New York University School of Medicine, New York, NY 10016
DAVID P. HAJJAR
Department of Pathology, Cornell University Medical College, New York, NY 10021

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Vaccination, Immunopathology, and Immunity

The idea that certain recombinant virus vaccines could be dangerous is close to the fears of both careful scientists and doubting laymen. S. Oehen *et al.* (*1*) interpret their results as showing that the worsening of disease after the use of a vaccine.

> happens usually not with whole virus vaccines exhibiting multiple protective T cell epitomes but may be induced when only one or few of the virus epitomes are used for vaccination, as is the case in the newer types of peptide or recombinant vaccines. . . .

We disagree with this reading of both the authors' results and of our own (*2, 3*). We showed more than 25 years ago that, with some strains of lymphocytic choriomeningitis virus (LCMV), peripheral inoculation and subsequent central challenge to the immune system could greatly increase sickness and death. Although one of our papers (*2*) is cited by Oehen *et al.*, they do not mention that we did indeed find "paradoxical effects" of vaccination with this whole virus vaccine.

With certain viral diseases (of which LCMV is the prime example), the viral infection itself is virtually harmless to cells, which subsequently recover and become virus-free (*4*). Disease, if it occurs at all, is mediated by autoimmune mechanisms, rather than intrinsic viral cytotoxicity. Initial sensitization of a specific cellular immune response by appropriate antigens (including both recombinant virus vaccines and nonlethal doses of intact whole virus) can—under certain conditions of timing, dose, and strain—cause marked exacerbation of the disease and increased mortality. This "paradoxical effect" is present not only during the early days after inoculation but also in waning immunity after wild-type viral infection (*5*). The phenomenon is intrinsic to the basic immunology of LCMV infection and no doubt of other viral diseases with a similar pathogenic mechanism.

It is unrealistic to impute these undesirable effects of vaccination to modern genetic techniques; they are as old as the viruses. If a vaccine can induce enhanced disease, this is, like immunity, good evidence of its efficacy. We should not confuse the vagaries of viral pathogenesis with advanced genetic procedures or we may foolishly condemn perfectly good weapons in the fight against human diseases.

JOHN HOTCHIN
LOIS (BENSON) HOTCHIN
18 Paxwood Road, Delmar, NY 12054

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Response: Hotchin *et al.* found accelerated disease when the immune system was challenged during the induction phase. Most mice challenged on the fifth day or thereafter were fully protected. In contrast, we evaluated an immunological memory model. We were interested in how different vaccines could influence susceptibility to LCM disease. Vaccination with whole virus three or more weeks before challenge infection usually did not accelerate disease. Under some conditions, with recombinant vaccines that expressed only a limited number of T cell epitopes, vaccination 3 weeks or less before intracerebral (i.c.) challenge accelerated LCM disease.

In this model the i.c. challenge infection occurred during an immune memory state that was characterized by increased amount of cytotoxic T lymphocyte precursor (CTLp). Frequencies of CTLp in LCMV-immune mice were 10 to 20 times higher than those in mice vaccinated with recombinant vaccinia virus. This could make the difference between prevention and aggravation of disease. Mice that were immune to LCMV showed a secondary immune response against LCMV isolate WE 3 to 4 days sooner than did mice that were vaccinated with a recombinant vaccinia virus. Vaccination with wild-type LCVM protected against high-dose i.c. challenge, whereas vaccination with some of the recombinant vaccinia viruses apparently shifted the equilibrium between immunosuppression and immune response only to a modest extent. This led to lethal LCM disease. Absence of vaccination would have ensured survival in the face of high zone immune paralysis.

The aim of our paper was not to discredit the development of recombinant vaccines. The "new" types of vaccines are promising, but the minimal safety requirements must be fulfilled. Multiple T or B cell epitopes, or both, induction of high neutralizing antibody titers, or induction of consistently high CTLp frequencies must be demonstrated. Recombinant hepatitis B vaccine serves as a good example of a vaccine that has met these requirements.

Our animal model demonstrated that, unless these requirements are met, a vaccine may not work as desired. The nonrecombinant, formalin-inactivated respiratory syncytial virus has also been found to induce damaging T cell responses (*1*). Even if a vaccine expresses a neutralizing determinant (as in the case of vaccinia-LCMV-GP recombinant virus), it may still not perform as expected. If limitations of efficacy or unwanted effects can be demonstrated in a vaccine model, such results should be studied carefully. Thus we caution that vaccination with recombinant vaccinia vaccines expressing only some T cell epitopes (but not wild-type virus) may enhance T cell–mediated immunopathology in the presence of a noncytopathic virus.

STEPHAN OEHEN
HANS HENGARTNER
ROLF M. ZINKERNAGEL
Institut für Pathologie der Universität Zürich, Universitätsspital, Zürich CH-8091, Switzerland

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