The Success of Hepatitis A Vaccine

Vaccines to prevent human hepatitis A and B viruses (HAV, HBV) have been developed rapidly, considering that these viral agents were discovered in 1973\(^1\) and 1965\(^2\), respectively. Such progress was made possible by the remarkable developments in microbiology since 1798 when Edward Jenner first described his work with cowpox vaccination.\(^3\) The evolution into the golden era of vaccine development began in 1949 with the discovery of virus propagation in cell culture. These breakthroughs made it possible to produce and license the first product developed by using the new cell culture technique: the Salk trivalent formalin-inactivated polio vaccine.\(^4\)

These events set the stage for the production of a hepatitis A vaccine. A crucial step towards this goal was taken by Provost and Hilleman (1979), who culti-
vated the hepatitis A virus in vitro. These investigators also showed the feasibility of a formalin-inactivated HAV vaccine, when they successfully tested a prototype HAV vaccine in marmoset monkeys. Several other investigators produced viable, formalin-inactivated, candidate vaccines using different HAV strains grown in diverse cell lines. Early clinical trials of these vaccines established that three doses were required to evoke an adequate antibody response and that the vaccines were safe and immunogenic in adult human populations. Dosage and immunization schedules may warrant revision, based on recent information, in which one or two vaccine doses were highly efficacious in children. Although the vaccines used in the latter studies were manufactured with different HAV strains, CR326 from Merck Sharp & Dohme and HM175 from SmithKline Beecham, the final products were remarkably similar, with efficacy rates of 100% and 97%, respectively. Both vaccines contain purified, cell culture-derived HAV antigen. In both cases, the HAV antigen was formalin inactivated, and both products contain alum as an adjuvant. The SmithKline Beecham vaccine was licensed in Europe early this year and is expected to be commercially available in the United States in the near future.

The report by Lee et al., published in this issue of GASTROENTEROLOGY, gives us necessary information to assess the safety and immunogenicity of the SmithKline Beecham vaccine in children. Although the efficacy trials cited above were performed in children, logistical problems did not allow the vigorous clinical and serological monitoring that smaller safety trials permit. The work by Lee et al. not only fills this information gap but also contributes important facts comparing antibody levels in children who received serum immunoglobulin (IG) as passive protection against HAV infection. We learn from reading this report that children aged 4-15 years "behave immunologically" like adults. Moreover, there are no differences in immune response between boys and girls. Minor reactions occurred; however, none merits discussion.

The vaccine was administered at times 0, 1 month, and 6 months. The antibody to HAV (anti-HAV) was observed in 97% of recipients after the first dose and in 100% of subjects after the second and third doses. The anti-HAV geometric mean titer (GMT) was 167, 465, and 4133 mIU/mL after each vaccine administration. In contrast, the nine children who received only IG, had a GMT of 155 mIU/mL, 5 days after receiving the product and 103 mIU/mL at 30 days. None of the children had detectable anti-HAV 4 months after IG administration. The follow-up period for this study is only 7 months, and important questions regarding longevity of anti-HAV remain unanswered.

Extended monitoring of hepatitis A vaccine recipients is not widely reported. The few communications bode favorably for HAV vaccines. Wiedermann et al. calculated the mean persistence of vaccine-induced anti-HAV based on 102 volunteers who received an inactivated CLF strain-derived HAV vaccine. The vaccine was administered at times 0, 1 month, 2 months, and at 6 or 12 months. He calculated the annual rate of antibody decay to be 42.5% and 44.3% by observing the anti-HAV decline between months 6 and 12, and 12 and 18, respectively. Wiedermann et al. established that after IG administration, 10 mIU anti-HAV mL of serum should be expected at the end of the protection period. They calculated that the mean persistence of vaccine-induced antibody to reach a concentration of 10 mIU anti-HAV mL of serum would be 10-11 years if a fourth dose (booster) was given and 6 or 7 years if no booster was administered.

Our own personal observations of eight volunteers who received four HAV vaccine injections showed that anti-HAV persists for at least 4 years past the initial immunization, although at a much lower GMT (1:20) than that observed 2 months after the fourth dose (1:320) (Figure 1). This finding is particularly encouraging because this initial vaccine contained only 17 ng/mL of HAV antigen. However, neither of these early vaccine preparations is available to the general population, nor will a four-dose immunization schedule be implemented. Therefore, it is most important that we monitor subjects who receive HAV vaccines in the schedule and formulation that are ex-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Neutralizing antibody to hepatitis A vaccine. Geometric mean titer in 8 humans after receiving 4 doses of vaccine at 0, 1, 2, and 6 months. All 8 had detectable anti-HAV by month 42. Data from Spiggen et al.
pected to be marketed for use in the general population. This is crucially important if we remember that acute hepatitis A is asymptomatic in a group of children, whereas the disease ranges from minimal morbidity to death in adults. If we were to immunize infants, the potential exists for the antibody to wane sometime during the second decade of life or earlier, hence rendering these subjects vulnerable to a time of expected increased morbidity. This possibility merits sensible thought and analysis. Although the role that immunological memory may play years after initial immunization needs to be ascertained, it is almost inevitable that booster injections will be required, because none of the inactivated vaccines in existence is able to induce life-long immunity. Studies in progress need to consider long-term evaluations of enrolled vaccine recipients. More studies of healthy and sick populations, including newborns and elderly subjects, are also needed. This knowledge will permit better understanding of the vaccine’s performance and permit the establishment of sound immunization policies. Meanwhile, research such as that done by Lee et al.16 will guide immunization strategy for school-age children and young adults living in or visiting endemic areas.

References