Gut, 1974, **15**, 581-597

Progress report

Chronic hepatitis

Chronic hepatitis is defined as a chronic inflammatory reaction in the liver as shown by liver function tests and histology and continuing without improvement for at least six months.[1] Morphologically, the two varieties of chronic persistent and chronic aggressive hepatitis (the latter better called active chronic hepatitis) can be described as 'chronic active liver disease'[2]. The aetiology of these conditions is only partly recognized. All may be associated with the presence of hepatitis B antigen in the serum and are then considered to represent sequelae of acute B virus hepatitis. The type A virus (or other agents) may also be responsible. Some are associated with marked disturbances in immunity and the term 'lupoid' is applied to this group.

Identical clinical, functional, and morphological features may be found associated with some drug reactions, for instance, to oxyphenisatin in laxatives, methyldopa, and isonicotinic acid hydrazide (INAH). Wilson's disease can also present as active chronic liver disease (101) as can alpha$_1$ antitrypsin deficiency (see fig).

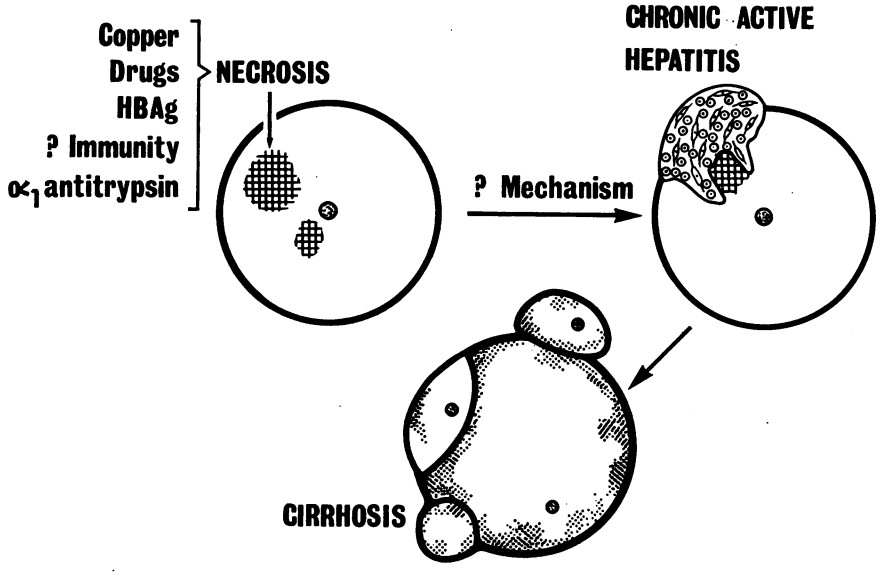

Fig *Aetiological factors concerned in active chronic liver disease.*

Chronic persistent hepatitis is characterized histologically by mainly portal inflammatory infiltration, preserved lobular architecture, and slight to absent fibrosis. Piecemeal hepatocellular necrosis is not conspicuous.

Chronic active hepatitis (formerly called aggressive hepatitis) is marked by

chronic inflammatory infiltration involving portal zones and extending into the parenchyma with piecemeal necrosis and formation of intralubular septa. Architecture is disturbed, theoretically there should be no nodular regeneration, but as this condition progresses to cirrhosis, some regeneration may sometimes be seen. Piecemeal necrosis and inflammation vary from moderate to severe. This progressive hepatitis is undoubtedly, in many instances, a precirrhotic one. The hepatocellular necrosis (piecemeal) is a key factor in initiating the active chronic hepatitis. This transcends zonal boundaries extending from one lobule to another and from portal zone to central zone, a feature which has been called bridging.

Hepatic cirrhosis, on the other hand, is an irreversible condition which is, in most instances, progressive. Nodular regeneration is constant and fibrosis is widespread. In general, cirrhosis can be regarded as a consequence of chronic active hepatitis.

This classification is based largely on morphological evidence, which is not always available; moreover, this evidence usually comes from small needle biopsies. These suffer a great deal from sampling error, particularly in patients with chronic hepatitis and cirrhosis. It is possible to show the appearances of a chronic persistent hepatitis in one part and in another a chronic active one. Interpretation of the morphological changes, particularly in relation to fibrosis and nodular regeneration, demands an expert pathologist, conversant with needle liver biopsy appearances. The distinction between chronic persistent and chronic active hepatitis is also difficult due to lack of uniformity of hepatic involvement. A falsely optimistic view may be taken if the biopsy is performed while the patient is receiving large doses of prednisolone.

Clinicians use the term active chronic hepatitis for the chronic aggressive hepatitis used by morphologists.

Chronic Persistent Hepatitis

Diagnosis is based on liver biopsy specimens[10]. If the biopsy is taken less than six months from the onset of acute symptoms, the changes are those of mild acute hepatitis. One to two years after the onset the changes are simply those of portal zone enlargement and infiltration with a variety of cells, mostly lymphocytes. Slender septa radiate from the portal zones in some instances, but the zonal architecture of the liver remains intact. Piecemeal necrosis of hepatocytes is virtually absent.

AETIOLOGY

Many pathological processes culminate in non-specific chronic inflammation of the portal zones.

The most usual association is with acute virus hepatitis. This may be of virus A or virus B type.[10,11] In one series of 20 patients, over half had an initiating attack clinically resembling an acute virus hepatitis and there was often a history of concurrent acute hepatitis among the patients' relatives.[10] Chronic persistent hepatitis may also be found as an association of chronic, longstanding ulcerative colitis. It is also possible that chronic persistent hepatitis is a complication of other longstanding chronic bowel disease, for instance, regional (granulomatous) ileitis (Crohn's disease) or infection with *E. histolytica* or salmonella. A chronic persistent hepatitis is seen accom-

panying infection with *Schistosoma mansoni* but here residua of ova are usually seen in the portal areas and these are diagnostic.

The alcoholic who has recently recovered from an attack of acute alcoholic hepatitis may show inflammation of the portal zone persisting for some months. Here centrizonal scarring is an important clue to the alcoholic aetiology.

CLINICAL ASPECTS

The patient may present following a mild or moderately severe hepatitis. He may be complaining of continuing fatigue, a poor appetite, intolerance to dietary fat and to alcohol, discomfort over the liver, and failure to regain the weight lost during the acute episode of hepatitis. The diagnosis may be made when serum transaminase values fail to return to normal after the acute attack or if tests of HB-Ag remain positive. Alternatively, the patient may complain of the same symptoms but without giving a history of an antecedent attack of acute virus hepatitis. Finally, the condition may present virtually without symptoms when abnormal biochemical tests of liver function are found incidentally, perhaps at a routine medical examination or perhaps when a patient visits a hospital in connexion with some other complaint. He may be diagnosed when a positive hepatitis B antigen test is found at the time of blood donation.

Physical examination may be completely normal or there may be slight hepatomegaly, the liver edge being tender. In particular, signs of chronic liver disease, such as vascular spiders, splenomegaly, or oedema of the ankles are not detected.

The serum bilirubin level is normal or slightly increased. Serum transaminase may be elevated. During the course of many years, the serum transaminase values may continue to fluctuate up to about four times the upper limit of normal. Serum alkaline phosphatase is usually normal.

Serum total globulin is usually within normal limits[10] and the serum immunoglobulin G (IgG) is but slightly increased. This is a point of distinction from the active forms of chronic hepatitis.

Positive HBAg tests imply an aetiological relationship with virus B (long-incubation) hepatitis.

Needle biopsy of the liver is an invaluable method of confirming the diagnosis and, particularly, of distinguishing the persistent from the more serious forms of chronic hepatitis. If there is any doubt in interpreting the first biopsy, it may be prudent to wait six months and perform a second one.

The condition must be distinguished from the 'post-hepatitis syndrome' which has similar symptoms but is not associated with organic liver disease.[12] The distinction is made largely on the hepatic histological appearances.

Active chronic hepatitis is distinguished by the physical signs of chronic liver disease and by the serum hyperglobulinaemia. Needle biopsy appearances are helpful.

The pericholangitis associated with ulcerative colitis or regional ileitis is distinguished by the association with chronic inflammatory bowel disease and by the serum biochemical changes, which usually include a raised serum alkaline phosphatase level. Liver histology shows that the portal zone inflammation is intimately related to small bile ducts in the liver.

Alcoholic liver disease is distinguished by the history of alcohol excess and by the physical stigmata of chronic alcoholism, including a large tender

liver. Histologically, the biopsy may show the features of alcoholic liver disease. However, if the patient has abstained from alcohol for some time acute appearances may have vanished and the picture can be indistinguishable from other forms of chronic persistent hepatitis.

Gilbert's syndrome is characterized by unconjugated hyperbilirubinaemia, the other tests of liver function, such as transaminase values, being normal, and hepatic histological appearances are completely normal.

TREATMENT

This is by reassurance after the fullest possible investigations which may have to include needle biopsy of the liver.

Corticosteroids or immunosuppressant treatment, such as with azothioprine, should not be given. No specific dietary regime is indicated. In particular, there is no scientific justification for a low-fat diet, avoiding eggs and butter. Additional vitamins and 'liver tonics' are not necessary. Activities should not be restricted.

Alcohol should be permitted within reason provided it is believed that excess is unlikely in that individual and that the persistent hepatitis has not followed alcohol excess.

PROGNOSIS

This is usually excellent. Twenty patients were followed for a mean period of 5·9 years (range 2-14 years)[10]. Sixteen are well and four were well when last seen. In no instance was there progression to cirrhosis. Nevertheless, there are occasional patients in whom serial hepatic biopsy show progression from a persistent to an active form of the disease.[13] Such exceptions may represent a sampling error in the interpretation of the first needle biopsy. Alternatively, it is conceivable that progression to a more severe form can occur although this is extremely rare.

The decision concerning the prognosis in those patients whose liver biopsies show mainly a persistent picture but also evidence of a mild aggressive hepatitis in one or two portal zones is very difficult indeed. Prognosis usually becomes easier when the clinical course has been followed for a few months and serial needle biopsies have been performed.

Active Chronic Hepatitis

The term 'active chronic hepatitis' or active chronic liver disease carries with it both a clinical and a pathological connotation. Clinically, it implies a chronic syndrome marked by progressive hepatocellular dysfunction, usually with jaundice and with the ultimate development of chronic liver disease. Pathologically, it is associated with the histological picture of a chronic active hepatitis. This combination can have more than one aetiology (see fig). The classical type is often called 'lupoid'. Another variety is associated with a positive hepatitis-B antigen test (HB-Ag) and is clearly posthepatitic. It can occasionally be seen with alcoholic liver disease and with hepatolenticular degeneration (Wilson's disease)[6]. Laxatives containing oxyphenisatin[3] may cause an active chronic hepatitis. Methyldopa can also cause it.[4] In neonates, virus infections, including rubella and cytomegala in addition to Australia antigen, can be related to an aggressive hepatitis. The

chronic liver disease associated with alpha$_1$ antitrypsin deficiency may be an active chronic hepatitis.[7,14]

Chronic Active Hepatitis (Lupoid Hepatitis)

This condition[15,16] has been described as chronic liver disease in young women[16,17], lupoid hepatitis,[18] plasma cell hepatitis,[19] active chronic hepatitis, active juvenile cirrhosis[20], and at the menopause as 'cirrhoses dysprotéiniques d'origine inconnue chez la femme'.[21]

The lesion throughout the liver is that of a chronic aggressive hepatitis. Activity is, however, variable from place to place and even in individual lobules. Near-normal areas within the liver can sometimes be encountered. This sampling difficulty makes assessment of activity and progress on the basis of needle specimens almost impossible. Cirrhosis develops rapidly. The chronic hepatitis and the cirrhosis seem to develop almost simultaneously and one cannot be regarded as a sequel to the other. Due to the difficulty in sampling it can never be certain whether or not cirrhosis can be excluded. In the majority of cases, when first diagnosed, there is indeed an irreversible cirrhosis present.

As time passes the activity subsides until, at necropsy in the longstanding case, the lesion appears that of an inactive cirrhosis. In most cases, however, a careful search will reveal areas of piecemeal necrosis and rosette formation remaining at the periphery of a nodule. Repeated episodes of necrosis with further stromal collapse and fibrosis lead to more severe cirrhosis. Eventually the liver becomes small and grossly cirrhotic.

AETIOLOGY AND PATHOGENESIS

There are considerable immunological changes. Serum globulin levels are grossly elevated. The finding of a positive LE cell phenomenon of some 12-15[20] led to the term 'lupoid hepatitis'[18]. Antinuclear factor is present in some half to one-third of patients[22,23].

About two-thirds of patients with active chronic hepatitis have a positive smooth muscle antibody test.[23,24,25] The mitochondrial (M) antibody, which is present in some 98 of patients with primary biliary cirrhosis[26], is found in 28% of patients with chronic hepatitis.

This disease was an obvious choice for an autoimmune disease since many non-specific antibodies had already been demonstrated in the serum of sufferers and a marked lymphocytic infiltration of the liver suggested the forbidden clones of autoimmunity. It was suggested that after viral or nutritional injury, liver cell components might become antigenic and so promote an autoimmune reaction that was responsible for the perpetuation of inflammation and progression to a macronodular cirrhosis.[18,27,28,29] Unfortunately, destruction of the liver cells as a response of this disturbance in humoral immunity has never been confirmed and this hypothesis remains unproven.

Immunization of animals with liver extracts has not given rise to a convincing form of hepatitis or to progression towards cirrhosis[79]. Many investigators have applied the complement-fixation reaction to studies of antibodies in liver disease and in no instance has there been evidence of an organ-specific liver antigen.[27,28,31,32,33] Destruction of liver cells as a response to an

autoimmune process and the possibility of autoaggression in liver disease now seem a little unlikely. Nevertheless, the demonstration of the various tissue antibodies, particularly mitochondrial and smooth muscle, have proved of considerable interest and led to useful procedures which are diagnostically valuable.

The histological changes in the liver are very similar to those in the rejecting hepatic transplant. There are lymphocyte accumulations, often in follicles, occasional granulomas and plasma cells, all features of the rejection reaction. Graft versus host ('runting') rejection reactions are believed to be mediated predominantly by destructive mononuclear cells (lymphocytes) hence disturbances of cell-based (delayed-type) hypersensitivity might be anticipated in active chronic hepatitis. It has been shown that peripheral lymphocytes from patients with chronic aggressive hepatitis could not be stimulated by phytohaemagglutinin in culture.[34] Patients with hepatitis of the alcoholic showed normal results. One of two patients with chronic active hepatitis gave a positive lymphocyte transformation reaction using as antigen their own liver tissue obtained by needle biopsy[35]. Depression of delayed type hypersensitivity was marked in 24 patients with active chronic hepatitis when tested by cutaneous methods and by transformation of blood lymphocytes with phytohaemagglutinin (PHA)[36]. The relationship of these changes to the stage of the disease and whether cause or effect and pathogenesis remain uncertain.

In about a quarter, the illness seems to begin with a typical attack of viral hepatitis. In others, however, the diagnosis of virus hepatitis remains presumptive. The likelihood is that acute virus hepatitis is one initiating factor in active chronic hepatitis. This type of active chronic hepatitis is unlikely to be related to long-incubation hepatitis with a positive Australia antigen test. Tests for this antigen have been consistently negative in the 'lupoid' type of active chronic hepatitis.[37,38,39] There could be a relationship with the short-incubation (infectious, virus A) type of acute hepatitis but, so far, as there are no satisfactory antigenic markers for this type of hepatitis, such a view is purely hypothetical.

A genetic predisposition is recognized in such 'autoimmune' conditions as pernicious anaemia, thyroiditis, and Addison's disease. A familial association has been found between 'lupoid' hepatitis and familial hypergammaglobulinaemia[40]. In another kindred, five members have chronic liver disease clinically resembling active chronic hepatitis while eight others have abnormal immunological results[41]. A dominant mode of inheritance, possibly at the level of immunoglobulin control, was suggested. Mitochondrial and other tissue antibodies have been found in the relatives of patients with primary biliary cirrhosis[42]. In another study, an increased prevalence of antinuclear factor and rheumatoid factor in the siblings of probands with cirrhosis was noted[43]. A further study of 33 patients with active chronic hepatitis showed that tissue antibodies—mitochondrial, antinuclear, and smooth muscle—were more often found in relatives than in their controls matched for age and sex.[44] Another genetic correlation is with the HL-A1 and HL-A8 tissue type groups in patients with active chronic hepatitis.[45] HL-A8 is also found with increased frequency in systemic lupus erythematosus. The nature of the precipitation of clinical disease in a genetically susceptible group remains uncertain.

CLINICAL FEATURES

The condition is predominantly one of young people, especially women. Of 139 patients, 48% were between 10 and 29 years of age and 70% were female[16]. Nevertheless, the conditions can occur in childhood, the youngest patients being 6 years old, and also on into later life, the oldest being 75 years.

The onset is usually insidious, the patient feeling generally off colour and is then noticed to be jaundiced. In about a quarter, the disease seems to present as a typical attack of acute viral hepatitis[15]. It is only when the jaundice persists despite adequate treatment that the physician is alerted to the possibility of more chronic liver disorder. Whether the disease does in fact commence as genuine viral hepatitis or presents with intercurrent infection in a patient who is already suffering from active chronic hepatitis remains uncertain.

In most instances, the hepatic lesion on presentation does not agree with the stated duration of symptoms. It is likely that active chronic hepatitis remains asymptomatic for some months or possibly years before the diagnosis is made, usually by the appearance of jaundice. Patients may be recognized sooner if a routine medical examination reveals the stigmata of liver disease or if, for some reason or another, biochemical tests of liver function are performed and found to be abnormal.

Although the serum bilirubin level is usually increased, the patient may be subicteric: 20% have an anicteric illness.[69] Frank jaundice is often episodic.

Amenorrhoea is usual and a return of the menses is a good sign. If a period does occur, it may be associated with increase of symptoms and deepening of jaundice. Epistaxis, bleeding gums, and bruising with minimal trauma are other complaints.

Examination shows a tall, healthy looking girl, often above normal stature[16]. Spider naevi are virtually constant. They tend to be small and to come and go with changes in the activity of the disease. Livid cutaneous striae may be found on thighs and abdominal wall, also in severe cases, on upper arms, breasts, and back. The face may be rounded even before the administration of corticosteroids. Acne is prominent and hirsuties may be seen.

Abdominal examination in the early stages shows a firm liver edge some 4 cm below the right costal margin. The left lobe may be disproportionally enlarged. In the later stages, the liver shrinks and becomes impalpable. Percussion confirms the decreased size. The spleen is universally enlarged. Ascites, oedema, and hepatic encephalopathy are late features. Recurrent episodes of active liver disease punctuate the course. Occasionally, the picture is frankly cholestatic, emphasizing the overlap between active chronic hepatitis and primary biliary cirrhosis[46].

ASSOCIATED CONDITIONS

The more careful the search the more likely is involvement in some system other than the liver to be detected. It is, of course, unsure how many of these are actually related to the active chronic hepatitis and how many are coincidental.

In those particularly ill, usually with a positive LE cell phenomenon, there may be sustained pyrexia.[20,47] Such patients may also have an acute, recurrent, non-deforming migrating polyarthritis of large joints.[48]

A specific skin lesion is a chronic eruption on trunks and limbs characterized by active inflammatory papules with central crusting and lesions in the form of depressed scars.[49] Urticaria is also described.[50] More non-specific are acne, erythematous lesions, lupus erythematosus, papules, and splinter haemorrhages[20]. There may be generalized lymphadenopathy[50].

The kidney may be involved in many ways and the relevant literature has been reviewed.[51] Renal changes may be present even if albuminuria is absent and the urinary deposits and creatinine clearance are normal.[52] Occasionally, lupus nephritis is severe and progressive and in one patient with a positive LE cell test this resulted in death in renal and hepatic failure[51].

Renal tubular acidosis in association with active chronic hepatitis has been described.[51,53,54,55]

Pulmonary changes, including pleurisy and transitory pulmonary infiltrate and collapse, are found when the disease is active.[20] The mottled chest radiograph is of particular interest[56] and may be related to dilated precapillary blood vessels[57]. The high cardiac output of chronic liver disease would add to the pulmonary vascular plethora[58]. Multiple pulmonary arteriovenous anastomoses are also found in association with active chronic hepatitis. Fibrosing alveolitis is another possibility[59]. Primary pulmonary hypertension is described in one patient[60].

Endocrine changes include the Cushing syndrome. Boys may develop gynaecomastia. Amenorrhoea is virtually constant. Hashimoto's thyroiditis may be seen[20] and other thyroid abnormalities include myxoedema and thyrotoxicosis. Five of 81 patients developed diabetes mellitus, three before and two after the diagnosis of chronic hepatitis.[20]

A positive Coombs' test with haemolytic anaemia is another rare complication and has been found with eosinophilia. Autoimmune neutropenia with a serum immunoglobulin G antibody has been demonstrated in one girl with active chronic hepatitis.[61]

Ulcerative colitis tends to present with the active chronic hepatitis or to follow it.[62] It tends to develop once colitis has remitted.

The sicca complex is perhaps more frequent with primary biliary cirrhosis than active chronic hepatitis.[54,63]

LABORATORY TESTS

Serum bilirubin levels are very variable usually between 2 and 10 mg/100 ml. Serum transaminases are markedly increased usually to at least ten times normal.

Serum albumin values, although in the lower range of normal, are relatively well maintained until late in the course of the disease.

Total serum globulin levels are markedly increased. Electrophoresis of the serum proteins shows that the great increase in gamma globulin is related to a polyclonal response. Rarely a monoclonal picture may be seen.[64] Serum immunoglobulin G (IgG) is particularly elevated in active chronic hepatitis but high values for serum IgA are also found[65].

Hepatitis B antigen is not found in the blood of patients with a classic active chronic 'lupoid' hepatitis.[37,38,39]

Thrombocytopenia and leucopenia are frequent even before the late stage of portal hypertension and a very large spleen. Prothrombin time is often prolonged even in the early stages when hepatocellular function seems preserved.

Needle biopsy of the liver is a very valuable diagnostic tool but may prove impossible to perform because of the blood clotting defect which is uncorrected by intramuscular vitamin K_1. If the biopsy is possible, the classical active chronic hepatitis is seen. There may, however, be problems arising from the small size of the biopsy sample.

TREATMENT

Prospective randomized clinical trials of corticosteroid treatment are difficult to set up and carry through, and results may not be meaningful for many months or indeed years. A controlled clinical trial of prednisolone in active chronic hepatitis was carried out at the Royal Free Hospital[66,67]. After six years, analysis of the results for the prednisolone-treated patients showed that only three of 22 died whereas 17 of the 27 control patients succumbed ($P < 0{\cdot}01$). Cure of the disease or prevention of the cirrhosis was not suggested but early deaths, particularly in the first two years, were fewer. The results so greatly favoured prednisolone therapy that it became unjustifiable to continue the trial.

Prednisolone had a marked effect on parameters which are apparently specific measures of hepatocellular function. In particular, the storage capacity for bromsulphthalein was significantly better in the treated than in the control group, although the transport maximum was unchanged[67]. Serum albumin concentration rose so that in one year it reached normal values whereas in the untreated the results were significantly lower. At three to five years, the difference had disappeared and the serum albumin concentration in both the treated and control subjects was equal. Results have been reported from the Mayo Clinic[68] of a well planned, double-blind trial of prednisolone therapy in chronic active liver disease. Patients were selected if the illness was of more than 10 weeks' duration, if liver biopsy had been performed, and if there was a persistent 10-fold increase in serum glutamic oxaloacetic transaminase or a five-fold elevation with a two-fold increase in gammaglobulin. There were 18 patients in the group given prednisone (20-30 mg daily) and 17 in the group receiving placebo therapy. Subjective improvement was the same in both groups. Prednisone showed significant advantages ($P < 0{\cdot}0{\cdot}5$) decreasing serum bilirubin, SGOT, and gamma globulin levels, and piecemeal necrosis. The initial dose should rarely exceed 30 mg prednisolone for the first week or two. Maintenance therapy is 10-15 mg daily. Twenty per cent fail to respond, deteriorate, develop hepatocellular failure, and die.[68] In such patients, a trial of higher doses of prednisolone (50-60 mg daily) is worth considering. Attempts are made to withdraw a therapy when serum bilirubin, transaminase, and if possible gamma globulin levels are normal. Relapses follow discontinuation of treatment in 50% usually within six months of stopping and necessitate reinstitution of the drug[68].

Azothioprine is an alternative method of treatment. In a clinical trial Mackay[69] found that azathioprine, 100-200 mg daily depending on the neutrophil leucocyte count, was as effective as prednisone in improving biochemical tests and maintaining quiescence. There was no significant improvement in any index after the initial zero to three-month period. The suppressive treatment served to maintain the initial improvement in liver function. In another study Mistilis and Blackburn[48] gave 6-mercaptopurine or azathioprine to 17 patients with active chronic hepatitis; in eight toxic reactions included anorexia, jaundice, coma, thrombocytopenia, and leu-

copenia. They seem to be related to both the dose and the severity of the underlying liver disease. One hundred mg appeared to be excessive for many patients with chronic hepatitis. In a small dose, 13 patients were treated for up to four and a half years with complete freedom from toxicity. 6-Mercaptopurine was given to 23 patients with active chronic hepatitis in the paediatric age range, and the results were compared with a previously published untreated series of patients.[70] A good therapeutic response was associated with positivity for four parameters, namely, onset of disease consistent with an attack of acute infective hepatitis, symptoms of disease in other systems, high serum levels of gamma globulin, and suspicious or positive lupus erythematosus cell tests. In the Mayo Clinic trial[68] one group of 14 patients was given azathioprine in a dose of 100 mg daily. On the whole, this group did not do as well as those receiving prednisone therapy. More patients developed jaundice and ascites and more died. Toxicity necessitated withdrawal of the drug in some patients. Azathioprine should be reserved for those in whom complications follow prednisolone therapy, when a coincidental condition such as diabetes precludes its use or when control is not achieved with prednisolone alone. Another controlled prospective trial has confirmed the benefit from prednisone[72].

Prednisolone usually requires to be used for at least six months. Relapses necessitate further treatment. These usually develop within three months of discontinuing treatment. A few more patients relapse later but rarely after a full clinical and biochemical remission lasting six months. Complications of long-term treatment include mooning of the face and obesity, and are particularly unwanted by young female patients. More serious complications include growth retardation, which is, however, unusual, unless the patient is less than 10 years old, diabetes, bone thinning, and serious infections. Alternate-day treatment may be used in children. Complications are not usually a problem if the maintenance dose of prednisolone is not more than 15 mg daily. If the dose has to be exceeded or serious complications have arisen, consideration must be given to alternative measures. In 14 patients a combination of 50 mg azathioprine with 10 mg prednisone has given equally good results to 20 mg prednisone.[68] This is surprising as azathioprine alone was ineffective. It may be related to prednisolone improving liver cell function so much that the conversion of azathioprine by the liver to its active components[72] is possible.

Prednisone has to be converted to prednisolone in the liver before it is active.[73,74] This may account for the observation that in the Royal Free Hospital study 10-15 mg prednisolone was adequate maintenance, whereas the Mayo Clinic patients required prednisone in a dose of 20 mg daily.

The later picture of cirrhosis is managed along the usual lines.[75] Portal hypertension with bleeding oesophageal varices may raise the question of portacaval anastomoses. The incidence of hepatic encephalopathy after portacaval anastomosis is greater in patients with cirrhosis following active chronic hepatitis than in other forms of chronic liver disease.[76] This may be related to continuing disease activity; portal hypertension is relieved but the hepatocellular necrosis continues.

COURSE AND PROGNOSIS

This is extremely variable. The course is a fluctuant one marked by episodes of deterioriation when jaundice and malaise are enhanced. The ultimate

effect of this continuing aggressive hepatitis is inevitably cirrhosis with very few exceptions. Serial needle biopsies show a progression towards this irreversible lesion. In one series the mean date from diagnosis to death was three and a half years.[20] In another it was stated that two-thirds die within five years of the onset of symptoms[15]. Mortality is undoubtedly greatest during the first two years when the disease is most active.

There are, however, plenty of examples of where the disease has burnt out and patients have survived 10 to 20 years. The question of inevitability of cirrhosis is under discussion. Certainly most patients end with cirrhosis, a lesion which is irreversible. The alternative view is that with adequate corticosteroid treatment a return to totally normal hepatic histology can take place[2]. This opinion may be based on results in patients studied very soon after an acute attack of acute hepatitis without the chronicity and duration of liver disease, and often already established cirrhosis, frequently associated with chronic active hepatitis. Corticosteroid therapy prolongs life but most patients eventually develop hepatocellular failure with or without the complications of portal hypertension. These are the causes of death in most instances.

Relationship between Active Chronic Hepatitis, Primary Biliary Cirrhosis, and Cryptogenic Cirrhosis

The regular and consistent demonstration in high titre of antibody tests such as antinuclear fluorescence (ANF), smooth muscle (SMA), and anti-mitochondrial (M) antibodies are virtually confined to three liver diseases—active chronic hepatitis, primary biliary cirrhosis, and cryptogenic cirrhosis—particularly in women[31]. Results are negative in such conditions as alcoholic liver disease, Wilson's disease, sclerosing cholangitis, and biliary atresia, even though the extent of hepatocellular or biliary damage may be as great. This suggests that the increases do not simply represent antibodies developing as a response to constituents of damaged liver cells or bile ducts.

There is considerable overlap between the hepatic histology of active chronic hepatitis and primary biliary cirrhosis. Both show marked mononuclear cell infiltration with accumulation into lymphoid follicles, but piecemeal necrosis is more conspicuous in active chronic hepatitis, whereas bile duct injury is more characteristic of primary biliary cirrhosis. However, I have under my care a young woman with chronic liver disease in whom multiple liver biopsy specimens show the classic features of active chronic hepatitis in one part and of primary biliary cirrhosis in another. In such patients the accompanying clinical picture is that of active chronic hepatitis and not primary biliary cirrhosis. The serum immunoglobulin patterns in active chronic and cryptogenic cirrhosis are very similar.

In many patients with chronic active hepatitis, cirrhosis ultimately develops. It is possible that cryptogenic cirrhosis may be the late stage of a subclinical active chronic hepatitis. The subclinical hepatitis with positive M test described in some patients with collagenoses[77] might represent an early stage of active chronic hepatitis or primary biliary cirrhosis may progress towards damage to hepatocytes or to bile ductules.

Hepatitis B Antigen (HB-Ag)-Associated Chronic Active Hepatitis

In general, HB-Ag-associated chronic active liver disease resembles the 'lupoid' type very closely and the description of 'lupoid' hepatitis already given can be applied to the HB-Ag-positive type. Indeed, accounts of active chronic liver disease often include patients who have a positive HB-Ag test.[68] In an individual patient, apart from the positive test for HB-Ag, there may be no clinical, biochemical, serological, or hepatic-histological differences. In such patients, this might be related to a fortuitous positive HB-Ag test in a patient with active chronic hepatitis of 'lupoid' type. Alternatively, the 'lupoid' type could also be related to virus hepatitis, perhaps to type A for which no antigenic marker is available or perhaps type B, the antigen test being negative. Such considerations remain hypothetical.

The incidence of antigen-positive active chronic hepatitis is high in areas where there is a high percentage of the population carrying the antigen. In 40 such patients seen in the United Kingdom, only four in fact came from that country. Three came from the United States, four from South America, six from Africa, four from Italy, one from Belgium, one from Turkey and 17 from Greece[78]. This is in keeping with previous studies from Yale[79], where positive tests were found in 25 patients with active chronic hepatitis, and from the United States where the Mayo Clinic reported that the antigen was positive in three of 31 patients with chronic active liver disease[2]. In Melbourne, only two of 56 patients with active chronic hepatitis gave positive tests for HB-Ag[39]. Australia probably has a low incidence of HB-Ag antigen in the population whereas in urban areas of the United States and in certain parts of Africa it is up to 10% and in Greece about 5%. These differences make it difficult to distinguish between the two groups in an area where there is a high incidence of a positive HB-Ag test in the general population. There are, however, certain differences both clinical and immunological that make it probable that the 'lupoid' and the HB-Ag positive types of active chronic liver disease represent different conditions.

HEPATIC PATHOLOGY

The general picture is of active chronic liver disease (aggressive hepatitis). The histological picture may be completely indistinguishable from that of the 'lupoid' type. The only hint may come from histological evidences of old hepatitis. This is manifest by centrizonal hepatocellular dropout, variation in cell size, and by cell infiltration and the presence of acidophil bodies. The presence of ground-glass-appearing hepatocytes, 'induction cells', in haematoxylin-eosin-stained sections is suggestive[80]. Immunofluorescence studies confirm that these cells contain HB-Ag.

PATHOGENESIS

The development of chronicity seems unrelated to the dose of antigen or to its subtype[81]. Virulence is clearly important, but has been little investigated. The progression to chronicity may also be related to genetic factors. It seems more likely that progression to chronic hepatitis depends on the immunological status of the patient. The liver injury could be related mainly to disturbances of humoral immunity. Antibody to HB-Ag forms complexes which, in the presence of complement, lead to lysis and cell death. Immune complexes involving IgG, HB-Ag, and complement have been demonstrated

in the tissues of patients with chronic HB-Ag disease[82]. However, the presence of complexes correlates poorly with the degree of liver damage and this seems an unlikely mechanism. It is more probable that disturbances of cell-mediated immunity are predominantly involved. The immune response, especially the cell-mediated one, is important in determining the clinical manifestations and course of viral infections. This depends largely on T-lymphocyte function. In patients with HB-Ag-positive chronic liver disease, this is probably defective.[83,84,85,86] This view is compatible with the observation that patients with renal failure or having immunosuppressive therapy when exposed to HB-Ag often develop chronic hepatitis. Similarly, neonates who are known to have impaired cellular immunity, are liable to develop chronic HB antigenaemia and cirrhosis when exposed to HB-Ag from their mothers[87]. Finally, corticosteroids inhibit the cellular immune response and the administration of these drugs during the acute stage of type B hepatitis does seem to favour the progression to chronic disease[83].

CLINICAL FEATURES AND ASSOCIATIONS[88,89]

Males are much more often affected than females and are often diagnosed when more than 30 years old. The disease is frequent in hospital and medical and dental staff generally, perhaps because of exposure to HB-Ag or frequent testing of their blood.

The condition may be recognized when an episode of acute virus hepatitis fails to resolve and transaminase and other biochemical tests remain elevated or fluctuate. There may be intermittent jaundice. The patient may be symptom-free with only biochemical evidence of continued activity. In about one half, presentation is as established chronic liver disease, which cannot be related to a previous acute attack of hepatitis. Some present as primary liver-cell carcinoma. Jaundice is unusual in the cases presenting later. Splenomegaly and signs of chronic liver disease such as vascular spiders are less evident than in the 'lupoid' variety. Episodes of jaundice with fever and arthralgias are also rare.

Associated lesions such as acne, striae, diabetes, ulcerative colitis, and thyroiditis are unusual.

Elevations of total serum bilirubin, gamma globulin, and transaminase levels are less marked than in the classical 'lupoid' type. In the cases presenting later, evidences of hepatocellular disease may be very mild.

Serum smooth muscle antibody, if present, is in low titre[86]. Serum mitochondrial antibodies are negative. Lupus erythematosus cells are very rarely found.

TREATMENT

Prednisolone therapy may be of value in the established chronic disease, perhaps by reducing the injurious effects of sensitized T-lymphocyte function and hence the extent of hepatic necrosis. The benefit in this type, however, has not been confirmed by large prospective controlled trials. The Mayo Clinic investigation[68] using prednisone, did include HB-Ag-positive patients and benefit was shown in this group. Prednisolone should probably be used where there is histological evidence of continuing active hepatocellular necrosis. A biochemical remission in the serum is certainly induced. The dose should be sufficient to suppress the activity of the liver cell damage (usually 10-20 mg prednisolone daily). Therapy should be continued for six months

after liver function tests have returned to normal. Slow withdrawal of prednisolone should then be attempted, the physician maintaining close observation for signs of relapse. This recommendation is based on limited experience[89]. The final therapeutic role of corticosteroids and immunosuppressant drugs generally in these patients must await both further research, prolonged follow up, and prospective controlled trials.

PROGNOSIS

Progression is both slow and insidious. Thirty-three patients were studied for an average of two years and there was no clinical or biochemical deterioration in any of them[89]. Progression was slow and this was in marked contrast to HB-Ag-negative chronic active hepatitis where there is a high early mortality. Those with chronic active liver disease (chronic aggressive hepatitis) may progress to cirrhosis after which the aggressive features may not be obvious. In most instances, the cirrhosis was probably present from the outset. A long-term risk is the development of primary liver cell carcinoma and the patient may present with this complication.

Other Types of Active Chronic Liver Disease

WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

This may present as an active chronic hepatitis[6]. A family history is important. Clinical and biochemical features may be very similar to those of lupoid active chronic hepatitis and hepatic biopsy difficult to distinguish. This emphasizes the need to examine the cornea with a slit lamp for Kayser-Fleischer rings and to estimate serum copper and caeruloplasmin levels in all patients less than 30 years old with active chronic hepatitis. If necessary the copper content of the liver biopsy may be measured.

OXYPHENISATIN REACTIONS

Chronic administration of laxative preparations containing oxyphenisatin may cause a picture very similar to classical lupoid active chronic hepatitis.[3] The patient has usually taken the drug for at least two years. The biochemical features and hepatic histological appearances are similar. A positive LE cell test and antinuclear smooth muscle antibodies have been seen.

METHYLDOPA

The reaction is a hepatic one usually developing within the first three months of starting treatment. The patient usually promptly recovers on stopping the drug[4]. However, there have been fatalities from acute hepatic necrosis[92] and active chronic hepatitis has developed[91].

ISONIAZID

The introduction of antituberculous chemotherapy (INH) for those having positive tuberculin skin tests allowed identification of the hepatic reaction[5]. The picture is usually that of an acute hepatitis, but 'bridging' necrosis and even cirrhosis have developed.

ALPHA$_1$-ANTITRYPSIN DEFICIENCY

This inherited deficiency alpha$_1$-antitrypsin is associated with progressive hepatic damage at all ages which may lead to cirrhosis.[7,93] In adults there

is usually associated emphysema. Inheritance is codominant and hepatic disease appears with the PIZ type. Liver biopsies show clumped pink material in the hepatocyte.

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