REFERENCES AND NOTES

1. B. B. Johnson and V. T. Covello, Eds., *The Social and Cultural Construction of Risk* (Reidel, Dordrecht, 1987); W. R. Freudenberg, *Science* **242**, 44 (1988); P. Slovic, *ibid.* **236**, 280 (1987).
2. N. D. Weinstein, *J. Behav. Med.* **10**, 481 (1987).
3. L. J. Bauman and K. Siegel, *J. Appl. Soc. Psychol.* **17**, 329 (1987).
4. J. G. Joseph *et al.*, *J. Appl. Soc. Psychol.* **17**, 231 (1987).
5. N. D. Weinstein, M. L. Klotz, P. M. Sandman, *Am. J. Public Health* **78**, 796 (1988).
6. N. D. Weinstein, *J. Pers. Soc. Psychol.* **39**, 806 (1980).
7. W. B. Hansen and C. K. Malotte, *Prev. Med.* **15**, 363 (1986); B. C. Leigh, *J. Stud. Alcohol* **48**, 467 (1987); J. P. Kirscht, D. P. Haefner, F. S. Kegeles, I. M. Rosenstock, *J. Health Hum. Behav.* **7**, 248 (1966); J. A. Kulick and H. I. M. Mahler, *Health Psychol.* **6**, 15 (1987); L. S. Perloff and B. K. Fetzer, *J. Pers. Soc. Psychol.* **50**, 502 (1986); N. D. Weinstein, *J. Behav. Med.* **5**, 441 (1982); *Health Psychol.* **3**, 431 (1984); in *Psychological Approaches to the Primary Prevention of Acquired Immune Deficiency Syndrome*, V. M. Mays, G. W. Albee, S. Schneider, Eds. (Sage, Beverly Hills, CA, in press); D. Zakay, *Acta Psychol.* **53**, 271 (1983).
8. D. Dolinski, W. Gromski, E. Zawisza, *J. Soc. Psychol.* **127**, 511 (1987).
9. A. G. Greenwald, *Am. Psychol.* **35**, 603 (1980); J. V. Wood, S. E. Taylor, R. R. Lichtman, *J. Pers. Soc. Psychol.* **49**, 1169 (1985); T. A. Wills, *Psychol. Bull.* **90**, 245 (1981).
10. C. S. Weinstein, *J. Teacher Ed.* **40**, 53 (1989).
11. N. K. Janz and M. H. Becker, *Health Ed. Q.* **11**, 1 (1984).
12. J. P. Kirscht, in *Health Behavior: Emerging Research Perspectives*, D. G. Gochman, Ed. (Plenum, New York, 1988), pp. 27–41.
13. H. Leventhal, in *Advances in Experimental Social Psychology*, L. Berkowitz, Ed. (Academic Press, New York, 1970), vol. 5, pp. 119–186.
14. S. E. Taylor and J. D. Brown, *Psychol. Bull.* **103**, 193 (1988).
15. R. F. Baumeister, paper presented at American Psychological Association convention, Atlanta, GA, August 1988; R. Janoff-Bulman, *ibid.*
16. L. B. Alloy and A. H. Ahrens, *J. Pers. Soc. Psychol.* **52**, 366 (1987).
17. M. F. Scheier *et al.*, *J. Pers.* **55**, 169 (1987).
18. I thank H. Leventhal, M. Pfeffer, P. Sandman, and C. Weinstein for suggestions during the preparation of this manuscript.

Progress in Vaccines Against AIDS

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JUST AS OTHER CONCEPTUAL BARRIERS IMPEDING THE RESOlution of the acquired immunodeficiency syndrome (AIDS) crisis have been overcome—such as the nature of its etiology, a diagnostic blood test, and a drug that would have a beneficial effect on the disease—the pessimism shadowing the development of an AIDS vaccine is showing some signs of receding. This is a result of advances on several fronts including: (i) the first examples of efficacy of killed virus vaccines in various animal models, (ii) the identification of important immunological targets on the virus and the infected cell, and (iii) information that humans respond favorably to certain candidate immunogens (*1, 2*). Indeed, as a result of these and other studies, apparent obstacles are being lifted and new concepts on how to approach a vaccine are evolving. Nowhere was this more apparent than at a recent international gathering of scientists at the Annual Meeting of the Laboratory of Tumor Cell Biology (Bethesda, Maryland, 21 to 26 August 1989).

The most striking results were the animal model studies with simian immunodeficiency virus (SIV) by Desrosiers, Murphy-Corb, Gardner, and colleagues (*3–5*), as well as studies with equine infectious anemia virus (EIAV) by Montelaro (*6*). In each example, whole killed virus vaccines were able to delay the onset of disease for a significant period of time (possibly permanently, as the experiments may eventually demonstrate). Notably, protection against the respective diseases caused by experimental challenge with SIV and EIAV could be achieved even in cases where entry of the virus was not prevented. The importance of this development is underscored because it suggests that the same general rules apply to human immunodeficiency virus (HIV) vaccines as have existed for other viruses; namely, that it may not be necessary to completely block infection in order to have a successful vaccine. If some degree of infection with HIV can indeed be tolerated, a vaccine against the virus is much more within reach. It also suggests that some of the studies already performed in chimpanzees with HIV (which were considered failures because infection was not prevented) might have had a more favorable outcome had a disease end point been available.

That is not to say that one should not strive to develop mechanisms to clear the virus. Indeed, some of the examples with both SIV and EIAV apparently were also able to prevent infection (*3, 4, 6*). In this regard, an experiment by Gibbs and Salk, presented at the Vth International AIDS Conference at Montreal (*7*), achieved a surprising result when whole killed virus was administered to two chimpanzees having long-term infections with HIV; the infection appeared to have cleared within the bloodstream. Postexposure immunization in humans with the same preparation has also been studied by Salk and colleagues, although the results are still equivocal (*8*). However, long-term studies, initiated in 1986 and still in progress by Zagury, Gallo, and their colleagues, in which autologous cells expressing HIV antigens were used have resulted in clinical and biological benefit including stabilization or increase of CD4 lymphocytes in some AIDS-related complex (ARC)–AIDS patients (*9*). Taken together, these results suggest that the immune system might be harnessed to protect humans from HIV infection and perhaps to improve the course of the disease.

Although the animal model studies with SIV are of extreme importance for providing concepts and strategies for vaccine development, SIV is not HIV and subhuman primates are not the equal of humans. The SCID-Hu mouse chimeras in which components of the human immune system are able to survive for several months show some promise in this regard (*10, 11*), particularly as infection models for HIV. However, a clear demonstration that these animals can mount an immune response to the virus is lacking. Until that is achieved, their use is limited primarily to testing the protective effects of immune responses generated in other systems through adoptive transfer.

Although instructive during preclinical development, whole virus vaccines do not represent a practical avenue for a vaccine against HIV because of the possibility of infectious particles. For this reason many laboratories are using the reductionist approach which seeks to define the essential components of the virus that would confer protection. Along these lines, advances have been made in several directions including a vast array of neutralizing epitopes, T cell epitopes that are targets for cytotoxic lymphocytes, and regions of the virus envelope that can target antibodies which mediate antibody-dependent cell cytotoxicity (ADCC). In total, nearly 20 such sites have been mapped as linear epitopes (*12*).

The principal neutralizing epitope of HIV is situated within the third hypervariable region, the V3 loop of the external envelope glycoprotein (gp120). Studies by Emini and colleagues have shown that when given with the virus, neutralizing antibodies to the loop can protect chimpanzees against HIV infection (*13*). Nevertheless, the usefulness of this segment in vaccine design appeared limited

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because of its apparent extensive variability. However, recent studies by a number of groups (led respectively by Putney, Goudsmit, Gallo, Haynes, and myself) have provided evidence that in natural isolates of HIV there is considerable pressure to conserve a critical portion of this loop, suggesting that certain serotype classes may indeed exist in the population (*14*). Studies by McKeating *et al.* (*15*) and more recently by Nara *et al.* (*16*) indicate that conformational constraints imposed by other changes in gp120 may be as important as primary sequence variation within the loop in regulating susceptibility to neutralizing antibodies.

Other neutralization targets also exist on the virus envelope, and one of these, situated within the transmembrane component (gp41), is highly conserved. Originally described by Chahn *et al.* (*17*), it has resurfaced as a more powerful epitope when inserted in the VP1 domain of poliovirus (*18*). Of interest is that neither this region nor the loop is involved in the binding of the virus to its receptor; therefore the respective antibodies do not have to compete against the high-affinity interaction occurring between gp120 and CD4.

A number of unique sites involved in T cell interactions have been defined on the virus envelope, in its internal components, and in its regulatory elements. Some of these can be targets for cytotoxic lymphocytes isolated directly from HIV seropositive individuals. Along with a number of sites on the envelope that serve as targets for ADCC, a substantial arsenal is thus available with which to attack virus-infected cells. This is important for two reasons: (i) natural transmission of HIV occurs both through free virus and virus-infected cells, and (ii) some degree of infection of host cells probably cannot be avoided even with the ultimate vaccine strategy. Thus, to be effective against the various modes of natural HIV transmission, a clearance mechanism for the infection must be established through vaccination.

Just as targets for protective immunity are being defined, one is beginning to understand the features of the virus that produce undesirable responses by giving rise to immunosuppressive effects and antibodies which enhance rather than prevent infection. Enhancement of HIV infection has thus far been limited to observations in vitro (*19*). It has not been documented in animal model studies of HIV or SIV vaccine testing; more specifically, it has been looked for but not found in humans immunized with HIV antigens, as reported by Zagury and colleagues (*20*). Nevertheless, in order to guarantee safety and maximal efficacy it is important to eliminate any potentially harmful epitopes from vaccine regimens.

These encouraging steps notwithstanding, the challenges standing before the development of an HIV vaccine are prodigious. Ways to present HIV antigens to the human immune system so as to evoke protective humoral and cellular immunity are still being perfected. Much more has to be done along the lines of development of safe and effective adjuvants or constructions of innocuous replicating vectors into which critical HIV target epitopes can be incorporated. Also, more has to be known about the role of secretory immunity in a protective response against transmission of HIV across mucous membranes. However, by far the most formidable barrier will be the evaluation of efficacy of a vaccine candidate in humans, given issues such as the low transmission rate of HIV infection in the population and the long and variable interval between infection and disease (*21*). As research produces more compelling vaccine candidates, such obstacles will hopefully also be overcome.

REFERENCES

1. D. Zagury *et al.*, *Nature* **332**, 728 (1988).
2. J. A. Berzofsky *et al.*, *ibid.* **334**, 706 (1988).
3. R. C. Desrosiers *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 6353 (1989).
4. M. Murphy-Corb *et al.*, *Science* **246**, 1293 (1989).
5. S. Sutjipto *et al.*, Vth International Conference on AIDS, Montreal, Canada, June 1989 (abstr. C. Th. C.O. 45).
6. R. C. Montelaro, personal communication.
7. C. J. Gibbs *et al.*, Vth International Conference on AIDS, Montreal, Canada, June 1989 (abstr. C. Th. C.O. 46).
8. A. Levine *et al.*, *ibid.* (abstr. B. Th. B.O. 44).
9. D. Zagury, personal communication.
10. J. M. McCune *et al.*, *Science* **241**, 1632 (1988).
11. D. E. Mosier, R. J. Gulizia, S. M. Baird, D. B. Wilson, *Nature* **335**, 256 (1988).
12. D. P. Bolognesi, *AIDS*, in press.
13. E. A. Emini *et al.*, Vth International Conference on AIDS, Montreal, Canada, June 1989 (abstr. Th. C.O. 30).
14. For example, S. D. Putney *et al.*, *ibid.* (abstr. W.C.O. 18).
15. J. A. McKeating *et al.*, *in Retroviruses of Human A.I.D.S, and Related Animal Diseases*, M. Girard and L. Valette, Eds. (Fondation Marcel Merieux, Lyon/Pasteur Vaccins, Marnes-la-Coquette/Paris, 1988), pp. 159–164.
16. P. Nara *et al.*, Vth International Conference on AIDS, Montreal, Canada, June 1989 (abstr. T.C.O. 22).
17. T. L. Chahn *et al.*, *EMBO J.* **5**, 3065 (1986).
18. D. J. Evans *et al.*, *Nature* **339**, 385 (1989).
19. D. P. Bolognesi, *ibid.* **340**, 431 (1989).
20. J. Bernard *et al.*, *AIDS Res. Hum. Retroviruses*, in press.
21. W. C. Koff and D. F. Hoth, *Science* **241**, 426 (1988).