Understanding Smallpox Vaccination

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(See the article by Gordon et al., on pages 1043–53.)

In a report in this issue of the Journal [1], Gordon and her colleagues at the National Cancer Institute use a rhesus macaque model of smallpox vaccination to examine a question first raised by researchers in the 1950s: what component of the immune response is required for the containment and elimination of the vaccination lesion? By ablating either B cells or CD4+ and CD8+ T cells at the time of inoculation with the licensed Dryvax vaccine, they found that the skin lesion resolved normally in the absence of a humoral response, but in animals depleted of T cells, it became larger and took longer to heal. In some T cell–depleted macaques, satellite lesions formed around the expanding vaccination site, so that it resembled the early stage of progressive vaccinia (PV), a severe vaccination complication of humans in which the inoculation site forms an expanding ulcer and similar lesions appear on other parts of the body [2]. The authors also found that the attenuated LC16m8 vaccinia virus, developed in Japan in the 1970s as a candidate smallpox vaccine, did not produce an enlarged lesion in T cell–depleted macaques, supporting its safety for immunodeficient persons [3].

The current article complements an earlier study from the same group at NCI, headed by Genoveffa Franchini, which used ablation of B or T cells from macaques to determine the basis of the cross-protective immunity to smallpox induced by vaccinia virus [4]. Macaques that were depleted of B cells at the time of Dryvax vaccination failed to produce neutralizing antibodies and developed lethal disease when challenged a month later with monkeypox virus, an orthopoxvirus related to variola, the causative agent of smallpox. In contrast, vaccinated macaques that were depleted of CD4+ or CD8+ T cells at the time of Dryvax vaccination failed to produce neutralizing antibodies and developed a more benign course of disease when challenged with monkeypox virus [5]. Unvaccinated animals that were pretreated with vaccinia immune globulin (VIG), a pooled immunoglobulin product from multiply vaccinated donors, developed only a mild illness. Together with clinical observations of humans with congenital and acquired immunodeficiency (see below) and data from murine models, these reports define the basic immunology of smallpox vaccination: T cells, not antibodies, are required for the resolution of the vaccination lesion, but the immunity to smallpox elicited by vaccination is based on antibodies, not T cells.

Even though a humoral response is not needed for the resolution of a vaccination lesion, would treatment with anti-vaccinia antibodies benefit a person with cell-mediated immunodeficiency who develops PV? A recent case suggests that antibody therapy is only weakly beneficial. In the only instance of PV that has occurred since smallpox vaccination was reinstated for the US armed forces, a recruit was vaccinated just as he was developing acute myelogenous leukemia [5]. Once his enlarging vaccination lesion was recognized and a diagnosis of PV confirmed, he was started on intravenous doses of VIG, which has been the only approved therapy for smallpox vaccination complications since the 1950s. VIG is packaged in single-dose vials containing at least 50,000 units; by the time the patient’s lesion resolved, he had been given almost 17 million units, and 2 investigational antiviral drugs had been added to his treatment regimen.

The fact that antiserum is the only approved therapy for a disease that is caused by deficient cell-mediated immunity reflects the history of research on smallpox vaccination. When Edward Jenner introduced his novel method of cowpox inoculation in the late 1790s, it was such a marked improvement in safety over the previous technique of variolation that little attention was paid to any adverse reactions. By the early
20th century, however, 2 distinct conditions had been recognized in which the inoculated virus spread to produce severe or fatal disease. One was PV, described above, a slow, relentless and usually fatal process that occurred most often in infants. The other, seen in children and adults with eczema or atopic dermatitis, was characterized by the rapid dissemination of virus to produce a smallpox-like disease (eczema vaccinatum, EV). In contrast to PV, many people with EV survived and were immune to repeat infection. Though uncommon, both EV and PV were recognized in large-scale surveys of smallpox vaccination. In 1947, for example, when the introduction of smallpox into New York City resulted in the vaccination of more than 5 million people, there were 2 deaths from smallpox, but 38 cases of EV, almost all in children under the age of 5, of which 2 were fatal [6]. A lethal illness consistent with PV was also observed.

The deaths of those “innocent bystanders” set the stage for Henry Kempe, a young pediatrician who on leaving the Army after World War II decided to dedicate his career to research on smallpox vaccination. In 1950, he reported that some infants of recently vaccinated mothers failed to develop a skin lesion (“take”) when inoculated with vaccinia virus, and showed that they possessed high titers of antivaccinia antibodies that they must have acquired transplacentally [7]. This led Kempe to hypothesize that, if antibodies could prevent the development of a vaccination lesion, then antibody treatment should be able to block the replication of vaccinia virus when it was not wanted. With the help of the American Red Cross, he obtained large amounts of immune globulin from multiply vaccinated volunteers and started using it to treat patients with vaccination complications. Because the practice in the 1950s was to vaccinate infants during the first few days of life, before immunodeficiency or eczema could be diagnosed, he and his colleagues received a steady flow of cases.

Even as Kempe was beginning his campaign, new findings challenged his concept of the role of the humoral response in smallpox vaccination. In 1952, Bruton published his discovery of X-linked agammaglobulinemia, and reports soon showed that boys who could not make antibodies responded normally to vaccination [8]. However, other children who lacked a humoral response developed fatal PV, and further examination showed that they differed from patients with agammaglobulinemia by lacking cellular infiltrates in the margins of their vaccination lesions and by their inability to generate a delayed-type hypersensitivity (DTH) response. They thus lacked both humoral and cell-mediated immunity. Interestingly, a few children were also identified who had circulating immunoglobulin but lacked a DTH response; they developed an expanding vaccination lesion that did not spread to other sites, suggesting that antibodies were blocking the systemic dissemination of virus [9, 10].

As these “experiments of nature” clarified the roles played by cells and antibodies in vaccination, additional data were obtained from attempts to treat PV. Kempe and others found that VIG therapy was only rarely able to rescue infants with severe, combined immunodeficiency, even when the antiviral compound methisazone was added to the treatment regimen [10]. Recognizing that a cellular response might be needed to halt viral replication, they gave their young patients whole blood from recent vaccinees, but only succeeded in produced lethal graft-versus-host disease [11]. Better success was achieved treating PV in adults with acquired immunodeficiency resulting from cancer or leukemia, as a combination of VIG with a temporary decrease in chemotherapy often resulted in resolution of the vaccinia lesions [10]. Matters stood at that point in the late 1970s, when the cessation of universal vaccination and the global eradication of smallpox largely ended interest in developing new therapies. It is only in the past 15 years that concern about the possible reintroduction of smallpox through bioterrorism has caused researchers to return to questions of vaccination safety.

The model of PV in T cell–depleted macaques described by Gordon et al. should prove useful for assessing the role of antibodies in therapy and to test new antiviral drugs or immunomodulators. The management of vaccinia virus infection in severe immunodeficiency can also be tested in mice [12]. More problematic, however, is the other complication resulting from excessive virus replication, EV, for which good animal models have not been developed. In contrast to the relatively small number of persons with severe cell-mediated immune deficiency, a recent survey found that some 18–30 million people in the United States meet the criteria for a diagnosis of eczema or atopic dermatitis [13]. Although careful screening has prevented the occurrence of EV in vaccinees since the US military smallpox vaccination program was resumed in 2002, and only a single accidental transfer of infection to an eczematous infant has been reported [14], this excellent safety record has come at the cost of withholding vaccination from numerous service members.

As Gordon and her coauthors note, one approach to the problem of EV is to administer an attenuated smallpox vaccine. In 1968, Kempe and his colleagues led the way by giving the multiply passaged CVI-78 vaccinia virus to almost 1000 patients with active eczema or a history of childhood eczema, and saw no cases of EV [15]. Similarly, the highly attenuated modified vaccinia Ankara vaccine (IMVAMUNE), which is now being stockpiled by the US government, is being evaluated for safety in persons with atopic dermatitis [16]. Because it is clear that only
a subset of persons with eczema or atopic dermatitis is susceptible to severe cutaneous viral infections, research is also needed to more precisely define the risk factors for EV [17]. More than 200 years after Jenner published the results of his vaccination experiments, the quest for a safe and effective smallpox vaccine continues.

**References**