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CHRONIC HEPATITIS

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The term *chronic hepatitis* is used to include prolonged inflammation of the liver following an attack of acute viral hepatitis, either icteric or anicteric, or chronic active hepatitis, of unknown aetiology. We accept the Fogarty proceedings (Leevy and Tygstrup, 1976) definition of chronic hepatitis as inflammation of the liver for six months or more, although the duration of the biochemical or histological abnormalities before the term *chronic hepatitis* has been used by different authors has varied from ten weeks to six months or even one year. The diagnosis is based on clinical, biochemical, histological and immunological findings. It is important to assess these carefully, often with serial liver biopsy, to determine the clinical course and prognosis and therefore the need for treatment in a particular patient. In prolonged or unresolved viral hepatitis the outlook is good, providing certain adverse prognostic features are not present. In chronic active hepatitis of unknown aetiology, the prognosis is poor, and in some cases established and irreversible liver damage is present at clinical presentation.

It must be emphasized that the distinction between these different types of chronic hepatitis, both clinically and histologically, is not always clear-cut, and frequent review and reassessment of the patient is necessary for correct diagnosis and treatment.

Not until it became feasible to test for hepatitis B-associated antigens was it clear that acute icteric or anicteric viral hepatitis could progress to chronicity and a post-hepatitic cirrhosis. The earlier evidence was based on rare instances where progression of acute viral hepatitis to chronic liver disease could be demonstrated clinically and sometimes histologically on serial liver biopsy (Krarup and Roholm, 1941; Kelsall, Stewart and Witts, 1947; Sherlock, 1948: Schaefer, Schiff et al, 1967). In a series of careful clinical and histological studies, Klatskin (1958) emphasized the importance of anicteric infection in the progression of acute viral hepatitis to cirrhosis. Evidence for a viral aetiology also arose from the repeated transmission of acute hepatitis to recipients by the transfused blood from a donor with cirrhosis (Creutzfeldt, Schmitt et al, 1962). When follow-up studies were undertaken of outbreaks of hepatitis, chronicity and cirrhosis were rarely observed (Cullinan, King et al, 1958; Nefzger and Chalmers, 1963), but this is not surprising since most of these outbreaks were due to hepatitis A and it is now recognised that hepatitis A infections do not proceed to chronicity.

It is customary to exclude alcoholic liver disease, Wilson's disease, primary biliary cirrhosis, alpha-1-antitrypsin deficiency and drug-induced chronic active liver disease in any definition of chronic hepatitis, although they may show clinical, biochemical and histological features indistinguishable from chronic active (aggressive) hepatitis of unknown aetiology or that due to viral infection. The commonest viral infection producing chronic hepatitis is that due to hepatitis B, but chronicity can also occur with non-A non-B hepatitis, although the hepatic lesion is usually less severe.

It is essential to distinguish chronic persistent hepatitis, where the prognosis is good, from chronic active (aggressive) hepatitis, where the prognosis may be poor. It is customary to use the term *chronic active hepatitis* to imply a clinical syndrome which

is associated with the histological lesion of chronic aggressive hepatitis. Chronic active hepatitis can be due to hepatitis B, non-A non-B hepatitis, or can be of unknown aetiology, possibly arising on an autoimmune basis. Cirrhosis may or may not be present at the time of clinical presentation. Minor non-specific chronic inflammatory changes in the liver can also occur in carriers of the hepatitis B virus in the absence of the more severe lesions described above.

CHRONIC PERSISTENT HEPATITIS

Following a typical attack of acute viral hepatitis, a proportion of patients with hepatitis B or non-A non-B hepatitis develop persistent symptoms or biochemical abnormalities which may continue for months or years. The distinction between chronic persistent hepatitis and chronic active hepatitis following an attack of acute viral hepatitis is based on histological examination of liver biopsy material, although there are certain clinical, biochemical and immunological features which may provide a clue to the nature of the underlying liver disease.

Clinical, biochemical and immunological features

Patients may present following a typical acute icteric attack of viral hepatitis, or the initial attack may have been anicteric. Symptoms of fatigue, malaise, lassitude and anorexia with intolerance of fat and alcohol may fluctuate in severity for months or years after the acute attack. Patients may fail to regain weight lost during the acute attack. Pain over the liver may be present, particularly after exercise. The liver may be enlarged, tender and slightly firmer than normal, but splenomegaly is unusual. Slight jaundice and dark urine are occasionally present, but this usually indicates a frank relapse of the hepatitis. Palmar erythema, spider naevi, oedema or ascites are not present. Serum transaminase levels are elevated but seldom more than four or five times the upper limit of normal. The prothrombin time is not prolonged. The albumin level is well maintained and hyperglobulinaemia is slight. Autoantibodies, including the smooth muscle antibody, are usually negative or present only at low titre.

An increasing number of cases are being detected incidentally in the course of investigation for an enlarged liver or spleen or abnormal liver function tests, or during the investigation of patients who are found to have HBsAg in their serum as the result of screening of high risk groups. Many cases follow hepatitis B infection, usually with persistence of the HBsAg in the serum, although occasionally it may be cleared, but liver cell necrosis and elevated transaminases persist. In a proportion of patients there is no evidence of previous infection with hepatitis B and the chronic persistent hepatitis is presumably due to a non-A non-B virus. There is no evidence that hepatitis A can proceed to chronicity, or that chronicity is associated with EB virus infection or cytomegalovirus infection.

The frequency with which chronic hepatitis follows acute icteric hepatitis B infection is difficult to determine. There is general agreement that anicteric or relatively mild infections are more likely to proceed to chronic liver disease (Sherlock, 1976). Follow-up of hospitalized biopsy-documented HBV infections will therefore not reflect the true frequency in the community. Of 429 patients with acute HBV infection followed by Redeker (1978) for one to five years, 30 (6.9%) developed persistent viral hepatitis and 13 developed chronic active hepatitis. Similar figures were reported by Nielsen, Dietrichson et al, (1974), though somewhat higher figures were reported by Klatskin (1975).

Following a fulminant or severe acute attack, chronic liver disease rarely develops (Karvountzis, Redeker and Peters, 1974). Follow-up studies of patients who had anicteric infections, on the other hand, have shown a higher risk of development of a persistent hepatitis than those who were icteric (Barker and Murray, 1971; Nielsen,

Dietrichson and Juhl, 1974). Furthermore, only a small proportion of patients with HBsAg-positive chronic persistent hepatitis or chronic aggressive hepatitis give a previous history of an acute attack of icteric viral hepatitis. There is also some evidence that men are more likely to develop chronic persistent hepatitis than women, and that corticosteroid therapy during the acute attack may predispose to the development of chronicity

In HBsAg-positive chronic liver disease, neither the titre of the HBsAg nor the nature of the predominant particle in serum, that is, small 23 nm. particles, filaments or full or empty Dane particles, provide a good guide to the nature of the underlying lesion. Similarly, although antibody to the core of the Dane particle and anti-HBs, even in the absence of HBsAg, imply recent or remote infection with HBV, they give no guide to the underlying hepatic damage. On the other hand, patients with chronic persistent hepatitis often have high titre HBsAg in the serum (Bianchi, Bianchi Porro et al, 1972; Chiaramonte, Heathcote et al, 1977), whereas patients with chronic aggressive hepatitis may have low titres of the antigen. Similarly, chronic carriers who have persistence of the 'e' antigen and full Dane particles in their serum are more likely to have severe hepatic damage (Table I).

Table 1

Hepatitis B markers in blood in relation to type of liver disease

	'e' Ag	Anti-'e'	Anti-HBc	Anti-HBs	CMI to HBsAg
Viral hepatitis					
acute early	high	0%	low	low	51%
acute late	low	12%	high	high	70%
Chronic active hepatitis	49%	7%	90%	90%	53%
Chronic persistent hepatitis	39%	23%	90%	90%	5%
Carriers («Normal»)	<10%	67%	90%	90%	0%

After Edginton and Chisari, Immune Reactions in Liver Disease, Pitman Medical, 1979.

Histopathology

The histological appearance in chronic persistent hepatitis is characterised by a normal liver lobular architecture, but with expansion of the portal tract and infiltration with inflammatory cells, mainly lymphocytes. There may or may not be superimposed features of acute hepatitis in the rest of the liver lobule. The portal tracts may be expanded by fibrous spurs, but there is no destruction of the limiting plate by piecemeal necrosis, which distinguishes this condition from chronic aggressive hepatitis (De Groot, Desmet et al, 1968). These histological features, persisting for six months or more, taken in conjunction with the clinical picture, described above and the absence of evidence of cirrhosis, provide strict criteria for the definition of chronic persistent hepatitis. It has to be distinguished from resolving acute viral hepatitis, relapsing hepatitis and chronic lobular hepatitis, where the florid changes of acute viral hepatitis may remain a prominent feature. It is difficult to know whether relapsing cases are due to a varying immunological response to HBV infection, reactivation of the virus (Nagington, Cossart and Kohn, 1977) or a superimposed non-A non-B infection.

Although chronic persistent hepatitis as defined above should be regarded as a benign condition, histological progression can occur to a mild or moderate chronic aggressive hepatitis. In one study, this was not associated with progression to cirrhosis (Chadwick, Galizzi et al, 1979), but in others (van Waes, Segers et al, 1974; Dietrichson, 1975) progression to chronic active hepatitis and cirrhosis apparently occurred, although there must be some doubt about sampling errors in the initial biopsy specimen.

In chronic persistent HBV infection, the surface antigen can usually be demonstrated in the cytoplasm of some of the hepatocytes by the orcein stain (Deodar, Tapp and Scheuer, 1975).

Prognosis

It would seem reasonable to regard chronic persistent HBV infection as defined above as being benign, and in the absence of the availability of therapy to terminate the infection, the patient should be reassured. It is, however, possible that some cases (perhaps initially misdiagnosed) may progress to cirrhosis or other late sequelae such as hepatoma.

HBsAg-POSITIVE CHRONIC ACTIVE HEPATITIS AND CIRRHOSIS

The discovery of the Australia antigen and the recognition of its clear association with hepatitis B infection had a profound effect on our knowledge of the importance of hepatitis B as a cause of chronic active hepatitis and cirrhosis. In our original study from Yale, six of 24 patients with chronic active hepatitis were shown to have HBsAg in their serum, even though an insensitive immunodiffusion technique was used (Wright, McCollum and Klatskin, 1969). A similar proportion was reported by other workers in the United States, but it was only rarely found to be a cause of chronic active hepatitis in residents of the United Kingdom (Fox, Niazi and Sherlock, 1969; Wright, 1970; Eddleston, Stern et al, 1973) and in Australia (Mathews and Mackay, 1970). It soon became clear that the proportion of cases of chronic active hepatitis seen in a community which were due to hepatitis B was related to the carrier rate of HBsAg in that community. High carrier rates were reported in chronic active hepatitis with or without cirrhosis in Italy (Bianchi, Bianchi Porro et al, 1972), Greece (Theodoropoulos, 1974) and Japan (Hirayama, Tominaga et al, 1972), and in our own studies from Iraq (Holdstock, Rassam et al, 1978) over 80% of patients with chronic active hepatitis were HBsAg-positive.

Clinical, biochemical and immunological features

The clinical features of HBsAg-positive chronic active hepatitis vary considerably, depending on the activity of the disease and the presence or otherwise of a post-hepatitic cirrhosis. In most series, males have predominated, accounting for over 80% of cases. Presentation usually occurs after the age of 20 years, but rarely it may present in infancy (Wright, Perkins et al, 1970).

The majority of cases probably arise as a result of vertical transmission from mother to baby, but with clinical signs and symptoms only presenting much later in life. Others arise from acute icteric or anicteric hepatitis B infection during the postnatal period in infancy, childhood or adult life. A previous history of acute icteric viral hepatitis usually occurs in less than 10%. An increasing number of cases are being detected when liver biopsies are performed in the investigation of patients found to be positive for HBsAg in the serum, as a result of routine testing or because of the investigation of physical signs such as hepatosplenomegaly or abnormal liver function tests.

Some patients will only present with a complication of chronic active hepatitis and cirrhosis late in the disease, with oedema, ascites, variceal bleeding, liver failure, septicaemia or a hepatoma. Another mode of presentation is with the extrahepatic manifestations of chronic active infection such as glomerulonephritis, polyarteritis or an arthropathy.

Chronic active hepatitis is associated with non-A non-B infection (Galbraith, Dienstag et al 1979), but the frequency with which this occurs is unlikely to be clear until serological tests for non-A, non-B infection are established (Vitvitski, Prince et al, 1979).

On clinical examination, patients may show features such as spider naevi and palmar erythema, but these are less common than with chronic active hepatitis of unknown aetiology, and other putative autoimmune diseases, as well as acne and endocrinopathies, are rare. Tattooing, scarification of the skin, a history of drug abuse or blood transfusion, homosexuality and medical or paramedical employment may lead to suspicion of the disease. Only a small proportion of patients give a history of jaundice. In others there are strong suggestive features of anicteric hepatitis, clinically or epidemiologically. Usually the jaundice fades and the major biochemical abnormality is the persistent elevation of the transaminases, other liver function tests being relatively little deranged until decompensation occurs. Occasionally there are intermittent attacks of acute on chronic hepatitis, but these are relatively infrequent. Hyperglobulinemia is often not pronounced, and autoantibodies such as the smooth muscle antibody and antinuclear antibody are absent or only present at low titre. DNA-binding antibodies, however, may be present, whether or not the patients are HBsAg-positive, and do not necessarily reflect an autoimmune response (Kingham, Rassam et al, 1978).

HBV markers in serum and liver tissue (Table I)

As indicated earlier, although markers of HBV infection in serum imply that the chronic active hepatitis is due to this infection, they provide no clear evidence of the histological lesion. The titre of HBsAG is significantly lower in patients with chronic active hepatitis than in chronic persistent hepatitis or carriers (Bianchi, Bianchi Porro et al, 1972; Chiaramonte, Heathcote et al, 1977; Dudley, Fox and Sherlock, 1971).

Reports of the significance of the persistence of the 'e' antigen have been conflicting. Eleftheriou and associates (1975) detected HBeAg in 44% of patients with chronic active hepatitis, whereas only two of 79 patients had 'e' antibody. A similar correlation between chronicity, the 'e' antigen and DNA polymerase was reported by Nordenfeld and Andrén-Sandberg (1976) and Feinman and associates (1975). Others have been more cautious in accepting that the persistence of HBeAg implies chronic aggressive disease or that anti-'e' implies quiescence of the infection (Smith, Murphy et al, 1976; Vogten, Schalm et al, 1976; Redeker, 1978).

Antibody to the core of the Dane particle (anti-HBc)is regarded as a more sensitive indicator of HBV replication than HBsAg itself, and may persist in the serum after HBsAg has disappeared. It has been suggested that in patients with chronic active hepatitis who have anti-HBc in their serum but are HBsAg-negative the disease is initiated by HBV infection and perpetuated by an autoimmune response. However, the frequency with which anti-HBc is detected in the serum of patients with HBsAg--negative chronic active disease has varied considerably. For example, in France Bories, Coursaget et al, (1978) found that one third of their HBsAg-negative patients had anticore in the serum, whereas Grady, Kaplan & Vyas (1977) rarely found core antibody in such patients, and this has been our own experience in Southampton and Iraq (Holdstock, Rassam et al, 1978).

Histopathology of HBsAg-positive chronic aggressive hepatitis

The histological features are characterised by an inflammatory cell infiltrate and piecemeal necrosis with or without cirrhosis. The inflammatory cell infiltrate varies in intensity and is usually maximal in the portal tracts, but it may extend into the hepatic parenchyma. It consists of lymphocytes and plasma cells with macrophages. Kupffer

cell hyperplasia is often seen, and there is every evidence of fibroblastic activity, a prelude to the development of cirrhosis. The combination of inflammatory cell infiltrate and fibroblastic activity destroying the hepatic parenchyma and isolating hepatocytes at the interface between the parenchymal cells and bands of collagen has been termed *piecemeal necrosis*. Acidophilic and ballooning degeneration of hepatocytes may be present, with cell drop-out resembling bridging hepatic necrosis. The bridging hepatic necrosis may be a prominent feature, particularly during the acute icteric or anicteric infection. Regenerative activity with twinning of cell-plates and rosette formation may be a prominent feature.

Hepatitis B surface and core antigens can be demonstrated in the liver in chronic active hepatitis, but are usually randomly distributed throughout the parenchyma, predominating in areas where there is minimal necrosis. HBsAg can be demonstrated by the orcein stain and both HBcAg and HBsAg by immunoperoxidase and immunofluorescence techniques. Another antigen, the delta antigen, has been described in HBsAg-positive liver disease, and it is of prognostic significance in that it is associated with the development of chronicity (Rizzetto, Fhih et al, 1979).

Table 2

Immunological abnormalities in chronic active hepatitis

Raised globulins	IgG++ IgM+ IgA+
Autoantibodies:	
anti-nuclear	40-60%
smooth muscle	40-60%
DNA-binding	<20%
microsomal	<20%
mitochondrial	<20%
hepatocyte membrane	40%
Bacterial and viral antibodies:	
E. coli	
Bacteroides	
Salmonella	
Measles	
Rubella	
Cytomegalovirus	
Cell-mediated immunity to liver-specific lipoprotein:	
K cell cytotoxicity	
increased incidence of HLA-B8	

After Wright, Immunology of Gastrointestinal and Liver Disease, Edward Arnold, 1977.

HBsAg-positive carriers

Patients who are found to have HBsAg in their serum and who have liver biopsies have a wide range of hepatic abnormalities, including chronic persistent hepatitis, chronic aggressive hepatitis with or without cirrhosis, an inactive cirrhosis, or only mild changes such as ground-glass hepatocytes (Hadziyannis, Gerber et al, 1973).

Irrespective of the severity of the hepatic damage, a number of interesting features have arisen as a result of studies of HBV-positive patients. There is a striking geographical distribution, ranging from 1: 1000 in an apparently healthy population in North America and Britain to 10-15% in Southeast Asia. Familial clustering occurs, and there is some evidence that carriage of the antigen is inherited as an autosomal recessive trait. It seems likely that both environmental and genetic factors contribute (Maz-

zur, 1976; Szmuness, Harley and Prince, 1975; Blumberg, Friedlaender et al, 1969). There have been some reports of an association between HBsAg positivity and HLA locus B specificity, but further studies are required (Hillis, Hillis et al, 1977).

The age at which infection occurs appears to be important in the development of the carrier state of HBsAg. In Western communities, It is unusual to detect carriers in childhood, and the carrier rate increases with age, although it is less common in the elderly, presumably because of spontaneous clearing of HBsAg (Szmuness, Hearley and Prince, 1975). In tropical communities, vertical transmission due to perinatal infection is common, and the carrier state develops at an earlier age. In chronic hepatitis and in asymptomatic carriers there is a striking male predominance. While this may be due to a greater liability of males to become infected with HBV because of their lifestyle, it has recently been postulated that it is due to cross-reactivity between the HBsAg and a male-determined tissue antigen (Drew, London et al, 1978), so that the male is tolerant of HBV antigens and therefore has an impaired tissue defence against it.

Extrahepatic manifestations of HBV infection

Recently there has been much attention focused upon the extrahepatic manifestations of HBV infection, such as polyarthralgia or arthritis, vasculitis, cryoglobulinaemia, glomerulonephritis and acrodermatitis, which can occur with any form of chronic HBV hepatic infection. There is strong immunological evidence to support immune complex deposition of HBsAg as the pathogenic mechanism involved.

Arthritis and arthralgia

Although most of the observations have been made in the arthritis and arthralgia associated with acute HBV infections, a similar syndrome can occur with chronic active hepatitis (Wands, Alpert et al, 1975). Low complement levels can be detected, both in the serum (Alpert, Isselbacher and Schur, 1971) and synovial fluid (Onion, Crumpacker and Gilliland, 1971).

Vasculitis and cryoglobulinaemia

An association between polyarteritis nodosa and HBsAg was reported by Gocke, Hsu et al, (1970) and Trepo and Tivolet (1970), and this is now well recognised (Duffy, Lidsky et al, 1976; Gocke, 1978). The liver disease is usually chronic but relatively insignificant, and patients present with some of the classic features of a polyarteritis nodosa, such as fever, polyarthralgia, rashes, peripheral neuropathy, hypertension and azotaemia. Circulating immune complexes of HBsAg can be demonstrated in the serum and in the vessel walls with a decrease in total serum haemolytic complement. Some patients show features resembling a hypersensitivity angiitis (Sergent, Lockshin et al, 1976), and there is also some evidence that the ischaemia may be on the basis of deposition of cryoproteins (McIntosh, Koss and Gocke, 1976).

Glomerulonephritis

The association between glomerulonephritis and HBsAg was first described by Combes, Stastny et al, (1971) and may be a common cause of glomerulonephritis in certain parts of the world, particularly in children (Brzosko, Krawcznski et al, 1974).

Deposits of IgG and complement can be demonstrated in the glomerular basement membrane by immunofluorescence and are nodular, showing a membrano-proliferative or membranous pattern.

Althoug the demonstration of HBsAg immune complexes in blood vessels or glomeruli provides strong suggestive evidence that immune complex deposition is the cause of these extrahepatic manifestations, it does not provide conclusive proof, but nevertheless has important implications in relation to arteritis, glomerulonephritis and arthritis of unknown aetiology.

CHRONIC ACTIVE HEPATITIS OF UNKNOWN AETIOLOGY

Clinical, biochemical and immunological features

Attention was first focused on chronic liver disease in young women with jaundice, acne, amenorrhoea, hepatosplenomegaly and hyperglobulinaemia by Waldenstrom (1950). Several similar reports of chronic active liver disease in young women (Bearn, Kunkel and Slater, 1956; Kunkel, Ahrens et al, 1951) soon followed, as well as in women at the menopause (Cattan, Vesin and Bodin, 1957). A feature emphasized by all these groups, including others in Australia (Joske and King, 1955; Mackay, Taft and Cowling, 1956) was the presence of immunological disturbances, including a positive LE cell phenomenon, and this led to the term *lupoid hepatitis*, although the predominance of plasma cell infiltrate in the liver was also emphasized by others (Good, 1956), who used the term *plasma cell hepatitis*. It is likely that such patients were previously described under the term *sub-acute or chronic hepatitis of insidious onset* by Kelsall, Stewart and Witts (1947) and *subchronic atrophy of the liver* by Bjorneboe and Raaschou (1949).

The clinical, biochemical and immunological features of chronic active hepatitis of unknown aetiology are now well recognised, although it is becoming increasingly apparent that, quite apart from hepatitis B, non-A non-B hepatitis and other viruses may induce a similar histological lesion, although there may be important clinical distinctions. The clinical features include a female predominance, particularly in adolescence or at the menopause, so that the former group was referred to by Read, Sherlock and Harrison (1963) as *juvenile cirrhosis*. In about 20% of patients the onset is acute, resembling viral hepatitis, but in the remainder it is insidious with the slow development of jaundice, signs of liver failure and fepatic pain. In some patients, extrahepatic manifestations such as thyroid disease, arthralgia, ulcerative colitis or renal disease may be the predominant presenting feature.

On physical examination, the patients often look well but have mild jaundice, prominent spider naevi and palmar erythema. Cutaneous striae and gynaecomastia occur in young males. The spleen is usually palpable, the liver usually enlarged, though occasionally when cirrhosis is present it may be reduced in size. Endocrine manifestations such as amenorrhoea and acne may be prominent features, particularly in the adolescent girls, and there may be other skin rashes, including those resembling lupus erythematosus with purpura.

In untreated patients, progressive deterioration of liver function was the rule, with anorexia, marked fatigue, abdominal pain, the development of new spider naevi, fever, haemorrhagic phenomena and ascites. Death usually occurred from liver failure, with or without bleeding varices, and in an Australian series (Mistilis, Skyring and Blackburn, 1968) half the deaths occurred within the first few years when the disease was most active, and only six patients survived ten years.

The biochemical severity of jaundice was variable. Serum transaminases are usually moderately elevated to a peak of 500 and 800 I.U., but hyperglobulinaemia was usually pronounced with lowering of the serum albumin and a prolongation of the prothrombin time as the disease progressed.

Anaemia, which was often normochromic, and sometimes a Coqmb's positive haemolytic anaemia and leucopenia was often observed.The positive LE cell phenomenon is present in 10-15% of cases.

Associated putative autoimmune conditions include Sjögren's syndrome, renal tubular acidosis (Golding, Smith and Williams, 1973) and pulmonary diffusion defects as well as peripheral neuropathy and thyroid disease. Fibrosing alveolitis (Turner-Warwick, 1968) and ulcerative colitis (Mackay and Wood, 1962; Holdsworth, Hall and Sherlock, 1965), arthropathy and arthralgia, myasthenia gravis and Coomb's positive haemolytic anaemia, as well as cryoglobulinaemia and monoclonal gammopathies, are well recognised.

A wide range of immunological abnormalities has been described in chronic active hepatitis of unknown aetiology. These have been fully reviewed elsewhere in this issue by Triger and are summarised in Table II. Hyperglobulinaemia is striking, all three major immunoglobulin classes being involved, although the rise is less pronounced in IgG. Serum complement levels may be low, but are probably due to defective synthesis by the diseased liver, although there is some evidence for *in vivo* inactivation of C3 in chronic active hepatitis, favouring the utilisation of complement in immune complex formation (Teisberg and Gjone, 1973).

A wide range of circulating aotoantibodies occur, including anti-nuclear antibody, DNA-binding antibody and antibodies to smooth muscle. The latter occur in 40-60% of HBsAg-negative cases and are often present at high titre and in the IgG class. In some patients, an antibody reacting with microsomal membranes occurs, particularly in young women with active disease (Smith, Williams et al, 1974). In addition, high titre antibodies to a variety of bacterial and viral antigens, particularly enterobacteria, measles, rubella and cytomegalovirus, have been observed in chronic active hepatitis. There is an overall correlation between the presence of antinuclear antibody, smooth muscle antibody and these viral antibody titres but no cross-reactivity (Triger, Kurtz and Wright, 1974).

Of special interest is a serum autoantibody which is directed against the hepatocyte membrane as demonstrated by indirect immunofluorescence of isolated rabbit hepatocytes. This has been observed in about 40% of patients with HBsAg-negative chronic active hepatitis, but only very rarely in other forms of liver disease (Tage-Jensen, Arnold et al, 1977). The significance of these liver-specific antibodies as well as antibodies reacting against cytoplasmic liver-specific lipoprotein in the pathogenesis of chronic active hepatitis has been critically reviewed by Dienstag and Isselbacher (1978).

Cell-mediated immunity to autologous and heterologous liver tissue has produced evidence for specific sensitization, but as with circulating antibodies it is uncertain whether this is causally related to liver disease or is a consequence of cell damage. Specific lymphocyte transformation and leucocyte migration inhibition have been used to a variety of antigens, but paticularly liver-specific lipoprotein. Studies of lymphocyte cytotoxicity have also produced a wealth of immunological data which is difficult to interpret. The target cells used have included Chang liver cells, human hepatocytes and rabbit hepatocytes.

The possibility that genetic factors are important in the pathogenesis of chronic active hepatitis arises from the demonstration of an increased incidence of the histocompatibility antigen HLA-B8 (MacKay and Morris, 1972), and there is a correlation between this HLA antigen and the titres of autoantibodies as well as antibodies to

measles and rubella viruses (Galbraith, Eddleston et al, 1976). Further evidence suggesting that genetic factors are important stems from the demonstration of a high frequency of autoantibodies in the relatives of such patients (Galbraith, Smith et al, 1974), as well as high titre antibodies to measles and rubella (Salaspuro, Laitinen et al, 1976).

Pathology

The pathology of idiopathic chronic active hepatitis is indistinguishable from that described earlier for HBsAg-positive hepatitis, with the exception that there are no demonstrable hepatic markers of HBV infection. More active parenchymal inflammation and an increased proportion of plasma cells favour idiopathic rather than HBsAg-positive chronic active hepatitis.

DISTINCTION BETWEEN HBsAg-POSITIVE AND NEGATIVE CHRONIC ACTIVE HEPATITIS (TABLE 3)

This distinction should be made both on clinical and on epidemiological grounds and because treatment may differ in the two groups. Patients with HBsAg-positive chronic active hepatitis are frequently male and on average are older than the idiopathic variety, which occurs particularly in young women and women at the menopause. As indicated earlier, there is a striking association between chronic active hepatitis of the idiopathic variety and other forms of putative autoimmune disease. By comparison, the extrahepatic multisystem disease associated with HBsAg-positive chronic active hepatitis is due to the deposition of immune complexes of the surface antigen and antibody. As with other autoimmune diseases, there is an increased incidence of HLA-B8 in the idiopathic chronic active hepatitis, but not in HBsAg-positive patients (Lindberg, Lindholm et al, 1977). In idiopathic chronic active hepatitis, the globulin levels are usually higher and there is a greater prevalence of circulating autoantibodies, particularly antinuclear antibody and anti-smooth muscle antibody at high titre. It has been suggested, however, that these differences can be attributed to the large number of females in the idiopathic variety, and that in males the distinction falls away (Eddleston, Stern et al, 1973).

It has been proposed by some that chronic active hepatitis of unknown aetiology might be due to an abnormal immune response initiated by the hepatitis B virus which is no longer detectable. This possibility has been examined by studying late markers of HBV infection with conflicting findings. Grady, Kaplan and Vyas (1977) did not find an increased incidence of anti-HBc in patients with chronic active hepatitis who did not have the surface antigen in their serum, and therefore concluded that few if any such cases were induced by HBV. Our findings have been similar in that only one of 29 patients with HBsAg-negative chronic active hepatitis had anti-HBc in the serum. On the other hand, Bories, Coursaget et al, (1978) and others have found that about a third of their patients with HBsAg-negative chronic active hepatitis have detectable anti-HBc.

Striking epidemiological and geographical variations are observed in HBsAg-positive chronic active hepatitis, the condition being rare in the United Kingdom but common in parts of Europe, the Middle East, Africa and South East Asia. It is not known whether a geographical variation occurs with HBsAg-negative cases.

OTHER CAUSES OF CHRONIC ACTIVE HEPATITIS

Although it is likely that as other causes of chronic active hepatitis are identified the proportion that are idiopathic will be reduced, the numbers of such cases are small and include other viruses and drugs. Non-A non-B hepatitis, particularly following blood transfusion, can proceed to chronicity, and in one study four out of 80 such patients had chronic active hepatitis (Rakela and Redeker, 1979). There is no evidence that cytomegalovirus or EB virus infection proceeds to chronicity.

Drug-induced hepatitis is being recognised with increasing frequency and has been reviewed by Maddrey and Boitnott in 1977. These drugs include laxatives containing oxyphenisatin (Cooksley, Cowen and Powell,1973; Dietrichson, Juhl et al, 1974; Reynolds, Peters and Yamada, 1971), methyldopa (Goldstein, Lam and Mistilis, 1973; Toghill, Smith et al, 1974) and possibly isoniazid (Maddrey and Boitnott, 1973) and paracetamol (Bonkowsky, Mudge and McMurty, 1978).

Clinical and histological features of chronic active hepatitis may occur in Wilson's disease, alpha-1-antitrypsin deficiency and alcoholic liver disease, and there is an overlap between primary biliary cirrhosis and chronic active hepatitis of unknown aetiology.

Table 3

Clinical and immunological distinctions between HBsAg-positive and HBsAg-negative chronic active hepatitis

	HBsAg-positive	HBsAg-negative
Age	Often elderly	Often young
Sex	Mostly males	Usually females
Multi-system disease	Rare	Common
Anti-nuclear factor	Rare	Common
Smooth muscle antibody	Rare	Common
Anti-HBc	Common	Rare
Liver-specific antibodies	Rare	Common
Hyperglobulinaemia	Moderate	Marked
HLA-B8 distribution	Normal	Increased
Geographical distribution	Variable	Probably universal
Response to corticosteroids	Unknown	Favourable
Prognosis	Unknown	Usually poor

After Wright, Immunology of Gastrointestinal and Liver Disease, Edward Arnold, 1977.

TREATMENT OF CHRONIC HEPATITIS

Treatment of chronic persistent hepatitis

As indicated earlier, in this condition the prognosis is good and progression to chronic aggressive hepatitis or cirrhosis is unlikely to occur, though it may be necessary to follow these patients with serial liver biopsy to be certain that adverse prognostic features are not developing. Corticosteroid drugs or azathioprine should therefore not be used, and there is no need to restrict diet or physical activity. Alcohol is best avoided, although there is little evidence that it prolongs the hepatitis.

Treatment of chronic active hepatitis

The prognosis in this condition if untreated is poor, particularly in the idiopathic variety, and in most series more than 50% of patients die within five years. Because of the florid inflammatory changes histologically, immunosuppressive drugs were used in

treatment soon after they were introduced. Following uncontrolled studies, prospective randomized controlled trials of prednisolone and placebo groups were advocated by the Copenhagen Study Group for Liver Disease (Lancet, 1969). In one such trial, Cook, Mulligan and Sherlock (1971) showed that there was a significant reduction in mortality in the prednisolone-treated group, compared with controls. Three patients of the 22 in the treated group died of liver failure, compared with 13 of 27 receiving placebo. Furthermore, the general health of the treated patients at the end of the study was better than that of the controls, and they had significantly higher serum albumin levels. In another prospective trial of 63 patients from the Mayo Clinic, prednisone 20 mg daily or a combination of 10 mg prednisone and 50 mg azathioprine was shown to be superior to 100 mg of azathioprine or a placebo. However, prednisone in doses of 15-20 mg daily was often associated with significant and sometimes serious side effects (Soloway, Summerskill et al, 1972). In a further trial, Summerskill, Korman et al (1975) titrated the dose of prednisone to produce biochemical resolution and administered it on alternate days and were able to reduce the incidence of side effects, but this regimen was not as effective as prednisone 10 mg daily and azathioprine 50 mg daily in producing histological resolution. Other forms of therapy that have been tried include D-penicillamine, but this, too, is associated with a high frequency of side effects (Stern, Wilkinson et al, 1977).

It must be emphasized that these trials are not strictly comparable, and the difficulties associated with conducting such trials, where one is dealing with conditions of multiple aetiology and varying severity, have been emphasized by the Copenhagen Study Group for Liver Disease (Lancet, 1969) and in two recent critical reviews (Lancet, 1978; Wright, Seeff et al, 1977).

It is our practice to start with 20-40 mg of prednisolone daily, reducing to a maintenance of 10 mg daily over four to six weeks, and combining the low dosage prednisolone regime with azathioprine. In view of the Mayo Clinic experience that 20% of patients may resolve spontaneously, it is important to reassess therapy frequently by serial liver biopsy done six months after the start of treatment and thereafter at one to two-yearly intervals.

Most of the trials discussed above contained few cases of HBsAg-positive chronic active hepatitis, and adequate controlled clinical trials of the effect of corticosteroids in the treatment of such patients are not available. In one report it was considered that prednisolone might have a favourable effect (Dudley, O'Shea et al, 1973), but in another it was suggested that immunosuppressives have an adverse effect (Aronoff, Gault et al, 1973), in a recent analysis of the Mayo Clinic controlled clinical trials, Schalm, Summerskill et al, (1976) considered that the HBsAg-positive cases did not respond adequately to treatment with conventional doses of prednisone, but the numbers they studied were small.

Other approaches to the treatment of HBsAg-positive chronic active hepatitis include the infusion of high titre specific immune anti-HBs globulin (Reed, Eddleston et al, 1973) and transfer factor (Jain, Thomas and Sherlock, 1977; Shulman, Schulkind and Ayoub, 1974; Tong Nystrom et al, 1976), but results have been disappointing.

The most promising current approach has been the use of interferon, either alone or in combination with anti-viral agents (Greenberg, Pollard et al, 1976; Desmyter, Ray et al, 1976; Kingham, Ganguly et al, 1978). This has resulted in modification of the markers of hepatitis B infection, but no convincing evidence of resolution of the inflammatory process in the liver. Supplies of interferon are at present extremely limited, but the possibility for synthesis or bulk production has improved, and there is also evidence that the combination of interferon with a chemical antiviral agent such as adenine arabinoside may prove more effective.

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