## GENERAL REMARKS ON THE AGENTS CONSIDERED

This fifty-ninth volume of *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains monographs on three human hepatotropic viruses—hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV, also known as the delta agent). Until now, the subjects of *IARC Monographs* have been mainly single chemical compounds and, to a lesser extent, groups of chemicals, complex mixtures, cultural habits, occupational exposure circumstances and physical agents. The inclusion of biological agents in the programme was considered by an advisory group which met in 1991 (IARC, 1991). The report of that group recommended inclusion of biological agents, and the human hepatotropic viruses were given high priority for evaluation.

At least five viruses (hepatitis A virus, HBV, HCV, HDV and hepatitis E virus) cause a similar acute illness in humans and are known as hepatitis viruses. They are, however, very different in structure and biology. Serological testing is necessary for accurate diagnosis. A few other viruses, such as yellow fever virus, Epstein-Barr virus and cytomegalovirus, may also induce acute viral hepatitis.

The three viruses considered in this volume have as a common feature that the liver disease they cause can have a chronic course. Hepatitis A and E viruses induce an acute clinical illness similar to that caused by HBV and HCV, but they do not appear to induce chronic liver infection. The few studies that have been done found no association between infection with hepatitis A virus and hepatocellular carcinoma (Drucker *et al.*, 1979; Tabor *et al.*, 1980), and no studies of hepatitis E virus have been reported in this connection. Infection with these two viruses was therefore not evaluated in this volume.

Chronic infection with HBV is highly prevalent in many human populations, particularly in developing countries. Over 300 million people are estimated to be chronically infected worldwide (IARC, undated), and between 250 000 and 1 million people die annually from HBV-associated disease, including fulminant liver failure, cirrhosis and hepatocellular carcinoma. The worldwide prevalence of HCV infection is less variable than that of HBV. About 50% of those infected with HCV develop chronic disease. HDV occurs only in the presence of HBV infection; however, there is marked variability in the prevalence of HDV infection among HBV carriers.

The worldwide incidence of primary cancer of the liver (ICD 155) was estimated at some 300 000 cases in 1985, the sex ratio varying from 1.3 to 3.7 in different parts of the world (Parkin *et al.*, 1993). An overview of studies in which the presence of hepatitis B surface antigen was used as a marker of chronic infection suggests that the proportion of hepatocellular carcinomas that is attributable to chronic infection with HBV ranges from a few percent in industrialized countries to more than 50% in some populations in Africa and Asia (Tomatis *et al.*, 1990). Estimates of the burden of cancer associated with HCV infection are not yet available.

In the evaluation of the three viral agents considered in this volume, the same principles were used as in previous monographs (see Preamble). Exposure to the viruses, however, was evaluated in epidemiological investigations on the basis of viral markers in sera and other tissues of study subjects; in other monographs, exposure assessment was based on measurements in the environment of subjects, on data from records or on information reported by the subjects themselves. The biological markers used to determine exposure in the studies reported in the present monographs are thus more direct than the methods used in monographs on non-biological agents.

Of relevance to the assessment that chronic HBV infection introduces a risk for developing hepatocellular carcinoma in humans is identification of species-specific, HBV-related viruses in the woodchuck (woodchuck hepatitis virus) and the Beechey ground squirrel (ground squirrel hepatitis virus), which are associated with the development of hepatocellular carcinomas in those animals. The Working Group did not formally evaluate those viruses but considered that the studies provide biological and mechanistic information relevant to the understanding of the process of carcinogenesis of HBV in humans. The interpretation of studies in experimental animals in evaluating the carcinogenic risk of viral infection in humans poses further complications not ordinarily encountered with chemicals or physical factors: Each hepadnavirus infects only a limited host range; for example, convincing evidence that HBV infects species other than chimpanzees and man is lacking. It is therefore impossible to assess directly the carcinogenicity of HBV in two or more species of animal, as is done with chemicals and physical factors. Somewhat similar considerations apply to experimental studies of HCV and HDV.

Hepatocellular carcinomas can develop in transgenic mice genetically engineered to express selected portions of the HBV genome. A high rate of expression of some, but not all, HBV genes in hepatocytes of transgenic mice is correlated with the development of neoplasia in these animals. Nevertheless, it does not appear possible at this time to apply these observations directly to evaluation of the carcinogenic risk of HBV.

Evaluation of the carcinogenicity of HDV represents a special situation: HDV infection appears to occur only in people who are also infected with HBV. HDV is not, therefore, biologically active in the absence of HBV. In order to evaluate whether or not HDV is a cause of cancer, cancer incidence must be compared in people with both HBV and HDV infection and in people with HBV only; HDV infection may be considered to be a cause of cancer if the lifetime cumulative incidence of cancer in people with both infections is higher than in those with HBV alone, or if cancers occur earlier in those with both infections than in those with HBV infection alone.

## References

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