Editorial

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Vaccination Against Viral Hepatitis

Progress in the decade since Saul Krugman and his colleagues published their studies on the antigenicity of the MS-1 and MS-2 strains of viral hepatitis (1) has drastically altered the situation of physicians confronted with cases of viral hepatitis. Today’s physician can protect his or her patients against two of the three forms of viral hepatitis, hepatitis A (HA) and hepatitis B (HB), by passive, active or passive-active immunization. Immunization against the third form of viral hepatitis, non-A, non-B hepatitis (HNANB), is still not possible, and will probably not be possible until the causative agent(s) of this form of hepatitis have been identified.

Passive immunization against hepatitis A by the single inoculation of normal, pooled immune serum globulin (NIG) protects the patient for eight to twelve weeks, and if infection has already occurred, NIG given early enough (within two to four weeks) in the incubation period will still provide partial protection. In contrast, a special immune serum globulin (HBIG) with high antibody titers against the surface antigen of HB (HBsAg) is needed for passive immunization against HB virus (HBV); such immunization is effective when the HBIG is given prophylactically or within hours (< 6 hours) after infection has occurred; inoculation of HBIG at a later time has little or no value.

Active immunization against HA is still not possible; however, now that hepatitis A virus (HAV) can be grown (2, 3, 4) in those cell cultures suitable for producing vaccines, killed or live attenuated vaccines should be available within a few years. The situation for HB is quite different, and the most important single advance in the last decade of hepatitis research has been the development of an HB vaccine. More than ten years ago, Dr. Krugman showed that HBsAg was immunogenic in man, and that antibodies against HBsAg (anti-HBs) could neutralize virus, i.e. anti-HBs developed in response to HBsAg protected against a subsequent exposure to fully infectious HBV (1), and these observations led to the development of a non-infectious HB vaccine consisting of purified HBsAg. Large amounts of plasma are obtained from HBV carriers by plasmapheresis, the HBsAg is extracted biochemically, and, although in theory these purified preparations cannot be infectious as they should contain no complete virions, the final vaccine preparation is inactivated with formalin before use (5-8). Three inoculations of this vaccine induce anti-HBs in 97-98% of healthy individuals (9), although vaccine may have to be given more frequently and in higher doses in immunosuppressed individuals such as haemodialysis patients (10-11); the antibodies remain detectable for more than two years, and persons with anti-HBs as a result of vaccination are immune to HBV infection (7, 9). The vaccine induces no side-effects other than minor pain or swelling at the inoculation site, slight temperature elevation or headache, and these symptoms occur in fewer than 10% of the vaccinees and are not significantly different from those in individuals receiving placebos. No cases of hepatitis have been linked with the vaccines now certified or under consideration for certification. Several subtypes of HBV exist (a, y, d, w, r), but all subtypes carry a common antigenic determinant, the “a” antigen, and this antigen underlies the cross-immunity that exists between the various HB subtypes. A vaccine consisting of a single HBsAg subtype can therefore be expected to induce immunity against all HBV subtypes (6, 12, 13).

Under certain circumstances, immediate protection is needed, and this can be achieved by a passive-active schedule of immunization; it has been shown that simultaneous inoculation of HBIG with HB vaccine does not interfere with the development of active immunity (14-17), and this form of protection – with HBIG shielding an individual from infection with HBV while the long-term active immunity stimulated by the vaccine develops – is particularly important for several quite different population groups. It can be used to protect the close family members of a hepatitis patient to be discharged from hospital; it can protect HB-negative patients and personnel being introduced into dialysis units, or medical personnel entering any situation with a high risk of contracting hepatitis; it can avert infection after accidental exposure to HBV (as in needle-stick incidents or laboratory accidents), or prepare patients well in advance of elective surgery, and perhaps most important of all, it can be used to break the chain of transmission of HB from mother to child.

Collaborative studies during the last two years with the HB vaccine prepared by Hilleman’s group (5) between investigators in Hanover, Mainz, Munich and Zurich (14, 17 and Arnold, Deinhardt, Grob, Meyer zum Büschenfelde, Müller and Zachoval, unpublished data) have confirmed the safety and efficacy of this vaccine. In addition, these studies indicate that somewhat different vaccination schedules may protect immunosuppressed patients even better than schedules used previously, and that less than the currently recommended amount of vaccine per dose appears to protect normal healthy individuals, a schedule which would lead to a considerable saving of vaccine in the future.

The effort put into the development of an HB vaccine and the attempts to eliminate this disease need no justification: it is estimated that there are 200 million carriers of
HBV; HB is not an infrequent nosocomial infection and it endangers both patients and medical personnel. It occurs with a very high frequency in some population groups, particularly in Africa and Asia; it is transmitted readily by sexual contact and becomes a chronic infection in about 10% of the cases. The state of chronic hepatitis itself quickly leads to other, more intractable problems: chronic hepatitis may lead to cirrhosis and primary hepatocellular carcinoma, and it will prevent the development of the HBV carrier state with its inevitable consequence of disease spread. Considering the benefits such a vaccine brings, the price to be paid for being able to tackle a disease for which physicians have no specific treatment is low indeed.

Licensing has been granted already to two vaccines in their countries of origin, and no doubt the number of licensing countries will increase considerably in the next 12–24 months. Unfortunately, this will also exacerbate the already acute problem of vaccine supply which is already insufficient to meet demands, and until supplies increase, we must deal with the problem of deciding who is to be protected. Some general agreement has been reached: the groups of people with priority for vaccination are medical and dental personnel whose work places them in particular danger of contracting hepatitis, dialysis patients, patients who frequently receive blood or blood products, and those patients who have to undergo extensive surgery. In addition, both residents and staff of institutions for the mentally handicapped, in which it is difficult to maintain high standards of hygiene, and persons in very close contact with HBsAg-positive individuals, as is the case in family groups or between mothers and newborn babies, are considered to have a high priority for receiving vaccine. Groups at a particularly high risk, such as prostitutes, homosexuals, drug addicts and long-term prison inmates, have a special claim to vaccination, as do travellers to hepatitis-endemic areas who are likely to come into close contact with local inhabitants. Costs will also become a limiting factor, even when supplies become more available, and special consideration will have to be given to the special needs of developing countries where the incidence of disease, carrier state and hepatocellular carcinoma are very high.

Looking to the future, the present vaccine produced from the plasma of HBV carriers may be replaced by HBsAg produced by molecular cloning in bacterial (18–21) or mammalian cells (22, 23), or even by chemically synthesized peptides with HBsAg determinants (24–26). Until that time comes, however, the vaccines available now will already have heralded in a new era in the natural history of HB. This disease can become one of the past, and there is every reason to suppose that the same fate awaits HA and HNANB.

Literature