12. D. D. Richman, in *Antiviral Drug Resistance*, D. D. Richman, Ed. (Wiley, Chichester, UK, 1996), in press.
13. L. M. Mansky and H. M. Temin, *J. Virol.* **69**, 5087 (1995).
14. J. M. Coffin, *Science* **267**, 483 (1995).
15. L. Moutouh, J. Corbeil, D. D. Richman, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
16. R. Gulick *et al.*, 3rd National Conference on Human Retroviruses and Related Infections, Washington, DC, 29 January 1996 (abstract), p. 162.
17. Y. Cao, L. Qin, L. Zhang, J. Safrit, D. D. Ho, *N. Engl. J. Med.* **332**, 201 (1995).
18. G. Pantaleo *et al.*, *ibid.*, p. 209.

A Perspective on AIDS Vaccines

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At the 11th International Conference on AIDS, a formal debate is scheduled on the question of whether "more fundamental research on vaccine development is required prior to the implementation of phase III trials of certain HIV vaccines." After more than a decade of research without a single HIV vaccine deemed worthy of large-scale efficacy trials, it may be useful to reconsider some general questions about AIDS vaccines that are commonly, or uncommonly, asked (*1–3*).

Is a vaccine against AIDS really needed? This question is appropriate in light of the dramatic reductions in viral burden and increased survival recently achieved with multiple drug therapy (and the probability of new therapeutics). Clearly, childhood vaccines are among the most cost-effective medical interventions to prevent death and disease (*4*). Assuming the best cases for therapeutic efficacy and lack of drug resistance, the inhibitors of reverse transcriptase and protease will remain chemically complex and enormously expensive (*5*). The 90% of people infected with HIV who live in the developing world, and many in industrialized countries, will not have access to them. The best long-term hope for preventing AIDS in the United States and globally must be an effective vaccine.

Why is it so difficult to develop AIDS vaccines? As part of the National Institutes of Health (NIH) Office of AIDS Research (OAR) review of NIH AIDS programs, I met with graduate students and postdocs to discuss barriers in attracting the brightest young scientists into AIDS research. It was my impression that research on AIDS was considered more applied than basic, and that research on vaccines was not thought to be particularly intellectually challenging. My own perception is that AIDS vaccines represent the most formidable vaccine challenge of any infectious disease. In most natural viral infections, illness occurs, an immune response develops, and if the illness is not acutely fatal, recovery ensues. In AIDS, most patients develop antibodies and even killer T cells against the virus, yet they fail to clear the virus and inexorably succumb to AIDS. The challenge is how to achieve something that nature has not succeeded in doing. The hurdles are daunting: (i) HIV infection places the immune system in double jeopardy, from the virus and from immune attack. (ii) There are multiple genetic types or clades of the virus, and with the high mutation rates of RNA viruses, there are even more antigenic subtypes and variants against which to engender protection. (iii) A vaccine may have to protect not only against transmission of free virus but also against virus-infected cells that can transmit infection, an immunological task comparable to selective rejection of tumor cells. (iv) Animal models of HIV that are faithful to the human disease are lacking, and experiments with different models often yield conflicting findings. (v) The possibility of generating inappropriate immune responses that might enhance infection or cause pathology cannot be ignored. (vi) Any population in which a vaccine might be tested for efficacy must ethically be provided with the best counseling on preventing transmission and reducing high-risk behavior, and such counseling is likely to compromise the statistical power of any trial.

Is there hope for an effective vaccine? Long-term survivors of HIV infection who have controlled the virus for more than a decade (*6*) and high-exposure, uninfected sex workers who show no detectable virus or disease but have HIV-specific immune responses (*7*) have been identified. Encouraging data indicate that individuals infected with HIV-2 have some cross-protection against HIV-1 infection (*8*). A small number of children infected at birth with HIV appear to clear their virus (*9*). Understanding the mechanisms that contribute to the well-being of these individuals could provide valuable insights relevant to vaccines. Although the diseases may differ, effective vaccines against the feline leukemia virus, a related retrovirus, have been available for years (*10*). Finally, long-term protection has been achieved in macaques with live, genetically attenuated simian immunodeficiency virus (SIV) strains (*11*).

How good must an AIDS vaccine be? We commonly think of vaccines as preventing infection and producing "sterilizing" immunity. In fact, relatively few vaccines prevent infection of host cells. Rather, they confer protection by reducing the initial burden of pathogen, by accelerating clearance of the infection, or by preventing recurrence, sequelae, and transmission. In the context of a fatal disease that is devastating a major proportion of young people in many countries, even a partially protective AIDS vaccine—20 to 40% as effective as measles or polio vaccines—would save and extend millions of lives and would reduce secondary transmission to offspring and contacts. Public health use of a vaccine will be decided not only by its efficacy, but also by the magnitude and urgency of the problem in different countries.

What do we have to know to develop an effective vaccine? Historically, successful vaccines were created with little understanding of the molecular basis of pathogenicity. Pickled proteins, viruses and bacteria, or spontaneously arising attenuated strains worked in the past. Empirical trial and error is indeed crucial in the development of vaccines but can no longer be the paradigm. For AIDS vaccines, there is a clear need to better understand the mechanisms of pathogenesis and protection.

In a rational world, to design an effective vaccine one would like to know: (i) What are the necessary and sufficient immune responses required for protection? (ii) What are the antigens or immune targets to which they are directed? (iii) What is the best way to deliver the appropriate antigens to engender the protective immune responses? In the real world, that's not how it usually works. More likely, an antigen is identified, then patented and licensed, and the developer tries to show that it will produce some immune responses in some animal models. If any responses are seen in animals and then in a limited number of humans, the plea is inevitably made that the antigen might protect against the disease if only the federal government would run a large efficacy trial.

I would argue that two issues have been confounded: questions of fundamental knowledge and questions of vaccine efficacy. The question of what immune responses are essential for protection against HIV is fundamental. It is similar to, but distinct from, the practically important question of what the "correlates" of protection are—that is, what tests can be measured in a test tube that correlate with protection. Responses may correlate but may not be necessary for protection. Experiments that can

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test scientific hypotheses clearly could be very informative, particularly if they refute these hypotheses and reveal what will not be useful for vaccines. Are antibodies necessary or sufficient for protection? If so, must they "neutralize" primary patient isolates of virus, activate killer cells, or do something else? Passive transfer of purified or monoclonal HIV antibodies to pregnant women, to learn whether antibodies can protect against maternal transmission of HIV to fetuses (the highest risk group for AIDS transmission), does not represent a vaccine, but such experiments could indicate whether certain types of antibodies alone can be protective. Are T cells essential, and if so, what kind—cytotoxic T cells, lymphokine- or chemokine-producing cells, or memory T cells? Why are macaques that receive attenuated SIV vaccines protected only after 10 to 20 weeks, even though they make killer T cells and antibodies soon after immunization? Is a concerted immune response involving multiple immune mechanisms necessary for protection?

How can the fundamental knowledge needed be acquired? Much depends on models and assays that, for HIV, are very imperfect. For example, chimpanzees but not macaques can be infected with HIV-1. However, infected chimpanzees generally do not get AIDS, but only chronic infection. Macaques infected with SIV develop a fatal AIDS-like disease in 1 to 2 years, but how readily these results can be extrapolated to the 8- to 10-year course of HIV infection in humans remains unclear. Clearly, a strain of HIV that causes disease in macaques or even chimpanzees would be valuable for study, and hybrid viruses (SHIV) have been created to learn what genes are necessary to overcome the species barriers to pathogenesis. The recent finding that fusin can facilitate entry of HIV into cells expressing CD4 (*12*) could lead to transgenic animal models, which would allow protection against HIV infection to be studied simply in immunologically well-defined hosts. Research materials from these immunized and infected primates must be made accessible to a wider group of scientists. If we are to gain the most knowledge from these models, the time is right to use more standardized challenge strains and protocols, so that work from different labs can be compared.

The other critically necessary approach is detailed immunological studies in humans, particularly the long-term survivors and high-exposure, HIV-negative individuals as well as the recipients of new vaccines in phase II trials. Particularly informative will be "breakthroughs"—vaccine recipients who become infected. This suggests that phase II trials of promising candidates should be expanded to provide more information. Invaluable clinical material from vaccinees must be made available to a wider group of researchers, who ideally should participate intellectually, not just take samples and run. The ethical standard in clinical trials where human beings are at risk, after doing everything to ensure the safety and confidentiality of the participants, should be to gain definitive scientific knowledge. The great need in phase II trials is for the freedom to fail. Are we reluctant to ask clear reductionist questions because negative results may be seen as vaccine "failures" and discouraging to research or investment? The only truly failed trial is one that fails to produce an interpretable result.

When is a large-scale efficacy trial justified? Human clinical trials come in three stages. Phase I studies, which involve small numbers of people, assess the safety and tolerance of escalating doses of vaccine and provide some information regarding immunogenicity; phase II trials are formally expanded safety trials that include individuals at risk and seek to determine the ability of the vaccine to induce biological end points (generally, immunological correlates of protection); and phase III trials are large-scale efficacy and safety trials in individuals at risk, in which the number of people required is determined by the annual risk of infection or disease, the estimated efficacy of the vaccine, and the duration of the trial (and thus the numbers of people likely to drop out). In the United States, the highest rates of infection are about 2% for several high-risk groups; thus, phase III trials will require many thousands of high-risk individuals.

All vaccine trials require enormous care and concern for the safety and protection of the participants, and the larger a trial, the more expensive. Currently, more than 20 products are in phase I prevention trials, and one or two are in phase II trials (*2*). There are at present no phase III trials in the United States, because no vaccine has yet appeared to be sufficiently promising (*13*). Given the limitations of animal models, there is no way that knowledge about mechanisms required for human protection can be acquired other than in human vaccine trials with intense immunological analysis of the volunteers, but much of that can be done in stepwise expanded phase II trials. The question of when the use of large cohorts of people and public expenditures in efficacy trials is justified is one that I believe must be answered, in part, on the basis of the best scientific data and judgments about the likelihood of success.

Vaccine manufacturers have argued, not without justification, that there are no criteria to tell them when their products, representing large investments, will be eligible for phase III efficacy trials. Although some differences in criteria clearly must exist between a live attenuated vaccine—potentially able to revert to virulence—and a subunit protein vaccine, there could be general criteria that set a high but reasonable standard for public expenditure on phase III trials (*14*). When the criteria are set by industry lobbyists and Congress, as in one recent dismal case (*15*), misallocation of scarce public resources results. Without criteria, there is no way to assure that standards will not be changed when a company threatens to withdraw its candidate vaccine. Equally important is the need for a credible and fair process, with participation of the scientific community and industry, both to develop acceptable criteria and to recommend the most promising vaccines for efficacy trials. In that process, major consideration should be given to maximizing the probability that some efficacy will be achieved, even if it means combining different vaccines from different companies (*16*).

Where can AIDS vaccines be tested? In the United States, there are six AIDS Vaccine Evaluation Units that can carry out in-depth immunological analysis on small numbers of phase I and II trials, as well as a few well-organized high-risk cohorts in which one or two phase III trials could be carried out. For multiple efficacy trials, AIDS vaccines will have to be tested in high-incidence populations, and this will require international collaborations and testing in developing countries (*17*). In any trial, there is an ethical responsibility to ensure access to effective vaccines that are affordable to the trial populations. For efficacy trials to have the best chance of success, it is desirable that vaccines derived from strains prevalent in a given country be tested, not just those most common in the United States. The knowledge gained will be dependent on investments in training, cohort development, and infrastructures. It is expensive (*18*), yet some of those cohorts, in the absence of vaccines to test, are now providing valuable knowledge about disease risks and prevention, and the international collaborations will ultimately provide the greatest value-for-money in carrying out efficacy trials.

What can be done lacking interest from the vaccine industry? Investments in vaccine development have declined, largely because of two major disincentives. For complex vaccines containing more than the envelope protein, which will render the recipients seropositive, and for new vaccine approaches such as naked DNA and live attenuated strains (*19*), there are major liability issues that have to be clar-

ified. Because the major beneficiaries of vaccines would be people in developing countries, assuring markets and returns on long-term investments is also problematic. If there were more promising candidates, there would be greater interest. The current need is not for public-sector production of vaccines that neither industry nor the scientific community believe are likely to be effective; it is for public investment in research on understanding pathogenesis and developing better candidates, better correlates, and better cohorts for clinical trials. Further, unless we are prepared to accept vaccines to protect only the rich, global efforts to develop incentives for industry to produce AIDS vaccines—such as tax credits, patent extensions, assured markets, international loan guarantees, and harmonization of regulatory standards—must be initiated now.

What's in it for me? It's the wrong question! Variants: "How can a vaccine decision enhance the standing of my country/my institute/my company/my career/or, just me?" The most poignant iteration: Some young HIV-infected activists, concerned that vaccines will only help someone else, charge vaccine advocates with "writing them off" or diverting attention from research on treatment. Although therapeutic vaccines are not inconceivable, particularly if administered early after infection, they will be more difficult to produce; perhaps they will have to be tailored to the host's HIV strain.

What should we have learned? Vaccines remain the best long-term hope for the prevention of AIDS. The easy vaccines have already been made; AIDS vaccines represent a formidable scientific challenge. To meet this challenge optimally, some changes in the culture of research would be salutary. There is a disturbing lack of respect for applied and clinical research in the biomedical community. Everyone accepts the crucial need for basic scientific knowledge and new ideas, but vaccines aren't developed without innovative targeted research, and targeted research is currently targeted for low priority. Mechanisms for NIH funding and review ought to be reconsidered (*20*). Vaccine research currently receives less than 10% of AIDS research funding, the smallest budget allocation of all categories. The OAR review made two recommendations that I believe make good sense and should be implemented (*21*): (i) that AIDS vaccine research merits a greater share of AIDS funding; and (ii) that responsibility at NIH for AIDS vaccines be vested in the institute with the greatest expertise, the National Institute of Allergy and Infectious Diseases (NIAID), but that NIAID's decision processes be informed by the best outside scientific expertise and judgment available.

At another level, we are privileged to have some remarkable leaders in the field of AIDS research in the United States and abroad, as well as in the AIDS community, yet coherent leadership is lacking. Without greater coordination of the research of the different NIH institutes with that of the U.S. Centers for Disease Control and Prevention, the U.S. Army, the foundations, the private sector, and other countries, the vaccine effort will remain fragmented. AIDS vaccines must also be seen in a global context. Crucial knowledge will be dependent on international collaborations. Finally, in response to the question "When will we have an AIDS vaccine?" the most prudent answer may be, "An optimist is one who believes the future is uncertain" (*22*).

REFERENCES AND NOTES

1. Some excellent recent reviews of AIDS vaccines and issues include M. C. Walker and P. E. Fast, *AIDS* **8** (suppl. 1), S213 (1994); M. L. Clements, in *New Generation Vaccines*, M. M. Levine, Ed. (Dekker, New York, ed. 2, in press).
2. B. F. Haynes, G. Pantaleo, A. S. Fauci, *Science* **271**, 324 (1996); W. E. Paul, *Cell* **82**, 177 (1995); R. A. Weiss, *AIDS Res. Hum. Retroviruses* **12**, 465 (1996).
3. B. F. Haynes, *Science* **260**, 1279 (1993); P. Lurie *et al.*, *J. Am. Med. Assoc.* **271**, 295 (1994).
4. World Bank, *Investing in Health, World Development Report 1993* (Oxford Univ. Press, New York, 1993), pp. 62–63.
5. Estimates range from $12,000 to $20,000 per year per patient.
6. See reviews by L. K. Schrager *et al.*, *AIDS* **8** (suppl. 1), S95 (1994); S. L. Rowland-Jones and A. McMichael, *Curr. Opin. Immunol.* **7**, 448 (1995); A. Munoz *et al.*, *Am. J. Epidemiol.* **130**, 530 (1989); S. P. Buchbinder *et al.*, *AIDS* **8**, 1123 (1994); I. P. M. Keet *et al.*, *J. Infect. Dis.* **169**, 1236 (1994); Y. Cao, L. Qin, L. Zhang, J. Safrit, D. D. Ho, *N. Engl. J. Med.* **332**, 201 (1995); G. Pantaleo *et al.*, *ibid.*, p. 209.
7. S. Rowland-Jones *et al.*, *Nature Med.* **1**, 59 (1995); F. A. Plummer *et al.*, *Ninth International Conference on AIDS–STD World Congress*, Berlin, 6 to 11 June 1993, abstr. WS-807-3.
8. K. Travers *et al.*, *Science* **268**, 1612 (1995).
9. Y. J. Bryson *et al.*, *N. Engl. J. Med.* **332**, 833 (1995); S. S. Bakshi *et al.*, *Pediatr. Infect. Dis. J.* **14**, 658 (1995); P. A. Roques *et al.*, *AIDS* **9**, F19 (1995); O. P. Morris *et al.*, *J. Infect. Dis.* **173**, 68 (1996); M. L. Newell *et al.*, *Lancet* **347**, 213 (1996).
10. Colloquium on Feline Leukemia/Feline Immunodeficiency Tests and Vaccination, *J. Am. Vet. Med. Assoc.* **10**, 1392 (1991).
11. M. D. Daniel, F. Kirchhoff, S. C. Czajak, P. K. Sehgal, R. C. Desrosiers, *Science* **258**, 1938 (1992); B. L. Lohman *et al.*, *J. Virol.* **68**, 7021 (1994); N. Almond *et al.*, *Lancet* **345**, 1342 (1995).
12. Y. Feng, C. C. Broder, P. E. Kennedy, E. A. Berger, *Science* **272**, 872 (1996).
13. The World Health Organization's position is that any decision to proceed with phase III trials must be made by the national government of the host country [J. Moore and R. Anderson, *Nature* **372**, 313 (1994)]. Phase III trials of two gp120 subunit vaccine candidates are being planned for Thailand.
14. In the absence of known correlates of protection, some criteria that ought to be considered are induction of (i) antibodies that neutralize human isolates; (ii) cytotoxic T cells; (iii) mucosal immunity; (iv) immunologic memory; (v) persistence of immune responses for more than a few weeks; (vi) significant protection in a relevant primate model against challenge with homologous virus, heterologous virus, and virus-infected cells; and (vii) possible long-term adverse effects.
15. Former Senator Russell B. Long of Louisiana, engaged by MicroGeneSys, successfully lobbied Congress to provide $20 million to the Department of Defense to carry out a large-scale trial of its recombinant gp160 vaccine before demonstrating that it had any clinical benefit in a phase II therapeutic trial. It did not ("Maker of an AIDS vaccine says test found no benefit," *New York Times*, 19 April 1996, p. A18).
16. The current phase II trial strategies for priming T cells with a viral vector and boosting with subunit formulations to generate antibodies, combining products from different companies, represents an admirable approach to minimizing the risks of phase III "failure."
17. Incidence rates range from 6% in some cohorts to as high as 16% in the subpopulation of sex workers [H. L. Martin Jr. *et al.*, *AIDS Res. Hum. Retroviruses* **10** (suppl. 2), S235 (1994)].
18. Cohort studies (HIVNET) and AIDS Vaccine Evaluation Units represent 21% of NIAID AIDS vaccine expenditures. Whether that is an appropriate proportion of vaccine research funds, and whether the number of sites is appropriate in the absence of vaccines ready for phase III trials, are questions currently under review by NIAID.
19. One of the concerns common to naked DNA and attenuated retroviral vaccines is the possibility of their random integration into tumor suppressor genes, leading to induction of tumors, for which there is precedent with HIV itself [B. Shiramizu, B. G. Herndier, M. S. McGrath, *Cancer Res.* **54**, 2069 (1994)]. The major concern about live attenuated retroviral vaccine strains, even deletion mutants, is that they might revert to virulence upon superinfection with HIV, transplacental transfer to newborns, or transfer to immunodeficient hosts [R. M. Ruprecht *et al.*, *AIDS Res. Hum. Retroviruses* **12**, 459 (1996)] or by recombining with retroviral homologous sequences scattered across the human genome [see also R. C. Desrosiers, *ibid.* **10**, 331 (1994)].
20. The OAR review recommended that an NIH Study Section on Vaccines, not limited to AIDS vaccines, be established with panels of scientists with both academic and industry experience. Much of the AIDS vaccine effort is supported by contracts that may limit flexibility and innovation. Other kinds of funding mechanisms, such as cooperative agreements and program project grants, might be considered.
21. *NIH AIDS Research Program Evaluation, Summary Report, and Report on Vaccine Research and Development* (Office of AIDS Research, NIH, Bethesda, MD, 1996).
22. Attributed to atomic physicist Leo Szilard.

23. I wish to thank many colleagues for generously sharing their thoughts and knowledge, including D. Bolognesi, M. L. Clements, P. Fast, S. Berkley, D. Ho, B. Mathieson, J. Moore, and W. Paul.