56. Buendia MA, Etiemble J, Degott C, Babinet C, Tiollais P. Primary hepatocellular carcinoma in transgenic mice carrying a c-myc woodchuck gene activated by hepadnaviral insertion. In: Cilberto B, Cortese R, Schibler U, Schutz G, eds. *Gene Expression During Liver Differentiation and Disease*. IRBM. 1992: 187.
57. Pasquinelli C, Bavani K, Chisari FV. Multiple oncogenes and tumor suppressor genes are structurally and functionally intact during hepatocarcinogenesis in hepatitis B virus transgenic mice. *Cancer Res* 1992; **52:** 2823-2829.
58. Arbuthnot P, Kew MC, Fitschen W. c-fos and c-myc oncoprotein expression in human hepatocellular carcinomas. *Anticancer Res* 1991; **11:** 921-924.
59. Takada S, Koike K. Activated N-ras gene was found in human hepatoma tissue but only in a small fraction of tumor cells. *Oncogene* 1990; **4:** 189-193.
60. Witte ON, Rosenberg N, Paskind M, Shields A, Baltimore D. Identification of an Abelson murine leukemia virus encoded protein present in transformed fibroblasts and lymphoid cells. *Proc Natl Acad Sci USA* 1978; **75:** 2488-2492.
61. Slagle BL, Zhou Z-Z, Butel JS. Hepatitis B virus integration event in human chromosome 17p near p53 identifies the region of the chromosome commonly deleted in virus-positive hepatocellular carcinomas. *Cancer Res* 1991; **51:** 49-54.
62. Ochiya T, Fujiyama J, Fukushige S, Hatada I, Matsubara K. Molecular cloning of an oncogene from a human hepatocellular carcinoma. *Proc Natl Acad Sci USA* 1986; **83:** 4993-4997.
63. Hatada I, Tokino T, Ochiya T, Matsubara K. Coamplification of integrated hepatitis B virus DNA and transforming gene hst-1 in hepatocellular carcinoma. *Oncogene* 1988; **3:** 537-540.
64. Shirakata Y, Kawada M, Fujiki Y, *et al.* The X gene of the hepatitis B virus induced growth stimulation and tumorigenic transformation of mouse NIH3T3 cells. *Jpn J Cancer Res* 1989; **80:** 617-621.
65. Hohne M, Schaefer S, Seifer M, Feitelson MA, Paul D, Gerlich WH. Malignant transformation of immortalized transgenic hepatocytes after transfection with hepatitis B virus DNA. *EMBO J* 1990; **9:** 1137-1145.
66. Kim CM, Koike K, Saito I, Myamura T, Jay G. HB X gene of hepatitis B virus induces liver cancer in transgenic mice. *Oncogene* 1991; **31:** 317-320.
67. Wollersheim M, Debelka U, Hofschneider PH. A transactivating function encoded as the hepatitis B virus X gene is conserved in the integrated state. *Oncogene* 1988; **3:** 545-552.
68. Koike K, Shirakata Y, Yaginuma K, *et al.* Oncogenic potential of hepatitis B virus. *Mol Biol Med* 1989; **6:** 151-160.
69. Kekule AS, Lauer U, Meyer M, Caselmann MH, Hofschneider PH, Koshy R. The preS/S region of integrated hepatitis B virus DNA encodes a transcriptional transactivator. *Nature* 1990; **343:** 457-461.
70. Robinson WS, Klote L, Aoki N. Hepadnaviruses in cirrhotic liver and hepatocellular carcinoma. *J Med Virol* 1990; **31:** 18-32.
71. Lohiya G, Pirkle H, Hoefs J, Lohiya A, Ngo VT. Hepatocellular carcinoma in young mentally retarded HBsAg carriers without cirrhosis. *Hepatology* 1985; **5:** 824-826.
72. Zaman SN, Melia WM, Johnson RD, Portmann BC, Johnson PJ, Williams R. Risk factors in development of hepatocellular carcinoma in cirrhosis. *Lancet* 1985; **1:** 1357-1359.
73. Ferenc P, Dragosics B, Marosi L, Kiss F. Relative incidence of primary liver cancer in cirrhosis in Austria. *Lancet* 1984; **4:** 7-14.
74. Chisari FV, Klopchin K, Moriyama T, *et al.* Molecular pathogenesis of hepatocellular carcinoma in hepatitis B virus transgenic mice. *Cell* 1989; **55:** 1145-1156.
75. Wang JC. DNA topoisomerases. *Ann Rev Biochem* 1985; **54:** 665-697.
76. Kew MC, Miller RH, Chen H-S, Tennant BC, Purcell RH. Mutant woodchuck virus genomes from virions resemble rearranged hepadnaviral integrants in hepatocellular carcinoma. *Proc Natl Acad Sci USA* 1993; **90:** 10211-10215.
77. Wang HP, Rogler CE. Topoisomerase I-mediated integration of hepadnavirus DNA *in vitro*. *J Virol* 1991; **65:** 2381-2392.
78. Goto T, Wang JC. Cloning of yeast TOP 1, the gene encoding DNA topoisomerase I, and construction of mutants defective in both DNA topoisomerase I and DNA topoisomerase II. *Proc Natl Acad Sci USA* 1985; **82:** 7178-7182.
79. Obata H, Hayashi N, Moroike Y, *et al.* A prospective study of the development of hepatocellular carcinoma from liver cirrhosis with persistent hepatitis B virus infection. *Int J Cancer* 1980; **25:** 741-747.
80. Hoofnagle JH, Shafritz DA, Popper H. Chronic hepatitis B and the 'healthy' HBsAG carrier state. *Hepatology* 1987; **7:** 758-763.
81. Hsu H-C, Wu M-Z, Chang M-H, Su I-J, Chen D-S. Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 52 cases strongly associated with rapid development of liver cirrhosis. *J Hepatol* 1987; **5:** 260-267.
82. Gerber MA, Shieh YSC, Shim KS, *et al.* Detection of replicative hepatitis C virus sequences in hepatocellular carcinoma. *Am J Pathol* 1992; **141:** 1271-1277.
83. Jeng JE, Tsai J-F. Hepatitis C virus antibody in hepatocellular carcinoma in Taiwan. *J Med Virol* 1991; **34:** 74-77.
84. Simonetti RG, Cottone M, Craxi A, *et al.* Prevalence of antibodies to hepatitis C virus in hepatocellular carcinoma. *Lancet* 1989; **2:** 1338.
85. Alter HJ, Purcell RH, Shih JW, *et al.* Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. *N Engl J Med* 1989; **321:** 1494-1500.
86. Caporaso N, Romano M, Marmo R, *et al.* Hepatitis C virus infection is an added risk factor for the development of hepatocellular carcinoma in patients with cirrhosis. *J Hepatol* 1991; **12:** 367-371.
87. Vargas V, Castells L, Esteban JI. High frequency of antibodies to hepatitis C virus among patients with hepatocellular carcinoma. *Ann Intern Med* 1990; **112:** 232.
88. Nalpas B, Driss F, Pol S, *et al.* Association between hepatitis C and B infections in hepatocellular carcinoma and alcoholic liver disease. *J Hepatol* 1991; **12:** 70-74.
89. Poynard T, Aubert A, Lazizi Y, *et al.* Independent risk factors for hepatocellular carcinoma in French drinkers. *Hepatology* 1991; **13:** 896-901.
90. Kaklamani E, Trichopoulos D, Tzonou A, *et al.* Hepatitis B and C viruses and their interaction in the origin of hepatocellular carcinoma. *JAMA* 1991; **265:** 1974-1976.
91. Chuang W-L, Chang W-Y, Lu S-N, *et al.* The role of hepatitis B and C viruses in hepatocellular carcinoma in a hepatitis B endemic area. *Cancer* 1992; **69:** 2052-2054.

The laboratory diagnosis of acute viral hepatitis

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The definitive diagnosis of viral hepatitis depends on the demonstration of the virus or of serological markers of recent infection. The serological tests to establish the aetiology of viral hepatitis vary from laboratory to laboratory. Those commonly performed are discussed here. An algorithm (Fig. 1) is provided as a guide to the investigation of patients with suspected hepatitis. It is stressed that the choice of initial tests should be based on the clinical findings in each individual patient.

Hepatitis A

Hepatitis A virus (HAV) or viral antigen can be detected in stool and other body fluids by various techniques including electron microscopy and molecular hybridisation to radiolabelled cDNA probes or single-stranded RNA (viral RNA) probes. However, these techniques are time-consuming and expensive. By the time the patient presents with symptoms, the infection is established and the diagnosis is thus based on the detection of specific antibodies to HAV by radio-immunoassay (RIA)[1] or enzyme-linked immunoassay (ELISA).[2]

IgM anti-HAV antibodies are detectable in the serum at the onset of symptoms, the titres rise rapidly and may persist for 48 - 60 days after the onset of symptoms. False positives are rare. The presence of HAV IgG antibody alone indicates previous exposure and thus immunity, and excludes current infection.

Hepatitis B

Commercially available tests for the diagnosis of hepatitis B virus (HBV) infection include tests for the detection of HBsAg, HBeAg, HBV DNA (by hybridisation techniques), anti-HBs, anti-HBe, IgM anti-HBc and IgG anti-HBc. For research purposes, tests are available to detect HBV DNA by polymerase chain reaction (PCR), HBV DNA polymerase activity, pre-S_1 and pre-S_2 antigens and their antibodies.

In acute hepatitis B, HBsAg is detectable during the prodromal phase prior to the elevation of transaminases. Although the presence of HBsAg in the serum implies active infection, the absolute level has no clinical significance and does not correlate with the degree of infectivity.[3] However, in an individual patient, a decreasing HBsAg titre is indicative of a resolving infection. In a minor infection, HBsAg is cleared rapidly and the only evidence of infection may be

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INVESTIGATION OF ACUTE VIRAL HEPATITIS

CLINICAL ASSESSMENT
↓
BIOCHEMISTRY
↓
AST, ALT, alkaline phosphatase, total and conjugated bilirubin
↓
SEROLOGY

a. Hepatitis A
(HAV IgM +ve = recent infection)

b. Hepatitis B
(i) HBsAg if +ve
↓
(ii) HBeAg if +ve suggests active viral replication
If HBsAg -ve and clinical evidence strongly suggests acute hepatitis B, e.g.
1. Minor infection with rapid clearing of HBsAg
2. Fulminant liver failure
3. 'Window period'

then
Determine anti-HBc
If IgM +ve = acute hepatitis B
If IgG +ve = previous infection or chronic hepatitis B

Repeat serology in 3 and 6 months
HBeAg +ve at 3 months = chronic hepatitis B
HBsAg +ve at 6 months = healthy carrier or chronic hepatitis B
↓
LIVER BIOPSY

c. Hepatitis C
Screening test — Anti-HCV if +ve
↓
Confirmatory test for specificity — HCV - RNA PCR +
If persistent anti-HCV and HCV RNA PCR positive for > 6 months = chronic infection
↓
LIVER BIOPSY

If HCV RNA PCR -ve and Anti-HCV -ve and the patient is from a high-risk group repeat tests in 3 months.

d. Hepatitis E
Total anti-HEV Ab +ve = acute or previous infection
IgM anti-HEV +ve = acute infection

Fig. 1. Algorithm for the investigation of patients with suspected acute viral hepatitis.

the subsequent development of anti-HBc and anti-HBs antibodies. Soon after HBsAg is detectable, HBV DNA and DNA polymerase, HBeAg and anti-HBc antibodies appear in the circulation. ELISAs are the most widely used tests for detecting HBsAg and anti-HBs as they are easily performed and have similar sensitivities to RIA.[4]

IgM anti-HBc antibodies usually develop early in acute infection; they remain positive in high titres for up to 6 months and in low titres for longer periods after acute hepatitis B.[5] Total and IgM anti-HBc antibodies are present during the 'window' period after HBsAg is lost but before anti-HBs appears. IgM anti-HBc is useful in distinguishing recent and current HBV infection[6] from remote previous infection and in diagnosing HBV infection when HBsAg is negative, i.e. during the window period of acute hepatitis B and in some cases of fulminant hepatitis B. Anti-HBc antibodies are usually measured by ELISA. ELISA for detecting IgM anti-HBc is designed to detect it above a pre-defined level and is thus indicative of recent infection as IgM anti-HBc may persist in low titres for a prolonged period.

Detection of HBeAg in the serum is important in the clinical evaluation of a patient with HBV infection as it usually correlates with viral replication, active liver damage and infectivity.[3] HBeAg is detected in the serum early in acute hepatitis B and its disappearance is followed by the appearance of anti-HBe in resolving infection.[7] The persistence of HBeAg is usually associated with ongoing viral replication, liver damage and the development of chronic liver disease. It is important to note that some patients who are HBeAg-negative and anti-HBeAb-positive may still develop chronic active hepatitis. These patients are HBV DNA-positive and have other positive markers of viral replication. This serological picture is also seen in individuals with HBV mutants that replicate in the absence of HBeAg. Seroconversion to anti-HBe may be associated with the development of mutant strains of HBV, characterised by high levels of HBV DNA but no expression of HBeAg. This is due to a single point mutation in the HBV DNA which does not permit translation of HBeAg but allows expression of HBcAg. The mutation (a single codon of the HBeAg, just upstream of the HBcAg initiation site, mutated to a stop codon) may be associated with clinically aggressive disease which responds poorly to interferon therapy. Both HBeAg and HBeAb are measured by commercially available RIAs or ELISAs.

HBV DNA can be detected in serum either by means of hybridisation techniques or PCR. PCR is extremely sensitive (1 - 3 virus genomes in serum sample) but is mainly a research tool. Clinically, detection of HBV DNA by hybridisation (10^6 genome equivalents) is more valuable as it correlates with a high level of viral replication and is associated with ongoing liver damage.

In acute hepatitis B, HBV DNA is not found during the incubation period but becomes detectable after HBsAg is present in serum at the onset of clinical symptoms. HBV DNA tends to be cleared rapidly in acute self-limiting HBV infection, and usually disappears before HBeAg and the transaminase levels return to normal.

HBV DNA polymerase activity is another marker of active viral replication but at present is used mainly as a research tool.

Anti-HBsAb is the last marker to appear, is detectable only after excess HBsAg has been cleared from the serum and usually persists long-term. There may be a window period between the loss of HBsAg and the appearance of anti-HBs. Ten per cent of patients with acute hepatitis B never develop anti-HBs despite clinical recovery, and occasionally chronic carriers have both HBsAg and anti-HBs.

Pre-S_1 and pre-S_2 antigens appear early in acute infection and their presence generally correlates with HBV DNA positivity and other markers of viral replication.[8] Pre-S antigens tend to disappear early and this may indicate subsequent clinical resolution.[9] Persistence of pre-S antigens has been associated with the development of chronic HBV infection.

Anti-pre-S antibodies also develop early in infection when HBsAg is detectable but before anti-HBs antibody appears. Persistence of pre-S_2 antigen and failure to develop pre-S_2 antibodies has been associated with a poor prognosis in fulminant hepatitis. At present, measurement of pre-S antigens and antibodies is limited to research purposes.

Patients in whom HBsAg persists for longer than 6 months and HBeAg persists for longer than 3 months are considered chronic carriers. Healthy carriers usually do not

have evidence of active viral replication. In symptomatic carriers with chronic liver disease HBsAg, HBeAg and HBV DNA are usually present in the serum or liver.

Hepatitis C

As 75% of patients with acute hepatitis C have a mild anicteric illness, the diagnosis is frequently not made. Moreover, the timing of seroconversion to anti-HCV is variable and may not be detected in patients with self-limiting disease. Patients with post-transfusion non-A, non-B (NANB) hepatitis usually remain anti-HCV-negative during the early phase of the illness, but anti-HCV tests may be transiently positive immediately after the transfusion due to passive transfer of antibodies from the donor.[10] Occasionally, anti-HCV antibodies appear 2 - 4 weeks after the onset of hepatitis but usually the anti-HCV antibody only appears months after the serum aminotransferase levels become elevated. Thus, in the acute setting, the diagnosis of HCV infection is still largely by exclusion of other causes.

Serological diagnosis of HCV infection depends on the detection of HCV antibodies or HCV RNA. The anti-HCV antibody tests include the first-generation ELISAs which utilise the recombinant C100-3 antigen to capture antibody. The C100-3 ELISA has low sensitivity and specificity although serum anti-C100-3 was a reasonable marker for chronic infection (in transfusion-related and sporadic NANB hepatitis) with persistently elevated ALT levels; in acute resolving hepatitis anti-C100-3 was only positive in 30% of cases with seroconversion occurring after 3 - 6 months. There is also a high false-positive rate among low-risk populations, e.g. blood donors; with frozen sera[11] and in the presence of hypergammaglobulinaemia. Assays for IgM antibodies to C100-3 are available and although IgM anti-C100-3 antibodies may be detected as early as 4 weeks after incubation, they are also detectable in chronic hepatitis C and thus cannot distinguish between acute and chronic hepatitis.

Second-generation ELISAs (Ortho) have increased sensitivity as they incorporate extra-HCV-derived recombinant proteins including c22c, c33c and c200 (a composite antigen).[12] Anti-c33c and anti-c22c antibodies occur more frequently in serum and earlier in the course of disease than anti-c100-3 antibodies.

Third-generation ELISAs, which test for antibodies to core, NS3 and NS5 antigens (combination of peptides from both structural and non-structural regions), further increase sensitivity of HCV detection in acute and chronic NANB hepatitis.

Supplementary tests involving recombinant immunoblot assays (RIBAs) have increased specificity. The second-generation RIBA4 (Ortho) tests for antibodies to C100-3, 5-1-1 (proteins from NS3/NS4 regions), c33c and c22-3. RIBA4 is useful in excluding false-positive ELISA results and there is good correlation between RIBA4 positivity and viraemia as determined by PCR detection of HCV RNA.[13,14]

Direct tests for HCV antigens in serum are not yet available. HCV RNA is at present the best marker of viraemia and infectivity. HCV RNA is measured by means of PCR. Detection of HCV RNA by PCR may confirm viraemia in patients who remain HCV antibody-negative and is also detectable in blood much earlier than other markers; tests may be positive within days of the infection. The sensitivity of the PCR depends on the primers used and primers derived from the 5′-UTR region are generally more sensitive as this region is highly conserved among HCV isolates. Quantitative HCV RNA tests have recently been developed which will enable HCV RNA titres to be correlated with serum aminotransferase values, response to antiviral agents and severity of liver disease.

Hepatitis D

Acute hepatitis D occurs either as superinfection in a chronic hepatitis B carrier or simultaneously with acute hepatitis B as a co-infection.

Total anti-HDV and IgM anti-HDV antibodies can be measured by ELISAs. Total anti-HDV antibodies are usually negative in the acute phase of the illness with seroconversion occurring late in the clinical course of the disease.[15] In patients with acute, self-limiting co-infection with both HDV and HBV, total anti-HDV titres are low and remain detectable for several months. Persistent high total anti-HDV titres usually occur in chronic disease where a patient with chronic HBV infection becomes superinfected with HDV.[16]

IgM anti-HDV antibodies are usually positive in acute cases but do not distinguish between HDV/HBV co-infection and superinfection.[17] In self-limiting co-infections, the IgM anti-HDV response is usually short-lived, whereas in chronic HDV infection, the IgM levels vary from being undetectable to fluctuating to high.

Delta antigen is detectable by ELISA during the late incubation period of acute hepatitis D and may persist into the symptomatic phase. In chronic HDV infection, delta antigen is often undetectable in serum with the ELISA technique but is usually positive if immunoblotting is used.

HDV RNA in serum can be detected by dot hybridisation using either cDNA or single-stranded RNA probes for HDV. In acute infection, HDV RNA is usually positive during the symptomatic phase, becoming negative after clinical recovery.

Hepatitis D is thought not to be a problem in South Africa, and tests for hepatitis D should be reserved for patients with chronic HBV infection who develop unexpected progressive liver disease.

Hepatitis E

Total anti-HEV antibodies (IgM and IgG) can now be measured by an ELISA (Abbott) which has a 98% sensitivity in acute infection. Specificity of the test is not yet known. This test should be limited to those cases of acute hepatitis with a likely epidemiological history and where viral markers for hepatitis A, B and C are negative.

Hepatitis F and G

There are no serological markers for either of these two hepatidides. Hepatitis F is an epidemiological entity that presents as fulminant or subfulminant hepatitis. Hepatitis G also presents as a subfulminant or fulminant hepatitis and is associated histologically with a giant cell hepatitis.

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

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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*.

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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