16. Vaccination Against Hepatitis B Virus: Past and Future Problems

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The possibility of immunization against hepatitis B virus (HBV) originated with B.S. Blumberg [1] who, in 1967, established the existence of a relationship between infection by HBV and the presence in the blood of an antigen of lipoprotein nature. This circulating antigen was eventually identified as the major constituent, or a major constituent, of the viral envelope, and was found to be discharged in great quantities into the blood. There is still no clear understanding of this mechanism. A considerable quantity of viral material, labelled HBs antigen (HBsAg) and occurring in the viral envelope, is secreted as if, in the hepatocyte where the virus replicates itself, it did not encounter the internal viral structures or the elements permitting assembly of the complete virus. In this respect, infection by HBV is unique. Other antigens may be liberated into the blood in viral infections, but their levels remain very low and the duration of their presence is limited. On the other hand, infection with HBV may lead to discharge into the blood of amounts of HBsAg 100 to 1000 times greater, levels possibly reaching 200–300 μg/ml. Moreover, infection with this virus has the special property that some individuals become chronic carriers of virus with or without pathological manifestations and therefore harbour more or less significant amounts of HBsAg in their serum. This condition is particularly common in immunodepressed patients, notably those on haemodialysis. There is every reason to suppose that the very large amount of virus or viral envelope produced in hepatitis B in comparison with the amounts of virus produced in other viral diseases is due to the fact that the liver is the bulkiest organ in the body and that the viral target, which is essentially the hepatocyte, represents the major assembly of specifically defined target cells in the organism. One reason why the viral envelope is produced in excess, and doubtless at times even in the absence of virus particles, may relate to a preferred integration of the gene coding for HBsAg without integration, or at least expression, of the remainder of the viral genome. Some recent results of molecular biology studies, in which the viral genome or its fragments were identified with radioactively labelled DNA originating from DNA cloned in Escherichia coli, point to this [2].

It is logical that administration of the surface antigen represented by the viral envelope should induce immunity. In fact, this need involve only one or a few of the antigens of the viral surface, since these must be accessible to the antibodies or protective cells which specifically recognise them.

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In 1971, Krugman showed that it was possible to guarantee protection of children exposed to the virus by immunizing them with serum heated for some minutes to 98°. However, this experiment did not formally establish that the HBsAg present was involved in the protection. Unequivocal demonstration of the immunizing power of HBsAg was delayed until the conclusion of the studies of Purcell and Gerin who, in 1975, immunized chimpanzees with a preparation of purified HBsAg and demonstrated resistance of the injected animals to test inoculation. In 1976, Maupas et al. took the risk of vaccinating the medical and nursing staff of haemodialysis units who suffered severely from hepatitis B. This boldness proved justified, since the risk of contracting infection was very significantly decreased in the inoculated subjects compared with what it had been before the introduction of such immunization. Nevertheless, the absence of a control group parallel to the immunized group still left some doubt as to the efficacy of the immunization. Clear demonstration of the effectiveness and harmlessness of inoculation in man had to await the simultaneous performance of two experiments in France and the United States.

In France, 318 persons belonging to the permanent medical and nursing staff of a number of haemodialysis units were selected for this study on the basis of absence of any evidence of hepatitis B virus or of previous transfusional hepatitis. All the subjects had normal levels of transaminases and none had received immunoglobulin within the previous four months. Persons for whom immunization is not generally indicated were excluded from the trial. A total of 184 subjects received the vaccine and 170 a placebo.

The vaccine given in this study was prepared from the plasma of an asymptomatic carrier of HBsAg, without HBeAg (index of viral replication), which suggests that the infectivity of the basic material was rather weak. Preparation involved adsorption of HBsAg on silica (aerosil) and its elution by sodium deoxycholate; after removal of the β-lipoproteins and immunocomplexes, the HBsAg was finally purified by ultracentrifuging to equilibrium with caesium chloride. Sterility was ensured by treatment with formol and filtration through a sterilising membrane. Immunochemical study of such a vaccine showed that it contained around 80% of host proteins (albumin, IgG, α1-lipoprotein, β1C). Alumina was used as an adjuvant and the subjects received three subcutaneous injections, each of which represented an effective amount of around 5 μg of a mixture of HBsAg of subtypes ad and ay.

Monthly study over 12 months of the serum indices for hepatitis and of the transaminases showed that 3.6% of the members of the group receiving the vaccine contracted an infection; the proportion was 12.6% in those who received the placebo. This difference was highly significant (P < 0.005). It was also significant that the 6 infections noted in the inoculated group occurred in the 63 days following the first injection and not subsequently, whereas the 19 infections in the placebo group were observed throughout the year of the trial. No secondary effects attributable to the vaccine were demonstrated. A response in anti-HBs antibodies was evident in 94% of those inoculated [3]. However, the results of inoculation appeared less promising as regards haemodialysed subjects, in whom immune capacity seemed impaired. Thus, a double-blind study conducted under the same conditions as before yielded 21% of