The successful development of any protective vaccine requires a knowledge of the immune correlates of protection. Rational targets for vaccine-elicited immune responses can only be established with an understanding of the immune responses that provide protection against infection by a pathogen. Defining such immune correlates of protection against HIV has proven extraordinarily difficult. Although powerful nonhuman primate models for HIV infection exist, impressive protection against AIDS virus challenges in these models has been difficult to achieve using safe, traditional vaccine strategies (1). Therefore, the results of studies done in nonhuman primates do not allow us to state with any degree of confidence whether humoral or cellular immunity will be needed to achieve protection against exposure to HIV. The few reported cohorts of multiply exposed HIV seronegative individuals are a focus of intense interest in the AIDS vaccine research community. The careful evaluation of multiply exposed, uninfected individuals may provide a means of defining the elusive immune correlates of protection. If the protection of these individuals against infection is immunologically mediated and the mechanism of this immune-mediated protection can be characterized, we will be able to define type and level of immunity that must be elicited by HIV vaccines to achieve protective immunity.

Initial reports of such cohorts of exposed, uninfected individuals were met with skepticism. Since a sizable percentage of individuals will escape infection by HIV after a single exposure, it is conceivable that a small but finite group of multiply exposed individuals may remain uninfected on the basis of chance alone. It is also plausible that undocumented behavioral differences in a group of exposed individuals may result in differences in susceptibility to infection. Some have even suggested that individuals categorized as uninfected in these cohorts may be cryptically infected. In African cohorts, individuals infected by isolates of HIV-1 or HIV-2 could escape detection by usual immunologic and virologic assays since the infecting viruses could differ substantially in their sequences from known AIDS virus isolates. In fact, AIDS virus infections that escape usual techniques of detection are well documented in nonhuman primate studies (2, 3).

However, incontrovertible evidence does exist to support the notion that there are exposed uninfected individuals. A homozygous genetic polymorphism in the structure of CCR5, a "second receptor" for HIV-1 entry into cells, has been defined in a subset of these individuals (4). This genetic polymorphism has been shown to be a significant barrier to infection by HIV-1. The report by Rowland-Jones and colleagues in this issue of *The Journal* suggests another mechanism for protection against infection in multiply exposed individuals (5). These investigators reported previously that a small group of HIV seronegative Gambian female sex workers had detectable HIV-specific cytotoxic T lymphocyte (CTL) responses (6). They suggested that such CTL may protect against infection during exposure to HIV. Problematic in that earlier study was the finding that CTL were only detected in three individuals using a limited number of epitope peptides presented to the immune system by the HLA-B35 MHC class I molecule. This finding raised the possibility that the rare positive CTL responses in this cohort may somehow reflect an artifact in the assay system used in the experiments. The present study overcomes that criticism, demonstrating CTL in seronegative, multiply exposed individuals that are specific for multiple HIV epitopes. These various peptide epitopes are presented to immune cells by multiple MHC class I molecules.

It is not immediately clear how such CTL responses could be generated in seronegative individuals. Virus-specific $CD8^+$ CTL are elicited through exposure to antigen that is processed through the MHC class I pathway. Virus-infected cells produce protein that undergoes proteosomal degradation. The resulting peptide fragments associate in the endoplasmic reticulum with MHC class I molecules and β2 microglobulin, and are transported complexed to these proteins to the cell surface. It is this MHC class I–associated peptide that is recognized as viral antigen by $CD8^+$ CTL. According to this paradigm, a productive viral infection must occur to elicit a virus-specific CTL response. One way to explain the initiation of an HIV-specific CTL response in seronegative individuals is that these individuals may have cells that undergo an abortive infection with sufficient viral protein synthesized to enter the MHC class I processing pathway, but a complete viral replicative cycle is not initiated. Although the possibility of abortive HIV infections has been discussed, such infections, in the absence of antiviral therapeutic interventions, have not been documented.

How does this finding by Rowland-Jones and colleagues inform the HIV vaccine effort? The observation that multiply exposed Nairobi female sex workers are protected from HIV infection by HIV-specific CTL alone may provide a rationale for pursuing an HIV vaccine strategy in which only CTL are elicited. There is no precedent for a successful viral vaccine that does not induce neutralizing antibodies. However, accruing data from a variety of studies support the notion that CTL rather than antibodies contain the spread of HIV in infected individuals. Containment of HIV-1 replication in vivo has been correlated temporally with the generation of virus-specific CTL (7). In addition, a potent CTL response in chronically infected individuals is associated with low viral load and a stable clinical status (8, 9). The studies of exposed uninfected female sex workers provide further evidence for the importance of CTL in controlling the replication of HIV.

Norman L. Letvin
Harvard Medical School

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