New Data in a 200-Year Investigation

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(See the article by Hsieh et al. on pages 86–9)

The article in this issue of Clinical Infectious Diseases by Hsieh et al. [1] on the longevity of T cell reactivity to vaccinia virus is the latest contribution to a more than 200-year effort to define the duration of protection provided by smallpox vaccination. When Edward Jenner announced his new cowpox vaccination method in 1798, he claimed that a single inoculation would protect for life [2]. Before developing vaccination, he had practiced variolation, in which material from smallpox pustules was inoculated into the skin. The technique had then been in use in Britain for some 80 years—sufficient time to show that it elicited prolonged immunity, as well as occasionally causing full-blown smallpox. Jenner’s assertion that his safer procedure provided equally durable protection helped lead to its rapid acceptance throughout Europe and the New World.

Jenner maintained his belief in the lifelong efficacy of a single vaccination until his death in 1823, but, by that time, numerous observations had already proven him wrong. Some physicians who continued to practice variolation challenged Jenner’s claim, and experience eventually proved them right. By the 1830s, countries that had instituted universal infant vaccination had noted a marked reduction in the number of smallpox-related deaths, but they had also discovered that adults who had been vaccinated in childhood could still acquire smallpox, although these persons usually developed a milder form of illness with a lower case-fatality rate [2]. Rather than prompting a return to variolation, such findings led many governments to require additional vaccinations after the first year of life. Extensive epidemiologic evidence soon testified to the soundness of this approach, including the definitive observation that soldiers who had been revaccinated at the time of entry into military service had much lower morbidity and mortality from smallpox than did those who had only been vaccinated during childhood.

The limited duration of vaccination-induced immunity was apparently unaffected by the change in vaccine strains from Jenner’s cowpox virus to the current vaccinia virus, which may have occurred at some time during the 19th century. Thus, studies of smallpox outbreaks during the first two-thirds of the 20th century reached conclusions essentially unchanged from those of public health investigators in the 1830s: resistance conferred by vaccination diminished over time, but a single vaccination given 20–50 years before infection still provided some protection against severe disease and death [3, 4]. This experience was distilled into simple vaccination schedules that took into account the likelihood of exposure to smallpox. In 1966 (6 years before childhood vaccination was discontinued in the United States), the Advisory Committee on Immunization Practices recommended that adults at particular risk of infection be revaccinated at 3-year intervals, whereas others should receive the vaccine every 10 years [5].

It was only shortly before the completion of global eradication that the first attempts were made to determine a more reliable correlate of immunity to smallpox than the presence of a vaccination scar or the nature of the visible response to revaccination. Two studies found that some persons who had low or absent levels of virus-neutralizing antibodies at the time of their contact with smallpox patients developed the disease, whereas those with higher antibody levels did not become ill [6, 7]. The critical role of cellular immunity in protection against poxvirus infections was not discovered until after smallpox had been eliminated, so studies to determine a protective level of specific cell-mediated immune function were never performed. Instead, immunologists have focused on assays of vaccinia-specific T cell function as a surrogate for activity.
against variola virus (the agent of smallpox), because vaccination is believed to evoke cross-protective cellular immune responses in addition to cross-reactive neutralizing antibodies.

Hsieh et al. [1] determined the longevity of vaccinia-specific immune memory by obtaining blood samples from a cohort of 220 individuals aged 18–70 years from the Taiwanese population and testing them for the presence of vaccinia-reactive CD4+ and CD8+ T cells. Universal childhood vaccination ceased in Taiwan in 1979, and, accordingly, the authors were unable to identify vaccinia-specific T cells in anyone <23 years of age. Reactive cells were easily detectable in persons aged 23–30 years, but they were less numerous in persons aged 31–40 years, and none were found in older individuals. Their findings differ somewhat from 2 previous studies, which showed that vaccinia-reactive T cells could be detected as long as 50–75 years after vaccination [8, 9]. The reason for this difference is not clear. Additional research is warranted, including the characterization of cellular responses to revaccination at various intervals after primary vaccination.

Studies of this type provide important information about immune system function. However, a cell-mediated correlate of immunity remains undetermined. As Hsieh et al. [1] observe, “It is difficult to determine how much T cell reactivity to vaccinia virus is enough to protect against smallpox” (p. 89). In the meantime, the nearly 2 centuries of experience summarized above indicate that repeated vaccination is of marked benefit for the prevention of severe illness after exposure to smallpox.

Hsieh et al. [1] propose that screening for vaccinia-specific T cell activity of the type they performed might become necessary if a shortage of vaccine made it impossible to immunize every at-risk person during a smallpox outbreak. The approach to this problem currently being taken in the United States is to prevent it from ever arising, by carefully maintaining the national stockpile of old, but effective vaccine, arranging for the production of additional stocks, and encouraging the development of a “next-generation” vaccine.

A recent attempt to use mathematical modeling to predict the effect of various interventions on the size and duration of a bioterrorist-induced outbreak of smallpox assumed that persons vaccinated before 1972 would have little residual resistance to infection and indicated a correspondingly increased potential for extensive spread of virus through the population [10]. However, recent success in containing the naturally occurring severe acute respiratory syndrome (SARS) epidemic appears to justify confidence that an outbreak of smallpox could be contained more quickly than such models suggest. The methods of contact tracing and isolation that were successfully used in the smallpox eradication campaign were also used to contain SARS, but, in the latter case, the methods were backed up by rapid internet communications, worldwide disease surveillance systems, modern biotechnology, and a global network of highly capable research and support laboratories. It would have been much easier to stop the spread of SARS if patients had developed a distinctive rash and remained uninfected until rash development, as occurs in the case of smallpox, and if health care workers attempting to control the outbreak had been protected by vaccination.

A striking similarity between the SARS epidemic and past outbreaks of smallpox in areas that were long free of infection was the large amount of disease transmission that occurred within hospitals, with doctors and nurses among the principal victims [4]. The vulnerability of these frontline defenders against infectious diseases is the rationale behind the current plan encouraging the voluntary vaccination of a large number of US health care workers. After more than 200 years, Jenner’s discovery remains the cornerstone of our defense against smallpox.

References


Note Added in Proof. Recent work by Crotty et al. [11] has shown that, in addition to the long-term persistence of vaccinia-specific T cells, specific memory B cells can also be identified more than 50 years after smallpox vaccination.