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Editorial

Non-A, non-B hepatitis

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Until the discovery of the hepatitis B virus in the mid-nineteen sixties, the pathology of viral hepatitis was thought to be similar irrespective of its cause. The discovery of a new antigen in serum, later shown to be the surface antigen of the hepatitis B virus (Blumberg et al. 1965), enabled patients with type B hepatitis to be identified, and the pathology of their liver disease studied in detail. In 1973, Feinstone and colleagues reported the finding of an antigen associated with type A hepatitis. Following these two discoveries, it became apparent that many patients with hepatitis, particularly those in whom infection followed blood transfusion or injection with blood products, had neither type A nor type B. This non-A, non-B hepatitis could also occur sporadically and in the absence of obvious parenteral infection. An epidemic form, clinically resembling type A hepatitis and spread by the faecal-oral route, was also described (Khuroo 1980). In the absence of identifiable virus particles and of reliable, reproducible serological tests, however, diagnosis rested on rigorous exclusion of hepatitis A virus, hepatitis B virus, cytomegalovirus and Epstein-Barr virus. Epidemiological and experimental evidence, the latter from cross-challenge experiments in chimpanzees, indicated the existence of at least two and possibly more separate viral agents (Bradley et al. 1980; Yoshizawa et al. 1981).

Descriptions of pathological changes in parenterally transmitted or sporadic non-A, non-B hepatitis have been hampered by lack of tests for the different viruses, and it has not always been clear whether one or several diseases were being studied. However, in spite of this uncertainty and of the lack of unique and diagnostic histological features, broad histological patterns of non-A, non-B hepatitis began to emerge. Acute and chronic infection proved surprisingly difficult to separate, because features traditionally regarded as "chronic", such as lymphoid follicles in portal tracts, could appear early in the course of the disease while lobular necrosis of a type often found in acute attacks was also seen in established chronic hepatitis. Clinically documented acute non-A, non-B hepatitis showed a variety of histological features including cholestasis, bile-duct damage and an unusual degree of fatty change. Lymphocytic infiltration of sinusoids was prominent in a group of haemophiliac patients developing a short-incubation hepatitis after receiving factor VIII concentrates (Bamber et al. 1981); lymphoid follicles in portal tracts, sometimes associated with damage to the epithelium of interlobular bile ducts (Schmid et al. 1982), have proved to be one of the most consistent histological features. In contrast to this lymphocytic pattern, others have described acidophilic degeneration of hepatocytes suggesting a possible cytopathic effect of a virus (Dienes et al. 1982). A number of different ultrastructural changes have been reported both in man and in experimentally infected chimpanzees (Shimizu et al. 1979; Busachi et al. 1981; De Vos et al. 1982; Spichtin et al. 1982; Weller et al. 1984). Nuclear particles are commonly found, but vary considerably in size and have not been positively identified as virus. Cytoplasmic findings include tubular structures, dense fused membranes and trilaminar structures consisting of an electron-dense layer sandwiched between two thinner membranes. These are also thought to represent non-specific markers of virus infection rather than components of an individual virus.

An important characteristic of parenterally-transmitted non-A, non-B hepatitis is its tendency to become chronic, up to a quarter of patients with chronic infection developing cirrhosis (Realdi et al.

1982). In spite of this, the histological picture in chronic post-transfusion non-A, non-B hepatitis is often that of a mild chronic active hepatitis on the borderline with chronic persistent hepatitis, with prominent lymphoid follicles, fatty change, focal necrosis and acidophil body formation. Cirrhosis appears to develop over a period of many years in most instances, probably as a result of the recurrent episodes of lobular necrosis accompanied by clinical and biochemical deterioration which are typical of the disease. It is likely that non-A, non-B hepatitis viruses will prove to be an important cause of cryptogenic cirrhosis, but the extent of the problem cannot be assessed, nor the histological pattern associated with each individual virus delineated, until there are reliable ways of identifying the viruses. A big step forward has been the recent development of a serological test for an antibody which has correctly identified patients with assumed post-transfusion hepatitis and the implicated donors (Kuo et al. 1989). The test was developed by preparing a cDNA library from infected material and identifying a clone producing a protein which was found to react with an antibody in the serum of infected patients (Choo et al. 1989). The virus identified by this approach contains a positive-stranded RNA genome, and has characteristics consistent with membership of the togaviridae or flaviviridae. The disease produced has been designated hepatitis C.

The agent of epidemic non-A, non-B hepatitis appears to be quite different (Ramalingaswami and Purcell 1988). The disease has been reported from many parts of the world including Asia, Africa and Mexico. The mortality is particularly high in pregnant women. Virus-like particles have been found in faeces of infected patients (Kane et al. 1984; Arankalle et al. 1988), and antibody tests are being developed. Infection can be experimentally transmitted to animals (Inoue et al. 1986). Histologically, a cholestatic picture is common, and Dienes and coworkers (1986) have described prominent portal and periportal inflammation. The disease therefore seems to resemble type A hepatitis not only epidemiologically but also histologically. With the identification of these two forms of viral hepatitis, type C and the epidemic form of non-A, non-B hepatitis, the stage is set for important preventive and therapeutic initiatives in the next few years.

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