4. Other Relevant Data

4.1 Pathology

HCC evolves through chronic HDV infection, which usually begins as acute viral hepatitis and may not be apparent clinically. Many patients with chronic HDV are identified through screening programmes, and the acute event is not documented. The transition of chronic hepatitis to cirrhosis may also be inapparent clinically.

4.1.1 *Acute infection*

The hepatocellular degenerative change and inflammatory reaction of HDV superimposed on chronic HBV (usually chronic persistent hepatitis) appear as acute viral hepatitis,

and the underlying carrier state is masked and not apparent by histological review. Prior biopsy samples may be available to demonstrate chronic active hepatitis or cirrhosis in some cases, but the acute HDV infection stimulates marked degenerative and inflammatory reactions (Govindarajan *et al.*, 1986a). Some patients with acute HDV have a fulminant course (Govindarajan *et al.*, 1984a). Some have combined acute viral infection with HBV and HDV, but the histological features are similar. Serological data and the clinical course are needed to identify patients with combined HBV and HDV infection, as the histopathology is not diagnostic.

4.1.2 *Chronic infection*

Prolonged inflammation and necrosis are common in patients with chronic hepatitis B and subsequent superinfection with HDV. During this prolonged inflammatory reaction, mild chronic liver disease often proceeds to cirrhosis. In a group of 106 consecutive chronic HBV carriers, 20 had HDV, were younger than the group without HDV and had more severe chronic liver lesions than those without HDV infection. Cirrhosis occurred in 55% and chronic active hepatitis in 45% of the patients with combined infection, whereas cirrhosis was documented in only 19% of the group with chronic HBV (Lok *et al.*, 1985; Govindarajan *et al.*, 1986a). In another group of 57 patients with chronic hepatitis B, 18 also had chronic HDV infection. In this group, the portal inflammation, lobular inflammation and necrosis were more severe in the presence of HDV. HDV staining in hepatocytes indicated current HDV replication, but the intensity of staining did not correlate with the inflammation and necrosis (Kanel *et al.*, 1984).

4.1.3 *Cirrhosis*

The continual necrotizing effect of chronic active hepatitis leads to cirrhosis within a few years in many patients with HBV–HDV co-infection. These patients may succumb to severe inflammatory and necrotizing reactions rather than have silent chronic liver disease, as is common with pure chronic HBV infection (Govindarajan *et al.*, 1986a).

4.2 Other observations relevant to possible mechanisms of action of HDV in carcinogenesis

HDV infection was transmitted experimentally to chimpanzees (Rizzetto *et al.*, 1980a) and eastern woodchucks (Ponzetto *et al.*, 1984a). Following experimental infection, the chimpanzees usually developed acute hepatitis of varying degree (Ponzetto *et al.*, 1987c; Negro *et al.*, 1988). The severity of the damage was not dependent on the infecting dose but rather on changes in the genotypes, favoured by serial passages in the host (Ponzetto *et al.*, 1988a). Characteristically, with increasing passage number there was a decrease in the incubation period for hepatitis, together with an increase in pathogenicity. During the peak levels of HDV, 90% of viral genomes were either defective or non-infectious particles. The acute phase of liver damage was characterized by fluctuations in serum alanine aminotransferase levels, which lasted for up to seven months (Ponzetto *et al.*, 1991). Long-term follow-up of infected chimpanzees revealed that 54% of the animals were still infectious and circulating low levels of serum HDV RNA in the absence of significant histological liver damage (Negro *et al.*, 1988). Those animals that apparently had cleared HDV were still susceptible to

reinfection with HDV, indicating lack of vigorous immune protection (Govindarajan *et al.*, 1986b).

Woodchucks persistently infected with WHV showed biological and pathological features similar to those seen in humans, with some differences. As in humans, superinfection of chronic WHV carriers resulted in persistent HDV infection of all animals. Viraemia developed after incubation periods of one to seven weeks, depending on the infecting dose, followed by cyclic fluctuations coincident with HDV RNA expression within the liver-cell nuclei. In the course of serial transmission, an increase in the degree of the infectious potential for HDV was observed (Ponzetto *et al.*, 1991). Animals immunized with purified cloned HDAg were not protected against infectious HDV inoculates (Karayiannis *et al.*, 1992).