THE HISTOPATHOLOGY OF VIRAL HEPATITIS AND ITS SEQUELAE

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The many viruses which cause hepatitis in man have already been enumerated (chap. 1). In the ensuing account the morphological features of viral hepatitis and its sequelae (table) are briefly reviewed; for more detailed descriptions and illustrations the interested reader is referred to the reviews by Bianchi *et al.*, 1971, 1977 and 1979; De Groote *et al.*, 1968; Desmet and De Groote, 1974; Ishak, 1976; MacSween, 1980. The mutual interactions between pregnancy and the described hepatic lesions are briefly summarised.

ACUTE VIRAL HEPATITIS

The changes to be described are those seen in infections by virus A, virus B and non A, non B. The pathological changes are essentially similar, although there are some reports, based on the more accurate serological diagnosis now available in the acute phase, that the distribution of the lesions, the intensity and composition of the inflammatory infiltrate and the presence or absence of fat, may distinguish the hepatitis due to these different agents. In hepatitis due to cytomegalovirus and Herpes virus hominis characteristic intranuclear inclusions may be found.

A) *Acute "classical" viral hepatitis*

The morphology of acute viral hepatitis comprises liver cell degeneration and necrosis, accompanied by a lymphocyte and histiocytic infiltrate of both

Table 1. — *Histopathology of viral hepatitis and its sequelae.*

Acute viral hepatitis
Acute "classical" viral hepatitis
Acute viral hepatitis with bridging necrosis
Acute viral hepatitis with massive necrosis
Acute viral hepatitis with possible transition to chronicity
Resolving viral hepatitis
Chronic viral hepatitis
Chronic carrier states
Chronic persistent hepatitis
Chronic active hepatitis
Chronic lobular hepatitis
Cirrhosis and primary hepatocellular carcinoma

the parenchyma and the portal tracts. The parenchymal changes tend to be more severe around the hepatic vein branches. Regenerative hepatocellular activity occurs virtually pari passu with the liver cell necrosis, and this also contributes to the so-called lobular disarray which characterises acute viral hepatitis (Ishak, 1976).

The degenerative changes which affect the hepatocytes comprise: (a) ballooning, in which the cells become swollen, with uniform finely granular dispersed cytoplasm and sometimes with a pyknotic nucleus; (b) acidophilic degeneration, in which single cells drop out of the liver cell plates and become intensely eosinophilic; the nucleus becomes pyknotic and is eventually extruded producing the acidophil or Councilman body. Giant cell transformation producing bizarre large multinucleate cells are a conspicuous feature in neonatal viral hepatitis. They may sometimes also be seen in neonatal hepatitis associated with metabolic disorders, and are sometimes seen in adults; they are thought to represent an unusual but non-specific feature.

Liver cell necrosis results from lysis of ballooned cells, a rapid process with breakdown of the cell membranes and "drop-out" of affected cells (Bianchi *et al.*, 1979). The lysis may affect single cells producing a pattern of spotty necrosis within the parenchyma; but with more extensive involvement areas of confluent liver cell necrosis result.

The inflammatory reaction comprises an infiltrate by lymphocytes, monocytes and some occasional plasma cells and neutrophil polymorphs, and a reactive Kupffer cell hyperplasia and hypertrophy. The monocytes and Kupffer

cells ingest cellular debris and aggregates of ceroid-containing macrophages are a conspicuous feature.

The portal tracts are also usually inflamed, with an inflammatory infiltrate of lymphocytes, macrophages and occasional plasma cells and neutrophil polymorphs. Occasionally the bile ducts show degenerative changes with stratification and vacuolation of the epithelium, basement membrane reduplication and an intense periductal inflammation; these lesions, however, are not of prognostic significance (Christoffersen *et al.*, 1970).

Regenerative activity is characterised by mitotic activity, and mesenchymal cells may also be seen proliferating. Cholestasis is usually mild, although in some cases, in which there is a more intense and more prolonged clinical jaundice, the histological changes include an acute cholangiolitis and may mimic large duct obstruction.

The extent and intensity of the features described change with the stage and evolution of the acute episode, and there is a considerable variation in the morphological spectrum. Additional features may develop and produce morphologically recognised sub-types as follows:

B) *Acute viral hepatitis with bridging hepatic necrosis*

This is characterised by confluent hepatocellular necrosis extending between the vascular structures in the liver i.e. between contiguous hepatic vein branches – central-central bridging, between contiguous portal tracts – portal-portal bridging, and between hepatic veins and portal tracts – central-portal bridging. In these areas of confluent necrosis there is extensive lysis of hepatocytes producing an empty reticulin framework which collapses. The presence of bridging necrosis is not thought to indicate a worse prognosis with progression to chronic liver disease.

C) *Acute viral hepatitis with massive necrosis*

There is very extensive liver cell necrosis resulting in clinical fulminant hepatitis. In this the mortality rate may be as high as 75 per cent; where there is clinical recovery, however, the liver architecture may be restored to normal or there may be post-necrotic scarring.

D) *Acute viral hepatitis with possible transition to chronicity*

The morphological feature which may suggest an eventual progression to chronicity is: i) piecemeal necrosis (v.i.), which occurs at the margins of

the portal tracts or at the interface between the intact parenchyma and the septa which may form following bridging necrosis. However, the morphological diagnosis of piecemeal necrosis is difficult in the presence of acute hepatitis. It must be emphasized, that transition to chronicity is also determined by the duration of clinical and histological abnormality, and following an acute episode, persisting abnormalities after 6 months suggest a less favourable outcome.

E) *Resolving viral hepatitis*

Resolution is manifest by quantitative changes in the features already described. The residual changes, which may persist for up to 6 months, consist of perivenular aggregates of pigment laden macrophages, acidophil bodies, and portal tract inflammation with some thin attenuated fibrous septa extending towards adjacent portal tracts.

CHRONIC VIRAL HEPATITIS

There is still no definite evidence that hepatitis A produces chronic liver disease. Approximately 10 per cent of patients with hepatitis B become chronically infected, half of these becoming chronic carriers with little clinical biochemical or histological evidence of liver disease while the remainder show some form of chronic liver disease, either chronic persistent or chronic active hepatitis. In hepatitis non A non B progression to a chronic course appears to be common, variously estimated at up to 30-40 per cent; histologically, some of these develop chronic lobular hepatitis. The precise definition of non A non B chronic states and their prognosis will remain uncertain until serological markers have been discovered.

A) *Chronic carrier states*

Persistence of hepatitis B infection may be histologically defined by the presence of surface antigen and of core antigen within affected liver cells. Excessive production of surface antigen, and its accumulations in the liver cell cytoplasm, is characterised by the presence of *ground glass hepatocytes* (Hadziyannis *et al.*, 1972, 1973). These cells are identifiable on routine histological sections but are more clearly defined by the orcein staining method (Shikata *et al.*, 1974); immunohistochemical methods can be used to specifically demonstrate that the cytoplasmic inclusions contain HBsAg. The

ground glass inclusions are of homogeneous very finely granular appearance and produce some cellular swelling and push the nucleus to the cell periphery. Accumulation of core antigen may produce *sanded nuclei* (Bianchi and Gudat, 1976) with eosinophilic inclusions pushing the nuclear chromatin to the periphery; immunohistochemical methods will specifically confirm the presence of HBcAg.

Carrier states for non A non B clearly exist but, as far as the Author is aware, morphological makers of this on liver biopsy have not been described.

B) *Chronic persistent hepatitis (CPH)*

In CPH there is a diffuse chronic inflammatory cell infiltrate of the majority of portal tracts, the infiltrate being predominantly lymphocytic with some plasma cells and ceroid-containing macrophages. The infiltrate is confined to the portal tracts, leaving the limiting plate intact and with no periportal liver cell injury. Parenchymal inflammation is minimal amounting to no more than a few small foci of liver cell necrosis. While CPH is in general thought to have a good prognosis (De Grotte *et al.*, 1968) there are some reports of progression to more active disease. In addition, reversion to a pattern of CPH may be found on biopsy of patients with CAH in spontaneous or drug-induced remission.

C) *Chronic active hepatitis (CAH)*

Morphologically CAH is a continuing inflammation of the liver in which liver cell degeneration and necrosis, accompanied by progressive fibrosis finally results in cirrhosis in the large majority of cases. The histological features commonly seen in the untreated cases are piecemeal necrosis, a chronic inflammatory cell infiltrate of the portal tracts and fibrosis. Piecemeal necrosis is defined as the destruction of liver cells at an interface between parenchyma and connective tissue, together with a predominantly lymphocytic or plasma cell infiltrate (Bianchi *et al.*, 1977). The distribution of the inflammation may vary, in some cases being predominantly portal and periportal, while in others there may in addition be piecemeal necrosis around bridging septa linking contiguous hepatic veins or hepatic veins and portal tracts. Fibrous tissue is laid down from an early stage, and in time this produces disturbance of the normal architecture with eventual progression to cirrhosis. The features of acute viral hepatitis may be superimposed and are often conspicuous during clinical relapse.

It must be emphasised that the histological features of CAH as just described are not peculiar to viral-associated chronic liver disease. The same morphological characteristics including piecemeal necrosis, may also occur in autoimmune hepatitis, Wilson's disease, drug-induced chronic liver disease and even occasionally in alcoholic liver disease.

D) *Chronic lobular hepatitis (CLH)*

The histological features in CLH closely resemble those found in acute "classical" viral hepatitis, but are recurrent and persistent for many years (Popper and Schaffner, 1976; Wilkinson *et al.*, 1978). Confluent necrosis may occur during relapse, but bridging necrosis, piecemeal necrosis and progressive fibrosis with progression to cirrhosis do not seem to occur (Wilkinson *et al.*, 1978). A proportion of cases are thought to be due to chronic non A non B infection.

CIRRHOSIS AND PRIMARY HEPATOCELLULAR CARCINOMA

Progression of CAH to cirrhosis results from the continuing liver cell necrosis, fibrosis, architectural disturbance and regenerative activity with nodule formation. The cirrhosis is usually of a macronodular pattern (Scheuer, 1979). Features of CAH may persist after the cirrhosis is established and one may then speak of an active cirrhosis or of cirrhosis with continuing active hepatitis. The demonstration of HBsAg or HBcAg will establish a hepatitis B aetiology.

Primary hepatocellular carcinoma may supervene as a complication in post-viral cirrhosis, and also in cirrhosis of other aetiologies. The strong association between HBV infection and primary liver cell cancer is currently of considerable interest and the topic has recently been well reviewed (Sumithran and MacSween, 1979; Hadziyannis, 1980).

ACUTE AND CHRONIC VIRAL HEPATITIS AND PREGNANCY

It is only possible to put this in a very brief perspective. The topic has recently been fully reviewed (Steven, 1981) and has been the subject of renewed clinical interest (Khuroo *et al.*, 1981; Williams and Ede, 1981).

The incidence and severity of acute hepatitis in pregnancy shows marked geographic variations. In Europe and America it is low, whereas in the Middle East and India it is greater than in non-pregnant women, is more

common in the second and third trimester and is more often complicated by massive necrosis and fulminant hepatic failure. The possible role of malnutrition in contributing to this geographical variation in severity remains speculative. Foetal loss is high when fulminant hepatic failure occurs and palliative caesarean section is indicated; in the uncomplicated case the outcome for the pregnancy does not appear to be affected. There is no evidence of any increase in congenital abnormalities. Transmission of viral hepatitis to the baby has not been established for hepatitis A or non A non B; vertical/perinatal transmission of hepatitis B is common when the mother is a chronic carrier and this has been discussed elsewhere (chap. 5).

As far as chronic liver disease is concernend it seems that the fertility rate is not affected in CPH, but is considerably reduced in CAH and cirrhosis. Pregnancies which do occur in CAH may progress normally, but there is increased foetal loss due to prematurity and perinatal death. The surviving babies are normal and caesarean section is only indicated for obstetric reasons. In the mother portal hypertension is aggravated during the pregnancy. Maternal mortality is considerably increased. Hepatic failure in pregnancy has a very poor outlook. There is an increased risk of post-partum haemorrhage. If the pregnancy is successfully completed the effect on the eventual maternal prognosis appears to be minimal.

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