boring populations within a species) but could hardly be maintained if the beach and river fish interbreed at random, and their offspring are fully viable and fertile. Thus, within half a century, both adaptive differences in morphology and some degree of reproductive isolation have evolved.

It is well established that natural populations can respond rapidly to selection (*7*). It is also well known that in the laboratory, selection for reproductive isolation can produce a rapid response, provided that it is not opposed by genetic exchange between the diverging populations (*8*). However, attempts to create species in the laboratory, by selection on a single interbreeding population, have usually failed (*8*). Neither of the examples presented by the Higgie and Hendry groups provide evidence that reproductive isolation evolved by the splitting of a single population; indeed, such evidence is almost impossible to obtain. But, because reproductive isolation can evolve so quickly, to levels that allow further divergence even after contact, this difficulty is perhaps not important. Populations must often become temporarily isolated for a few tens of generations, and this may suffice to allow divergence within an essentially continuous geographic range.

Socking it to the competition. Male red sockeye salmon (*Oncorhynchus nerka*) competing to spawn with a female.

The two reports provide strong evidence for the rapid evolution of reproductive isolation. This raises the question: Why do we not see more species? It may well be that new species (that is, reproductively isolated populations) do form often, but that only rarely do they evolve sufficiently to be recognized as separate species by biologists or such that they find a distinct ecological niche. For ecologists, the question is then whether the number of established species that we see is determined by a balance between the rate of speciation and the rate of extinction (*9*), or instead is set by the range of distinct niches that are available. The realization that evolution occurs on time scales accessible to experiment and observation may help bring together evolutionary and ecological approaches to address such questions.

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PERSPECTIVES: AIDS

Preventing AIDS But Not HIV-1 Infection with a DNA Vaccine

Xuefei Shen and Robert F. Siliciano

Individuals infected with human immunodeficiency virus–1 (HIV-1), the cause of AIDS, develop strong immune responses against the virus but never completely eradicate the infection. The extraordinary mutation rate of HIV-1, its ability to evade immune responses by establishing a latent (silent) infection, and the progressive destruction of the $CD4^+$ T helper cells that it infects all contribute to the inability of the immune system to completely destroy this virus. These characteristics also complicate the development of vaccines to prevent HIV-1 infection. Indeed, it is currently unclear whether it will be possible to develop a vaccine that can actually prevent infection. Nevertheless, an important study by Barouch *et al.* (*1*) on page 486 of this issue suggests that vaccine-induced immune responses may control the virus effectively enough to prevent clinical disease even if they fail to prevent or eradicate infection.

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The authors are in the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. E-mail: rsilicia@welch.jhu.edu

Most vaccines against viruses prevent infection by inducing antibodies that stop the virus from infecting host cells. It is difficult to induce antibodies to HIV-1 that serve this protective role. This is a reflection of the enormous variation in the HIV-1 envelope (env) protein and the failure of most antibodies that recognize this protein to neutralize the virus. For these reasons, investigators developing vaccines to protect against AIDS have concentrated on boosting the response of $CD8^+$ cytolytic T lymphocytes (CTLs). These lymphocytes provide resistance to infection with HIV-1 by inducing lysis of virally infected cells. Numerous studies implicate virus-specific $CD8^+$ CTLs as crucial players in the control of HIV-1 replication (*2*–*4*). Confirmation of the importance of CTLs has come from a well-established animal model of AIDS: rhesus monkeys infected with simian immunodeficiency virus (SIV). Last year, Schmitz *et al.* (*5*) and Jin *et al.* (*6*) demonstrated that virus replication is not controlled in monkeys depleted of $CD8^+$ lymphocytes during SIV infection (see the figure).

Barouch and colleagues use a similar animal model to determine whether vaccine-induced immune responses, especially CTL responses, could prevent infection or ameliorate the course of disease. In this case, the virus used to infect rhesus monkeys was a chimeric simian/human immunodeficiency virus (SHIV) consisting of the SIV genome containing the HIV-1 *env* gene instead of the SIV *env* gene. Rhesus monkeys were immunized with a vaccine that contained DNA encoding the SIV gag and HIV-1 env proteins as well as human interleukin-2 (IL-2), a cytokine that enhances the immune response. Although immunized monkeys developed CTL responses that could be readily measured, they were not protected against intravenous challenge with a large dose of a highly pathogenic form of SHIV. However, the pattern of infection and the course of disease were altered markedly compared with control monkeys receiving a sham DNA vaccine. Sham-immunized animals generated only weak CTL responses after infection and showed high levels of viral replication and a rapid loss of $CD4^+$ T cells. There was clear disease progression in the control monkeys, and half of them died within 140 days of being exposed to SHIV. In contrast, monkeys immunized with optimal doses of the vaccine had a slightly blunted initial increase in virus levels in the blood (viremia) and then

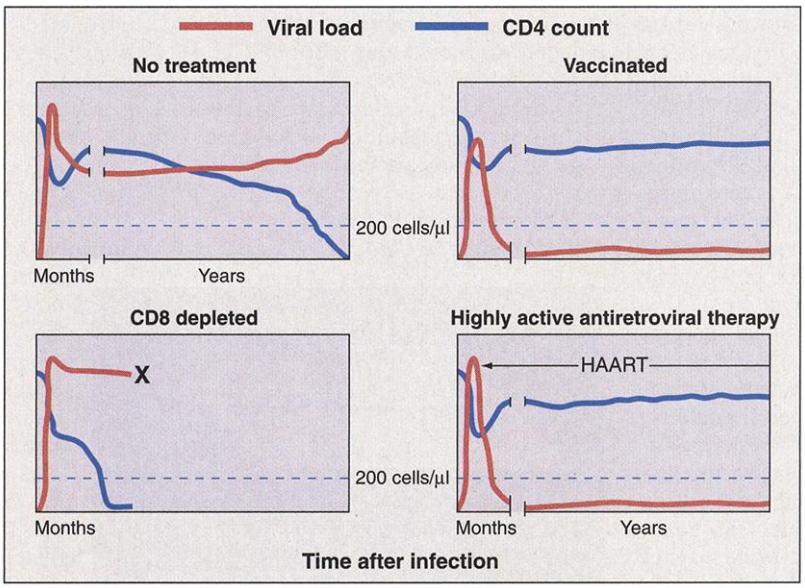
developed potent secondary CTL responses, with gag-specific CTLs comprising an astonishing 18 to 40% of the circulating $CD8^+$ T cells. Most important, these animals showed suppression of viral replication to low or undetectable levels with stable $CD4^+$ T cell counts (see the figure). There was no evidence of clinical disease, and all immunized monkeys survived for at least 140 days. The magnitude of the CTL response induced by vaccination correlated with the degree of suppression of viral replication after challenge with SHIV. Neutralizing antibody responses could not be detected before challenge and appeared in some infected animals only when the viremia had already been partially controlled. These results strongly suggest that a vaccine-induced increase in the number of CTLs was responsible for the control of viral replication (although the part played by neutralizing antibodies and nonspecific innate immune effector responses modulated by IL-2 cannot be excluded).

One of the most interesting aspects of this study is that optimal vaccine-induced immunity required the inclusion of IL-2—in the form of either a recombinant divalent IL-2–immunoglobulin fusion protein or the genes encoding such a protein. The idea of including cytokines as immune response promoters (adjuvants) grew out of work with tumors (*7*) where locally delivered cytokines have been identified as potent stimulators of an antitumor immune response. The IL-2–immunoglobulin fusion protein incorporated into the Barouch *et al.* vaccine presumably provides the second signal needed to drive the proliferation and differentiation of virus-specific CTLs (the first signal is provided by the gag and env antigens).

When interpreting the results of Barouch and colleagues, it is important to keep in mind that the authors have used an animal model in which there is very rapid depletion of $CD4^+$ T cells in control infected monkeys that are not immunized. In six of eight sham-immunized animals, the depletion of $CD4^+$ T cells was almost complete by day 20. Thus, there is not the prolonged asymptomatic period characteristic of HIV-1 infection in humans. In a model infection where so many critical events happen in the first 20 days, the advantages of a vaccine-induced "head start" may be more dramatic than in an infection that progresses less rapidly. Additional studies will be needed to determine whether the same beneficial effects will be observed in vaccinated humans.

The findings of Barouch *et al.* shed new light on what can be reasonably expected from the candidate AIDS vaccines that are currently under development. If the results can be generalized to immunization of humans with HIV-1 vaccines, then we can expect to have vaccines that do not prevent infection with HIV-1 but nevertheless have a significant effect on the course of the disease, potentially improving the quality of life and the lifespan of infected individuals. According to the most recent estimates by the Joint United Nations Programme on AIDS (UNAIDS), about 5.4 million people became infected and about 2.8 million died of AIDS in 1999 (*8*). If vaccine-induced CTL responses allow long-term suppression of viremia to undetectable levels, the rate of transmission (*9*) and number of AIDS deaths could be substantially decreased.

This is especially important in countries where effective drug therapy is not readily available. In the United States, the introduction of highly active antiretroviral therapy (HAART)—triple drug therapy consisting of two reverse transcriptase inhibitors and a protease inhibitor—has resulted in a substantial decrease in deaths from AIDS (*10*). However, eradication of the virus does not appear to be possible (*11*), and HIV-1–induced immune responses may decline in patients on long-term HAART because of decreased antigenic stimulation. Thus, there has also been tremendous interest in the idea that therapeutic vaccination might be combined with anti–HIV-1 drug treatment. With the enhanced immunity engendered by vaccination, it is possible that infected individuals immunized while on HAART will eventually be able to contain the low level of persistent virus even in the absence of drugs, as the immunized animals in this study appear to be able to do.



The immune system fights back. Possible effects of a vaccine-induced CTL response on the course of HIV-1 infection. Variations in viral load (red) and number of $CD4^+$ T cells (blue) during the normal course of HIV infection in an untreated individual (**upper left panel**). Viral load, as measured by the amount of free virus in the blood, peaks during the first few weeks after exposure and then declines as the immune response to HIV-1 develops. The viral load then becomes stable at a level that determines the rate of $CD4^+$ T cell loss. The higher the steady-state viral load, the more rapid the loss of $CD4^+$ T cells. When the number of $CD4^+$ T cells falls below 200 cells/μl (dotted line), clinical immunodeficiency develops. Studies with SIV in monkeys demonstrate that in the absence of $CD8^+$ T cells, the viral load does not decline after primary infection, resulting in rapid depletion of $CD4^+$ T cells and disease progression (**lower left panel**). According to Barouch *et al.* (*1*), it is reasonable to expect that individuals who develop robust CTL responses as a result of vaccination may still become infected with HIV-1 but may have some blunting of the initial peak of viremia (upper right panel). Vaccine-induced immune responses may then bring the viral load down to very low levels, preventing depletion of $CD4^+$ T cells. This is essentially the outcome achieved by continuously treating infected individuals with HAART (triple drug therapy), beginning during primary HIV-1 infection (**lower right panel**). The time scale is based on HIV-1 infection in humans, for which the typical time between infection and the development of severe $CD4^+$ T cell loss is 10 years. In primate models, particularly the SHIV model, the disease course is more rapid than in human HIV patients.

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