with ulcerative colitis will develop PSC. Many patients have pANCA antibodies, but diagnosis is by imaging, showing a characteristic 'pruned tree' appearance on cholangiogram. Liver biopsy shows chronic cholestatic changes (similar to those in long term obstructive jaundice above) and ductopenia (disappearing bile ducts – no longer a duct in every portal tract).

3. Cirrhosis

1. Definition
2. Aetiology
3. Pathogenesis
4. Key clinical features

3. Cirrhosis - definition

Cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

Liver cells still present, but portal vein blood bypasses the sinusoids so the liver cells cannot perform their functions.

Pressure inside the liver increases, portal hypertension.

3. Cirrhosis
= end point of chronic liver disease

Cirrhosis develops over months – decades

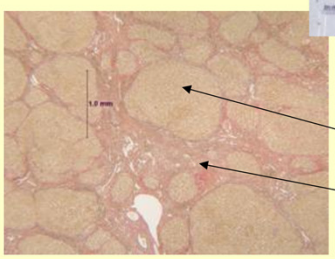
(rate of progression is very variable)

Causes of cirrhosis – the cause does not go away.

- Alcohol
- Non-alcoholic steatohepatitis (metabolic syndrome)
- Chronic viral hepatitis – B, C
- Autoimmune liver disease – autoimmune hepatitis,
  - primary biliary cirrhosis, primary sclerosing cholangitis
- Metabolic – iron, copper, alpha 1 antitrypsin

Although conventionally regarded as the irreversible end stage of chronic liver disease, it is now recognized that some fibrosis is reversible if the cause of the disease is treated, e.g. hepatitis C. How much fibrosis is reversible is unclear, but some scars usually remain. The risk of developing HCC after treating cirrhosis is currently unclear.

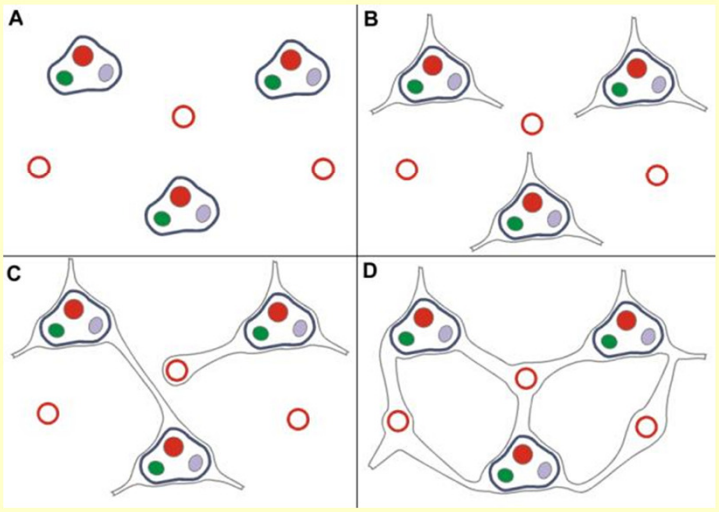
Cirrhosis – the end stage of all chronic liver disease
The liver is converted into a mass of regenerating nodules wrapped by fibrous scar tissue

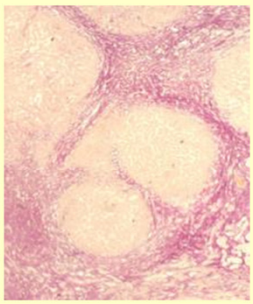


Microscopically,
Regenerative nodules of hepatocytes
Surrounded by sheets of fibrous tissue

3. Progression of fibrosis in chronic liver disease

– encircles nodules of regenerating hepatocytes

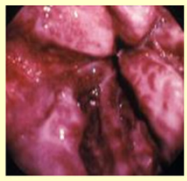


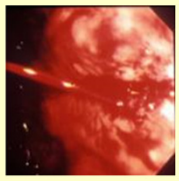


Van Gieson stain – collagen red, parenchymal nodules yellow.

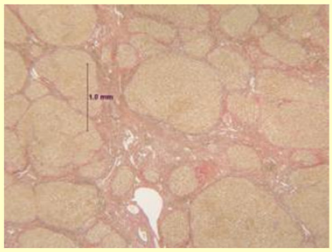
3.2 Complications of cirrhosis - pathogenic mechanisms

- Structural changes, fibrosis
  - Portal hypertension – see below
  - Increased blood flow, stiff liver
  - Pressure rises in portal vein
  - Oesophageal varices





- Liver cell failure
  fewer hepatocytes +/- blood bypasses sinusoids
  - Synthetic - oedema, bruising, muscle wasting
  - Detoxifying – drugs, hormones, encephalopathy,
  - Ascites – low albumin, portal hypertension, hormone fluid retention (aldosterone)
  - Excretion
    - Bile - jaundice
    - Bile salts – itching
- Reticulo-endothelial cells
  - Vulnerable to infection



Cirrhosis is the end stage of chronic liver disease – the patient may not have been aware of any symptoms of liver disease, and diagnosed with liver disease for the first time from complications of cirrhosis.

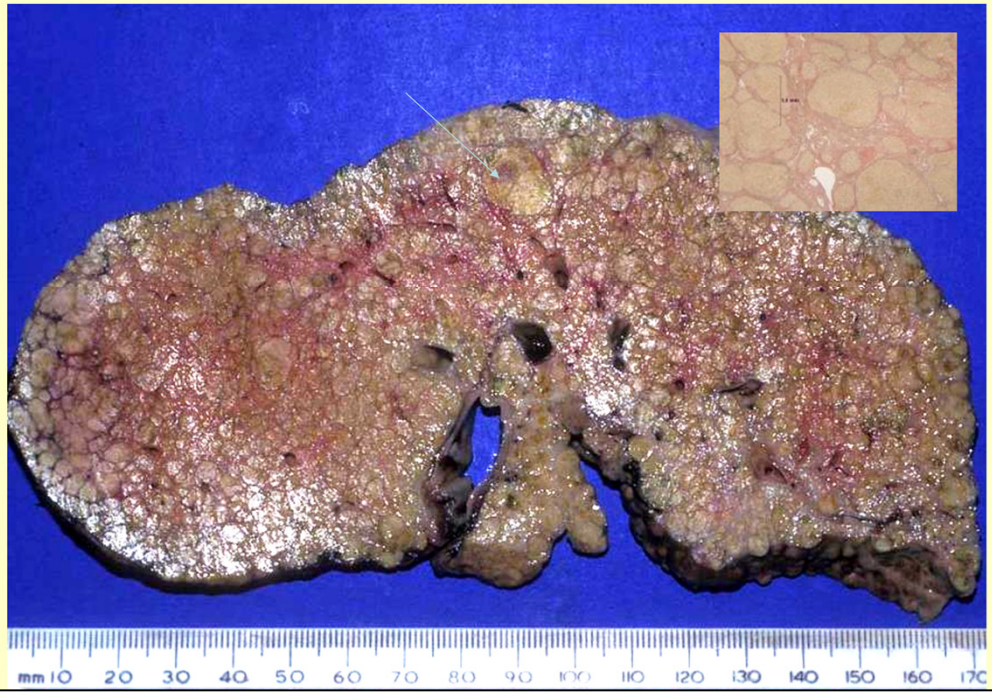
Complications of cirrhosis are a result of the pathological processes in the liver.

Structural changes, fibrosis, increased liver stiffness – results in portal hypertension. Bleeding oesophageal varices can cause massive haemorrhage.

Inefficient liver cell function due to shunting of blood and fewer hepatocytes, results in liver cell failure

Patients are also vulnerable to infections because the liver is an important site of immune response.

Cirrhotic liver with hepatocellular carcinoma



Macroscopic appearance of cirrhotic liver. This is a slice taken from a liver removed at transplant.

The HCC is visible as a larger, different coloured, bulging nodule against the background of the diffusely nodular liver.

The insert is a microscope slide showing the fibrosis and parenchymal nodules at low magnification.

4. Hepatic Failure

Acute hepatic failure – rare,

- severe rapid liver injury

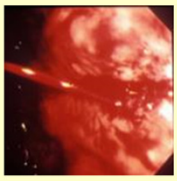
Chronic hepatic failure –

- end stage chronic liver disease

- Ascites
- Muscle wasting
- Bruising
- Gynaecomastia
- Spider naevi
- Caput medusae = variceal umbilical vein collaterals

4. Chronic liver failure - pathogenic mechanisms

- Structural changes, fibrosis
  - Portal hypertension
  - Increased blood flow, stiff liver
  - Pressure rises in portal vein
  - Oesophageal varices
  - Caput medusae



- Liver cell failure
  fewer hepatocytes +/- blood bypasses sinusoids
  - Synthetic - oedema, bruising, muscle wasting
  - Detoxifying –hormones – gynaecomastia
    . encephalopathy – 'liver flap,
  - Ascites
  - Excretion (especially chronic biliary disease)
    - Bile - jaundice
    - Bile salts – itching
- Reticulo-endothelial cells
  - Vulnerable to infection

Cirrhosis is the end stage of chronic liver disease – the patient may not have been aware of any symptoms, and diagnosed with liver disease for the first time from complications of cirrhosis.

Complications of cirrhosis are a result of the pathological processes in the liver.

Structural changes, fibrosis, increased liver stiffness – results in portal hypertension. Bleeding oesophageal varices can cause massive haemorrhage. Distension of veins at site of portal – systemic shunt include dilated veins on the abdominal wall radiating from the umbilicus – so called 'caput medusae' after the Greek mythical lady with snakes for hair.

Inefficient liver cell function due to shunting of blood and fewer hepatocytes, results in liver cell failure. Liver cells carry out many metabolic functions, and insufficient functioning liver cells result in consequences due to failure of synthesis of albumin (oedema, ascites), clotting factors (bruising) proteins (muscle wasting), or failure to remove substances from the blood – encephalopathy (confusion and 'liver flap' tremor of outstretched hands), hormones (gynaecomastia).

Patients are also vulnerable to infections because the liver is an important site of immune response.

Role of liver biopsy in chronic liver disease?

When knowledge of liver pathology is necessary to decide on clinical management – diagnosis, treatment and follow-up

consider risks and benefits of biopsy

Information on:

- Stage of disease,
  ? Cirrhosis
- Cause of disease,
- Current activity,
- Response to treatment
  (if previous biopsies)

Liver biopsy is used in many patients with chronic liver disease.

The benefits of a definite diagnosis (rather than presumed from non-invasive investigations) is balanced against the risks of haemorrhage and puncture of other organs – liver biopsy is performed under ultrasound guidance, and risk of medical liver biopsy is very low. There is a slightly higher risk with targeted liver biopsy taken to diagnose a tumour in the liver.

Biopsy gives diagnostic information on the cause, severity and stage of disease. In some patients, repeat biopsy is used to determine the response to a treatment.

Summary

- Jaundice
- Acute and chronic hepatitis
- Cirrhosis
- Hepatic failure

- How liver disease pathology is manifested in the clinical signs and investigations of the patient.

- Powerpoint, notes and Underwood chapter – for future reference