

Malcolm Granger, aged 48, has just left hospital. He was hit by a car as he inebriatedly weaved his way home by bicycle from a rugby club dinner (he lost his licence for drink-driving a year ago). His injuries were mild, but he had hit his head and cracked his skull so he was kept in for observation. After a day the nurses noted that he was plucking agitatedly at his sheets and cringing from ‘vultures’ circling him. He was also sweating, with a tachycardia and rapid breathing. The registrar diagnosed delirium tremens, caused by acute alcohol withdrawal. Malcolm’s claim at the time of admission was that he only ‘drank socially’! Malcolm recovered with medication (diazepam, then clomethiazole, plus multivitamins) over the next two

days. A psychiatric referral was made, but Malcolm denied an alcohol problem and discharged himself.

Question 1

What features of alcoholism can you recognize from this history?

Answer 1

- Drink-driving
- Accidents: road traffic, domestic
- Lack of awareness: denies alcohol problem

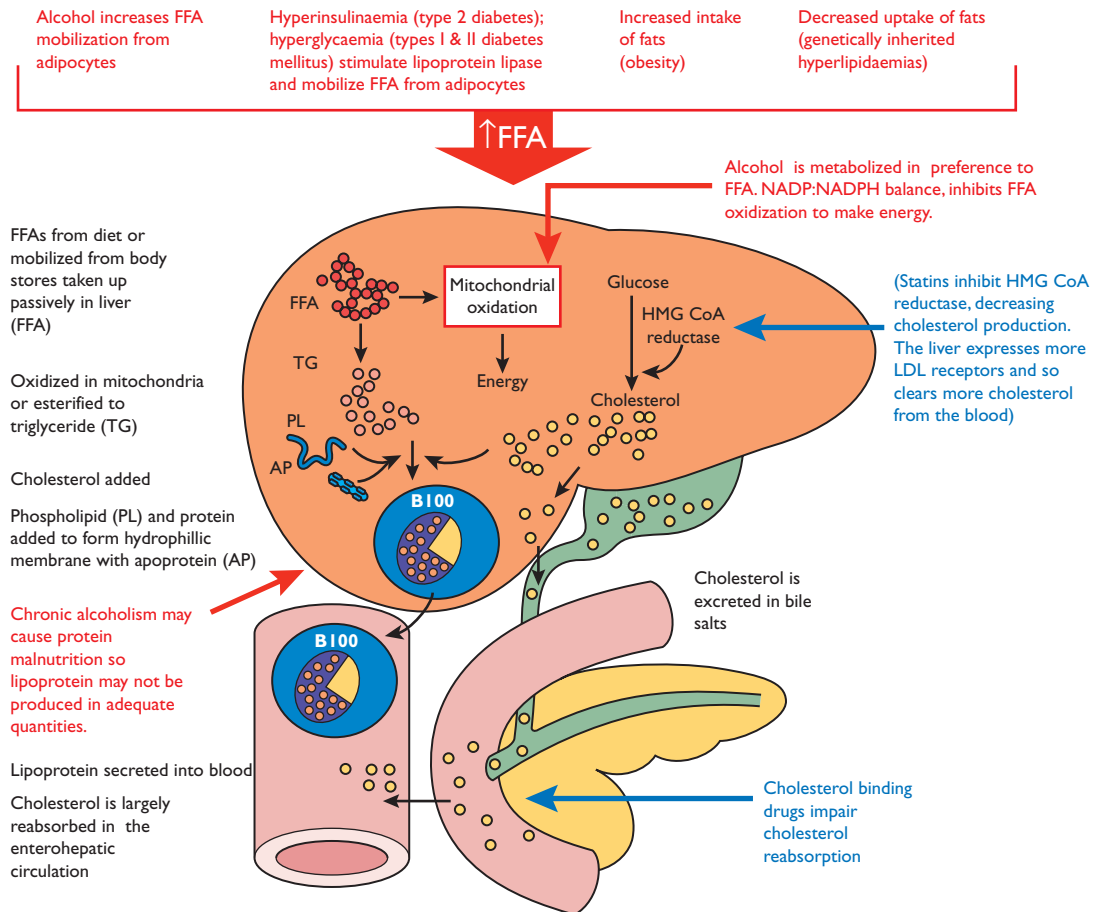


Figure 19.1 Normal liver metabolism of free fatty acids (FFA) is shown in black. The cholesterol pathway is also shown – cholesterol is also brought to the liver by high-density lipoproteins (HDL) and low-density lipoprotein (LDL). The points at which alcohol interacts are shown in red. The effects of drug treatment are shown in blue.

- Withdrawal symptoms: plucking bedclothes as if picking off ants is typical, also paranoid delusions.

Also may have:

- Dependence on alcohol early in the day, before meeting people
- Inability to cope at work
- Marital breakdown.

Question 2

Why treat with clomethiazole?

Answer 2

Clomethiazole stimulates increased release of GABA (gamma-aminobutyric acid), a neurotransmitter

which induces sleepiness and controls anxiety. Some effects of alcohol are mediated through GABA receptors and rapid withdrawal may therefore cause problems. Clomethiazole also inhibits alcohol dehydrogenase.

One year later, Malcolm is rushed to intensive care in a weak, jaundiced and semi-comatose state. His breath is foul-smelling ('foetor hepaticus'). His sclerae are deep yellow and his liver is enlarged and tender. He is dirty and unshaven. He demonstrates asterixis. Investigations show that he is in fulminant liver failure.

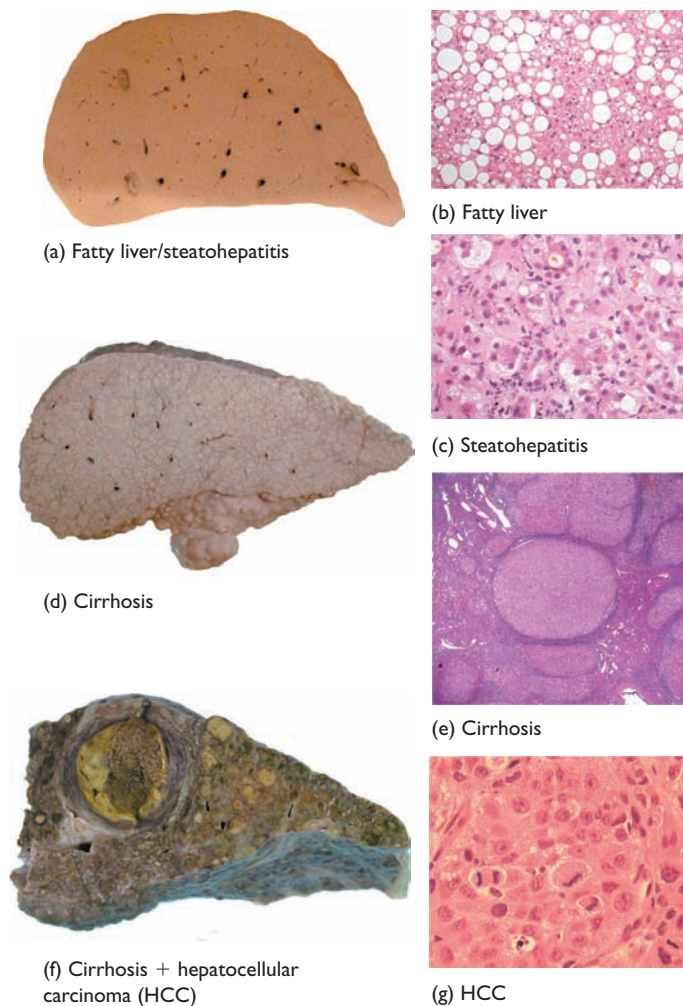


Figure 19.2 Around 60% of chronic alcoholics will develop fatty liver (a,b); 40% will develop steatohepatitis, which looks similar macroscopically but shows inflammation and early fibrosis microscopically (c); 10–15% will develop cirrhosis, usually micronodular type (d,e); only 10% of people with cirrhosis will develop hepatocellular carcinoma (f,g).

Question 3

What are the clinical features of fulminant acute liver failure?

Answer 3

- Encephalopathy
 - grade I, mild confusion, euphoria or depression
 - grade II, drowsy and semi-comatose
 - grade III, stupor (marked confusion but rousable)
 - grade IV, coma (unrousable)
- Jaundice
- Bleeding tendency (often this is generalized oozing into the gastrointestinal tract)
- Asterixis ('liver flap'), a curious phenomenon which is demonstrated with the arms outstretched and the hands dorsiflexed – it reflects uraemia.

Question 4

What investigations would you perform and why?

Answer 4

1. Liver function tests (see Case 33 (p. 125) for further information):
 - metabolic function tests – transaminases (ALT and AST)
 - inducible liver enzymes – alkaline phosphatase, GGT
 - synthetic function tests – albumin, prothrombin time or INR
 - bilirubin.
2. Blood glucose: hypoglycaemia due to loss of gluconeogenesis carries a poorer prognosis.
3. Blood urea and creatinine levels: nitrosourea compounds are metabolized by the liver, so failure leads to high circulating blood levels. Interference with neurotransmitters causes confusion and coma. Nitrosourea compounds excreted in the breath cause foetor hepaticus.
4. Blood cultures, chest X-ray, urine culture: alcoholics are at increased risk of bacterial and fungal infection.
5. Ultrasound of the abdominal organs.
6. Liver biopsy: to demonstrate liver cell necrosis, inflammation and fibrosis.

Ultrasound scan shows a smoothly enlarged liver.

Investigations

(Indications for immediate referral for transplantation in bold.)

Bilirubin (>300)	437 µmol/L	(3–17 µmol/L)
ALT	1097 IU/L	(5–35 IU/L)
AST	997 IU/L	(5–35 IU/L)
ALP	443 IU/L	(30–150 IU/L)
Albumen	32 g/L	(35–48 g/L)
GGT	640 IU/L	(0–50 IU/L)
Urea	8.8 mmol/L	(2.5–6.7 mmol/L)
Creatinine	240 µmol/L	(70–170 µmol/L)
(>300)		
Glucose	3.3 mmol/L	(3.5–5 mmol/L (fasting))
pH (<7.3)	7.35	(7.4)
INR (>6.5)	6.3	(1.0)
PaO ₂	11.4 kPa	(13.3 kPa)

The consultant hepatologist notes that the test results do not quite fulfil the criteria for referral to a liver transplant centre. He reads the result of a transjugular liver biopsy.

Summary of liver findings:

- marked fatty change with Mallory's hyaline
- confluent hepatocyte necrosis
- acute inflammation and ballooning degeneration of hepatocytes
- cholestasis
- evidence of liver cell regeneration
- very mild fibrosis.

Conclusion: appearances are those of florid steatohepatitis, compatible with an alcoholic aetiology.

Question 5

Discuss the factors that can generate a fatty liver, and its consequences.

Answer 5

Causes of fatty liver:

- Raised free fatty acids: alcohol excess, diabetes mellitus, obesity, genetic hyperlipidaemia
- Lowered metabolism of fatty acids and triglycerides (competition with drugs, e.g. alcohol or pathway interference, e.g. hepatitis C)

- Lowered excretion, e.g. due to lowered protein for synthesis of lipoprotein (chronic alcoholism, protein calorie malnutrition) or paralysis of the secretory apparatus (e.g. drugs of various types).

Consequences of fatty liver:

- Mechanically impaired blood flow in the hepatic sinusoids
- Oxidation of fat causes free radical formation, stimulating inflammation and fibrosis
- Hepatocyte insulin resistance (leads to type 2 diabetes mellitus)
- Fat can activate angiotensin, leading to hypertension.

Question 6

Compare fatty liver disease, steatohepatitis and acute liver failure.

Answer 6

Fatty liver shows fat with minimal inflammation and no fibrosis. This is reversible but about 50 per cent of patients later develop fibrosis. *Steatohepatitis* features fatty change, inflammation and ballooning of hepatocytes (a feature of toxic damage), often with fibrosis. Patients risk acute liver failure or advanced fibrosis/cirrhosis. *Acute liver failure* features massive hepatocyte necrosis due to a toxic insult such as alcohol, paracetamol overdose or acute viral (or other) hepatitis. The mortality in acute liver failure due to steatohepatitis is around 40 per cent. Recurrent attacks are common, each with 40 per cent risk.

After many weeks in hospital, Malcolm is ready to return home. He is warned that another episode could be fatal. If he continues to drink he will almost certainly develop cirrhosis.

Question 7

Compare the risk of severe liver disease due to alcohol with other aetiologies.

Answer 7

- Alcohol – 50 per cent steatohepatitis of whom 10–15 per cent have cirrhosis
- Non-alcoholic fatty liver disease – 40 per cent steatohepatitis of whom 5–10 per cent have cirrhosis
- Hepatitis B virus – 10 per cent chronic hepatitis of whom 10 per cent have cirrhosis

- Hepatitis C virus – 80 per cent chronic hepatitis of whom 10 per cent have cirrhosis.

Malcolm worries when 72-year-old Bill Barlow from his Alcoholics Anonymous group misses several meetings. Bill knew that his liver was cirrhotic but if he kept away from alcohol he should be all right for years. Bill found this impossible.

Question 8

Describe the microscopical features of cirrhosis.

Answer 8

Cirrhotic scarring is a diffuse process involving the entire liver. There is liver architectural destruction by nodules of regenerating hepatocytes separated by fibrous septa. If inflammation is present it indicates ‘active’ cirrhosis and further damage and scarring are likely.

Question 9

Is it true that someone with cirrhosis can remain well?

Answer 9

A patient with established cirrhosis but no inflammation may remain surprisingly well (‘compensated cirrhosis’). Anything which causes inflammation or toxic damage to hepatocytes can precipitate liver failure.

Question 10

What are the main causes of cirrhosis?

Answer 10

Globally hepatitis B and C and alcohol are the main causes of cirrhosis. Common causes of cirrhosis in the UK are:

- Alcohol 60 per cent
- Hepatitis C: 5–10 per cent
- Hepatitis B: 5–10 per cent (viral hepatitis is the largest cause globally)
- Autoimmune hepatitis: 10 per cent
- Biliary disease: primary biliary cirrhosis, sclerosing cholangitis: 5–10 per cent
- Non-alcoholic steatohepatitis/metabolic syndrome: 5–10 per cent
- Metabolic causes, such as haemochromatosis or Wilson’s disease are rare.

Malcolm learns that Bill has been rushed to hospital after vomiting blood. Bill is jaundiced, with ascites and spider naevi over his scrawny chest. Scans show a large