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LETTERS

Alloimmunization as an AIDS Vaccine?

In a Special News Report (28 May, p. 1265), Jon Cohen describes a study by James Stott and his colleagues (*1*) which demonstrated that macaques immunized against a normal human cell line, like those immunized against a human cell line infected with simian immunodeficiency virus (SIV), were protected when challenged with cells from that same SIV-infected line. Although Stott's observations, confirmed by A. J. Langlois *et al.* (*2*), were initially disappointing to those working on virus-specific immunity, they opened the possibility of a new approach for acquired immune deficiency syndrome (AIDS) vaccines (*3*). Stott suggests the possibility of an HIV vaccine based on cellular proteins, and the work of Larry Arthur *et al.* (*4*) demonstrating and identifying many of these cellular proteins as human lymphocyte antigens (HLAs) supports such a possibility. These cellular proteins, either associated with free virions or on the surfaces of infected cells, could be recognized as HLA alloantigens (or "xenoantigens" in the study by Stott *et al.*) when first introduced into the host during initial HIV infection. It was recently shown that protection of macaques against SIV infection was correlated with the presence of antibodies against HLA class I antigens (*5*). F. A. Plummer *et al.* have suggested that recognition of HLA alloantigens could account for their observation that many of the prostitutes in Nairobi who appear to be resistant to HIV infection express rare HLA types (*6*). These individuals might have rejected, by alloantigen recognition, HIV-infected leukocytes introduced in semen before efficient HIV infection could occur.

Alloimmunization offers some unique advantages as a potential HIV vaccine. For example, the allogeneic response (i) is the strongest known antigen-specific immune response; (ii) is responsible for foreign tissue allograft rejection, and could therefore destroy allogeneic leukocytes introduced by parenteral exposure; (iii) elicits both strong cellular and humoral immunity and could thereby destroy (by cellular immunity) infected allogeneic cells, including those not expressing HIV antigens at the time of cell transfer, as well as free virus expressing HLA antigens (by antibody); (iv) is well developed in the newborn; (v) does not require preimmunization (as do viral antigens), although it can be efficiently boosted; and (vi) exhibits long-term immunologic memory.

Furthermore, it has been reported that (i) the three-dimensional structure of certain regions of the protein gp120 may be similar to regions of HLA class I and class II molecules (*7*); (ii) human cellular and antibody responses can be generated to HLA-like epitopes of gp120 (*8*); (iii) anti-gp120 antibodies in vaccines can compete with anti-HLA class I antibodies, which also recognize soluble gp120 (*9*); and (iv) human cytotoxic T lymphocytes, generated in response to HLA alloantigens, lyse autologous targets that are pulsed with synthetic peptides that correspond to the shared HLA and gp120 epitopes (*10*).

Many individuals have been primed to HLA alloantigens without exhibiting harmful side effects. Albert Sabin suggested that a sterilized HIV vaccine is not a realistic option for a first-line defense against HIV infection because the virus can remain hidden in the genetic material of infected cells (*11*). However, the initial infective event could involve the interaction between host $CD4^+$ T cells and HIV-infected cells from an allogeneic donor. A strong allogenic immunity might destroy foreign donor cells before efficient HIV infection could occur; this should happen even in infected leukocytes that do not express HIV antigens. Furthermore, HLA-specific antibodies could neutralize free virions through their relatively high concentrations of HLA antigens (*4*).

Alloimmunization as an AIDS vaccine has at least three potential disadvantages. First, alloantigen-immunized individuals might not be good candidates to receive allografts. However, in several parts of the world, effective immunization against HIV infection might take precedence over the unlikely prospect of a future organ transplant. In fact, blood transfusion has been used in certain renal transplant combinations to prevent kidney allograft rejection (*12*). Second, it is not possible to determine the HLA antigens that would need to be recognized, because the HLA types of the infecting cells and the prospective recipient would not be known. Third, immunization with foreign leukocytes presents a risk of infecting the vaccinee with other viruses. However, these latter two potential problems could be resolved by

immunizing with a pool of solubilized class I and class II HLA antigens, including those shared with gp120. Such an approach would maximize the number of immunizing determinants and minimize the risk of infecting the prospective vaccinee with blood-borne viruses.

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A Magic Bullet Against AIDS?

A prophylactic vaccine against infection by the human immunodeficiency virus (HIV) is years away at best (*1*) and once developed will face formidable obstacles to successful deployment (*2*). Although many researchers are promoting behavioral interventions to diminish the spread of acquired immune deficiency (AIDS), as noted in the news article by Jon Cohen, the prevailing attitude is that such interventions—the use of condoms or the sterilization of drug injection equipment, for example—are inherently inferior to the "magic bullets" proffered by biomedical science. The veracity of this proposition, however, has received little critical examination.

In order to demonstrate the importance of behavioral risk reduction, one can pose the question, How large a proportion, ϕ, of the sexually active population would