It is important to establish the aetiology of acute viral hepatitis in order to treat patients and their contacts appropriately and to limit the spread of infection. Although a careful clinical history and biochemical markers are important, diagnosis depends on specific serological testing.

REFERENCES

1. Lemon SM, Brown CD, Brookes DS, *et al.* Specific IgM response to hepatitis A virus determined by solid-phase radioimmunoassay. *Infect Immun* 1980; **28:** 927-936.
2. Duermeyer W, Van der Veen J. Specific detection of IgM antibodies by ELISA applied in hepatitis A. *Lancet* 1978; **2:** 684-685.
3. Hoofnagle JH, Di Bisceglie AM. Serologic diagnosis of acute and chronic viral hepatitis. *Hepatology* 1991; **11:** 73-83.
4. Wolters G, Kuijpers LPC, Kacaki J, Schuurs HW. Enzyme-linked immunosorbent assay for hepatitis B surface antigen. *J Infect Dis* 1977; **136:** 311-317.
5. Irwin GR, Allen RG, Segal HG, *et al.* Serodiagnosis of hepatitis B virus infection by antibody to core antigen. *J Infect Dis* 1977; **136:** 31-36.
6. Lindsay KL, Nizze JA, Karetz R, Gitnick G. Diagnostic usefulness of testing for anti-HBc IgM in acute hepatitis B. *Hepatology* 1986; **6:** 1325-1328.
7. Hoofnagle JH, Dusheiko GM, Seef LB, *et al.* Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. *Ann Intern Med* 1981; **94:** 744-748.
8. Kuijpers L, Koens M, Murray-Lyon I, *et al.* Pre-S proteins in hepatitis B. *J Med Virol* 1989; **28:** 47-51.
9. Delfini C, Colloca S, Taliani G, *et al.* Clearance of hepatitis B virus DNA and pre-S surface antigens in patients with markers of acute viral replication. *J Med Virol* 1989; **28:** 169-175.
10. Ciach RD, Stevens CE, Hollinger BF, *et al.* Hepatitis C virus infection in post-transfusion hepatitis. An analysis with first and second-generation assays. *N Engl J Med* 1991; **325:** 1325-1329.
11. Ellis LA, Brown D, Conradie JD, *et al.* Prevalence of hepatitis C in South Africa: detection of anti-HCV in recent and stored serum. *J Med Virol* 1990; **32:** 249-251.
12. McHutchison JG, Pesan JL, Govindarajan S, *et al.* Improved detection of hepatitis C virus antibodies in high-risk populations. *Hepatology* 1992; **15:** 19-25.
13. Nakatsuji Y, Matsumoto A, Tanaka E, *et al.* Detection of chronic hepatitis C virus infection by four diagnostic systems: first generation and second generation ELISA, second generation recombinant immunoblot assay and nested polymerase chain reaction analysis. *Hepatology* 1992; **16:** 300-305.
14. Van der Poel CL, Cuypers HTM, Reesink HW, *et al.* Confirmation of hepatitis C virus infection by new four-antigen recombinant immunoblot assay. *Lancet* 1991; **337:** 317-319.
15. Buti M, Esteban R, Gardi R, *et al.* Serological diagnosis of acute delta hepatitis. *J Med Virol* 1986; **18:** 81-85.
16. De Cock KM, Govindarajan S, Redeker AG. Serological response to hepatitis delta virus in hepatitis D. *Lancet* 1987; **1:** 1438.
17. Buti M, Esteban R, Gardi R, *et al.* Serological markers for delta hepatitis. *Lancet* 1987; **1:** 815.

Chronic hepatitis

R. J. Hift

Most cases of hepatitis which are due to viral infection or drug injury will resolve promptly. Indeed, in most instances elevated transaminases may be expected to return to normal levels within 3 months. However, in some instances inflammation does not settle but becomes established as a chronic illness. Although the patient may be asymptomatic, the transaminases are intermittently or permanently elevated, liver biopsy shows continuing damage, and there may be evidence of ongoing viral replication. The whole process is associated with a high risk of progression to cirrhosis, chronic liver failure and hepatocellular carcinoma. These then are the parameters which define the entity of *chronic hepatitis*.

MRC/UCT Liver Research Centre, Department of Medicine, University of Cape Town

R. J. Hift, M.B. CH.B., M.MED., (MED.), F.C.P. (S.A.)

Clinically the disorder is defined by demonstrating evidence of inflammation that has been present for at least 6 months.[1] The terminology of chronic hepatitis is confusing. For many years the terms *chronic persistent hepatitis* (CPH) and *chronic active hepatitis* (CAH) have been employed.[1,2] The two were distinguished histologically by the degree and morphological pattern of inflammation. Thus, in CPH inflammation was confined to the portal tracts with no periportal inflammation or inflammation within the hepatic lobule, whereas in CAH hepatocyte necrosis and fibrosis were evident. The distinction was believed to have important clinical and prognostic consequences, CPH denoting a relatively benign disease, whereas CAH was likely to progress to cirrhosis. The terms were originally applied to the auto-immune variety of chronic hepatitis, but have been extended to other forms of hepatitis, and to chronic viral hepatitis in particular, where the distinction is less useful.[3] Histological changes may not be uniformly distributed throughout the liver — thus being open to sampling error — and may also change with time; hence demonstration of the features of CPH now offer no guarantee that the course will be benign, or that a repeat biopsy will not show aggressive changes. Indeed, it is the presence of virus and its replicative status that will determine the progression of the disease,[4] and histology is at best an indirect reflection of this. Thus the terms CPH and *chronic lobular hepatitis* (a later addition to the family) are now discouraged. It is appropriate to consider *all* cases as chronic hepatitis (CH), and to qualify the term further by cause, severity and histological appearance. Thus one may speak of mild CAH secondary to chronic hepatitis B viral infection with inflammation limited to the portal tracts, or of severe auto-immune CAH showing hepatocyte necrosis and fibrosis linking adjacent portal tracts.

Causation

The important causes of chronic hepatitis are listed in Table I. The major categories are type B and C viral hepatitis, auto-immune chronic hepatitis (AICH) and drug-induced chronic hepatitis. Although both primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) may present with some of the histological features of CH, they are usually distinguished from AICH by their other characteristic features. There are in addition a few other

Table I. Differential diagnosis of chronic hepatitis

Accepted causes
Viral hepatitis B
Viral hepatitis C
Immune hepatitis
Overlap with primary biliary cirrhosis, primary sclerosing cholangitis
Drug-induced hepatitis
Similar conditions to be excluded
Wilson's disease
Alpha-1-antitrypsin deficiency
Alcoholic hepatitis
Non-alcoholic steatohepatitis
Haemochromatosis, haemosiderosis
Cryptogenic

conditions characterised by ongoing hepatic inflammation, some with specific reversible causes which must be identified and treated. These include alcoholic steatohepatitis, non-alcoholic steatohepatitis, Wilson's disease, α_1-antitrypsin deficiency and the iron overload states haemosiderosis and haemochromatosis.

Several of these conditions are discussed in more detail elsewhere in this issue. Those aspects relevant to their diagnosis are described below.

Viral hepatitis B

Hepatitis B virus infection is the most common cause of chronic hepatitis, and indeed of cirrhosis, in the world.[5] Recent findings have yielded insights into the biological mechanisms which predispose to chronicity in hepatitis B infection. Chronic hepatitis is established where the host immune response is sufficiently aggressive to result in hepatocyte damage, yet inadequate to eradicate the virus.[6] Were the immune response stronger, the virus would be eradicated and the disease self-limiting; were it less efficient, tolerance would ensue with viral persistence but no liver damage. Thus chronic hepatitis appears to arise in those people whose immune response falls between these two extremes.

Although symptoms and signs are nonspecific, extrahepatic manifestations of HBV infection such as arthritis or glomerulonephritis may occasionally point to hepatitis B as the cause of a chronic liver problem. The hallmark of chronic hepatitis B is persistence of hepatitis B antigenaemia. CH may be diagnosed where HBe antigen or HBs antigen are present for more than 6 months. Since, in acute infection, HBe antigen is normally cleared as early as 2 weeks after the onset of the illness, persistence of this antigen for more than 3 months strongly suggests that the infection has entered a chronic phase. HBs antigen is almost invariably present in chronic hepatitis B. Most cases of chronic hepatitis will also be HBe antigen-positive; the presence of this antigen always denotes active viral replication and the continuing liver damage, albeit perhaps mild.[7] Increasingly, however, HBe antigen-negative mutant viruses are being recognised, which fail to express HBe antigen (and usually demonstrate anti-HBe antibody) yet cause severe and rapidly progressive liver damage. Thus the absence of HBe antigen does *not* exclude hepatitis B as the cause of a chronic hepatitis. In such cases the diagnosis can be confirmed by quantitating HBV DNA, since high levels of this reflect viral replication. Determination of HBV DNA polymerase activity or of low-titre IgM anti-HBc antibody may also confirm HBV as the cause of the chronic hepatitis, but are not routinely available. These three markers of viral activity are becoming increasingly important in determining the need for antiviral therapy with α-interferon and in assessing a patient's response to it.

The diagnosis of chronic hepatitis B is in most instances readily made on biopsy. The degree of hepatic inflammation and damage varies. Typical features are the presence of ground-glass hepatocytes which stain positively with orcein.[8] Immunohistochemical techniques may show the presence of surface antigen and HBc antigen in the hepatocytes.[9] Newer techniques of *in situ* hybridisation may demonstrate the genomic sequences of viral DNA in infected cells. Such features confirm the presence of HBV in the liver; the effect of the virus may be gauged by assessing the extent of the accompanying inflammation, necrosis and fibrosis.

Unfortunately some patients with hepatitis B CH fail all these tests. Cases are reported where livers removed at transplantation have proved to be infected with HBV, despite the absence of all antigens and antibodies, negative immunohistochemical tests and inconclusive histological features despite an extensive search for the cause of the liver disease before the operation.[10]

Viral hepatitis C

Hepatitis C is currently the most frequent cause of chronic hepatitis in the USA.[11] A large proportion of cases previously labelled 'cryptogenic' CH have subsequently been identified as cases of HCV infection.[12] A major feature of chronic hepatitis C is that the disease itself is often mild, with low levels of transaminases and few if any symptoms, whereas the eventual outcome may be severe with cirrhosis and chronic liver failure.[11] Hepatitis C should perhaps be the first diagnosis entertained in an otherwise asymptomatic individual who is found to have a chronically but mildly elevated alanine transaminase (ALT). The diagnosis of chronic hepatitis C is complicated by the poor specificity of the serological tests employed for its diagnosis. The first-generation enzyme-linked immunosorbent assays (ELISAs) which detected antibodies directed against the C100-3 antigen of HCV were of low sensitivity and specificity. They are, however, still widely employed for screening of patients. A positive result (which may represent a false positive in as many as 70% of cases) demands a subsequent confirmatory test; conversely, a negative result where the clinical suspicion for hepatitis C, is high should be independently checked with another test.[13] The second-generation ELISAs, which in addition to the C100-3 recognise antibodies directed against additional epitopes, typically C33 and C22, have a much higher sensitivity and specificity, but are still not entirely specific for hepatitis C. Other confirmatory diagnostic tests include the synthetic peptide ELISAs and the recombinant immunoblot assay (RIBA), which offer further increases in sensitivity and specificity.[13] Unfortunately some patients will show intermediate responses, with reactivity to some but not all of the epitopes offered, and there remain a core of about 10% of all cases with chronic HCV infection who remain persistently antibody-negative.[13] The gold standard for the diagnosis of chronic hepatitis C is therefore the demonstration of RNA sequences by the polymerase chain reaction (PCR). Physicians faced with a positive hepatitis C result from a laboratory should never accept that result without checking with the laboratory concerned by what method the test was performed and whether confirmatory tests are necessary.

The histological picture in chronic hepatitis C may vary from mild to severe CAH and cirrhosis. Certain features on biopsy are suggestive of hepatitis C infection. These included lobular lymphoid aggregates, lymphocyte infiltrate of the sinusoids, focal bile duct damage, microvesicular fatty change and hepatocytes showing eosinophilic granules with eosinophilic bodies.[7] The use of immunohistochemistry and *in situ* hybridisation for the diagnosis of chronic hepatitis C is as yet undetermined. Although patients showing more severe inflammation are likely to proceed to cirrhosis more

rapidly, the presence of apparently benign changes, which it is tempting to label chronic persistent hepatitis, does not imply a benign outcome; in many of these, progression to cirrhosis is also noted.[14]

Auto-immune chronic hepatitis

This is considerably less common than chronic hepatitis B and C infection, but it is nevertheless not infrequently encountered and was in fact the first form of chronic hepatitis described.[15]

AICH is commonly symptomatic. The age of onset is usually between 10 and 40 years and 75% of patients are female.[4] Symptoms include malaise, anorexia, fatigue, amenorrhoea, and eventually features of portal hypertension or liver failure. Occasionally AICH presents with fulminant hepatic failure. Other forms of auto-immune disease such as Sjögren's syndrome and thyroiditis may be present. The condition is often characterised by the presence of markedly elevated transaminases, hypergammaglobulinaemia and a variety of auto-antibodies. The serological features of AICH are not uniform and allow subclassification of this disorder. In type 1 AICH, antinuclear antibodies (ANA) are present, as may be anti-smooth-muscle antibodies. Type 2 AICH is characterised by the presence of anti-liver/kidney microsomal (LKM1) antibodies without ANA. While up to 30% of patients also show positive antimitochondrial antibodies, these are usually present in low titre and the condition is easily distinguished from primary biliary cirrhosis.[16] Although demonstration of the LE cell phenomenon in some patients led to the term lupoid hepatitis being applied as a synonym for AICH, there is no association with systemic lupus erythematosus. A new classification to be recommended shortly also allows a seronegative subtype where no auto-antibodies are present and there is no evidence for HCV infection, yet the presence of hypergammaglobulinaemia, severe inflammation and a positive response to corticosteroid therapy suggest that the disorder is similar to the seropositive disease (P. Scheuer — personal communication).

The association between chronic HCV infection and AICH has attracted much interest. There is evidence that in some patients with type 2 AICH (classified as type 2b) the immune phenomena are probably triggered by hepatitis C virus infection. The distinction is important in that such patients may respond better to antiviral therapy with α-interferon than to corticosteroids.[17-19]

As with most forms of CH, the histological picture is nonspecific. More active parenchymal inflammation as well as larger numbers of plasma cells tend to suggest immune hepatitis rather than viral hepatitis.[7]

In the absence of therapy, AICH is usually a progressive disorder with a poor outcome. The condition often responds well to immunosuppressive therapy with corticosteroids and azathioprine. Where AICH is strongly suspected, a trial of corticosteroid therapy is indicated.

Occasional patients with two other auto-immune disorders of the liver, primary biliary cirrhosis and PSC, may show evidence of an overlap syndrome with histological features indicative of CH in addition to the typical features of the parent disorder. The clinical features, a disproportionate increase in alkaline phosphatase, gamma-glutamyl transpeptidase and 5'-nucleotidase, demonstration of histological changes, predominantly in the bile ducts, and an abnormal cholangiogram may help to differentiate these patients from those with pure AICH.[20]

Drug-induced chronic hepatitis

Although many drugs may induce an acute hepatitis, few have been reported as causing a true chronic hepatitis which might be confused with other forms of CH.[21,22] One of the more common offenders in South Africa is α-methyldopa, which is widely prescribed for hypertension.[23] Although methyldopa may be associated with benign prolonged cholestasis[24] and a transient mild hepatotoxicity,[25] it more commonly induces a severe CH which appears indistinguishable from AICH both clinically and histologically. Even ANA may be positive and the liver disease may be accompanied by auto-immune haemolytic anaemia.[26] The disease will usually remit once methyldopa is withdrawn, but some patients will develop fatal acute or subacute liver failure, and rechallenge may be fatal.[23] Long-term use of oxyphenacetin,[27] a component of laxatives, and nitrofurantoin[28] may result in a similar syndrome of chronic hepatitis. Other drugs which have been linked (but rarely) with CH include isoniazid, sulphonamides, aspirin, paracetamol, chlorpromazine and propylthiouracil.[4] There are no specific features to allow a confident diagnosis of drug-induced CH and the most appropriate test is an assessment of the response to withdrawal of the drug.[7]

Conditions that may resemble chronic hepatitis

Alcoholic liver disease

Alcohol abuse is a prominent cause of persistently disordered transaminases. The histological changes are usually sufficiently typical to point to alcohol as the cause. Occasional patients, however, show histological lesions suggestive of CH.[29] It is not yet clear whether this reflects the effects of alcohol alone, and some patients may in fact have concomitant viral hepatitis, which is probably due to HCV in most cases, though as yet uncharacterised non-B, non-C viruses may be implicated.[30] Increasingly it appears that alcohol and viral infection may act synergistically to induce more severe liver disease than can be ascribed to alcohol alone.

Non-alcoholic steatohepatitis

This disorder is described in patients who take little or no alcohol but have consistently raised transaminases and histological changes indistinguishable from those of alcohol-induced liver injury.[31,32] These may include fatty change, portal and globular inflammation and even Mallory's alcoholic hyaline. Patients are often obese, female and diabetic, and may be hyperlipidaemic. They tend to be asymptomatic but may have hepatomegaly and some right upper quadrant tenderness. Unfortunately there is no reliable method of distinguishing such patients from those with alcohol-induced liver disease, and the diagnosis must rely on the exclusion of alcohol abuse by circumstantial means.

Metabolic diseases

Wilson's disease may present as CH before the onset of neurological illness. A reduced plasma caeruloplasmin concentration[33] and a raised hepatic copper concentration are typical of the condition, but neither alone is specific for Wilson's disease,[34] although the two together are diagnostic. In the absence of hepatic copper measurements, the diagnosis is suggested by the finding of Kayser-Fleischer rings on ophthalmological slit-lamp examination, reduced caeruloplasmin concentrations and an increased urinary copper excretion in excess of 1,6 µmol/24 h.[35] The serum copper value itself is unreliable, and the morphological appearances on hepatic biopsy, ranging from CH on a background of micronodular cirrhosis to massive necrosis, are not specific. The diagnosis of Wilson's disease is not straightforward and several pitfalls remain to trap the unwary. Thus severe hepatic necrosis from any cause may cause a reduced caeruloplasmin level as a result of decreased synthesis leading to an erroneous diagnosis of Wilson's disease; patients with PBC or chronic cholestasis may show Kayser-Fleischer rings, increased hepatic copper concentrations and an increased urinary copper excretion,[36,37] although the caeruloplasmin value will be normal.[34]

Alpha-1-antitrypsin deficiency will also occasionally produce features suggestive of CH.[38] The diagnosis is suggested by detecting periodic acid-Schiff-positive globules in the liver which test positive for α_1-antitrypsin by immunohistochemical techniques. Further confirmation will come from the demonstration of the abnormal α_1-antitrypsin phenotypes associated with disease, particularly the PiZ allele. PiZZ homozygotes are most severely affected.[39]

Also to be considered as causes of persistently abnormal transaminases are the iron overload states, haemosiderosis and haemochromatosis. The first is common in black South African males and is often associated with moderately elevated serum transaminases. A high serum ferritin level and transferrin saturation are suggestive; since these tests alone are not specific for iron overload, liver biopsy should be performed to confirm the diagnosis. Staining for the pattern and degree of iron deposition is helpful, and spectrophotometric quantitation of hepatic iron content is diagnostic.[40]

Approach to the diagnosis of CH (Table II)

In most instances history is of limited help. However, in the case of drug-induced CH it is vital, since there is seldom evidence to implicate drugs either on physical examination or on special investigations. For the same reason a history of alcohol consumption is important; since patients may deny the amount of alcohol they take, independent information should be sought from family and colleagues. Symptoms suggestive of auto-immune disease, such as the dry eyes and dry mouth of the sicca syndrome, may point to AICH. Most patients in South Africa with chronic HBV or HCV infection will not give a history of blood transfusions, tattooing and other risk factors for parenteral viral transmission, so a history here is of low sensitivity. An important aspect of the history, however, is an assessment of the severity of the disease as manifested by its effects on the patient; thus marked fatigue or symptoms of early encephalopathy may point to a severe process.

Table II. Approach to the patient with presumed chronic hepatitis

History
Alcohol, drug therapy
Examination
Biochemical assessment of liver damage and function
Bilirubin, transaminases
INR and albumin
Viral serology
Hepatitis B
HBs antigen, HBe antigen, anti HBe antibody
Hepatitis C
Anti-HCV antibody, confirmatory RIBA or PCR
Auto-immune serology
Antinuclear antibodies, anti-smooth-muscle antibodies
Special biochemistry
Transferrin saturation, ferritin
Alpha-1-antitrypsin levels
Serum copper, caeruloplasmin, urinary copper excretion
Histology.
Assessment of response to therapy

Physical examination is usually unhelpful in assigning a cause to CH. There may be no abnormalities at all; other patients may have nonspecific findings such as hepatomegaly, jaundice or features of chronic liver disease such as spider angiomas. However, occasional patients will show highly diagnostic features such as Kayser-Fleischer rings in Wilson's disease or pigmentation and arthropathy in haemochromatosis. Thus one cannot assess a patient with suspected CH without adequate biochemical and serological screening.

In the first instance, the presence of hepatitis is confirmed by demonstrating a sustained or fluctuant elevation of the transaminases. Disproportionately high alkaline phosphatase and gamma-glutamyl transpeptidase or 5′-nucleotidase should arouse suspicion of biliary obstruction or a cholestatic process such as PBC or PSC; this will require further investigation, including imaging of the biliary tree and liver biopsy.

Liver function should be assessed by determining bilirubin levels, serum albumin and the prothrombin time or international normalised ratio (INR). Following confirmation of the presence of chronic hepatitis and an estimation of its functional severity, further investigations are directed towards determining the cause.

It is necessary in every case to exclude viral infection. As a screen, HBs antigen and anti-HCV antibody should be sought. Where HBs antigen is present, HBV is a likely but not necessarily definite cause of the CH. Further confirmation of this must be sought by testing for HBe antigen and, where possible, HBV DNA levels. Final confirmation will come from biopsy. A positive HCV antibody result must be confirmed; preferably by detection of HCV RNA by PCR, or at least by RIBA or one of the newer ELISAs. Here histological changes may also be suggestive.

Serological markers for auto-immune disorders should be sought. The important tests are the ANA and anti-smooth-muscle antibodies, which are positive in most cases of type I AICH. It is not necessary to test the antimitochondrial antibody unless there are pointers towards PBC. Histological examination will add useful information. Where the ANA are

negative and there is a strong suspicion of AICH, anti-LKM antibodies or positive tests for HCV may suggest type 2 AICH.

In the absence of other positive results metabolic disorders must be excluded. Serum copper, urinary copper excretion and plasma caeruloplasmin will help to exclude Wilson's disease. Serum ferritin and transferrin and α_1-antitrypsin levels should be determined to exclude iron storage diseases and α_1-antitrypsin deficiency.

In most instances liver biopsy is important. An adequate core is essential to ensure that sufficient representative tissue is present for a valid assessment to be made. Biopsies should be interpreted by an experienced pathologist to whom all the patient's clinical and biochemical findings should be available. Immunohistochemical techniques can be important in confirming a diagnosis; where such expertise is absent, the specimen should be sent to a centre of excellence for review. The block itself should accompany the slides so that further preparation is possible.

Where all diagnostic approaches fail to define an obvious cause, a 'non-diagnosis' of cryptogenic CH may have to be made. It is, however, important to remember that HCV infection, HBV infection and AICH will in some cases fail to yield definitively positive results. Here a trial of steroids should be undertaken, under strict supervision since viral CH may advance rapidly on steroid therapy.

In all but the most straightforward cases patients may benefit from review by a specialist centre interested in liver disease. It is our experience that many patients referred to the Liver Clinic of the University of Cape Town for consideration of a transplant for apparently 'end-stage' liver disease have on review turned out to have diseases amenable to medical therapy; in many instances this has made surgery unnecessary.

REFERENCES

1. DeGroote J, Desmet J, Gedigk P, Korb G, Popper H, Poulsen H, *et al.* A classification of chronic hepatitis. *Lancet* 1968; **2:** 626-628.
2. Geall MG, Schoenfield JJ, Summerskill WHJ. Classification and treatment of chronic active liver disease. *Gastroenterology* 1968; **55:** 724-729.
3. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991; **13:** 372-374.
4. Maddrey WC. Chronic hepatitis. *Dis Mon* 1993; **34**(2): 53-126.
5. Brown JL, Carman WF, Thomas HC. The hepatitis B virus. *Baillieres Clin Gastroenterol* 1990; **4:** 721-747.
6. Lavine JE, Bull FG, Millward-Sadler GH, Arthur MJP. Acute viral hepatitis. In: Millward-Sadler GH, Wright R, Arthur MJP, eds. *Wright's Liver and Biliary Disease*. London: WB Saunders, 1992: 679-786.
7. Jacyna MR, Millward-Sadler GH, Thomas HC. Chronic hepatitis. In: Millward-Sadler GH, Wright R, Arthur MJP, eds. *Wright's Liver and Biliary Disease*. London: WB Saunders, 1992: 787-820.
8. Deodhar KP, Tapp E, Scheuer PJ. Orcein staining of hepatitis B antigen in paraffin sections of liver biopsies. *J Clin Pathol* 1975; **28:** 66-70.
9. Hadziyannis SJ, Gerber MA, Vissoulis C, Popper H. Cytoplasmic hepatitis B antigen in 'ground-glass' hepatocytes of carriers. *Arch Pathol* 1973; **96:** 327-330.
10. Chazouilleres O, Mamish D, Kim M, Carey K, Ferrell L, Roberts JP, *et al.* 'Occult' hepatitis B virus as source of infection in liver transplant recipients. *Lancet* 1994; **343:** 142-146.
11. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, *et al.* The natural history of community-acquired hepatitis C in the United States. *N Engl J Med* 1992; **327:** 1899-1905.
12. Jeffers LJ, Hasan F, De Medina M, Reddy R, Parker T, Silva M, *et al.* Prevalence of antibodies to hepatitis C virus among patients with cryptogenic chronic hepatitis and cirrhosis. *Hepatology* 1992; **15:** 187-190.
13. Trépo C, Zoulim F, Alonso C, Petit M-A, Pichoud C, Vitvitski L. Diagnostic markers of viral hepatitis B and C. *Gut* 1993; **34**(2): suppl, S20-S25.
14. Mattsson L. Chronic NANB hepatitis. *Scand J Infect Dis* 1989; suppl 59, 7-55.
15. Waldenstrom J. Leber blutproteine und Nahrungeiweiss. *Dtsch Z Verdau Stoffwechselkr* 1950; **2:** 113.
16. Kenny RP, Czaja AJ, Ludwig J, Dickson ER. Frequency and significance of antimitochondrial antibodies in severe chronic active hepatitis. *Dig Dis Sci* 1986; **31:** 705-711.
17. Todros J, Touscoz G, D'Urso ND, Durazzo M, Albano E, Poli G, *et al.* Hepatitis C virus-related chronic liver disease with autoantibodies to liver-kidney microsomes (LKM). *J Hepatol* 1991; **13:** 128-131.
18. Magrin S, Craxi A, Fiorentino G, Fabiano C, Provenzano G, Pinzello GB, *et al.* Is autoimmune chronic active hepatitis a HCV-related disease? *J Hepatol* 1991; **13:** 56-60.
19. Lenzi M, Johnson PJ, McFarlane IG, Ballardini G, Smith HM, McFarlane BM, *et al.* Antibodies to hepatitis C virus in autoimmune liver disease: evidence for geographical heterogeneity. *Lancet* 1991; **338:** 277-280.
20. Williamson JMS, Chalmers DM, Clayden AD, Dixon MF, Ruddell WS, Losowsky MS. Primary biliary cirrhosis and chronic active hepatitis: An examination of clinical, biochemical, and histopathological features in differential diagnosis. *J Clin Pathol* 1985; **38:** 1007-1012.
21. Seeff LB. Drug-induced chronic liver disease with emphasis on chronic active hepatitis. *Semin Liver Dis* 1981; **1:** 104-115.
22. Maddrey WC. Drug-induced chronic liver disease. *Gastroenterology* 1977; **72:** 1348-1353.
23. Seggie J, Saunders SJ, Kirsch RE, Campbell JA, Gitlin N, Clain D, *et al.* Patterns of hepatic injury induced by methyldopa. *S Afr Med J* 1979; **55:** 75-83.
24. Moses A, Zahger D, Amir G. Cholestatic liver injury after prolonged exposure to methyldopa. *Digestion* 1989; **42:** 57-60.
25. Stanley P, Mijich A. Methyldopa: an often overlooked cause of fever and transient hepatocellular dysfunction. *Med J Aust* 1986; **144:** 603-605.
26. Breland BD, Hicks GS Jr. Hepatitis and hemolytic anaemia associated with methyldopa therapy. *Drug Intell Clin Pharmacol* 1982; **16:** 489-492.
27. Reynolds TB, Peters RL, Yamada S. Chronic active and lupoid hepatitis caused by a laxative, oxyphenisatin. *N Engl J Med* 1971; **285:** 813-820.
28. Sharp JR, Ishak KG, Zimmerman HJ. Chronic active hepatitis and severe hepatic necrosis associated with nitrofurantoin. *Ann Intern Med* 1980; **92:** 14-19.
29. Maddrey WC. Alcoholic hepatitis: pathogenesis and approaches to treatment. *Scand J Gastroenterol Suppl* 1990; **175:** 118-130.
30. Brillanti S, Masci C, Siringo S, *et al.* Serological and histological aspects of hepatitis C virus infection in alcoholic patients. *J Hepatol* 1991; **13:** 347-350.
31. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. *Prog Liver Dis* 1986; **8:** 283-298.
32. Powell EE, Cooksley GE, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990; **11:** 74-80.
33. Scheinberg IH, Sternlieb I. *Wilson's disease* (Major Problems in Internal Medicine, vol. 23). Philadelphia: WB Saunders, 1984.
34. LaRusso NF, Summerskill WHJ, McCall JT. Abnormalities of chemical tests for copper metabolism in chronic active liver disease: differentiation from Wilson's disease. Gastroenterology 1976; **70:** 653-655.
35. Sternlieb I, Scheinberg IH. Wilson's disease. In: Millward-Sadler GH, Wright R, Arthur MJP, eds. *Wright's Liver and Biliary Disease*. London: WB Saunders, 1992: 965-975.
36. Fleming CR, Dickson ER, Wahner HW, Hollenhorst RW, McCall JT. Pigmented corneal rings in non-Wilsonian liver disease. *Ann Intern Med* 1977; **86:** 285-288.
37. Kaplinsky C, Sternlieb I, Javitt N, Rotem Y. Familial cholestatic cirrhosis associated with Kayser-Fleischer rings. *Pediatrics* 1980; **65:** 782-788.
38. Sharp HL. Alpha-1 antitrypsin: an ignored protein in understanding liver disease. *Semin Liver Dis* 1982; **2:** 314-328.
39. Triger DR, Carlson J, Millward-Sadler GH. Alpha-1-antitrypsin deficiency and liver disease. In: Millward-Sadler GH, Wright R, Arthur MJP, eds. *Wright's Liver and Biliary Disease*. London: WB Saunders, 1992: 1170-1188.
40. Summers KM, Halliday JW, Powell LW. Identification of homozygous haemochromatosis subjects by measurement of hepatic iron index. *Hepatology* 1990; **12:** 20-25.

Management of chronic hepatitis B and C

G. M. Dusheiko

Chronic viral hepatitis caused by hepatitis B, C or D may lead to cirrhosis, hepatocellular failure and hepatocellular carcinoma. The morbidity of these diseases has necessitated a prolonged search for effective therapy. Although many antiviral compounds have been evaluated for the treatment of chronic viral hepatitis, few have achieved clinical applicability. Alpha-interferon has been widely studied, and remains the mainstay of treatment. A number of other cytokines, including thymosin, are being evaluated. Nucleoside analogues, alone or in combination with alpha-interferon, may prove useful adjuncts to the treatment of chronic hepatitis B and C.

University Department of Medicine, Royal Free Hospital and School of Medicine, London, UK

G. M. Dusheiko, M.B. B.CH., F.C.P. (S.A.), F.R.C.P.