Liver biopsy in chronic hepatitis: 1968-78

P. J. SCHEUER

From the Department of Histopathology, Royal Free Hospital, London

SUMMARY The classification of chronic hepatitis introduced in 1968 is still current, but has been modified. The concept of bridging hepatic necrosis has been incorporated, and is recognised as an important feature of both acute and chronic aggressive (active) hepatitis (CAH). In the pathogenesis of the latter, piecemeal necrosis is, however, thought to be the more important factor. The histological picture of CAH varies widely. Several causes of CAH have been identified, including hepatitis B virus. Recognition of surface and core components of the virus in tissue sections has facilitated study of the relationship between host response and pathological lesion in chronic hepatitis. CAH and primary biliary cirrhosis share histological features, and a mixed form has been postulated. Staining for copper sometimes helps to distinguish the two lesions. A third histological category, chronic lobular hepatitis, comprises patients with histological lesions like those of acute hepatitis, but with a chronic or recurrent course.

Ten years ago De Groote *et al.* (1968) emphasised the need to subdivide chronic hepatitis, according to histological criteria, into categories with differing prognosis. The more benign form, chronic persistent hepatitis (CPH), was characterised by inflammation largely confined to portal tracts, with or without superimposed features of acute hepatitis in the lobules. The essentially benign nature of the lesion has since been confirmed (Becker *et al.*, 1970; Chadwick *et al.*, 1977), although progression to more serious liver disease is recorded (Vido *et al.*, 1969). The other category in the classification of 1968, chronic aggressive hepatitis (CAH), was defined by the presence of piecemeal necrosis, a process of liver-cell destruction at the interface between parenchyma and connective tissue. This category corresponded approximately but not in every respect to the clinical diagnosis of chronic active hepatitis, a term now preferred by many authors for both histological and clinical description. Cirrhosis develops in a variable and often high proportion of patients with CAH (Dietrichson and Christoffersen, 1977).

This classification of chronic hepatitis, though not universally accepted, is still widely used and 10 years after its publication liver biopsy continues to play a major part in the diagnosis and management of patients with chronic hepatitis. The purpose of the present paper is to review the changes which have taken place since 1968 in the nomenclature and classification of chronic hepatitis, in the techniques

which can be applied to biopsy tissue, and in the understanding of biopsy findings.

Aetiology of CAH

In 1968 the aetiology of CAH was largely a matter for speculation, although a relationship between some instances of CAH and viral hepatitis was assumed. The hepatitis B surface antigen (HBsAg) had been discovered a few years previously (Blumberg *et al.*, 1965), and proved to be present in a variable proportion of patients with CAH (Dudley *et al.*, 1972). Techniques became available for demonstrating HBsAg by empirical and specific immunological methods in liver tissue: by means of these and electron microscopy, surface components of the virus could be identified in the cytoplasm of some liver cells (Gerber *et al.*, 1974; Shikata *et al.*, 1974; Ray and Desmet, 1975; Burns, 1975). The virus core antigen (HBcAg) can be identified by electron microscopy and by immunological methods, mainly in liver-cell nuclei. The relationship between HBcAg and HBsAg in the various forms of chronic hepatitis has been studied by Gudat *et al.* (1975) and Ray *et al.* (1976). Gudat and coworkers postulate that four main patterns of distribution of the virus components reflect different immunological responses of the patients to the virus infection. The normal response is elimination of the virus, and a short self-limiting attack of acute hepatitis. In a minority of patients virus continues to multiply

in the liver. Either surface or core antigens may predominate, the latter typically in the patient on immunosuppressive drugs. Presence of both components in approximately equal amounts (the equivalence pattern) is characteristic of the more severe forms of chronic liver disease. Since the immunological patterns do not correspond exactly to the histological categories of chronic hepatitis, demonstration of virus components in liver biopsies may provide useful prognostic information, not obtainable by conventional light microscopy alone.

It has not proved possible so far to distinguish other aetiological types of chronic active hepatitis histologically with any degree of certainty. In addition to type B hepatitis, other causes to be considered include an immunological reaction, possibly directed against liver-cell-membrane components ('lupoid hepatitis'), drugs such as alpha-methyldopa, isoniazid and oxyphenisatin (Goldstein *et al.*, 1973), and Wilson's disease (Sternlieb and Scheinberg, 1972). More recently, it has been pointed out that patients with chronic hepatitis may give a history of excess drinking, and alcohol is now considered as one of the many agents that are capable of triggering the immunological reaction visualised in liver biopsy specimens as CAH (Goldberg *et al.*, 1977).

Relationship of CAH and bridging hepatic necrosis

Soon after 1968, Boyer and Klatskin (1970) pointed out that in a group of patients with viral hepatitis the presence of necrosis linking the various vascular structures of the hepatic lobule carried a poor prognosis. Patients with bridging hepatic necrosis were much more likely to die of liver failure within months of the onset of the hepatitis than were those with the classical lesion of viral hepatitis, characterised by spotty necrosis. Patients with bridging also developed chronic liver disease more often. The bridges linked adjacent centrilobular veins, adjacent portal tracts, or both. Peters (1975) has argued that the poor prognosis of patients with bridging necrosis may reflect their greater age and hence the impaired regenerative capacity of their livers, but, whatever the underlying mechanism of the worse prognosis, there is no doubt that confluent bridging necrosis may be found in the livers of patients with CAH, and that it modifies the histological picture.

The term bridging necrosis has been used for different kinds of bridges, and it is necessary to clarify the part played by each kind. Bianchi *et al.* (1977) consider that bridges linking centrilobular veins to each other or to portal tracts are qualitatively

different from those joining portal tracts. They postulate that the first two are examples of confluent necrosis, whereas the last represents a form of piecemeal necrosis. Bridges linking centrilobular veins to each other probably play little part in the pathogenesis of CAH. In the remainder of this review, the term bridging hepatic necrosis (BHN) will be restricted to bridges of confluent necrosis linking centrilobular and portal structures. Their location is difficult to explain on the basis of the lobular concept of hepatic structure, and they are thought to represent confluent necrosis at the periphery of Rappaport's simple acinus; bridging between adjacent efferent (centrilobular) veins is postulated to occur as a result of similar necrosis at the periphery of complex acini (Rappaport, 1976).

Bianchi *et al.* (1977) favour the view that BHN is not by itself an important prognostic or pathogenetic feature in the development of chronic liver disease, and that uncomplicated BHN normally undergoes healing with partial or complete resolution. This is supported by the observation of Karvountzis *et al.* (1974) that the livers of some patients with massive hepatic necrosis who survive the acute attack return to normal. In drug-induced hepatic necrosis, which may include BHN, healing is the rule (Portmann *et al.*, 1975). Piecemeal necrosis, including the form seen as portal-to-portal bridging, is thought to be the more important pathogenetic factor and can be recognised early in the course of acute viral hepatitis. The ensuing lesion of chronic active hepatitis varies greatly in severity and in the extent to which lobular structure is altered. It is assumed that the presence of BHN leads to more rapid progression to cirrhosis, by altering the hepatic architecture and forming intrahepatic portal-systemic shunts, and possibly by facilitating immunological reactions deep within the lobules.

CAH and primary biliary cirrhosis

Piecemeal necrosis, mononuclear-cell infiltration, and fibrosis are common to CAH and primary biliary cirrhosis (PBC), and both may end in cirrhosis. There is therefore overlap in the histological features of the two diseases, occasionally leading to difficulty in distinguishing them on liver biopsy. This difficulty is compounded by the fact that not all patients with PBC have antimitochondrial antibodies in the serum, and in a minority the typical clinical features of PBC, such as pruritus, are absent (Sherlock and Scheuer, 1973). Usually, attention to histological details enables the correct diagnosis to be made even in the absence of clear-cut clinical, biochemical and immunological data. Helpful features suggesting PBC include bile duct damage,

granuloma formation, partial preservation of lobular or acinar structure, irregularly distributed fibrosis, paucity of bile ducts, proliferation of ductules, and focal accumulations of lymphocytes. These mark the sites of destroyed bile ducts. Staining for copper may also be helpful. Copper is largely excreted in the bile, and in diseases with chronic cholestasis such as PBC large amounts of copper accumulate in the liver (Hunt *et al.*, 1963; Fleming *et al.*, 1974). A copper-associated protein can be demonstrated in liver cells in such patients by means of staining with orcein (Salaspuro and Sipponen, 1976). Jain *et al.* (1977) have found good correlation between liver copper levels as estimated by neutron activation, and staining for copper or copper-associated protein. Intense staining appears to favour a diagnosis of PBC over CAH.

The existence of a third category, with features of both PBC and CAH, has recently been supported by a study of antibodies against different mitochondrial fractions (Klöppel *et al.*, 1977). Liver biopsies of patients with antimitochondrial antibodies unlike those of classical PBC commonly showed very active hepatocellular damage and intense ductular proliferation.

A third category of chronic hepatitis

An international group sponsored by the John E. Fogarty International Center and the International Association for the Study of the Liver (US Government Printing Office, 1976) has defined chronic hepatitis as 'inflammation of the liver continuing without improvement for at least six months'. There are patients, who according to these criteria have chronic hepatitis, whose liver biopsy appearances are not those of CPH or CAH. Liver-cell necrosis and degeneration, Kupffer-cell proliferation, and inflammatory-cell infiltration are seen in the lobules as in acute viral hepatitis, but portal and periportal inflammation are inconspicuous. Popper and Schaffner (1971) designated this lesion chronic lobular hepatitis (CLH), a term which corresponds to the other categories of chronic hepatitis. Prolonged or protracted hepatitis is used in a similar way. Ishak (1973) and Peters (1975) refer to persistent viral hepatitis and unresolved viral hepatitis, using these terms to include both portal and intra-lobular changes. Their categories are thus an amalgam of CPH and CLH. CLH without substantial portal inflammation appears to be relatively rare, and is sometimes marked by a distinctive clinical picture of repeated episodes resembling acute hepatitis but responding to corticosteroids (Wilkinson *et al.*, 1977). Theoretically, CLH is of considerable interest, as it presumably represents

an immunological response to hepatitis virus infection that is different from the one responsible for CAH. The long-term outlook for patients with CLH appears to be good, but more studies are needed to confirm or refute this impression.

Liver biopsy and clinical course of chronic hepatitis

Finally, it is necessary to reassess the current histological classification of chronic hepatitis in the light of 10 years' use. The need to recognise bridging hepatic necrosis and to incorporate it into the concept of CAH has already been discussed. The presence of bridging necrosis between portal tracts and efferent veins, as well as the extent of piecemeal necrosis and the associated mononuclear-cell infiltration, determine the character and severity of the disease. CAH may thus vary from a minimal lesion, distinguishable with difficulty from CPH, to one with complete disruption of hepatic architecture, widespread necrosis and inflammation, formation of liver-cell rosettes and nodular regeneration. Between these two extremes are examples of CAH of moderate severity, without cirrhosis, and therefore at least potentially reversible. All three varieties fulfil the criteria of CAH as proposed by De Groote *et al.* (1968) and modified by Bianchi *et al.* (1977). Their effect on the patient, their prognosis, and the need for active treatment, however, differ. It is therefore suggested that there are significant subcategories within the histological spectrum of CAH, ranging from a minimal lesion more akin to CPH to an active cirrhosis. This heterogeneity of CAH should be kept in mind when therapeutic and other studies of CAH are assessed.

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