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ISSUES -
Vaccine
- Initiative

until it's over

virtualvaccine

A Ten Point Plan to Reinvigorate our National Commitment to HIV Prevention

THE VIRTUAL VACCINE

A Ten-Point Plan to Reinvigorate Our National Commitment to HIV Prevention

1. INCREASE FEDERAL HIV PREVENTION FUNDING BY TWENTY-FIVE PERCENT TO STEM THE RATE OF NEW INFECTIONS

- Federal prevention funding at the CDC including education has been flat during the past three years ($617 million in FY97, $634 in FY98 and $634 proposed in FY99).

- Infection rates since 1996 have increased, especially among young people and communities of color. Women accounted for over one quarter (28%) of the HIV diagnoses compared to 17% of AIDS diagnoses from a recent analysis by the CDC of 25 states from 1994-97. The trends also indicate that African-Americans accounted for the majority (57%) of HIV diagnoses, compared to 45% of AIDS diagnoses.

- There are approximately 40,000 new infections every year, half of which are estimated to be among young people (under the age of 25). Despite a drop in death rates in other categories, AIDS remains the number one killer of African-Americans and Latinos age 25-44.

- The Congressional Black Caucus recently declared a "State of Emergency" because of the alarming rates of HIV/AIDS in the black community. Blacks and latinos make up 66% of AIDS cases, and blacks account for more AIDS cases than any other racial/ethnic group.

- Only 3,995 infections must be prevented annually to actually result in cost-savings.

- Increased funding should support a reinvigorated and renewed national HIV prevention effort that targets highest risk communities.

2. PROVIDE "TREATMENT ON REQUEST" TO HELP STEM THE TWIN EPIDEMICS OF DRUG ABUSE AND AIDS

- Providing treatment on request for those using drugs would help fight both the wars on AIDS and illegal drug use.

- Nearly a third of all AIDS cases and approximately half of all HIV infections are attributed directly or indirectly to substance abuse.

- A Massachusetts study of young people revealed that teens were less likely to use condoms if sex followed drinking or drug use.

- The Clinton Administration should lift the federal ban on needle exchange funding and veto any bills that would jeopardize states from implementing needle exchange programs. Also, states and local communities should implement needle exchange programs, fully fund them, and facilitate access to clean syringes.

- As the first step toward treatment on request, Congress should pass and the President should sign into law $275 million in funding increases for substance abuse programs.

- Engage the U.S. Drug Czar, General McCaffrey, to strike a more equitable balance between treatment and interdiction in the fight against illegal drug use.

3. LAUNCH NATIONAL ROLL-OUT OF PROVEN HIV PREVENTION COUNSELING

- A June study released by the NIH's National Institute of Mental Health revealed the extraordinary effectiveness of small-group counseling sessions. The 37-city study of 3,705 men and women of color demonstrated that targeted prevention including multiple group counseling sessions cut high-risk behavior in half and doubled regular condom use.

- The CDC should provide grants to community-based organizations to implement a nationwide roll-out of small-group educational and counseling sessions targeted to at-risk populations.

- Research illustrates vital need for comprehensive HIV prevention programs for adolescents. Effective programs will inform adolescents that making right decisions often takes more than knowledge, it also includes support from peers, parents, and the public health and at-large community.

4. MAKE HIV TESTING SAFE, SWIFT AND SIMPLE

- The CDC should launch a new testing campaign by improving the accessibility of HIV testing and ensuring that it is anonymous, confidential and private.

- As a part of this new testing campaign states and territories would be required, as a condition of receipt of federal funds, to have in place easily accessible HIV anonymous testing sites. In an AIDS patient survey, anonymous testers showed up for testing and medical care earlier in their HIV disease course than did confidential testers, demonstrating that anonymous testing contributes to enhancing early access to HIV testing and medical care.

- Studies indicate that ensuring the availability of anonymous testing increases the likelihood that people at risk would seek testing. An Oregon study demonstrates that there was an overall increase in testing by 50%: 125% for homosexual/bisexual men; 56% for female prostitutes; 17% for injection drug users; and 32% for other clients.

- The CDC should encourage testing vans and testing-mobiles that can help reach those who might otherwise not get tested at a clinic or doctor's office.

- The American Hospital Association should encourage hospitals to offer better HIV testing, including rapid and non-invasive procedures.

- Testing centers should implement rapid testing (results in 10 minutes vs. current week). Rapid testing would eliminate the high rate of patient return failure for results appointments. Under current tests, results are not available for at least a week. According to the CDC, 700,000 people who are tested each year do not return for their results.

5. USE STATE OF THE ART MARKETING TO SELL PREVENTION

- The CDC should oversee the implementation of an independent and vigorous new HIV prevention ad campaign.

- The marketing of these ads should follow the epidemic and should appeal to the communities most at-risk, giving fresh, accurate information.

- Enlist the help of adolescents to design and test ads intended for their generation. The Illinois Department of Public Health recently launched a prevention campaign using teens as messengers about the consequences of bad decisions.

- Instead of sensationalizing sex on TV, networks should portray sexual reality, not just fantasy. In addition, networks should allow condom ads on programs rated "S" for sexual content under the new TV rating system.

- Build comprehensive sexuality education curricula that include, but are not limited to abstinence only.

6. PUT THE AIDS HOTLINE ON-LINE TO REACH YOUNG PEOPLE

- Create an enhanced HIV/AIDS Prevention Web Page with links from popular web sites used by at-risk populations that would ensure widespread accessibility among young people.

- Deploy new technologies to allow individuals to access anonymous e-mail for prevention information as well as a national testing referral database.

- Urge states to gather accurate data including questions about same-sex behavior in a 1999 national youth risk behavior survey.

- In the anonymity of cyberspace, young people are 14 times more likely to reveal personal information, according to recent study from the Program in Health and Behavior Measurement at the Research Triangle Institute. The study demonstrates that respondents may be uncomfortable divulging potentially embarrassing information about themselves to a live interviewer, so researchers developed a computerized, self-administered survey designed to work around these problems.

7. "DO ASK, DO TELL" – LAUNCH ANTI-STIGMA AND HEALTHY LIVING CAMPAIGN FOR PEOPLE LIVING WITH HIV

- As part of HIV social marketing, the CDC should include a campaign to reduce HIV stigma and promote HIV-positive people working to protect their health and the health of others.

- Modify prevention programs to alter peer norms and reach young men at highest risk in social settings. At the World AIDS Conference, a study showed that nearly two-thirds of gay men reported engaging in unprotected anal sex at least once during the previous 18 months. Additionally, 56% of gay men under the age of 25 reported having unprotected receptive anal intercourse, a behavior that poses substantial risk for HIV infection, compared to 46% of older men.

- The CDC should develop ways to ensure that people living with HIV and receiving treatment adhere to drug regimens and work to prevent new infections among HIV-negative populations as well as their own re-infection.

- Public health departments should implement innovative programs to help eradicate STD's (e.g. syphilis) because of their role in facilitating transmission of the HIV virus.

8. THE SURGEON GENERAL SHOULD LAUNCH NATIONWIDE CAMPAIGN FOR HIV PREVENTION FOR WOMEN AND PEOPLE OF COLOR

- The Surgeon General should launch a mailing to all African-American and Latino households with information about HIV infection risks, stigma, sexually transmitted diseases and testing.

- African-Americans comprise 57 percent of new HIV infections in 25 states, despite accounting for only 13 percent of the total U.S. population.

- Young African-Americans have an even higher rate; those aged 13 to 24 years accounted for 63 percent of new HIV cases between January 1994 and June 1997.

- HIV has also increasingly affected women of all races. Of those aged 13 to 24 years, women now make up 44 percent of infections.

- Women of color are often the hardest to reach since many perceive themselves at low or no risk, yet are unaware of their sex partner's homosexual behavior or drug use.

- A majority of African Americans (52%) and one in two Latinos (50%) believe AIDS is the nation's leading health crisis, according to a survey by the Kaiser Family Foundation. Most African Americans (56%) say AIDS is a very serious problem.

9. PROMOTE PHYSICIAN PATIENT DIALOGUE ABOUT HIV RISKS

- Physicians could do more to determine a patient's risk of contracting HIV, a recent report suggests. In 73% of doctor-patient encounters, "physicians did not elicit enough information to characterize patients' HIV risk status," according to the study conducted by Dr. Ronald Epstein of the University of Rochester School of Medicine and Dentistry and colleagues.

- Grants should be made available to AIDS Education and Training Centers to promote better HIV/AIDS knowledge in the medical community.

- A recent National Health Council survey found that a greater percentage of people named television as a primary source of their medical and health news (40%) than named doctors (36%).

- The AMA, ANA and other health provider organizations should work with the NIH to develop guidelines for better physician training so that HIV risks are better identified.

10. ADVANCE FROM THE VIRTUAL VACCINE TO THE MEDICAL VACCINE

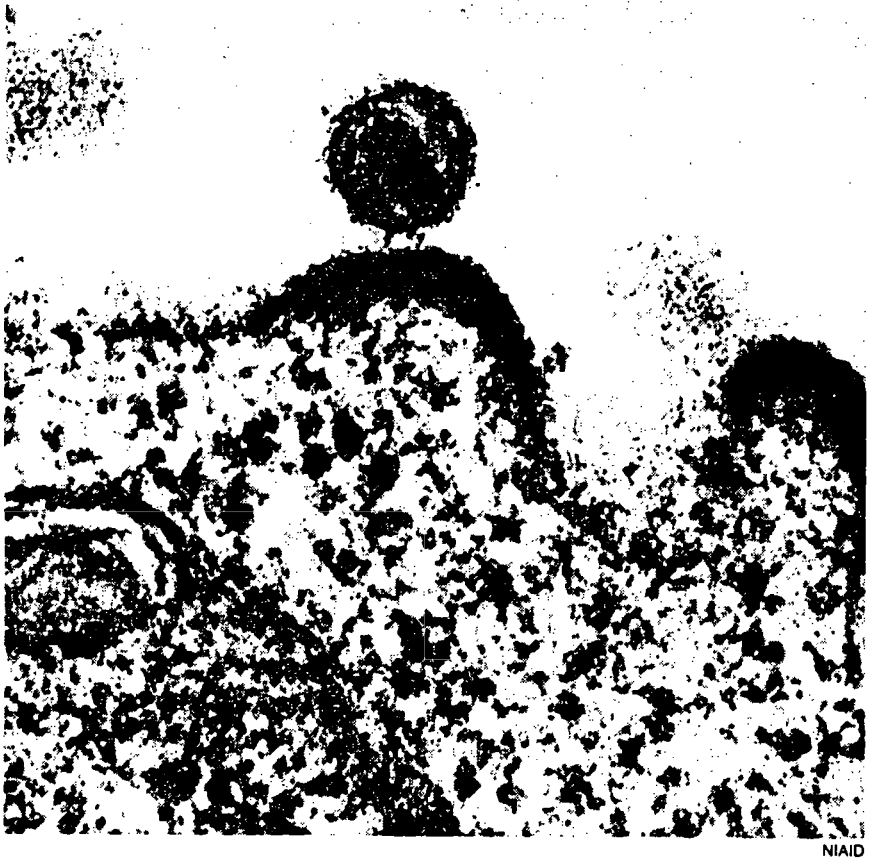
- HIV Vaccine development should be a top priority of the federal government. Increased commitment to the development of a vaccine should be accompanied by increased funding.

- In May 1997, President Clinton issued a challenge to the nation to develop an HIV vaccine within a decade.

- One year later, the President hasn't even named a director for the project. The President should act immediately to name a director and ensure a genuine commitment to the project.

The Challenge of Developing An AIDS Vaccine

by Colin Lowry



NIAID

HIV budding from the membrane of a T-cell.

The rapid spread of the AIDS epidemic throughout the world in the past year underscores the need for an effective vaccine against the HIV virus. In 1997, the World Health Organization estimated there were 5.8 million new cases of HIV infection, 30.6 million people infected, and 2.3 million deaths due to AIDS worldwide.

Research toward developing a vaccine against HIV has given scientists new insights into how the immune system responds to this virus, while presenting formidable obstacles scientists will have to overcome if they are to succeed in creating an effective vaccine. At present, the increased specialization of biology has led to the isolation of much of the research, preventing scientists from other fields from effectively contributing to AIDS research. A crash research program, implemented with policies similar to those of the Apollo Program, would be an important step toward overcoming many of these obstacles.

Vaccination is one of the great breakthroughs of modern medicine, starting with vaccines against smallpox, diphtheria, and then polio, which led to the control or elimination of these diseases. However, modern medicine confronts an unyielding enemy in HIV, a retrovirus that turns the immune system against itself. Science cannot fully explain how the HIV virus causes massive immune defects when it infects only a small percentage of immune cells. Also, the HIV virus's ability to mutate frequently, may undermine the effectiveness of a vaccine.

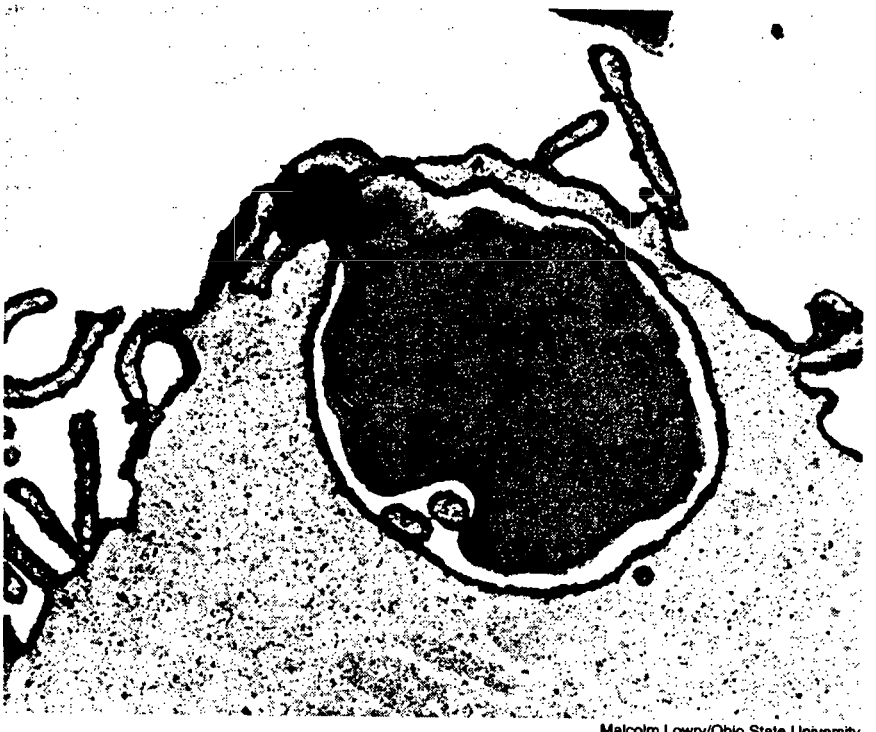
A vaccine generally works by educating the immune system in advance about a specific infectious agent, stimulating a response that creates a reserve of immune cells designed to attack the infectious agent. When these reserve cells encounter the active infectious agent, they mobilize the immune system to defend the body from infection. In order to understand how the HIV virus destroys the immune system, and the difficulties in developing an effective vaccine, a closer look at the immune response is necessary.

The Immune Response

The immune system responds to a pathogen in two ways: The first is humoral immunity, which involves the production of antibodies. The second is called cellular immunity, and involves the killing of infected cells, which is key in clearing viral infections.

Humoral immunity is a primary defense against viruses, bacteria, or other pathogens that are in circulation in the blood or lymph. Antibodies are produced by B-cells, and bind specifically to the pathogen, neutralizing it, and tagging it for destruction by other immune cells. The B-cell can bind soluble proteins, or engulf invaders, chopping up these foreign proteins, which are processed and then presented on the membrane surface of the B-cell on a specific receptor. Surface receptors are produced inside the cell, and protein fragments that are being processed there are bound by the receptor, which is then shipped to the membrane surface for presentation.

In order to become active, and start producing a specific antibody, the B-cell needs the help of another immune cell, known as the CD4 T-cell (or helper T-cell). The B-cell presents a protein fragment (antigen) from the pathogen on its membrane receptor known as MHC II, which is found only on immune cells. The CD4 T-cell can bind to MHC II receptors, and it will bind to the antigen presented by the B-cell, if the variable region of its T-cell receptor has the spe-



Malcolm Lowry/Ohio State University

Electron micrograph of a monocyte engulfing an antibody-coated target.

cific binding affinity for that antigen. Once the T-cell and B-cell have bound together, the clustering of other receptors on the membrane produces signals that activate the B-cell to produce antibodies, as well as to proliferate. The activated T-cell will also secrete molecules known as cytokines, which cause the proliferation of this T-cell, and the production of a line of memory T-cells specific for this antigen.

To complete the process of humoral immunity, the antibody-secreting B-cells indirectly recruit the help of other immune cells, including macrophages, monocytes, and neutrophils, that engulf and chemically destroy targets bound by the antibody.

Cellular immunity is responsible for destroying cells that are infected with viruses or have become damaged or cancerous. The CD8 T-cell, often called a cytotoxic lymphocyte, identifies infected cells by the presence of foreign proteins on the membrane surface. The CD8 T-cell binds to the MHC I receptor, reading the antigen held by the receptor, which is found on the surface of almost all cell types. As an example, a virus-infected cell will produce viral proteins internally, and fragments of these proteins will be presented on the MHC I receptor. A CD8 T-cell with the correct specificity, can bind to MHC I presenting a viral antigen. Once bound to the MHC I receptor, the clustering of coreceptors may activate the CD8 T-cell, which will then kill the infected cell, by lysing (bursting) it with chemicals. The activated CD-8 T-cell will then proliferate, and memory cells specific to the antigen will also be produced. CD-8 T-cells are restricted to killing cell targets that express the MHC I receptor, and are not involved in attacking free viruses or bacteria in the circulatory system.

HIV's Devious Attack

By studying the progression of patients from initial infection with HIV, to total immune suppression characteristic of full-blown AIDS, scientists have learned what damage HIV does to the immune system, but how this damage occurs is not completely understood.

The HIV virus uses many of the immune system's defense mechanisms to its own advantage, infecting responding T-cells, and relentlessly suppressing and defeating the immune system as a whole. HIV is a retrovirus, which uses RNA as its genetic material, but transcribes this into DNA using a special enzyme. A retrovirus can integrate its DNA into the genome of the host cell, and remain dormant, or it can force the cell to replicate the virus until the cell is killed, and the new viruses are released.

One of the ways HIV destroys the immune system is by infecting CD4 T-cells, disabling their function, and eventually killing them. HIV can bind to the CD4 receptor on the membrane surface of the T-cell, and, with the help of another coreceptor, gain entrance into the cytoplasm of the cell intact. This is very unusual, in that the virus escapes any enzymatic cleavage or processing by the host cell, by entering through these receptors. Once inside, the virus may replicate, killing the cell, or may integrate into the genome and lie dormant.

The destruction of CD4 T-cells, is reflected by the low T-cell counts in the bloodstream of AIDS patients. The CD4 T-cell acts mostly as a mediator for activation of immune responses. Communication within the immune system is necessary for mobilizing a response. HIV disrupts this communication, altering the normal production of signalling molecules, called cytokines, which would be produced in response to infection. By destroying CD4 T-cells, HIV also damages the function of B-cells, which require the help of CD4 T-cells to produce antibodies.

HIV also directly destroys another important immune cell, known as the dendritic cell. Dendritic cells reside in the mucous membranes, in lymph nodes, and in epithelial tissue generally. These cells act as surveillance against viruses or bacteria, by taking in foreign antigens, and presenting them to T-cells. Dendritic cells normally take in pathogens, digest them with proteolytic enzymes, and display the protein fragments on their surface within the MHC II receptor. A CD4 T-cell with the correct specificity can then bind to the MHC II receptor of the dendritic cell, becoming activated to proliferate. In this way, dendritic cells activate a T-cell response to pathogens encountered within mucous membranes, often before the pathogen gets into the bloodstream.

The HIV virus uses the ability of the dendritic cell to pass antigens to T-cells, as a direct route to infect the CD4 T-cell population. HIV can also bind to and enter the dendritic cell intact. When an infected dendritic cell contacts a CD4 T-cell, it often passes intact HIV to it, infecting the T-cell. In AIDS patients, the number of dendritic cells remaining in

the mucous membranes decreases rapidly, as the disease progresses.

Cytotoxic T-lymphocytes, predominantly CD8 T-cells, responding to HIV proteins on the surface of infected cells, are activated to destroy infected CD4 T-cells, dendritic cells, and others, also contributing to the decline in immune function. However, cells infected with HIV that are in latency, with no viral proteins being expressed on their cell surface receptors, will not be detected and killed by CD8 T-cells, leaving a reservoir of the virus. Once the HIV virus has infected enough immune cells to suppress immune function, the amount of virus present in the blood increases, accompanied by the loss of CD8 T-cell response to HIV antigens, overwhelming the system in the final phase of AIDS.

Vaccine Problems Specific to HIV

The HIV virus presents some special problems for scientists who are designing an effective vaccine. The virus mutates frequently, disguising itself, so variants may escape detection by the immune system. The coat proteins of the virus are not highly antigenic; they are not recognized well by B-cells, meaning that they do not elicit a strong antibody response. Also, most of the antibodies to HIV coat proteins isolated from AIDS patients, do not neutralize the virus, or are antibodies to viral debris or immature coat proteins, that are not found on the actual infectious virus.

An effective vaccine would have to stimulate an antibody response, and a strong cytotoxic T-lymphocyte (CTL) response. Vaccination with HIV coat proteins may be able to generate an antibody response, but not a CTL response, because CTLs recognize foreign proteins made within cells that are presented on the cell surface. By the time antibodies in the blood can bind to HIV, it is usually too late, because the virus has infected the CD4 T-cell population, through the dendritic cell pathway.

Many vaccines against viruses have been based on live, non-pathogenic, weak versions of the infectious virus. Application of a live, weakened HIV virus vaccine in human beings would be very dangerous, for several reasons. No one knows what the long term effects of retroviruses are in human beings, and the fact that retroviruses can integrate into the host DNA, means they may create mutations which, in the long term, would lead to cancer. Also, there is the possibility of causing an active infection using a live HIV vaccine.

Experiments in monkeys using weakened versions of the simian SIV, which is related to HIV, have shown that viruses that were supposed to be non-pathogenic, when used as vaccines, caused full-blown AIDS symptoms in some of the monkeys. However, in monkeys that did not get sick, the live virus vaccines produced a strong immune response, which protected them from infection when the monkeys were challenged with the pathogenic SIV virus. Scientists are not sure how the weakened SIV caused disease, because several genes believed to be involved in pathogenicity had been deleted from it. When researchers analyzed the virus present in the sick monkeys, it was clear that the virus had undergone genetic changes. Because there are so many unknowns, and a high risk of causing infection, use of a live, attenuated HIV vaccine in human beings remains only a remote possibility.

The first vaccine designs, tested about 10 years ago in animals, involved injection of the coat proteins of HIV/SIV under the skin. These vaccines could elicit an antibody response in roughly 40 percent of the animals, but did not induce any cytotoxic lymphocyte response. When the animals that produced antibodies to the SIV coat proteins were challenged with infectious virus, only a very small percentage were protected from infection. The problems with this type of vaccine stem from the fact that it does not produce a CTL response, and it is unlikely that any of the antibodies produced will neutralize the infectious virus. Other problems with us-

Glossary

Antibody: A special protein, made with specific capacity to bind to a region of another protein. Produced by B-cells. Antibodies bind to foreign proteins on invaders, and target them for destruction by other immune cells, such as macrophages and monocytes, which engulf and chemically destroy the target.

B-cell: Responsible for production of antibodies. The B-cell binds to soluble proteins, or engulfs invaders whole, then presents these antigens on its surface within MHC II. Requires T-cell help for activation to proliferate, and secrete antibodies.

CD4 T-cell: Binds to antigens presented by the MHC II receptor. When active, helps B-cells by providing second activation signal for production of antibodies. Secretes cytokines which promote proliferation of T-cells.

CD8 T-cell: Acts as a cytotoxic cell, kills infected cells. Binds to antigens presented by the MHC I receptor. The CD8 reacts to proteins produced internally by other cells, that are held on the surface by MHC I.

Dendritic cell: A specialized immune cell, found within membranes and epithelial tissue. It engulfs pathogens, and presents antigens to T-cells on MHC II. It is easily infected by HIV.

Macrophage: A professional engulfing cell. Destroys foreign bacteria, viruses, etc. Can also present antigens on MHC II to T-cells.

M-cell: A mucosal membrane immune cell, found in the lining of the gut. It takes antigens from the gut, and passes them to immune cells in associated lymph nodes.

MHC I receptor: This cell surface receptor is known as the "self recognition" receptor. It presents protein antigens from proteins produced within the cell. It is found on almost all cell types. An HIV-infected cell will present viral protein antigens on this receptor.

MHC II receptor: This cell surface receptor is found only on immune system cells. It is used to present antigens from one immune cell to the next. CD4 T-cells recognize antigens held by this receptor. Immune cells interact by cell-to-cell contact.

Monocyte: A lymphocytic cell. It is also an engulfing cell. It can present antigens on MHC II to T-cells.

ing the whole HIV coat proteins as immune stimulators have only recently come to light.

Several scientists have pointed out that the degree of immune suppression in HIV-infected individuals before the development of AIDS is quite high. The percentage of infected immune cells, including CD4 T-cells, in these patients is too low to account for the immune defects observed. A study by K.J. Weinhold and D.P. Bolognesi et al., demonstrated that the purified HIV coat protein gp120 can suppress T-cell activation, and may set up the CD4 T-cell for cytolytic destruction by CD8 T-cells. The coat protein, gp120, is a glycoprotein, meaning it contains carbohydrate residues attached to its surface. The gp120 protein binds directly to the CD4 molecule on the surface of the T-cell. The binding of gp120 to CD4 may act to block the T-cell from receiving antigens presented to it within MHC II, which would result in a complete lack of T-cell activation. The binding of gp120 to the CD4 molecule of the T-cell, may also initiate programmed cell death (apoptosis), in the absence of another activating signal.

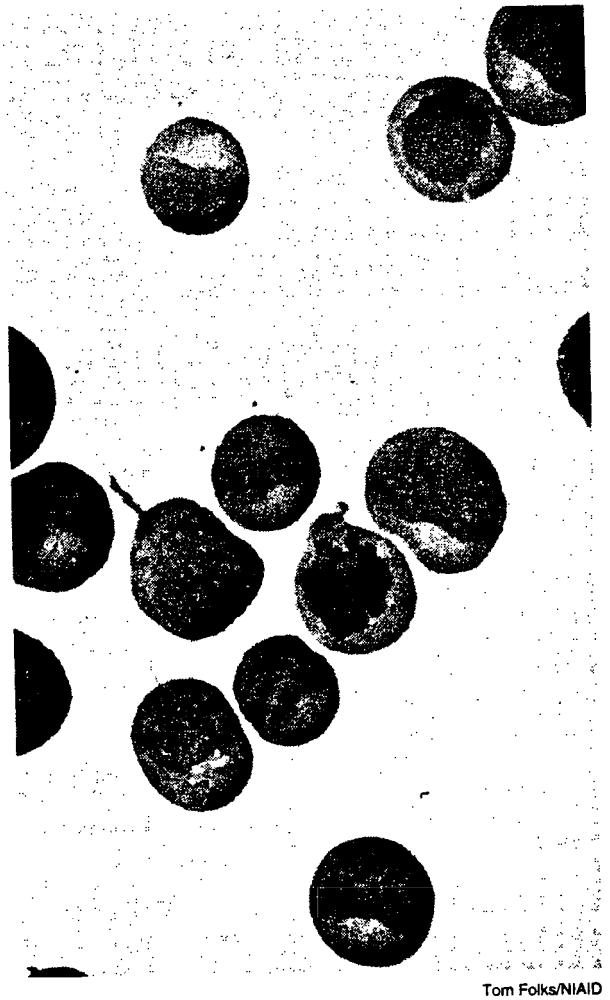
This is consistent with what was found in a study by J.J. Eron, in which individuals already infected with HIV, were given an immunization of recombinant gp120, which failed to slow the course of the disease. A trend that was perceptible but just under statistical significance, was that many of the immunized patients actually progressed to full-blown AIDS faster than the non-immunized group.

A DNA Vaccine Approach

The idea of using viral DNA as a vaccine offers several advantages over using viral proteins alone. The goal is to introduce a portion of viral DNA, such as a gene for the HIV coat protein, into cells using a vector such as a harmless virus, so that the DNA is translated into protein made inside the cell. Once the protein is produced inside the cell, portions of it will be displayed by MHC I surface receptors, which could activate a cytotoxic T-cell response. Also, the protein could be secreted by the cell, or cells already lysed (killed) by CTLs may release the viral protein, which would activate an antibody response.

Studies by E.L. Cooney and P.D. Greenberg compared the ability of a DNA-based vaccine and a protein vaccine, to induce an immune response against HIV in human beings. A vaccinia virus containing the HIV gene for the full length coat protein, gp160, was used as a DNA vaccine. Used alone, this vaccine elicited a low T-cell proliferative response in 8 of 11 patients. However, the response was not sustained, and 12 months after immunization, T-cells from these patients did not respond to HIV antigens. This vaccine also elicited a poor antibody response, with only 3 of 11 patients producing antibodies, none of which neutralized the virus. The antibody response was no longer measurable 12 months after immunization.

Results using gp160 protein alone gave even lower percentages of immune response. Only 1 of 4 patients produced antibody to HIV, and this response also disappeared within 12 months after vaccination. T-cell responses were even lower, and more fleeting than with the DNA vaccine alone. These unsuccessful results prompted the researchers to try a vaccine regimen combining the HIV gp160 DNA and gp160 protein.



Tom Folks/NIAID

Normal T-cells.

Combined vaccination with the vaccinia virus containing gp160 DNA, followed by injections of the gp160 protein, produced stronger and longer-lasting immune responses to HIV. Neutralizing antibodies to HIV were found in 7 of 13 patients. T-cell responses, primarily CD4 T-cell proliferative responses, were found in 12 of 13 patients. Cytolytic T-cells were detected in several patients, but the study, done in 1993, had difficulty determining if any of these were CD8 T-cells.

More recently, experiments conducted in 1996 by B. Fleury and Y. Riviere et al., at the Pasteur Institute in Paris, have shown that a combined vaccine regimen does induce a CD8 cytolytic T-cell response against HIV antigens. In these experiments, a canarypox virus containing HIV gp160, followed by two injections of recombinant gp160 protein, elicited CD8 T-cell responses in 7 of 18 immunized patients. In two of these seven subjects, the CD8 T-cell response was still present two years after immunization.

Peptides and Fusion Proteins

Vaccines containing the coat proteins of HIV suffer from their inability to activate a cytotoxic T-cell response, because the coat proteins are not internalized by cells. Several strategies are currently being worked on to use fusion proteins or peptides, that can get inside the cell, and be presented on the MHC I receptor, to elicit a CTL response. The immune system recognizes and reacts strongly to certain bacterial proteins, such as coat proteins from tuberculosis, or other common infectious bacteria. These bacterial proteins are often used

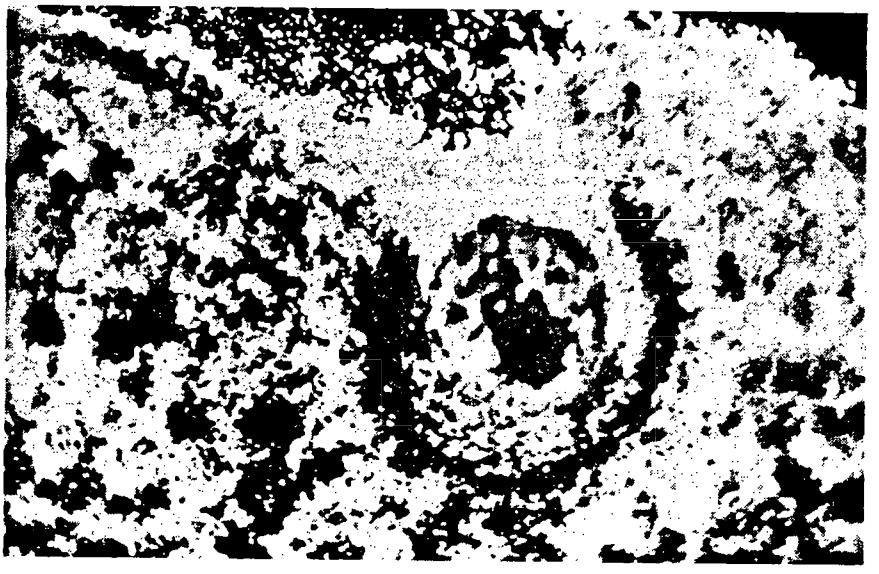
as an adjuvant, mixed with the vaccine antigens, designed to recruit an immune response that recognizes the vaccine antigens. Because the HIV proteins do not produce a strong immune response alone, fusing the HIV proteins to highly antigenic bacterial proteins would cause a mobilization of the immune system, and strong recognition of accompanying HIV proteins.

One of the more ingenious approaches uses the natural ability of proteins from the toxic anthrax bacteria, to cross cell membranes and enter the cytoplasm. Experiments by T.J. Goletz and J.A. Berzofsky, constructed genetic fusions of the HIV gp120 with the anthrax lethal factor, which had its catalytic domain deleted, making it non-toxic, and tested whether this fusion protein could be processed and presented on MHC I. The anthrax fusion protein acts as a "molecular syringe," delivering the gp120 protein inside the cell, which is then processed and presented on MHC I. This was shown to produce a strong CTL response in mice.

In experiments not related directly to HIV, heat shock fusion proteins have also been shown to be effective immune stimulators of antibody and CTL responses, and promising candidates for vaccines. Heat shock proteins are produced by cells under stress, and have the ability to chaperone other proteins across cell membranes. Heat shock proteins from mycobacterium act as their own adjuvant, stimulating a strong immune response, activating the immune system by triggering the production of cytokines, which enhance the proliferation of immune cells, such as T-cells.

Experiments by K. Suzue and R. Young, tested whether a tumor cell protein fused to mycobacterium heat shock protein could induce CTL response against the tumor cells. Mice were first immunized with the fusion protein, and then injected with tumor cells. These immunized mice produced strong CD8 CTL responses against the tumor cells, and 80 percent of the immunized mice survived, as compared to 100 percent fatality in the control mice, 21 days after injection of the tumor cells. The use of heat shock fusion proteins for HIV vaccines is very promising, and is currently under development.

A very different approach to vaccine design involving synthetic peptides is being developed by Jay Berzofsky and Jeffrey Ahlers. This approach requires knowing what parts of the HIV coat proteins actually bind to MHC receptors, and stimulate a strong response. The idea is to synthesize peptides that correspond to these HIV protein areas, which can then directly bind to MHC I and MHC II, and stimulate a neutralizing antibody response. By directly binding to MHC I, the peptide tricks the system, in that normally only internal protein fragments would be presented on this receptor, which is key to stimulating a CTL response.



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AIDS virus penetrating a cell, magnified many thousands of times.

Another variable in immune responses is that there are many different varieties of MHC receptor genes in the general population. The slight differences in variety influence what portion of an antigenic protein is strongly bound by the MHC receptors. Through careful study in mice and in infected humans, Ahlers and Berzofsky have identified regions of the coat proteins of HIV, that are recognized by multiple MHC types. By analyzing segments of these protein regions, they have identified specific sections, called determinants, that stimulate CTL response, neutralizing antibodies, and helper T-cells. These protein sections are usually 20 to 30 amino acids long, and can be synthesized in the form of peptides.

The vaccines based on this approach are composed of peptides that contain multiple determinants for several MHC binding types, consisting of protein regions common to several HIV subtypes. The peptides are mixed with an adjuvant, containing bacterial proteins known to elicit a strong immune response, which helps the peptides to be recognized by the immune system. Experiments with these vaccines in mice have been successful in stimulating neutralizing antibody and helper T-cell responses, as well as CTL responses to HIV coat proteins.

The stimulated T-cells from these mice were tested against various strains of HIV. These T-cells were found to react to two HIV strains common in Europe and North America, but not to two strains from Africa and Haiti, which differed enough from the peptide determinants used in the vaccine, to escape detection. This problem of recognition of several different HIV strains affects any vaccine design, but by adding peptides that represent determinants of more strains, this synthetic peptide approach may be able to overcome it.

HIV Variants Escape Detection

One of the most troublesome problems with HIV, is that small variations in its proteins occur rapidly as a result of mutation, which often allows these variants to escape detection by the immune system. This is one of the ways vaccines made against a specific subtype of HIV, can fail to protect against infection by a variant strain.

A case of a vaccine failure involving an unusual phenomenon known as T-cell antagonism, was documented in a study by S.J. Kent and M.J. McElrath. An

individual immunized with a vaccinia virus vector containing gp160 DNA, and boosted with recombinant gp160 protein, produced strong CD4 proliferative and CTL responses, as well as neutralizing antibodies to HIV. Researchers assumed that this level of immune response would provide protection against HIV infection. However, this individual later became infected with an HIV strain that differed slightly from the one used to make the vaccine.

T-cells that recognized a specific region of the HIV gp160 were removed from the immunized individual, before he became infected, and cultured. These cultured T-cells were compared to the T-cells present in the immunized individual after he became infected, for their ability to recognize and lyse target cells bearing the gp160 sequence used in the vaccine. Surprisingly, the T-cells taken after the individual became infected with the variant HIV, failed to recognize or lyse cells bearing the original gp160 sequence, to which they had previously responded. The strain of HIV that infected this individual had two mutations in the region of gp160 that was used to make the vaccine. This phenomenon of T-cell antagonism, where a variation in the region of the HIV protein bound by the MHC receptor, causes the T-cells to lose the ability to recognize the original strain, is not fully understood.

Other studies of T-cell antagonism have provided clues to its importance in the progression to AIDS. Experiments by D.A. Price and R.E. Phillips, have demonstrated that the immune system's CTL response in initial HIV infection, exerts a selective pressure on the virus, which promotes the survival of variants that can escape detection. These escape variants, were shown to have mutated the sites that were recognized by CTLs in proteins of the viral envelope. However, the escape variants did not become the dominant viral species. The variants' ability to antagonize T-cells, which causes the T-cell to fail to recognize the original, dominant form of the virus, does not require large numbers of variants. These escape variants provide protection for themselves, and the dominant species of virus, by disrupting T-cell function.

T-cell antagonism has been found to occur in hepatitis B infection, and the mechanism by which it inactivates T-cells has only been partly defined. Experiments using peptides, as substitutes for variant viruses, have shown that peptides with only 1 or 2 sequence changes, can bind to MHC I, but do not trigger activation of T-cells. Normally, immune cells require two signals for activation, as a safeguard to avoid over-responding to rare antigens or nonspecific binding of a receptor. A signal from an isolated receptor will be ignored, and no activation will occur. HIV isolates the components of the signalling network, cutting off activation, and turning the immune system against itself by interfering with this signalling. T-cells that have a variant peptide bound to MHC I, often go into programmed cell death in the absence of a second activation signal. This leads to inactivation of the T-cells, and by unexplained mechanisms, to the loss of recognition of the original protein to which they first responded.

THE FOUR MAIN WEAPONS OF HIV

(1) Infect the immune cells that respond to it. Gain entrance intact into CD4 T-cells and dendritic cells.
(2) Mutate coat proteins, use as disguise, and escape detection by immune system.
(3) Coat glycoproteins can bind and inactivate T-cells, disrupt T-cell communication.
(4) Use *nef* protein to rip down MHC I receptor from surface of infected cell. Allows HIV to hide and replicate undetected in the cell.

HIV has some other tricks to escape detection by the immune system. The virus can infect types of neuronal cells, which do not display MHC I receptors, allowing the virus to hide from immune responses. Latently infected neurons are tolerated by the immune system, which provides a reservoir of viruses which can be reactivated at a later time. This strategy is used by many viruses other than HIV, such as herpes.

Recently, HIV was shown to have a unique method of escaping detection once inside a cell. The HIV *nef* protein, critical to its pathogenicity, was shown to be capable of forcing the infected cell to eliminate the expression of MHC I receptors on its membrane surface. Without MHC I receptors, the cell cannot signal to immune cells that it is infected, as no viral proteins can be presented to CD8 T-cells. The virus can then replicate in the camouflaged cell undetected, until it is ready to kill the cell, and release more viruses. This effect requires some incubation time, and does not always occur.

An unexpected property of CD8 T-cells has been found through the study of their response to HIV-infected CD4 T-cells. Usually, CD8 T-cells lyse infected CD4 T-cells, but it has now been discovered that CD8 T-cells can secrete a soluble factor that inhibits viral replication in the infected CD4 T-cells in close proximity. This factor is believed to inhibit the transcribing of the viral genes, although it has not yet been identified.

Stimulating Mucosal Immunity

One of the main routes for the HIV virus to invade the body is through mucous membranes. A vaccine that can elicit mucosal immunity to HIV may provide effective protection against infection. Researchers are experimenting with salmonella bacteria as a vector for delivering HIV antigens specifically to the immune cells that reside in mucous membranes, and the gastro-intestinal tract. Within the gastro-intestinal tract membranes lie special clusters of immune cells, called Peyer's patches. These patches contain M-cells, which sample the antigens in the gut, and are associated with underlying lymph nodes, containing monocytes, T-cells, B-cells, and macrophages. M-cells act by presenting antigens to the cells in the associated lymph node. Salmonella is unusual in that it crosses the mucosal barrier, and targets M-cells. Salmonella is highly antigenic, and elicits strong mucosal immune responses. These characteristics make it a good vector for a mucosal vaccine to HIV.

Experiments by S. Wu, D. Pascual, and D. Hone, tested a salmonella vector expressing HIV gp120 in animals for its ability to stimulate mucosal immunity. Oral doses of this vaccine induced T-cell proliferative responses, and the secretion of IgA antibody, which is found in the

gut, and differs from the IgG antibodies found in the bloodstream. It was unclear whether any CD8 T-cells were stimulated by this vaccine, although they are present in the lymph nodes beneath M-cells, and are often stimulated by salmonella infection. The development of salmonella vectors as HIV vaccines is in an early stage, and has not been tested in humans, although animal experiments have shown it to be a promising approach.

Will a Vaccine Protect a Population?

Significant unanswered questions remain concerning the effectiveness of any of the HIV vaccines in protecting a large population from infection. There have been only small trials of vaccines in humans, from which it is very difficult to extrapolate results to a larger population. The first large-scale trial of an HIV vaccine, based on recombinant gp120 protein, is scheduled to begin in Thailand this year. Whether or not this vaccine will protect against infection from multiple strains of HIV, and how the genetic background of the population influences the vaccine's effectiveness, will only be partly known once the trial is over. Unfortunately, the gp120 vaccine being tested in Thailand, has shown poor results in small trials in the United States. The vaccine has been shown to be safe, and without side effects, and as such has been approved for further testing. However, some of the better vaccine designs, which have provided excellent results in small trials, should be accelerated to large-scale trials, especially in areas of the world where the HIV virus is spreading most rapidly.

Research on treating HIV-infected patients has led to treatments which do prolong their survival. However, the much touted "triple drug therapy" has been shown to leave reservoirs of the virus in the patient's infected T-cells. Even when this drug therapy eliminates the virus from the bloodstream, experiments have shown that resting CD4 T-cells from infected individuals, contain HIV, that when stimulated, actively replicates, as shown by T.W. Chun and Anthony Fauci.

Is the lack of more complete knowledge of the immune system, one of the largest obstacles to the effective treatment of AIDS, and the development of a vaccine against HIV? The problem with much of the research being done today, is that it rests on mechanistic, often linear, concepts of the immune system, and living systems in general. Key parts of the biological picture are missed by this mechanistic approach. The application of technologies usually reserved for physics, such as advanced spectroscopy, could provide scientists the means to explore the fundamental electromagnetic processes characteristic of living systems.

Proposals for a crash research program in biology using advanced biophysics, were made by this magazine's predecessor, *Fusion,* in 1985 and 1986, as part of a strategy to stop the spread of AIDS, and find a cure. Researchers have barely opened up investigations into the electromagnetic interactions between cells, which may provide insight into a new level of organization in the immune system. Perhaps if scientists can overcome these conceptual problems, the problems of creating an HIV vaccine will be solved.

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file Vaccines

QUOTES SUPPORTING THE PRESIDENT'S CHALLENGE FOR AMERICA TO DEVELOP AN AIDS VACCINE WITHIN TEN YEARS

"AIDS Action Council is anxious to work with you to ensure that this era of hope--raised to a new level by your call to re-energize our nation's search for an AIDS vaccine--touches the life of every American living with, and affected by, HIV and AIDS."

-- AIDS Action Council 5/20/97

"The President has set a difficult goal for the research community, but NIH is ready to bring its scientific expertise and resources into play...recent advances in immunology and virology have increased optimism that (creating an AIDS vaccine) can be done."

-- Dr. Harold H. Varmus, NIH Director

"The International AIDS epidemic will only be overcome by the development of an effective HIV vaccine, and American science has a critical role to play in developing one. But this vaccine can be made only if the scientific community receives strong support from the federal government to overcome the very real obstacles that will exist for years to come. The President's intellectual endorsement of our efforts is very welcome."

-- David D. Ho, M.D.

"For millions of people at-risk for HIV infection across the globe, the simple knowledge that the greatest nation on earth will lead the effort to develop a preventive vaccine is very powerful."

-- National Association of People With AIDS 5/21/97

"Your extraordinary leadership in setting the goal for the development of an AIDS vaccine in the next ten years merits sincere praise. Mr. President, we pledge UNAIDS to work with you...in the forefront of this crusade against AIDS."

-- UNAIDS 5/20/97

"I am absolutely convinced that we will have a vaccine (for AIDS) that is safe and effective."

-- Dr. Anthony Fauci, National Institute of Health 5/19/97

"It's like polio in the iron lung days. People were overjoyed to have the iron lungs, but that was no way to live if you had the opportunity to be protected. So protection is the right response."

-- David Baltimore, chairman of the NIH Vaccine Commission 5/19/97

"I like the idea of setting a goal."

-- Robert C. Gallo, co-discoverer of HIV 5/19/97

"We salute your use of the Presidency to keep issues related to the worldwide AIDS pandemic at the forefront...We acknowledge the importance of a targeted initiative for vaccine development and recognize that a vaccine is critical to preventing new infections in youth and adults at risk for infection."

-- Cities Advocating Emergency AIDS Relief 5/19/97

"The IAVI strongly supports your call for an urgent increased and time-bound effort to develop safe and effective HIV vaccines. We also applaud your plans to call for the leaders of the G-7 countries and Russia to join the U.S. in a global effort to create a vaccine."

-- International AIDS Vaccine Initiative 5/19/97

"There are still many unexplored or only partly explored avenues of research that could lead to an effective vaccine within a few years...Our planned research institute will be eager to participate with the U.S. government in its effort to speed up the development of an AIDS vaccine."

-- Luc Montagnier, discoverer of the virus that causes AIDS and head of the Swiss-based World Foundation for AIDS Research

"Mr. President, AMFAR strongly supports your goal to develop a successful vaccine for the prevention of HIV infection by the year 2007. We believe that this is a realistic goal...AMFAR will provide grant support for selected promising research projects...We hope to join with the federal government in further increasing our financial commitment until, like smallpox and polio, HIV infection is brought under full control throughout the world."

-- The American Foundation for AIDS Research (AMFAR)

"The development of a vaccine against AIDS will be an accomplishment of the greatest importance to humankind. Advances in biomedical research supported by the National Institutes of Health have created new opportunities and encouragement in our search for an effective AIDS vaccine. The NIH is committed to allocating the resources necessary to move us forward."

-- Dr. William E. Paul, Director of Office of AIDS Research of NIH

LIVE ATTENUATED VACCINES: BEST HOPE TO PREVENT HIV DISEASE?

Ronald C. Desrosiers, PhD

Since Edward Jenner devised a vaccine against smallpox 200 years ago this year, vaccination has proved to be medical science's most potent weapon against viral diseases. Smallpox, yellow fever, measles, mumps, rubella, polio, influenza, rabies, and hepatitis B can all be prevented by vaccination. Smallpox, in fact, has been eradicated.

When HIV was determined to be the cause of AIDS in 1983, some predicted that scientists would rapidly develop a vaccine to prevent this viral disease. AIDS, however, turned out to be difficult to prevent through vaccination. A major problem in developing an effective vaccine against HIV is the unique ability of this retrovirus to replicate persistently and relentlessly in almost all persons infected, despite a strong host immune response. A second problem is the extensive variability in the viral target of neutralizing antibody responses, the envelope protein.

With the benefit of hindsight and an increasing understanding of the pathogenesis of this disease, it is not surprising that researchers have yet to produce a vaccine candidate likely to be safe and effective enough for large-scale efficacy trials in humans. That the natural immune response ultimately fails suggests that a successful vaccine must provide highly stringent protective immunity. In other words, we are asking a vaccine to induce an immune response that is better than the natural immune response to infection. To complicate matters, antibodies to one strain of HIV cross-neutralize other strains poorly or not at all.

In animal models of AIDS—the focus of our study at the New England Regional Primate Research Center—one vaccine candidate after another proved unequal to the task of protecting monkeys from disease. Inactivated whole virus particles in adjuvant, recombinant envelope protein in adjuvant, recombinant viral vectors, and several vaccines containing a cocktail of viral antigens performed poorly or failed totally. A particularly sobering aspect of these failures is that they occurred despite use of highly idealized laboratory conditions. Challenge doses were minimal, were of the same strain used in the vaccine, and were given precisely when the vaccine-induced response was judged to be maximal. Such conditions would rarely be duplicated in the field.

The failures of these early experiments, coupled with an unexpected finding in our laboratory, have led us to consider another path to protection from AIDS. A review of the vaccines that are effective against human viral disease shows that the most consistently successful strategy has been vaccination with live attenuated virus. Vaccines for yellow fever, measles, and mumps and the Sabin polio vaccine all use live attenuated virus. Only vaccines for influenza and rabies and the Salk polio vaccine use an inactivated virus, and only the hepatitis B vaccine uses a recombinant subunit of the virus—the approach studied most vigorously in human trials of an HIV vaccine.

Viral subunit vaccines stimulate the immune system with one or more pieces of the virus. One piece is usually part of the viral envelope protein, the protein that HIV uses to dock to its primary cellular receptor, CD4. The hope is that the resulting stimulation will be enough to prime the immune system to recognize a later actual infection with HIV. If that tactic worked, as it has with the vaccine against hepatitis B virus, it would be the preferred strategy because these subunits or components of HIV cannot themselves cause HIV infection. So far, however, the subunit strategy has not shown great promise.

Vaccination with live attenuated viruses has been the favored means of preventing several human viral diseases because the strength, breadth, nature, and duration of the immune response that they elicit is difficult to match with other vaccine approaches. They are so potent because, rather than presenting mere components of the virus to the immune system, they present nearly intact virus that can replicate and that actually causes infection.

However, the level at which attenuated virus replicates in the host is generally much lower than the level of replication of wild-type or field strains of virus. When a live attenuated vaccine is successful, the level of replication is so low that disease almost never develops, yet the level is great enough to prevent disease following exposure to field strains of the virus. Still, the possibility of causing HIV disease with a vaccine and the certain prospect of causing low-level infection have placed live recombinant vaccines at the bottom of many scientists' lists of HIV vaccine candidates.

In 1992, I proposed that a live attenuated virus vaccine be studied as a strategy to prevent HIV disease.[1] Recognizing the risks posed by live attenuated vaccines, my colleagues and I

nonetheless believed that in many instances the risks could be justified if such a vaccine substantially outperformed others. And work we were doing at that time in monkeys suggested that this approach could do just that.

As our early work on simian immunodeficiency virus (SIV) vaccines in monkeys proceeded, we were also trying to determine how SIV and HIV actually destroy the immune system. To solve that mystery, scientists have been studying the nine genes of HIV and corresponding SIV genes in an attempt to define their precise contribution to pathogenesis. One of the genes on which our group was focusing was *nef*, which partially overlaps one end of the genome called the long terminal repeat (LTR) (Figure).

We isolated a clone of a highly virulent strain of SIV designated SIVmac239.[2] Using recombinant DNA procedures, we then deleted sequences in the *nef* gene of the virus to create a derivative called SIVmac239/*nef*-deletion or SIVmac239Δ*nef* (see Figure). We then injected six rhesus monkeys with the *nef*-deleted virus to assess how *nef* affects the course of disease in these monkeys compared with others that we infected with wild-type *nef*-containing virus. The monkeys who were given unaltered SIVmac239 began to die with the simian equivalent of AIDS, whereas those who were given the *nef*-deleted SIV stayed healthy. This attenuated virus replicated in the six animals; yet, the level of circulating virus remained very low, and CD4 lymphocyte counts remained normal.

The effect was so strong and sustained that we soon began wondering whether we had inadvertently created a live attenuated SIV vaccine. To find out, we challenged four of the six animals with 10 rhesus monkey infectious doses of fully pathogenic *nef*-containing SIV, either SIVmac239 or SIVmac251.[3] The challenge doses were administered 2 years and 3 months after these monkeys had been injected with *nef*-deleted SIV. Four control monkeys who had not been given SIVmac239*nef* were also given 10 infectious doses of one or the other pathogenic strain of SIV.

The four control monkeys had a spike in plasma antigenemia 2 weeks after injection with SIV, the response expected after infection. But none of the four monkeys who had been "vaccinated" with *nef*-deleted SIV had such a spike or any detectable plasma antigenemia at any time.[3] All four control monkeys had high levels of virus in peripheral blood mononuclear cells (PBMCs). Only 1,000 to 20,000 PBMCs were needed from these animals to recover SIV in culture. With one of the "vaccinated" monkeys, we detected SIV 4 weeks after the challenge in 74,000 PBMCs, but later the virus could not be detected even in 10^6 cells. In the other three test monkeys, viral loads were invariably low. Recovery of SIV was consistently difficult even with 10^6 or more PBMCs.

We used sensitive amplification assays, necessary because of the low viral burdens in the test monkeys, to examine the viral sequences of these four animals in PBMCs sampled at several points over the ensuing 40 weeks. Sequences corresponding to the wild-type *nef*-containing SIV were not detected in any of the four monkeys.

Two of the four test animals were rechallenged 37 weeks after the first challenge with 1000 rhesus monkey infectious doses of wild-type SIVmac251. Even at this dose, 100 times higher than the original dose, we could not recover the challenge virus from 10^6 PBMCs. Again, amplification of SIV sequences showed only the original *nef*-deleted virus.

These protective effects were far and away the most impressive we have seen with any SIV vaccine. To this day, viral loads in these four monkeys remain low, their CD4 counts remain stable, and they remain asymptomatic. Other workers have since confirmed the substantial level of protection attainable with a live attenuated SIV vaccine.[4] But attenuated vaccines are not universally successful in the SIV model,[5,6] and such failures attest to the difficulty of protecting against challenge with a highly pathogenic strain of SIV. However, the protection achieved with live attenuated vaccines in monkeys is clearly more potent than the protection achieved with any other strategy advanced to date.

HIV and the simian viruses related to it are unique among retroviruses. In addition to the genes required for replication, they carry auxiliary genes—such as *nef*, *vpr*, and *vpu*—that are not absolutely essential for replication. Yet, because these auxiliary genes have been conserved as HIV and SIV evolved, they must enhance the ability of these viruses to reproduce. Our work demonstrated that SIV requires *nef* to cause AIDS in monkeys.[2] In the past 2

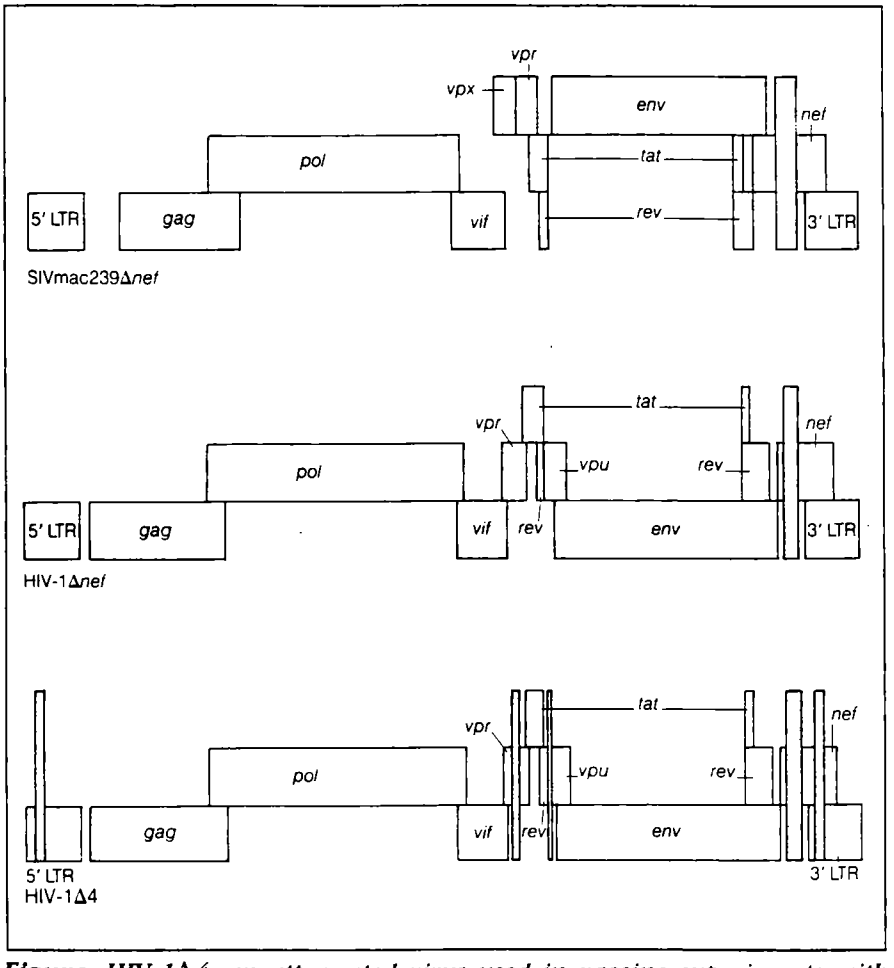

Figure. *HIV-1Δ4, an attenuated virus used in vaccine experiments with chimpanzees (bottom), is missing segments of the* vpr, vpu, *and* nef *genes, as well as a segment of the long terminal repeat (LTR) overlapping* nef. *In comparison, only a segment of* nef *is missing from the mutant HIV-1 found in a long-term progressor (middle) or in SIVmac239*Δnef *(top), the attenuated virus that has been protective in monkeys.*

years, several cases of humans infected with *nef*-deleted HIV suggest that this gene also facilitates progression to AIDS in HIV-infected humans.

In collaboration with colleagues at the University of Massachusetts, we published the first such report.[7] By amplifying the *nef* sequences of five individuals with long-term nonprogressive HIV infection, we found one with consistently defective *nef* sequences in PBMCs sampled from 1983 through 1993 (see Figure).

This patient, a man with severe hemophilia, has been HIV positive by Western blot assay since at least 1983.[7] However, he has had no symptoms of HIV infection and has never taken antiretroviral drugs. His CD4 count has remained stable and only slightly below normal since 1983, in a range between 600 and 900 cells/μL. We could detect only 1 viral DNA copy per 100,000 PBMCs in his stored samples, a level 10 to 3500 times lower than those measured around the same time in six individuals with slowly progressive HIV infection. Yet the persistence of HIV-specific antibodies and cytotoxic T-lymphocyte activity in this man indicates continuing, low-level replication of HIV.

Late last year, investigators at the MacFarlane Burnet Centre for Medical Research in Australia reported the cases of an HIV-positive blood donor and six persons who became infected by blood products from him.[8] Yet, all remained asymptomatic and maintained stable CD4 counts 10 to 14 years after infection. Three of the individuals infected with the donor's virus eventually died, but apparently none of the deaths was caused by the HIV infection. These researchers demonstrated that the seven people in this cohort were all infected with the same virus because they all had deletions in the *nef* gene and in the overlapping region of the LTR. No other genomic abnormalities were apparent. The Australian team concluded that their findings "support the importance of *nef* and the U3 region of the LTR in determining the pathogenicity of HIV-1."[8]

Clearly, virus with *nef* deletions is

a rare finding even in persons with long-term nonprogressive HIV infection. We found such virus in only one of the five long-term nonprogressors we studied,[7] and other workers have not found it in other cohorts of individuals with nonprogressive disease. Even the occasional finding of *nef*-deleted virus in persons with nonprogressive HIV infection, however, suggests that *nef* does indeed contribute to disease progression in humans. It is reasonable to speculate that the other genes not required for replication have similarly important roles. If that is true, vaccination with a virus from which more of this auxiliary genetic material is deleted may be even more attenuated than the *nef*-deleted virus we had studied in monkeys.[2,3]

We have begun testing the properties of various mutants of SIV with different combinations of deletions (Table).[9] The levels of attenuation of these strains were evaluated principally by measuring viral loads in experimentally infected animals and by measuring the strength of antibody responses. These studies have enabled us to rank the virulence, or aggressiveness, of these mutant strains from not detectably infectious, to infectious but extremely attenuated, all the way through to only marginally attenuated and still pathogenic (see Table).

Next we asked how much the level of attenuation influences the ability to serve as a protective vaccine. SIVmac239Δ*nef*, SIVmac239Δ*vpx*Δ*vpr*, and SIVmac239Δ3 have all demonstrated good protective efficacy as vaccines. However, the highly attenuated SIVmac239Δ4 has not functioned well as a protective vaccine when tested under similar conditions (see Table). Thus, there may be an inverse correlation between level of attenuation and ability to serve as a protective vaccine. For practical application, this means striking a balance: attenuating the virus enough to help ensure safety but not attenuating it so much that protective efficacy is greatly diminished.

We also investigated the effects of duration of vaccination on protective efficacy. Monkeys vaccinated with live attenuated SIV were challenged with pathogenic virus at 8, 20, and 79 weeks.[9] There was a clear trend of increased protection with increasing time since vaccination. Animals vaccinated for 79 weeks were completely protected against challenge by a slightly different (heterologous) strain, but only a portion of them were protected at 20 weeks. It is possible, although not yet demonstrated, that the time needed to achieve complete protection may vary with how different the challenge virus is. In any event, level of attenuation and duration of vaccination appear to be critical variables that influence the protective efficacy observed with the live attenuated approach.

What mechanisms enable live attenuated vaccines to achieve such solid protection when other approaches have failed miserably? Is the protection immune mediated or simply the result of viral interference?* If protection is immune mediated, what arms of the immune system are principally responsible? These questions are important not only for vaccine development but also for the fundamental understanding of the pathogenesis of AIDS because they strike at the core of how SIV and HIV infection can be controlled. If we understand the mechanisms by which this impressive protection can be achieved, perhaps we can find some way to achieve it other than a live attenuated vaccine.

In addition to theoretic considerations, several lines of evidence argue that the protection of live attenuated vaccines is immune mediated. Since viral loads with the vaccine strains are maximal only a few weeks after vaccination, the prolonged time dependence of protection is consistent with immune mediation. Also, we have found that in at least some animals there is a clear, readily measurable replication of the challenge virus in the early weeks after challenge but that this replication is quickly and effectively suppressed.[9] Considerable effort is being expended to identify the immunologic responses principally responsible for this vaccine protection. Preliminary results suggest that high-avidity antibodies with neutralizing activity to the challenge virus may correlate with protection.

We have now begun testing attenuated HIV in a different host, the chimpanzee. HIV-1Δ3 has deletions in *vpr*, *nef*, and a portion of the LTR; HIV-1Δ4 (see Figure) lacks these sequences as well as parts of *vpu*. The preliminary results suggest that one chimpanzee who was given HIV-1Δ4 was strongly protected from challenge with wild-type HIV-1 56 weeks after vaccination and that another animal given HIV-1Δ4 and one given

*Viral interference can occur when the presence of one virus inhibits, or interferes with, the replication of another virus by a non–immune-mediated mechanism.

TABLE. Level of attenuation of SIV mutants

Virus strain*	Gene(s) deleted	Pathogenicity/ infectivity	Relative virulence†	Protective as vaccine?‡
Wild-type	None	Pathogenic	1.00	Not applicable
Δvpr	*vpr*	Pathogenic	0.95	Not tested
Δvpx	*vpx*	Pathogenic	0.1	Not tested
ΔvpxΔvpr	*vpr*, *vpx*	Nonpathogenic	0.01	Yes
Δnef	*nef*	↓	0.01	Yes
Δ3	*nef*, *vpr*, US	↓	0.005	Yes
Δ3X	*nef*, *vpx*, US	↓	0.001	Testing ongoing
Δ4	*nef*, *vpr*, *vpx*, US	↑	0.0005	No
Δvif	*vif*	Infectious for monkeys	0.0001	Testing ongoing
Δ5	*nef*, *vpr*, *vpx*, *vif*, US	Not detectably infectious	0	Not applicable

US, upstream sequences of the long terminal repeat.

*All derived from wild-type SIVmac239.

†Relative virulence is based on viral loads after infection (vaccination) and on strength of antibody response.

‡Based on results of intravenous challenge with the slightly heterologous, pathogenic strain SIVmac251, 6 to 18 months after vaccination.

HIV-1Δ3 had lower viral loads after challenge (R.E.D., unpublished data, 1996).

Safety is the principal concern of many who might otherwise endorse aggressive development of a live attenuated HIV vaccine. Five issues are commonly raised:

- An attenuated virus may revert to a fully virulent form once it establishes low-level infection in the host.
- An attenuated virus may not cause AIDS in the usual 6 to 10 years, but low-level persistent infection might cause AIDS 15, 20, or 30 years later.
- Even if it does not cause AIDS, long-term low-level infection may have other unwanted effects.
- Proviral DNA from a vaccine virus could insert itself near a key cellular gene—a process called insertional mutagenesis—and so alter cellular function, differentiation, or growth potential. One result of this could be cancer.
- The low-level infection induced by an attenuated vaccine may not harm an adult. But if that infection is transmitted from a mother to a newborn, it may overwhelm the infant's immature immune system.

When considering such concerns, one must first remember that live attenuated vaccines do not have to be, and never are, absolutely safe. Every year in the United States, there are an average of 10 vaccine-associated cases of paralytic poliomyelitis.[10] Our society accepts this risk as the price it must pay for nearly complete control of a once-devastating disease. At this point, a live attenuated HIV vaccine would not be appropriate for most people in developed countries because they have a low lifetime risk of HIV infection. But for populations in which the risk of HIV infection is substantially higher, the potential benefit of an attenuated HIV vaccine might easily outweigh the risk.

The large, gaping deletion mutations in the vaccine strains we have studied essentially rule out the possibility that an attenuated virus may revert to a virulent form at the genetic level. But live attenuated HIV could

capture a cellular gene that may substitute for a missing gene, or compensatory changes in the viral genome itself could return it to a state of virulence. Such possibilities—even if they are unlikely—must be looked for closely in continuing animal studies. They have not been detected yet.

The safety record of live attenuated SIV vaccine strains in juvenile and adult rhesus monkeys has been excellent over more than 7 years of observation. More than 78 monkeys vaccinated with SIVmac239Δ*nef*, SIVmac239Δ*vpx*Δ*vpr*, and SIVmac239Δ3 have been observed for a total of more than 178 rhesus monkey years. Nonetheless, the long-term consequences of live attenuated HIV vaccine strains in humans can be assessed only in human studies. In the absence of actual safety trials of live attenuated HIV strains in people, studies of long-term nonprogressing survivors who fortuitously harbor gene-defective strains of HIV-1, as described above,[7,8] can be most informative. It will be important to continue to follow the courses of individuals who harbor *nef*-defective HIV-1 for their continued stability in CD4 counts and general health. Further characterization of virologic and immunologic parameters is also needed. These unusual individuals can be viewed as already having received a live attenuated HIV-1 vaccine strain 13 or more years ago, and while their numbers are small, the studies are already long term. It will also be important to identify other such individuals and to focus on genes other than *nef*.

Despite intense study, there is little evidence to suggest that even unmutated HIV causes cancer. Most scientists agree that the principal HIV-associated cancers—B-cell lymphoma, cervical carcinoma, and Kaposi's sarcoma—are opportunists that take advantage of a weakened immune system, not direct results of HIV itself. Type C retroviruses—a subgroup distinct from the lentiviral family to which HIV and SIV belong—can cause cancer because of insertional mutagenesis. Because the insertion of retroviral genes into host DNA near an oncogene is a chance event, it is more likely to happen with high-level replication and less likely with the low-level infection caused by attenuated virus.

One safety concern with live attenuated vaccines has gone beyond theory into the realm of scientific experimentation. Ruth Ruprecht and colleagues[11] at the Dana-Farber Cancer Institute reported last year that SIV from which *nef*, *vpr*, and a portion of the LTR had been deleted—SIVmac239Δ3—caused terminal disease in a newborn monkey. The newborn was exposed orally to the virus 1 hour after delivery by cesarean section from an SIV-negative mother. Before the monkey was sacrificed, it had persistently high viremia, depletion of CD4 lymphocytes, follicular hyperplasia, and hemolytic disease. When a healthy infant was exposed orally to blood from the infected newborn monkey, high-level persistent viral replication resulted. That infant's mother became virus positive 1 week after being injected with the same blood, but after 8 weeks no virus could be isolated from 10^6 PBMCs. Ruprecht and her colleagues concluded that multiply deleted viruses are too unsafe to be tested as candidate vaccines in humans because of the risk of perinatal transmission.

We disagree with this conclusion for several reasons:

- Transmission of attenuated virus from a mother to her newborn is much less likely than is transmission of unmutated virus, which is present at much higher levels than attenuated virus. As Yvonne Bryson and coworkers[12] have demonstrated in humans, the possibility of perinatal transmission of HIV decreases as the maternal viral load decreases. Viral loads in adult monkeys exposed to attenuated virus are well below the levels at which one would expect transmission.
- Infants born to infected mothers are born with maternal antibodies that could ameliorate the effects of infection. The neonates in the Dana-Farber study were delivered by cesarean section from SIV-negative mothers. Therefore, they did not have SIV-specific antibodies that might have prevented or contained their infection.
- The dose used to infect the neonates in the Dana-Farber study, 5 mL of undiluted high-titer tissue-culture supernatant, is extremely high and unlikely to occur naturally. Although the course of infection with wild-type or mutant virus is not dose dependent in adult monkeys, dose dependency may influence the course of infection in neonates.
- Virus even more attenuated than that used in the Dana-Farber study may be even less likely to be transmitted or to cause disease.

Work done collaboratively by our laboratory and TSI Mason Laboratories of Worcester, Mass, recently confirmed many of these assertions

(R.C.D., unpublished data, 1996). We observed high viral loads and disease in only 2 of 18 neonatal monkeys infected with gene-deleted vaccine strains of SIV. Pathogenicity was restricted to those neonates who were born to unvaccinated mothers and who received extremely high oral doses of SIVmac239Δ3. Neonates who received lower doses of SIVmac239Δ3 became infected but had low viral loads and no disease progression, an outcome very similar to what is observed in juvenile and adult rhesus monkeys. We observed no in utero transmission of vaccine virus in four neonates born to mothers vaccinated during the second trimester. Our results suggest that the live attenuated vaccine approach should remain an option to be considered for preventing HIV infection and disease in high-risk human populations.

No one would suggest that safety concerns surrounding live attenuated vaccines should be cavalierly dismissed. However, fixation on a desire for absolute safety, which is probably not attainable, has distracted attention from the potential merits of this approach. As the foregoing summary of animal studies indicates, live attenuated virus has offered by far the most potent protection against disease in experimental testing. A live attenuated vaccine would be much less expensive to produce than recombinant subunit vaccines and therefore much more likely to be used in developing countries where the lifetime risk of HIV infection is highest. And it would have to be given only once. The only effective subunit vaccine for viral disease, the hepatitis B vaccine, is largely unused in resource-poor countries.

In some parts of Africa and Asia, seroprevalence rates between 30% and 80% have been recorded among sex workers and injection drug users.[13] Seroprevalence rates exceeding 20% have also been demonstrated in selected larger populations. Such populations may well deem the risk of disease from a live attenuated virus minuscule by comparison. The magnitude of that risk will never be determined, of course, until safety trials in humans begin. I believe that the harmful effects associated with a virus from which *nef*, *vpr*, *vpu*, and 250 base pairs of the LTR have been deleted are likely to be considerably less than the effect of not vaccinating such high-risk populations.

Despite the apparent logic to the live attenuated approach for groups at extremely high risk, it has not received much support from the AIDS scientific community, particularly from among the most prominent scientists whose opinions carry the most weight. Additional evidence of safety and/or the failure of other vaccines in field trials will probably be necessary before the live attenuated vaccine approach for AIDS receives more serious consideration.

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RONALD C. DESROSIERS, PhD

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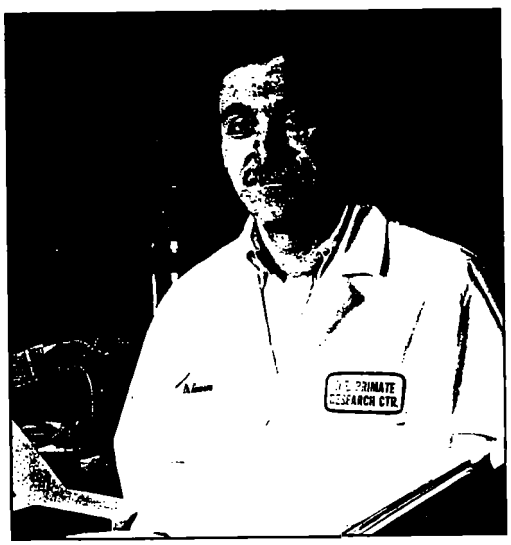
On November 11, 1783, Jean-François Pilâtre de Rozier and two colleagues became the first men to fly. Their craft was a hot-air balloon. A few years later, de Rozier became one of the first men to die in flight, when his hot-air and helium balloon exploded. Ballooning drifted along for the next 2 centuries without anyone mixing hot air and helium. But it turns out that, with a little tinkering, de Rozier's highly combustible idea was not so bad after all. Today, several highly financed, scientifically scrutinized plans to circumnavigate the globe with no stops rely on hot-air and helium balloons.

In another field of scientific endeavor, another Desrosiers is inflaming debate with another dangerous-sounding idea: a live attenuated HIV vaccine. Although live attenuated virus vaccines have eradicated smallpox and control numerous other viral infections, the thought of a live HIV vaccine has kindled little enthusiasm among most AIDS experts. Their primary fear is that even an attenuated form of HIV may prove too much for the human host to handle over the long term. But Ronald C. Desrosiers, PhD, contends that humankind should not wait 200 years, as it did with de Rozier's idea, to find out whether his idea might be right.



As Dr. Desrosiers argues in the following article, no live virus vaccine is completely safe. Society must always bargain with itself when weighing the risks of a medical intervention against its potential benefits. And with the life expectancy in some African countries descending into the 30s because of HIV, Dr. Desrosiers thinks the time has come to begin safety trials of live attenuated HIV in high-risk populations. What makes the argument compelling, he maintains, is that other HIV vaccine strategies in primates and humans have failed. And, so far, live attenuated vaccines have been protective in some animals.

Like it or not, other vaccinologists pay attention to Dr. Desrosiers because of his impressive portfolio. For starters, he discovered the primate cousin of HIV, simian immunodeficiency virus (SIV), just a year after scientists first started growing HIV in lab dishes. To unravel the pathogenic mysteries of these viruses, Dr. Desrosiers and his colleagues began deleting SIV genes and injecting monkeys with the resulting attenuated virus. When they excised *nef* from a particularly nasty strain of SIV and gave it to six macaques, they were surprised to see persistently low levels of circulating virus, normal CD4 counts, and utterly unruffled monkeys. They had inadvertently designed a live attenuated SIV vaccine.

Dr. Desrosiers began studying retroviruses in the early 1970s, just as the world was catching up with Howard Temin's idea that these "RNA viruses" managed to get things done backward via an enzyme called reverse transcriptase. He earned his PhD in 1975 at Michigan State University with a dissertation on the synthesis and methylation of messenger RNA.

After leaving Michigan State, Dr. Desrosiers worked as a postdoctoral fellow and research associate of Dr. Peter Lengyel at Yale University. In the late 1970s, he became an instructor and then assistant professor in microbiology and molecular genetics at Harvard Medical School. In the year he discovered SIV, he became chairman of the division of microbiology at the New England Regional Primate Research Center, a post he holds today. He is also coordinator of the AIDS unit there and now a professor of microbiology and molecular genetics at Harvard.

Dr. Desrosiers is frequently called on to organize prestigious meetings on HIV pathogenesis. His list of invited seminars and lectures is hypertrophic. He is the editor of *Current Biology*, a senior editor of the *Journal of Virology*, and a section editor of *AIDS Research and Human Retroviruses*.

Remaining stoic in his quest to see if the attenuated HIV vaccine balloon will fly, Dr. Desrosiers suggests that other prominent researchers share his views—privately. "Maybe," with accumulating evidence, he surmises, "some people will decide to 'come out,' so to speak." CE

Phase I Live-Attenuated HIV Vaccine Trial

Proposal by the Live-Attenuated HIV Vaccine Subcommittee
of the International Association of Physicians in AIDS Care (IAPAC)

September 1, 1997

In search of an HIV vaccine

Over sixteen years into the worst epidemic of our time, it seems painfully clear that efforts at educating populations at large to transform centuries-old practices of intimate behavior have not met with major and sustained successes. Indeed, the rate of new HIV infections continues its unimpeded upward spiral in both developing and developed countries – especially among the most organized in society. Worldwide, there are approximately 22 million people currently infected with HIV, and another 3 million people are becoming infected each year (UNAIDS, 1997). And, while many in the United States revel in the good news that drug therapy of HIV has been clinically beneficial for many people with HIV/AIDS, these expensive drugs are available only for those patients residing in relatively wealthy countries where the majority of the world population afflicted by HIV do not reside.

Even if the drugs were available to all, they will never eradicate the disease. We have vastly better treatments for tuberculosis and syphilis than we do for HIV but both diseases remain huge scourges worldwide. Theoretically, a preventive, or protective, HIV vaccine could eradicate HIV from the globe - as in the case of smallpox. It is difficult to conceptualize how the epidemic could be halted, let alone reversed, in the absence of an inexpensive and effective preventive vaccine which could be put into widespread usage. The search for a preventive HIV vaccine akin to the vaccine which eradicated smallpox is, therefore, an international priority. This fact was recognized by President Clinton in May of this year when he announced a goal to develop an AIDS vaccine within the next ten years. It is awful to contemplate, however, the devastation that HIV will have wrought across the globe if its rapid spread, especially in third world countries, is not halted before ten years from now.

After the President's announcement there were many pessimistic articles written about the state of vaccine development. Few of them, if any, stated that an effective live attenuated vaccine has actually been developed and been demonstrated to work in rhesus monkeys by Ronald Desrosiers. And, that an accidental "clinical" trial which began in eight human beings in Australia fourteen years ago, when a naturally occurring attenuated strain was disseminated by blood transfusion, has provided initial safety data for this approach in humans. Considering that no other vaccine approach has shown anything like a comparable level of protection against a variety of viral strains, it is amazing that the live attenuated vaccine did not receive more attention during this recent press coverage - especially considering the President's plea for speedy development.

Also, in the recent press coverage there was little discussion that the development of an effective "dead" vaccine may be an impossible goal - and that it is quite possible, if not likely, that the only form of vaccine that will ever protect against HIV, is a live attenuated vaccine. Consider that for all other diseases that successful vaccines have been developed against, a natural state of immunity has already been developed by millions of human beings who have been infected with the disease (eg measles, mumps, rubella etc), thrown off the infection, and been left with a state of "immunity" such that they could no longer be reinfected. The task of the vaccine developers was a relatively simple one of stimulating the immune system in the same way as the disease itself does and thus reproducing the same state of immunity that the disease itself produces. The problem with HIV however is that it does not behave like other infectious diseases. Infected individuals are

infected for life - few , if any, human beings have ever been infected with HIV, thrown it off, and been left with a state of "immunity." It is probably impossible to produce a vaccine that is a greater stimulus to the immune system than the disease itself, and if the disease itself does not result in an immune reaction great enough to eradicate the disease and leave an individual with protective immunity, then it may be naive to think that a dead vaccine of any kind could ever do so. Animal experiments, however, have proven that once infected with HIV an animal is protected from superinfection. Live attenuated SIV and HIV vaccines have been proven to work in animal models but their development in human beings is being blocked by safety concerns - whilst millions of dollars are being pumped into alternative approaches searching for the holy grail of an effective totally safe dead vaccine that quite possibly may never be found. Protection without ongoing infection may simply not be possible. For right now, and for the forseeable future, nothing can be seen to match a live attenuated vaccine for efficacy, and the likelihood for eventual ready availability to the worldwide population. That is why we need to start accumulating the needed safety data in human beings as soon as possible. We cannot afford the luxury of another five years of monkey data which ultimately will never be able to prove safety in humans anyway.

The development of a live attenuated vaccine has been stalled because of fear. Fear that an attenuated strain will attack the immune systems of some vaccine recipients and cause AIDS. Most successful vaccines in the world today are live attenuated micro-organisms and do cause disease some of the time. The highly successful Sabin oral polio vaccine causes a few cases of polio every year - but the risk/benefit ratio, considering the vaccine has protected millions of children every year from polio, has been deemed acceptable. The scenario may be similar with a live attenuated HIV vaccine. The vast majority of monkeys infected with highly attenuated stains of SIV, or the humans who have been infected with the naturally occurring attenuated Australian strain of HIV, have not developed AIDS, or high virus loads, which is encouraging - encouraging enough, we feel, to proceed with phase one safety trials in humans as soon as possible.

Recent developments in our ability to predict the course of HIV disease by the measurement of HIV viral load in the serum, and our ability to effectively suppress the disease with highly active antiretroviral therapy (HAART), make now a better time to proceed with a human trial than five years ago when the first attenuated organisms were engineered. Now we will not have to wait ten years to know if a vaccinated individual is likely to progress to AIDS. If in the first few months of infection he or she shows a very low viral load then we know the likelihood of disease in the next decade is remote- remote enough perhaps to persuade us that the risk benefit ratio would justify moving to a phase II efficacy study in populations at very high risk of acquiring HIV. Also, now should a vaccine recipient show a high viral load, and CD4 depletion, his or her disease could be effectively suppressed by HAART- vaccine strains being wild type for drug resistant mutations.

If as scientists and physicians many of us feel strongly that the live attenuated vaccine is the approach which is likely to work and likely to be safe, and that other approaches are unlikely to work, then we should, as physicians have done many times in history, be prepared to roll up our own sleeves first and perform the first safety trials on ourselves. With this in mind the International Association of Physicians in AIDS Care (IAPAC) presented a challenge to AIDS physicians in the August edition of its magazine for colleagues to join us as potential volunteers for an attenuated HIV vaccine study. In just a few weeks over fifty physicians from seven

countries have registered as potential volunteers confounding the arguments of some critics who have said that one could never recruit for such a study.

Our proposal is that an initial small safety study be performed on five volunteers, with the HIV construct deficient in the nef, vpr, vpu, nre and NFkB elements developed by Ron Desrosiers. This small study should occur promptly as soon as the product has undergone GLP and GMP production and safety testing. The five volunteers should be monitored very closely for viral load, immune function, immune response, and viral evolution in vivo - for a period of six months. If all five subjects remain well, with low viral set points (viremia), then the initial five should be expanded to ten subjects. If after a further six months all subjects are well, without concerning indices, then this group could be further expanded and placebo controlled studies planned in very high risk subjects in the USA and in the third world simultaneously.

Some have said that it is unethical to inject live HIV into human subjects. We think it is unethical with 8,500 new cases of HIV infection occurring every day in our world, not to start human trials when the animal data, and the human experience in Australia, looks so promising. We will never know if this promising approach is safe unless we try it and we could procrastinate for ever but we feel that the time is now.

Scientific concerns

I. Insertional mutagenesis

Some scientists have raised the concern that retroviruses insert their genetic material at random into the genome. Theoretically the insertion could be adjacent to an oncogene which could be activated - the result of which could be cancer. While this is a theoretical concern in sixteen years of the AIDS epidemic rare and unusual tumors are very seldom seen. With the exception of the opportunistic cancers Kaposi's sarcoma and lymphoma very few tumors seem to be in higher incidence in AIDS patients than in the general population. If insertional mutagenesis was a significant problem surely this would not be the case. Kaposi's sarcoma occurs secondary to immunosuppresion and probably HHV8 infection - lymphoma is probably secondary to a combination of immunosuppression, EBV infection, and increased mutation rates from rapid cell turnover secondary to destruction of lymphocytes by HIV. Probably neither of these tumors are the result of insertional mutagenesis. If wild type HIV does not appear to cause tumors by insertional mutagenesis, why would an attenuated strain? Also, transformation by insertional mutagenesis requires infected cells that are long lived - this is not generally the case with HIV when virus infected cells are constantly turning over. Also, insertion in front of an oncogene is a stochastic event - thus the likelihood is dependent on the level of viral replication, and viral loads are very low with attenuated strains.

II. Reversion of an attenuated strain to a virulent strain by mutation.

Use of large gaping deletions eliminates the possibility of reversion of the targeted genetic locus. Might mutation elsewhere in the genome allow the virus to compensate and acquire a more virulent phenotype? The more genes deleted from a strain of HIV, the less likely it could ever revert to wildtype by mutation. It is proposed to use a strain of virus deleted of three of its ten genes - and of a major controlling element. Reversion of such a depleted virus would appear highly unlikely. Observation to date, over time, on sequential isolates from the human beings found to be infected with the nef deleted strains of HIV, have shown that the nef deletion becomes larger with time, not smaller. Thus, there is no suggestion of reversion to wildtype.

III. Superinfection of a vaccinated subject with a virulent strain enabling gene transfer from virulent to attenuated virus.

The principal of the live attenuated vaccine, the reason it works, is because established superinfection is prevented. Superinfection of a human being, with established HIV infection, by a different strain of HIV, to our knowledge, has never been reported. Simultaneous infection with two strains at the same time has however been observed in individuals acquiring two different viruses on the same day - either via blood transfusion or sexual activity. Chimeric strains have also been observed in Thailand and how they occurred is unknown. Probably most likely they occurred as simultaneous infections. It would be very unlikely that if superinfection occurred it would not

now have been observed to have occurred many times in the USA where many HIV infected individuals are known to practice unsafe sex, frequently, with other HIV positive individuals.

IV. New born monkeys exposed to attenuated SIV developed AIDS

Ruth Ruprecht and colleagues from the Dana-Farber Cancer Institute reported two years ago that new born monkeys exposed to a nef/vpr deleted strain one hour after delivery developed immune depletion. From this work some have concluded that a live attenuated vaccine would be unsafe as a pregnant mother may transfer the virus to a fetus who may develop disease. This experiment is probably misleading. Any new born given a live attenuated vaccine of almost any type at high dose is likely to fall ill. If however the infant had acquired the virus from its mother in utero then it would also have acquired passive immunity from the mother. Also monkeys that have been vaccinated with live attenuated SIV and have given birth have not transmitted the vaccine strain - probably because of the very low viral loads that occur with an attenuated strain.

V. Some adult monkeys with attenuated strains of SIV have developed immune suppression.

Some monkeys infected with the "nef" deleted SIV strain (1 in 20 adult macaques after one year in Ruth Conner's experience), and some with the "delta 3" SIV (nef, vpr, nre deleted) strain (1 in 24 rhesus monkeys after 3-4 years in Ron Desrosiers experience, and 2 in18 after 2-5 years in Ruth Ruprecht's experience) have developed some immune deficit. It is proposed however that the human studies will use an HIV-1 strain that is equivalent to an SIV strain that is much more highly attenuated than SIVdelta3. The HIV-1 strain will be missing nef, vpr, vpu, nre and the NFkB sites.
Of the ten humans found to be infected with nef deficient HIV however, all are well ten or more years after infection, with the exception of three who have died of probably unrelated causes. One died in his eighties of a probably unrelated bowel cancer, another in her eighties of cerebrovascular disease - and another who had Systemic Lupus Erythematosis (SLE), and was on immunosupressive drugs, died of Pneumocystis carinii pneumonia (PCP). It is not uncommon for patients with SLE to develop low CD4 counts and die of PCP. Of the nine patients who remain alive none have any disturbance of immune function, three have detectable viral loads (all less than 3000c/ml), and the rest do not have a detectable viremia.
SIV causes a more rapid development of AIDS in macaques and rhesus monkeys than HIV does in humans. Whilst the monkey data is interesting and important, it must be realized that SIV is a different virus to HIV, and the monkey is a different animal to the human being. Whilst the SIV/monkey model has been very useful to enable us to establish the potential efficacy of the live attenuated approach surely we should look more to the human experience than the monkey experience when we are trying to predict safety. The good human experience to date with an HIV strain deficient only in nef, leads us to believe that a three gene deleted HIV would be extremely unlikely to cause disease in humans. We feel that the international crisis is such that we cannot wait any longer to do safety testing. Monkeys are not human beings, no amount of testing SIV in monkeys will tell us if a three gene deleted HIV is safe in humans, and human trials of well

informed consenting adults should proceed. If, as we suspect it will, the vaccine strain proves safe, then the world may well have a vaccine which could be used first in individuals highly at risk of disease. If on wider use of the vaccine the safety margin proves to be very high then eventually even its use in populations at only moderate or low risk of HIV infection may be considered.

VI. Long term toxicity.

Many scientists have expressed concern that long term toxicity may occur, Even if immune depletion has not occurred at all after fifteen years of infection with an attenuated strain what about twenty to thirty years later, perhaps when the immune system is failing with increasing age? This question can not be answered now but once again it is a theoretical concern - we know of no definite long term toxicity. Delayed development of immune depletion or HIV induced encephalitis presumably might be seen. It is comforting however that two elderly Australian patients died of unrelated causes, in their eighties, without having developed immunosuppression from the attenuated strain that they carried.
Can we afford to wait for 20-30 years of observation before embarking on these studies? And, considering the enormously high death rates in the third world within the first five years of HIV infection in an individual - huge benefits could be accrued by using a live vaccine even if it did result in occasional illness twenty to thirty years out. The risk/benefit ratio must be weighed carefully but at least for very high risk individuals it would appear to us to lie very much in favor of use of the live attenuated vaccine.

VII. The vaccine strain may transmit.

It is probably not very likely that an attenuated strain sustaining only very low viral loads in recipients would transmit. It is a moot point however as to whether this would be a bad thing. On the contrary, it may provide widespread herd immunity. It seems a much more attractive idea to have an attenuated strain of HIV spreading through a community than a virulent strain. The probability however is that the vaccine strain would have very poor ability to transmit.

Legal/Ethical concerns

1. Would the FDA ever approve such a trial?

We hope so. It is up to us to convince the FDA that with medically qualified study participants who can truly give informed consent that it is ethical to proceed. We would ask that with such good scientific data showing the efficacy and safety of live attenuated HIV to date, is it ethical not to proceed with such a trial?

2. Who would cover the medical expenses / litigation from any study participants who may fall ill?

This study must be well funded to ensure that any participants were well covered for any problems they might encounter. We would hope for government support.

3. Would study participants be subject to prejudice as they would now be HIV positive?

HIV infection is not the pariah it once was. Also, individuals who have been vaccinated would be able to carry proof of how they acquired their HIV status. It is more likely perhaps that they would be treated with respect for having taken part in such study, than with derision.

Objectives

To recruit bioethicists, biostatisticians, clinicians, community activists, and scientists to advise, and possibly join, IAPAC and its Live-Attenuated HIV Vaccine Subcommittee on HIV vaccine development issues.

To examine the scientific, ethical, economic, legal and social obstacles to the development of an effective live-attenuated HIV vaccine.

To develop an appropriate response to the scientific, ethical, economic, legal and social obstacles to the development of an effective live-attenuated HIV vaccine.

To recruit potential volunteers for a pilot human safety trial of a live-attenuated HIV vaccine, ensuring informed consent of said potential volunteers.

To secure Food and Drug Administration (FDA) approval of a pilot human safety trial of a live-attenuated HIV vaccine.

To assist in the implementation of a pilot human safety trial of a live-attenuated HIV vaccine as soon as possible.

To implement efficacy studies in human subjects at high risk of HIV infection in both the USA and in the third world as soon as possible.

Strategy outline

1. Goal: To implement a human safety trial of a live-attenuated HIV vaccine as soon as possible.

2. Scientific concerns
   a. Recruit clinicians and researchers to identify scientific concerns against live-attenuated HIV vaccine trial.
   b. Craft and articulate vaccine subcommittee responses to scientific concerns.

3. Ethical concerns
   a. Recruit bioethicists and community activists to identify ethical concerns against live-attenuated HIV vaccine trial.
   b. Craft and articulate vaccine subcommittee responses to ethical concerns.

4. Food and Drug Administration (FDA) concerns
   a. Determine all FDA concerns against live-attenuated HIV vaccine trial.
   b. Develop strategies to address FDA concerns.

5. Economic implications
   a. Recruit biostatisticians to assess the risk benefit ratio of using a live attenuated vaccine in high risk areas, and examine economic implications of developing an HIV vaccine (not limited to a live-attenuated HIV vaccine candidate).
   b. Establish a five-year epidemiological and economic model to determine impact in the US and other countries of not having an effective live-attenuated HIV vaccine by the year 2003.

6. Hold meeting between Live-Attenuated HIV Vaccine Subcommittee Members and the FDA to identify and possibly respond to FDA concerns and any other scientific, ethical or economic concerns against a human safety trial of a live-attenuated vaccine.

7. Work with live-attenuated HIV vaccine developers and manufacturers on the coordination of support for a human safety trial of the live-attenuated HIV vaccine. Develop cost estimates for vaccine trials.

8. Explore and secure funding to cover the cost of vaccine trials and to mitigate financial liability of providing healthcare and social services to any IAPAC-sanctioned live-attenuated HIV vaccine trial participant who may develop progressive HIV infection.

9. Roll-out the live-attenuated HIV vaccine initiative at IAPAC's Conference on Health Care Resource Allocation for HIV/AIDS and Other Life-Threatening Illnesses [Nov. 10-11 in Washington, DC]. Develop a comprehensive media strategy to maintain public interest in HIV vaccine issues through the *Journal of the International Association of Physicians in AIDS Care*

(*Journal*) and placement of vaccine-related articles/features/op-eds in mainstream and trade media outlets.

10. Mobilize scientific and community support around the urgent need for a human safety trial of a live-attenuated HIV vaccine.

11. Work with key federal and state legislators to enact federal legislation limiting liability for pharmaceut legislation.

12. Develop a model to guarantee the wide availability and accessibility of an effective HIV vaccine in those areas where the vaccine would be most practical.

POLICY: BIOMEDICINE

The Highest Attainable Standard: Ethical Issues in AIDS Vaccines

Barry R. Bloom

AIDS has had a devastating impact of almost unimaginable proportions on developing countries. Currently, the United Nations estimates that there are 16,000 individuals newly infected with the human immunodeficiency virus (HIV) each day, or 5.8 million per year. Ninety percent of new infections occur in developing countries, where ultimately almost all infected people succumb to the disease or opportunistic infections. By the end of this decade, it is estimated that 40 million people will have died from AIDS, and more than 9 million children will have been orphaned. Because many developing countries cannot afford to implement the new antiretroviral drug therapies—with a current cost of about $12,000 to $15,000 per patient each year in the United States—the only public health measure available to them is counseling against behaviors that increase the risk of the disease.

The scientific community has increasingly come to believe that the best hope for stemming the global epidemic is the development of preventive HIV vaccines. Even before clinical trials are undertaken, ethical guidelines require that "clinical testing must be preceded by sufficient laboratory experiments including, when appropriate, animal testing, to demonstrate a reasonable probability of success without undue risk." This standard must be considered carefully before initiating trials of vaccines containing live attenuated HIV in human volunteers, for example, which could revert to virulence and themselves cause disease.

Clinical vaccine trials, which are the next step, are carried out for multiple reasons, both scientific and practical: To gauge the safety of the candidate vaccine, to ascertain how well a vaccine protects against infection or disease, to better understand protection, to acquire data required for licensure, and to introduce vaccines into public health practice (*1*). Clinical trials of AIDS vaccines present complex ethical issues. A recent controversy (*2*) erupted over the ethics of including placebos in clinical trials designed to test simplified and less costly drug regimens for prevention of maternal-infant HIV transmission. These trials were conducted by investigators in several developing countries, in collaboration with scientists from the United States and other developed countries. There were charges that the existence of effective antiretroviral drugs made the use of placebos unethical and countercharges of ethical imperialism that ignored the realities of economic conditions in the developing world. These events only emphasize the need for the medical community to consider, in advance, critical ethical issues likely to arise in vaccine trials in developing countries.

Vaccine Expectations and Endpoints

Most vaccines currently in use—those for polio, tetanus, diphtheria, measles, hepatitis B, and influenza, for example—prevent disease without actually preventing infection. Instead, they reduce the number of invading microorganisms, increase the rate of clearance of the infection, prevent the secondary consequences of infection, or prevent transmission. Similarly, few of the candidate HIV vaccines appear promising for preventing infection, and the expectation that HIV vaccines will in fact prevent infection is yielding, in the scientific community, to the hope that they may prevent disease.

In developed countries, it will be ethically required that individuals in vaccine trials who are found to have acquired HIV infection will be offered antiretroviral therapy, which usually dramatically reduces virus levels. If vaccines cannot achieve protection against infection, however, treatment with antiretrovirals will compromise the ability of the trial to measure the efficacy of the vaccine in preventing disease. It may also obscure possible secondary endpoints of vaccine efficacy, such as reduction in viral loads [a promising correlate of disease progression (*3*)] or immunological correlates of protection. Delaying the drug treatment until viral loads can be determined at several time points may present another ethical problem.

Because of these complications, determination of the protective efficacy of HIV vaccine candidates may only be possible in trials in developing countries where the resources are not available to provide antiretroviral drugs. It is that circumstance, plus the fact that development of successful vaccines will be an incremental process requiring multiple trials, that presents the most challenging ethical issues.

The Ethics of Research on Humans

Codification of ethical precepts for experimentation on human beings derives from the Nuremberg Code of 1947, issued to prevent the kinds of medical abuses perpetrated on non-consenting prisoners by physicians in World War II. Many industrialized countries, including the United States, have established their own ethical guidelines for human experimentation (*4*, *5*), but that is rarely the case for developing countries. Because AIDS vaccine trials are likely to require collaborations between developed and developing countries, two documents on human experimentation in international research are most influential: The Declaration of Helsinki, promulgated in 1964 by the World Medical Association (*6*), and the "International Ethical Guidelines for Biomedical Research Involving Human Subjects," published by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) in 1982 (*7*). The most recent version of the CIOMS guidelines, prepared in 1993, is explicitly intended to indicate how the ethical principles of the declaration can effectively be applied in developing countries. Together these documents are accepted by the international medical community as providing for the highest standards of medical ethics in human experimentation, although in most countries they lack the force of law.

These and other guidelines rest on three general ethical principles, made explicit in 1988 in the Belmont Report (*4*): Respect for persons (including their autonomy and self-determination), beneficence (maximizing benefits and minimizing harms), and justice. The last principle also includes distributive justice, which demands "the equitable distribution of both the burdens and the benefits of participation in research." When applied to specific circumstances, these ethical guidelines may conflict with one another. Furthermore, they are silent on the issue of the economic and technical capacity of either the trial population or the host country to implement the recommendations.

The Best Proven Therapeutic Method

CIOMS Guideline 14 quotes Article II.3 of the Helsinki Declaration and states that, "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and

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therapeutic method" (7). This guideline is not easy to apply. Is combination antiretroviral therapy the best proven therapeutic for individuals in a vaccine trial who become HIV-infected? Indeed, is there a best proven therapeutic, especially when the national treatment guidelines of the United Kingdom, United States, and other developed nations differ (8)? No one has defined the criteria that would allow a judgment to be made on what constitutes the best proven therapeutic. What is the obligation to individuals who, after agreeing to enter a vaccine trial and giving informed consent to be screened for HIV, are found to be HIV-positive and are thus excluded from the trial? According to CIOMS Guideline 15, these individuals should be referred to medical care. Is it appropriate to refer them to a health service in a country where the standard of care does not include antiretroviral therapy?

Many scientists believe that the only short-term way to ascertain the beneficial effect of immunization on HIV transmission—which is the most important public health endpoint—is vaccination of uninfected sexual partners of HIV-infected individuals. If a HIV-positive, previously infected partner is identified, must he or she be offered and provided antiretroviral therapy as well as counseling? If so, can transmission blocking trials ever ethically be undertaken?

Another facet of this guideline relates to placebo-controlled trials, the focal point of the recent controversy in the maternal-infant transmission trials. The guidelines seem to be clear and unambiguous. Helsinki (Article II.3) states that "the best proven therapeutic" requirement "does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists." That is amplified in CIOMS Guideline 14 to say "If there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified." However, the interpretation of this guideline has also evolved (9).

The guideline is silent on preventive methods, but I shall assume they are implicit in the designation of "diagnostic or therapeutic method." Because no HIV vaccine has yet been tested for efficacy in a Phase III trial, there is no best proven preventive. But what if a vaccine existed that was clearly demonstrated to be 20% effective? Does that establish it as the best preventive method? Would all controls, or perhaps all vaccinees in future trials, have to be given the poorly effective vaccine rather than placebo, even though it may compromise evaluating the effectiveness of a vaccine candidate capable of engendering greater protection?

In a related circumstance, recent trials of acellular pertussis vaccines in Sweden and Italy generated a major ethical controversy regarding the use of a placebo. These countries were chosen in part because the use of whole-cell pertussis vaccine was very low (only 30 to 40% of the population), and so a definitive result could be obtained by studying 15,000 children in Italy and 10,000 in Sweden, rather than the hundreds of thousands or more that would have been required in the United States. Groups received a placebo and various acellular vaccines, and one group in each trial received the best proven preventive: whole-cell pertussis vaccine. The inclusion of the placebo group permitted the trial to reveal not only that the efficacy of the new acellular vaccines (76 to 89% protection) was significantly greater than that of the whole-cell vaccine, but that the standard whole-cell vaccine had far poorer protective efficacy (36 to 48%) relative to placebo than was thought to be the case (10).

Expectant mothers in a maternity clinic in Kampala, Uganda. [Reprinted with permission from A. W. Kigotho, *Lancet* **350**, 1456 (1997)]

Another question is whether it will be unethical to carry out placebo-controlled trials in countries that have not yet accepted vaccines proven to be effective elsewhere. In some instances, it is only after local testing that the demand for internationally accepted vaccines results in their adoption by national immunization programs.

A Requirement for Reasonable Availability

CIOMS Guideline 15 on Externally Sponsored Research requires that any trial "must be responsive to the health needs of the host country.... Any product developed through such research [should] be made reasonably available to the inhabitants of the host community or country at completion of successful testing" (7).

In the case of HIV vaccine trials, the ethical principles for provision of the best proven therapeutic and for reasonable availability appear to be in conflict. There are several facets of this conflict of principles. One is the cost of the best proven therapeutic. For example, Uganda is a country of 16 million people with a gross national product per capita of $170, one physician per 100,000 people, and an annual per capita expenditure on health of $6 (11). Uganda suffers one of the greatest burdens from AIDS, with 11 to 12% of pregnant women estimated to be already infected with HIV and at least 100,000 children orphaned by AIDS (12). It is also a country that has made a major commitment to health infrastructure over many years to be able to conduct HIV vaccine trials. When individuals become HIV-infected during the course of vaccine trials, would the $12,000 to $15,000 annual cost for antiretroviral therapy (if considered the best proven therapeutic) be assumed by the companies producing the candidate vaccines, the host country, or the sponsoring country or agency?

Although the problem might be obviated if antiretroviral therapy regimens were not considered the best proven therapeutic, this would be irresponsible circumvention of the issue by semantics. In my view, the question is more general than just the case of AIDS vaccines and relates to any trials of vaccines or drugs for diseases such as tuberculosis and pneumonia, or even for noncommunicable diseases. For example, chronic noncommunicable ailments (including cardiovascular, neoplastic, and psychiatric disorders) form the most rapidly rising category of disease in developing countries (13). Few, if any, clinical trials in developing countries have evaluated whether simple, inexpensive interventions, such as aspirin and β-blockers, will reduce mortality from heart attacks and strokes, as they do in the industrialized world; consequently, these treatments are not widely applied. Were the standard of best proven therapeutic method to be literally invoked in such a trial, many study subjects suffering heart attacks would have to be provided with either angioplasty or coronary artery bypass surgery, which are hardly reasonably available in countries where per capita expenditures for health are $10 per year or less. The more general question is that if the best proven therapeutic standard of the industrialized countries were literally applied without qualification, could there ever be efficacy trials of AIDS vac-

cines or of many other interventions? And if not, how would interventions most responsive to the health needs of the host country ever be developed and tested?

Who Controls Controlled Trials?

When ethical norms or standards of care differ among countries, whose ethical rules prevail? For AIDS vaccines, even the guidelines explicitly designed to protect populations of developing countries from exploitation are problematic. CIOMS Guideline 8, which states that "Phase I and II vaccine studies should be conducted only in developed communities of the country of the sponsor" (7) is particularly troubling to AIDS researchers and health leaders of countries where AIDS is endemic. Phase I early safety trials require only small numbers of volunteers (typically 20 to 60) and can and should be carried out quickly in the countries where the vaccines are developed. However, the question asked by scientists from developing countries is why, given the urgency of the epidemic, must we delay expanded safety (Phase II) trials until such trials are completed in a developed country, where accrual of patients into trials is often a very time-consuming process, sometimes requiring a year or more? The beneficent intent of avoiding exploitation is clear. The guidelines, however, are seen to be paternalistic or imperialistic and to preempt the sovereign right of developing countries to make decisions that profoundly affect the health of their people.

A Process for Resolving Ethical Issues

UNAIDS was created by the United Nations to lead and coordinate all UN agency activities in combating the AIDS epidemic. A group of bioethicists, human rights lawyers, community leaders, public health officials, physicians, representatives of CIOMS, and AIDS scientists from 13 countries was recently convened by UNAIDS to identify ethical issues in AIDS vaccine trials (*14*). The UNAIDS meeting raised many of the ethical issues discussed here, as well as others that must be considered in moving forward with vaccine trials, including the question of whether all ethical issues must be resolved before efficacy trials may be initiated. It was recognized that thoughtful people of good will can disagree on ethical interpretations of the guidelines and that most of the current guidelines will be applicable in their present form to the ethical questions of AIDS vaccine research.

Nevertheless, there are critical issues that require that the current guidelines be reconsidered, clarified, strengthened, further elaborated, or modified. In this context, UNAIDS has commissioned working papers to provide ethical, legal, and scientific background information. A process of consultation is being initiated with public health, science, ethical, and community leadership in countries and regions around the world that are involved in HIV vaccine research, with the aim of developing a consensus on these issues.

It would be inappropriate in this article to preempt in any way the findings of the UNAIDS process, but some personal thoughts on approaching the issues presented here may be helpful. The Helsinki and CIOMS guidelines have for decades been universally respected and should not lightly be changed. Nevertheless, they are living documents that must evolve to encompass and provide guidance for changing realities in global health. I believe that the guidelines stipulating the best proven therapeutic method and reasonable availability require clarification and perhaps modification. One framework for doing so might be to incorporate the basic concept of the Charter of the World Health Organization (WHO), which states that "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social conditions." Without changing the existing guidelines significantly, I believe it is possible and necessary to clarify what is attainable for their implementation in developing countries whose health care resources are severely constrained. Further, guidelines enjoining developing countries from carrying out Phase II trials until they are completed in developed countries are indeed paternalistic or worse, and ought to be modified. The general qualification I would suggest to ensure that trials are ethically carried out and are not exploitative is that UNAIDS, CIOMS, or WHO should provide independent review of the protocols to ensure that they are ethically and scientifically sound and as safe as possible. It is essential that research of the highest attainable ethical standard be carried out, with due recognition of the global needs and opportunities, burdens and benefits, and resource constraints for individuals and countries.

References and Notes

1. Trials can create a demand by proving to the local community that an effective treatment or vaccine is available. For example, although *Hemophilus influenzae B* and hepatitis B vaccines are highly effective and are recommended by WHO for universal immunization, they are currently used in only a minority of national vaccine programs.
2. M. Angell, *N. Engl. J. Med.* **337**, 847 (1997); P. Lurie and S. M. Wolfe, *ibid.*, p. 853; H. Varmus and D. Satcher, *ibid.*, p. 1003.
3. J. W. Mellors *et al.*, *Ann. Intern. Med.* **126**, 12946 (1997).
4. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* [U.S. Government Printing Office (GPO 887-809), 1988]; Code of Federal Regulations, *Regulations on the Protection of Human Subjects*, Title 45, Part 46 (45CFR46), Title 21, Parts 50 and 56 (21CFR50, 21CFR56); U.S. Public Health Service, *Consultation on International Collaborative Human Immunodeficiency Virus (HIV) Research* (Assistant Secretary for Health, Department of Health and Human Services, Washington, DC, (1990).
5. For Europe, see Council of Europe, *Convention on Human Rights and Biomedicine* (Strasbourg, 1997); M. A. M. deWachter, *Hastings Center Report* **27**, 13 (1997); and F. W. Dommel and D. Alexander, *Kennedy Inst. Ethics J.* **7**, 259 (1997).
6. Declaration of Helsinki [World Medical Association, Ferney-Voltaire, France, 1964 (revised 1974, 1983, 1989, and 1996)].
7. CIOMS, in collaboration with WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* [CIOMS, Geneva, Switzerland, 1982 (revised in 1993)].This document contains 15 guidelines that address fundamental ethical principles relating to the need for informed consent and freedom to withdraw from studies; the use of children, prisoners, and vulnerable populations in research; undue inducements to participate in trials; indemnification for injuries suffered as a consequence of the research; and mechanisms for ethical review, among others.
8. C. C. Carpenter *et al.*, *J. Am. Med. Assoc.* **277**, 1962 (1997). A draft set of revised Centers for Disease Control guidelines is currently under review. British HIV Association Guidelines, *Lancet* **349**, 1086 (1997). Early initiation of treatment with combination chemotherapy including protease inhibitors is recommended in the U.S. guidelines prepared by the International AIDS Society–USA Panel. In contrast, the U.K. guidelines recommend treatment initially only with anti-reverse transcriptase drugs and inclusion of protease inhibitors in therapy only at later stages of disease.
9. Povl Riis, chairman of the Central Scientific-Ethical Committee of Denmark, a member of the committee that drafted the Helsinki Declaration in 1974 and a co-author of the "best proven therapeutic method" sentence in the declaration, has indicated that "In the seventies we focused mainly on clinical-pharmacological trials in developed countries. During the last 15 years, the Danish Committee System has interpreted the above sentence" as implicitly qualified by ". . . in accordance with national accessibility," and "with the indispensable condition that the project is of great importance to the developing country and consequently is not intending to test drugs or methods of primary interest to the donating country." (P. Riis, personal communication).
10. D. Greco *et al.*, *N. Engl. J. Med.* **334**, 341 (1996); L. Gustafsson *et al.*, *ibid.*, p. 349 (1996). Another example is the cholera vaccine trials in Bangladesh in the 1960s, in which children in the unvaccinated experimental groups, if not protected by the vaccine, were at risk for rapid death from dehydration. A system was put in place for the trial to allow rapid oral rehydration to any child in the trial contracting cholera. That system remains in place. W. E. Van Heyningen and J. Seale, *Cholera: The American Scientific Experience, 1947–1980* (Westview, Boulder, CO, 1983).
11. The World Bank, World Development Report 1993, *Investing in Health* (Oxford Univ. Press, 1993).
12. UNAIDS Programme, Geneva, Switzerland.
13. C. J. W. Murray and A. Lopez, Eds., *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*, Vol. 1. (Harvard Univ. Press, Cambridge, MA, 1996).
14. UNAIDS, *Ethical Considerations in Clinical Trials of Preventive HIV Vaccines*, proceedings of a meeting held 23 to 24 September 1997 (UNAIDS. Geneva, Switzerland, 1997).

15. Many of the ideas in this article derive from discussions with the participants at the UNAIDS meeting (*12*). I thank R. Macklin for her critical reading of the manuscript; P. Riis for permission to quote from his letter to me; J. Esparza, D. Guenter, and S. Kalibala of UNAIDS for current AIDS statistics; J. Weber for guidelines for care in the United Kingdom; R. Glass for information on the cholera vaccine trials; and J. LaMontagne for information on the acellular pertussis vaccine trials. I thank D. Baltimore, M. L. Clements Mann, M Johnston, P. Fast, A. Fauci, C. Grady, D. Ho, J. Mann, D. Richmond, P. Smith, and H. Varmus for thoughtful comments on the manuscript and R. Levine, M. Sommerville, and E. Mbidde for helpful discussions.

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DRAFT #2 - 1/27/98

PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS
RESEARCH SUB-COMMITTEE
Recommendations concerning development of an effective AIDS vaccine

In the USA, approximately 100 people are infected with HIV each day; world-wide, 8,000 to 9,000 new infections occur on a daily basis. Despite institution of multiple behavioral risk reduction strategies, it has become apparent that only a preventive vaccine will ultimately be successful in stopping the AIDS pandemic. In recognition of these facts, President Clinton declared his goal of development of a successful AIDS vaccine within the next decade.

The scientific issues involved in vaccine development are extremely complex and controversial; the Presidential Advisory Council on HIV/AIDS has neither the expertise nor the desire to address these complexities. Further, the National Institutes of Health, the world's premier biomedical research agency, is well equipped to provide the scientific focus and leadership required. The recent re-organization of the AIDS vaccine program within the NIH, under the strong leadership of Dr. David Baltimore, is an extremely important step in meeting the President's stated goal, and will, in all probability, lead to the generation of a series of scientifically valid candidate vaccines for future testing.

Despite the newly organized vaccine effort within NIH, however, it has become apparent to the Council that an appropriate administrative structure will also be required, in order to address the myriad of public policy issues which must also be resolved, both nationally and internationally, prior to implementation of a successful AIDS vaccine program. These policy issues include development and implementation of mechanisms to assure active participation of the pharmaceutical industry, to address

issues such as intellectual property rights, regulatory and liability concerns, and to involve the international community, where candidate vaccines must be tested, and where the bulk of vaccine product will be used. Specific administrative mechanisms must be in place to assure scientifically and ethically appropriate field testing of candidate vaccines, while other mechanisms will be required to assure a fully coordinated effort among all relevant agencies of the US government. The recommendations which follow concern these administrative issues, which must be planned and coordinated simultaneously with the actual generation of candidate vaccines.

Administrative leadership and coordination

Scientific (NIH): The recent restructuring of the AIDS vaccine program within NIH represents an important step in defining the scientific leadership which will be necessary to expedite the development of candidate vaccines. The appointment of Dr. David Baltimore as Chair of the AIDS Vaccine Research Committee (AVRC), the institution of a new Vaccine Research Laboratory at the NIH, and the active and on-going participation of senior NIH leadership including its Director, Dr. Harold Varmus, have all served to invigorate the scientific process which will be essential to vaccine generation. The appointment of a full time Director of the Vaccine Research Lab provides another mechanism for coordination of the vaccine development effort within NIH. The Council supports these changes with enthusiasm.

Other Federal agencies: Aside from NIH, agencies such as the Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), and the United States Agency for International Development (USAID) have extensive experience and expertise in the area of field epidemiology, surveillance, and the conduct of vaccine efficacy trials, especially in developing countries. The Council agrees with the NIH-

commissioned Levine Report on AIDS Vaccines, that "...in parallel with basic development and preclinical testing of a variety of vaccine candidates, it is essential to prepare cohorts within different populations well in advance of efficacy trials". It is clear that the activities of all relevant Federal agencies must be coordinated simultaneously with the scientific efforts of the NIH. Although the Levine Report called for such coordination, although NIH vaccine meetings have been attended by DOD and CDC representatives, and although an informal interagency group was formed, this group is not comprised of senior leadership, and has not met on a regular basis. It is clear that no formal process of interagency coordination has yet been developed or implemented. **If the President's goal is to be met, such interagency coordination must occur, involving the highest levels of leadership from each Agency.**

Pharmaceutical industry, and regulatory agencies (FDA): It is clear that the scientific efforts of NIH must remain independent of the pharmaceutical industry in terms of the development of candidate AIDS vaccines. It is also clear, however, that eventual product development will require the infrastructure and expertise which resides primarily in the private sector (pharmaceutical and biotechnology industries). **Since industry will be called upon to further develop the more promising candidate vaccines, an administrative mechanism must be developed to assure coordination of the public and private sectors.** Federal leadership will be required to address a host of essential issues, such as intellectual property rights, financial incentives, tax rebates, subsidies for vaccine approaches not commercially attractive, patent extensions, and liability issues.

International community: Due to the higher prevalence of HIV/AIDS in developing nations, clinical testing for efficacy of candidate vaccines (Phase III) must be accomplished internationally. Further, the majority of AIDS vaccine use is expected to

occur in nations outside the USA. It if thus apparent that **mechanisms to exchange information and to coordinate international efforts must begin at once, if the President's goal is to be achieved.** Agencies such as the United Nations Program on AIDS (UNAIDS), the World Bank, the International AIDS Vaccine Initiative (IAVI), and the G-7 countries have critical roles to play in the final testing and implementation of an AIDS vaccine. A mechanism must be developed at once to provide a means for on-going communication among these groups, and among the other critical constituencies listed above.

Role of the President's Office in coordination of full vaccine effort: It is only within the Office of the President that sufficient authority exists to assure coordination of all requisite constituencies, including Federal agencies, private sector, and the international community. **A Vaccine Coordinator should be appointed within the Office of National AIDS Policy (ONAP), whose role will be to develop administrative mechanisms for mandatory on-going dialogue and coordination among all relevant parties.** This individual will be responsible for assuring the involvement of senior leadership in all constituencies, and for addressing problems or concerns as they arise; this individual will have no fiscal responsibility. The Vaccine Coordinator will serve in a purely administrative capacity, assuring that the appropriate constituencies are in communication, providing input to the President when problems arise, and assuring that all administrative mechanisms are in place to achieve the President's stated goal of an AIDS vaccine within one decade.

Candidate vaccines to be tested

The most logical way to assure the eventual development of a successful AIDS vaccine will be to proceed scientifically, with the generation of hypotheses, and the testing of these hypotheses by means of standard scientific inquiry. With such study,

the elucidation of protective immune responses to HIV can be determined, with subsequent design of appropriate candidate vaccines, and eventual human testing of promising candidates. The Council also acknowledges, however, that many of the currently used protective vaccines were initially developed without a clear understanding of the basic biological mechanisms which were likely to confer protection. With the gravity of the current AIDS pandemic in the world, and the need to proceed with vaccine development as quickly as possible, the Council acknowledges that it will be necessary to test various traditional and novel vaccine design strategies in human clinical trials, even before the scientific correlates of protection have been fully deciphered. **We thus advocate the simultaneous implementation of both hypothesis-driven scientific studies, as well as studies based upon thoughtful empiricism.**

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MEMORANDUM

TO	Members of Vaccine Sub-Committee Presidential Advisory Council on HIV/AIDS
FROM	Alexandra M. Levine, MD
DATE	March 9, 1998
INRE	NEXT DRAFT (final !?!?!)

Enclosed please find the 6th draft (dated 3/9/98) of the Recommnedations regarding AIDS vaccine. The changes are based upon our conversation on the conference call of 3/4/98, with the inclusion of verbiage which was sent to me by several members of our committee, as well.

I think we are just about there. This is the version which will go out to the entire Council. We do have another chance to make SMALL changes. Our Committee is scheduled to meet on Monday afternoon, 3/16. The final discussion in front of the full Council is scheduled for Tuesday morning at 9am.

I thank you all VERY, VERY much for all of your help and support throughout this process.

See you soon.

→ PS: Daniel Montoya: can you replace whatever is in the book with THIS version?

TOTAL PAGES FAXED=5, including this sheet

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PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS

RESEARCH SUB-COMMITTEE

Achieving the Goal of an AIDS Vaccine

DRAFT # 6: 3/9/98

Background

In the USA, approximately 100 new people are infected with HIV each day; world-wide, 16,000-17,000 new infections occur on a daily basis. Although behavioral change to reduce risk of HIV infection is a viable strategy for some, it is clear that this stragegy will not work for all. It has thus become apparent that only a preventive vaccine will ultimately be successful in stopping the AIDS pandemic. In recognition of these facts, President Clinton declared his goal of development of a successful AIDS vaccine within the next decade.

Since late 1995, the Research Committee of the Presidential Advisory Council on HIV and AIDS has devoted signficiant time and effort to issues concerning the development of an AIDS vaccine. The Committee consulted with numerous experts in AIDS research and vaccinology (Appendix A), and also solicited and received written input from these and other experts (Appendix B).

The scientific issues involved in vaccine development are extremely complex and controversial, and can best be addressed by existing Federal agencies, including the National Institutes of Health, the world's premier biomedical research agency. However, it has become apparent to the Council that an additional administrative structure will also be required, in order to address the myriad of public policy issues which must also be resolved, both nationally and internationally, prior to implementation of a successful AIDS vaccine program. These issues include development and implementation of mechansims to assure the active participation and coordination of all relevant agencies of the US government, as well as the pharmaceutical industry, and the international community, where candidate vaccines must be tested for efficacy, and where the need for an effective vaccine is the greatest. The recommendations which follow concern these administrative issues, which must be planned and coordinated simultaneously with the actual generation of candidate vaccines .

Requisite participants in vaccine development

Federal agencies: The proposed restructuring of the AIDS vaccine program within NIH represents an important step in expanding the scientific leadership which will be necessary to expedite the development of candidate vaccines. The appointment of Dr. David Baltimore as Chair of the AIDS Vaccine Research Committee (AVRC), the expanded vaccine budget, and the proposed institution of a new Vaccine Research Laboratory at the NIH, can all serve to invigorate the scientific process which will be essential to vaccine generation. The appointment of a full time Director of the Vaccine Research Lab could provide another mechansim for coordination of the vaccine development effort within NIH. However, the Council is very concerned that recent progress has been slowed substantially by the failure to appoint this individual, who must be at the highest level of expertise.

In addition to NIH, Federal agencies such as the Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), and the United States Agency for International Development (USAID) have extensive experience and expertise in the area of vaccine development, field epidemiology, surveillance, and the conduct of vaccine efficacy trials, especially in developing countries. It would thus seem prudent to assure the active cooperation, collaboration and communication of all relevant Federal agencies in the areas of candidate vaccine development and testing, if the President's goal is to be met. Similar recommendations were made by the Levine Commission. However, although various NIH vaccine meetings have been attended by DOD and CDC representatives, and although an informal interagency group was formed, this group does not include senior leadership, and has not met on a regular basis. It is thus clear that no formal process of interagency coordination has yet been developed or implemented. If the President's goal is to be met, such interagency communication and coordination must occur, involving the highest levels of leadership from each Agency.

Pharmaceutical and biotechnology industries: It is clear that development of a successful AIDS vaccine will also require the active involvement of the pharmaceutical and biotechnology industries, working in a coordinated manner with relevant federal agencies. The pharmaceutical industry has traditionally been a major leader in the creation and development of vaccines, and should be encouraged to participate actively in the pursuit of an AIDS vaccine. Further, eventual product development will require the infrastructure and expertise which resides primarily within the private sector of pharmaceutical and biotechnology industries. To

assure the requisite coordination of both public and private sectors, an administrative mechanism must be created. Multiple policy issues must also be addressed, in an attempt to overcome existing financial disincentives for involvement by the private sector. This may entail subsidies for targeted applied research, cooperative agreements for pilot manufacture of vaccine approaches not commercially attractive, support of phase III human efficacy trials, tax rebates, and/or patent extensions. Federal leadership will also be needed to address related issues, such as intellectual property rights, liability, and international vaccine development and purchase funds.

International community: Due to the higher prevalence of HIV/AIDS in developing nations, the majority of clinical testing for efficacy of candidate vaccines (Phase III) must be accomplished internationally. Further, the majority of AIDS vaccine use is expected to occur in nations outside the USA. It is thus apparent that mechansims to develop true partnerships between the international community and the federal AIDS vaccine effort must begin at once, with exchange of information and full coordination of combined efforts. Agencies such as the United Nations Program on AIDS (UNAIDS), the World Bank, the International AIDS Vaccine Initiative (IAVI), and the leading developed countries (G-8), as well as those countries most affected, have critical roles to play in the final testing and implementation of an AIDS vaccine. A mechanism must be developed to provide a means for on-going communication and collaboration among these groups, as well as the other critical constituencies listed above. Critical Issues which must be addressed by these groups include active involvement in the process by scientists living in the countries involved, assurance of scientifically and ethically appropriate field testing of candidate vaccines, and mechanisms to assure accoss to vaccine product after successful field testing.

Leadership and coordination

Role of the President's Office: It is only within the Office of the President that sufficient authority exists to assure coordination and collaboration of all requisite constituencies, including Federal agencies, private sector, and the international community. Responsibility for this effort should rest with the Office of National AIDS Policy (ONAP). The Council therefore recommends that the President formally charge the Director of the Office of National AIDS Policy with developing and maintaining administrative mechansims for accomplishing the requisite communication and coordination among all relevant parties, including assurrance of

the involvement of senior leadership from all constituencies. Adequate resources must be made available for this function.

Generation of a Comprehensive Federal Plan for AIDS Vaccine Development: A Comprehensive Federal AIDS Vaccine Plan must be developed and implemented. This plan must include the vision and process for vaccine development, and must also depict the specific objectives, responsibilities, strategies and outcomes for the implementation of the plan. Additional requisites of the plan should include the framework by which competing issues may be addressed, an over-all work schedule, and a specific time-frame in which certain milestones are to be accomplished. The Council recommends that the process for development of this plan be organized within the Office of AIDS Policy, working with relevant federal agencies.

Moving candidate vaccines into human trials

Conceptually, two divergent approaches may theoretically lead to the successful development of an AIDS vaccine; these include the basic scientific method, and the empirical scientific approach. Employing the basic scientific method, various hypotheses are generated and then tested which aim to elucidate the specific protective immune responses against HIV. Once such information is known, vaccine candidates can be developed, which are capable of inducing the specific immune responses which are likely to confer protection. The empirical scientific approach generates and tests hypotheses based upon in vitro or animal studies, even without a clear understanding of their biological mechanisms of activity. With the gravity of the current AIDS pandemic in the world, and the need to proceed with vaccine development as quickly as possible, the Council acknowledges that it will be necessary to test various traditional and novel vaccine design strategies in human clinical trials, even before the scientific correlates of protection have been fully deciphered. We thus advocate the simulataneous implementation of both basic scientific studies, aimed at elucidating protective immune responses, as well as studies based upon thoughtful empiricism. These parallel approaches should be recognized within the comprehensive Federal plan for AIDS vaccine development.

THE WHITE HOUSE

WASHINGTON

THE PRESIDENT INTRODUCES INITIATIVES TO FULFILL HIS COMMITMENT TO DEVELOP AN AIDS VACCINE

Today President Clinton challenged the nation to commit itself to the goal of developing an AIDS vaccine within the next ten years. The President also announced a number of important initiatives to help fulfill this commitment, including high-level international collaboration, a dedicated research center for AIDS vaccine research at the National Institutes of Health (NIH), and outreach to scientists, pharmaceutical companies, and patient advocates to maximize the involvement of both the private and public sectors in the development of an AIDS vaccine. The President has already taken steps to enhance the possibility of developing an AIDS vaccine by increasing funding for NIH vaccine research and development over 33 percent in the last two years. The initiatives the President announced today, which build on an exceptional commitment to develop better ways to prevent, diagnose, treat, and eventually cure AIDS, include:

- **A New NIH AIDS Vaccine Center.** A dedicated intramural HIV vaccine research and development center is being established at the National Institutes of Health. This vaccine center, which will be fully operational within the next several months, is uniting outstanding scientists in immunology, virology, and vaccinology to join in a highly-collaborative effort to develop an AIDS vaccine. Bringing together a broad array of researchers in an intensely-focused environment has been a successful way of developing vaccines in the past.

- **A Global AIDS Vaccine Research Initiative.** The United States is proposing that the leaders of the eight major industrialized nations meeting at the Denver Summit in June agree to support a worldwide AIDS vaccine research initiative. The proposal calls for each nation to make a commitment to provide the necessary investments in their country to accelerate research toward the development of an HIV/AIDS vaccine as a scientific and public health priority. Joint meetings of key scientists from participating nations will address research progress, identity scientific gaps and opportunities, and design collaborative programs.

- **A Challenge to Pharmaceutical Manufacture Industry to Invest in Innovative Research to Develop an AIDS Vaccine.** We can only be successful in developing an AIDS vaccine if private and public sectors make this goal a priority. The President is challenging the pharmaceutical industry to join the government in a partnership to realize this important goal.

Background on HIV/AIDS. HIV/AIDS remains a global public health threat. More than 29 million men, women and children around the world have been infected with HIV -- more than 3 million infections occurring within the last year. Without an effective vaccine, AIDS will soon overtake tuberculosis and malaria as the leading cause of death among persons between 25-44 years of age. Between 650,000-900,000 Americans are estimated to be living with HIV disease, and over 300,000 Americans have already died from AIDS.

Clinton Administration Accomplishments on HIV/AIDS. The Clinton Administration has made a sustained commitment to addressing the HIV epidemic through investments in prevention, research and treatment.

- **Increased funding for the NIH vaccine by 33 percent.** Funding for NIH vaccine research and development has increased over 33 percent in the last two years -- from $111.1 million in FY 1996 to $148 million proposed in the President's FY 1998 budget.

- **Funding for AIDS research, prevention and care increased by more than 50 percent in the first four years of the Clinton Administration.** Funding for AIDS Drug Assistance Programs (ADAP), which help low-income people purchase needed therapies, has tripled, while funding for the Ryan White CARE Act increased 158 percent. The approval of new AIDS drugs has greatly accelerated, with 16 new AIDS drugs and two diagnostic tests.

AIDS VACCINE Q&AS

Q: DOESN'T THE PRESIDENT'S CHALLENGE RING HOLLOW SINCE YOU ARE NOT INVESTING ANY NEW RESOURCES DEVELOPING AN AIDS VACCINE?

A: The President has committed additional resources to developing an AIDS vaccine. In the last two years, he has increased funding for the AIDS vaccine by 33 percent and his FY 1998 budget increases spending for AIDS vaccine research by $17 million.

Moreover, scientists have informed the President that it is not only money that we need to meet the challenge of finding an AIDS vaccine, but that we also need to promote collaboration between experts in this area. That is why the President has announced that there will be a new AIDS Vaccine Center at NIH which will unite scientists in immunology, virology, and vaccinology to join in a highly collaborative effort to develop an AIDS vaccine.

That is also why is he calling on the leaders of the eight major industrialized nations meeting at the Denver summit in June to support a worldwide AIDS vaccine research initiative. These important initiatives are what scientists believe we need to do to fully commit ourselves to the goal of developing an AIDS vaccine.

Q: IN 1985, MARGARET HECKLER PREDICTED THAT WE WOULD HAVE AN AIDS VACCINE IN TWO YEARS. THAT WAS OVER TEN YEARS AGO. MOREOVER, AT A RECENT CONFERENCE, DR. ROBERT GALLO INDICATED THAT WE MAY NEVER SEE AN EFFECTIVE AIDS VACCINE. WHY SHOULD WE BELIEVE THAT THE PRESIDENT'S PROMISE THAT WE CAN DEVELOP AN AIDS VACCINE IN A DECADE?

A: We know much more about the AIDS virus today than we knew in 1985 or even in 1995. Recent scientific advances have taught a great deal about how the AIDS virus infiltrates the human and begins to destroy the human immune system. We have developed a whole new series of drugs that inhabit the reproduction of the AIDS virus.

There are many credible scientists and medical researchers who are believe that it is not a question of whether we will ever get an AIDS vaccine but when. The scientific leaders at the National Institutes of Health have said that are extremely encouraged by recent progress in the AIDS vaccine and believe that the development of a vaccine is feasible. In fact, there were

numerous presentations at the conference that spoke about the tremendous progress we have made in the AIDS vaccine development and in vaccine development in general.

The President announced today that we should commit ourselves to developing an AIDS vaccine in the next ten years. He acknowledged that there are no guarantees. But he believes that we should commit our energy, our focus, and the efforts from our greatest minds to finding an AIDS vaccine.

Q: HOW ARE THE INITIATIVES THE PRESIDENT ANNOUNCED TODAY BEING PAID FOR? ARE THEY A PART OF THE BALANCED BUDGET AGREEMENT?

A: All of the costs for developing an AIDS vaccine are being paid for by NIH's existing budget. NIH has already increased funding for AIDS vaccine research by 33 percent in the last two years -- from $111 million in FY 1996 to $148 million proposed in the President's FY 1998 budget. The President's FY 1998 budget alone calls for a $17 million increase.

Q: IF WE ARE INVESTING MORE TO DEVELOP AN AID VACCINE AREN'T WE TAKING AWAY FROM INVESTMENTS ON TREATING PEOPLE WHO ALREADY SUFFER FROM THIS DISEASE?

A: Since he took office, the President has made an extraordinary commitment to increasing our investments in AIDS. Funding for AIDS research, prevention and care increased by more than 50 percent in the first four years of the Clinton Administration. Funding for AIDS Drug Assistance Programs (ADAP), which help low-income people purchase needed therapies, has tripled, while funding for the Ryan White CARE Act increased 158 percent. The President believes that we need to continue to increase our investments in all of these areas and his FY 1998 budget reflects that commitment, with additional investments in AIDS research, prevention and care.

Q: THE BALANCED BUDGET AGREEMENT CALLS FOR CAPS ON DISCRETIONARY DOMESTIC SPENDING. WON'T ADDITIONAL FUNDING FOR AN AIDS VACCINE MEAN LESS FOR OTHER IMPORTANT PRIORITIES? WHY NOT EXPEND THIS KIND OF ENERGY AND RESOURCES ON A CURE FOR BREAST CANCER OR HEART DISEASE OR DIABETES?

A: This Administration has made a strong improving biomedical research an extremely important priority. We have increased investments in biomedical research at the National Institutes of Health by an impressive 16 percent since the President took office.

These additional investments has been used to increase investments in biomedical research in a number of important areas. For example, funding for breast cancer research has increased by 76 percent since the President took office .

Developing an AIDS vaccine is one important priority in our investments in biomedical research. Without an effective vaccine, AIDS will soon take over as the leading cause of death for persons between the ages of 25 and 44. Between 650,00 and 900,000 Americans are estimated to be living with HIV and over 300,000 have died of AIDS.
While we have made enormous strides in the last year in treating AIDS, these treatments are not always effective and are often prohibitively expensive both for Americans and throughout the world. Also scientists at NIH believe that it is only a matter of time before we develop an AIDS vaccine.
Increasing our commitment to developing a vaccine could make an enormous difference and save millions of lives both in this country and throughout the world.

STATISTICS ON THE AIDS EPIDEMIC

National Trends

- Between 650,000 and 900,000 Americans are living with HIV.
- Since the AIDS epidemic began 500,000 Americans have been reported with AIDS -- 300,000 have died.
- An estimated 40,000 to 60,000 Americans are being infected with HIV each year.
- An average of 100 Americans are diagnosed with AIDS each day and 100 to 150 become infected with HIV every 24 hours.
- AIDS is the leading cause of death among Americans aged 25 to 44.
- Women now comprise 14% of people with AIDS. If the current trends continue, an estimated 80,000 children will have been orphaned as a result of this disease by the end of the decade.
- In 1994 alone, 1,000 new pediatric cases of AIDS were reported.
- One in four new HIV infections in the U.S. occur among people under the age of 21.
- People of color have been disproportionately impacted by AIDS. As of October 1995, 38 percent of newly reported AIDS cases were with people of color

International Trends

- More than 29 million men, women and children around the world have been infected with HIV -- more than 3 million infections occurring within the last year.
- In 1995, 1.1 million adults and 350,000 children in the world died of AIDS.
- 8,500 people become infected with AIDS each day, including nearly 1,000 children.

- It has been estimated in some countries in subsaharan Africa that life expectancy has decreased by up to twenty years because of the AIDS epidemic.

- In 1992, in South Africa 2% of all women who came in for prenatal treatment were HIV positive and that number is up to 14%.

- Without an effective vaccine, AIDS will soon overtake tuberculosis and malaria as the leading cause of death among persons between 25-44 years of age.

THE PRESIDENT INTRODUCES INITIATIVES TO FULFILL HIS COMMITMENT TO DEVELOP AN AIDS VACCINE

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- Since the AIDS epidemic began 500,000 Americans have been reported with AIDS -- 300,000 have died.
- An estimated 40,000 to 60,000 Americans are being infected with HIV each year.
- It is the leading cause of death among Americans aged 25 to 44.
- Women now comprise 14% of people with AIDS. If the current trends continue, an estimated 80,000 children will have been orphaned as a result of this disease by the end of the decade.
- In 1994 alone, 1,000 new pediatric cases of AIDS were reported.
- One in four new HIV infections in the U.S. occur among people under the age of 21. Between 27 and 54 Americans under the age of 21 are infected with HIV each day.
- People of color have been disproportionately impacted by AIDS. As of October 1995, 38 percent of newly reported AIDS cases were with people of color

INTERNATIONAL

- India has the largest growing AIDS population
- There are also terrible problems in subsaharan Africa. It has been estimated in some countries that life expectancy has decreased by up to twenty years because of the AIDs epidemic.
- In 1992, in South Africa 2% of all women who came in for prenatal treatment were HIV positive and that number is up to 14%.

Office of
National AIDS Policy

Correspondence Routing Slip

Tracking Number: G3824

Date Rcvd: 06-06-97

From: Mathilde Krim

Letter addressed to the President from AMFAR
cc Sandra Thurman

file - vaccines

Staff Action:

Reviewed By Sandy:_____ Reviewed By: _____

Assigned To:_____

RCVD:_____ DONE:_____

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Recommendations/Instructions:

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To Support Staff:_____

Date of Response:_____

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cc: S. Thurman

AmFAR
733 Third Avenue
New York, NY 10017-3204
Tel 212-682-7440
Fax 212-682-9812

May 28, 1997

The President
The White House
Washington, D.C.

Dear Mr. President:

The American Foundation for AIDS Research (AmFAR) strongly supports your goal to develop a successful vaccine for the prevention of HIV infection by the year 2007. We believe that this is a realistic goal.

Soon AmFAR will publicly announce its own targeted support for research on certain aspects of the immune system in which more knowledge is needed for the development of an HIV vaccine. Working together with the National Institutes of Heath, its Office of AIDS Research and industry, we will help coordinate research efforts. And AmFAR will provide grant support for selected promising research projects. As new scientific discoveries are made, we hope to join with the federal government in further increasing our financial commitment until, like smallpox and polio, HIV infection is brought under full control throughout the world.

Looking back on the HIV/AIDS epidemic, we have seen that many "unreachable" goals have been met successfully.

Initially, many felt that the cause of AIDS would not be discovered, but, in 1984, HIV, the virus that causes AIDS was identified by three research groups. Subsequently, there were many who said that treatment of HIV would not be possible, but in 1986, AZT was shown to decrease the number of AIDS related complications and now, in 1997, we have 11 drugs to control the virus. Some have stated that we would never be able to prevent HIV transmission from mothers to infants, but now maternal HIV transmission to infants can be prevented with AZT, and HIV transmission following accidental HIV inoculation in health care workers can be reduced with AZT and 3TC. All of this

has been extraordinary progress, some of which is having an impact even beyond the field of HIV/AIDS. As only one example, the drug 3TC developed against HIV is also effective in the treatment of Hepatitis B.

And, sometimes predictions do come true. In November 1995, at the White House Conference on AIDS, you stated that "by the year 2000 we can bring the pediatric epidemic under control. If we offer counseling and HIV testing to all pregnant women and provide treatment to HIV-infected women and their newborns we will have virtually no newly infected infants." Today, less that two years since you made this statement, it is estimated that from 2000 cases in the early '90s there are now fewer than 100 newly HIV infected infants born in the United States each year. We are already in sight of the goal you set for the year 2000.

The dramatic progress made against HIV/AIDS is the result of the combined efforts of research scientists in academia and industry along with the cooperation of the entire HIV/AIDS community. Without funding from the government, industry and private sector foundations, these advances would not have occurred. Therefore, we believe that your plans to target efforts and funding on the development of an HIV vaccine will greatly accelerate the control of the epidemic.

Each day, 7,500 individuals become infected with HIV throughout the world. For 90% of the 25 to 30 million people already infected with HIV worldwide, there is no treatment today and no treatment they will be able to afford in the foreseeable future. A vaccine is needed for the protection of huge populations now at risk as it is needed for Americans as well. Indeed, we live in a global incubator and unless we prevent HIV infection worldwide we will remain at risk of a continuing epidemic at home.

Respectfully yours,

Mathilde Krim, Ph.D.
Founding Co-Chair and
Chairman of the Board

Arthur J. Ammann, M.D.
President

AMERICAN FOUNDATION FOR
AmFAR
AIDS RESEARCH

733 THIRD AVENUE
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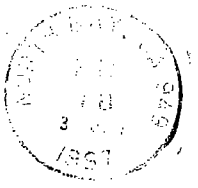
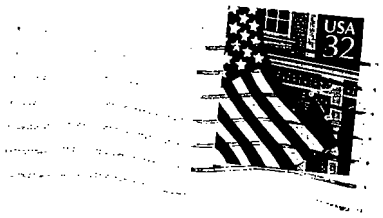
NEW YORK, NY 10017-3204





Sandra Thurman
Office of National AIDS Policy
808 17th Street NW, Suite 820
Washington D C 20006

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Subject: 1997-05/16 Remarks by President re: Tuskegee

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release May 16, 1997

REMARKS BY THE PRESIDENT
IN APOLOGY FOR STUDY DONE IN TUSKEGEE

The East Room

2:26 P.M. EDT

THE PRESIDENT: Ladies and gentlemen, on Sunday, Mr. Shaw will celebrate his 95th birthday. (Applause.) I would like to recognize the other survivors who are here today and their families: Mr. Charlie Pollard is here. (Applause.) Mr. Carter Howard. (Applause.) Mr. Fred Simmons. (Applause.) Mr. Simmons just took his first airplane ride, and he reckons he's about 110 years old, so I think it's time for him to take a chance or two. (Laughter.) I'm glad he did. And Mr. Frederick Moss, thank you, sir. (Applause.)

I would also like to ask three family representatives who are here -- Sam Doner is represented by his daughter, Gwendolyn Cox. Thank you, Gwendolyn. (Applause.) Ernest Hendon, who is watching in Tuskegee, is represented by his brother, North Hendon. Thank you, sir, for being here. (Applause.) And George Key is represented by his grandson, Christopher Monroe. Thank you, Chris. (Applause.)

I also acknowledge the families, community leaders, teachers and students watching today by satellite from Tuskegee. The White House is the people's house; we are glad to have all of you here today. I thank Dr. David Satcher for his role in this. I thank Congresswoman Waters and Congressman Hilliard, Congressman Stokes,

the entire Congressional Black Caucus. Dr. Satcher, members of the Cabinet who are here, Secretary Herman, Secretary Slater, members of the Cabinet who are here, Secretary Herman, Secretary Slater. A great friend of freedom, Fred Gray, thank you for fighting this long battle all these long years.

The eight men who are survivors of the syphilis study at Tuskegee are a living link to a time not so very long ago that many Americans would prefer not to remember, but we dare not forget. It was a time when our nation failed to live up to its ideals, when our nation broke the trust with our people that is the very foundation of our democracy. It is not only in remembering that shameful past that we can make amends and repair our nation, but it is in remembering that past that we can build a better present and a better future. And without remembering it, we cannot make amends and we cannot go forward.

So today America does remember the hundreds of men used in research without their knowledge and consent. We remember them and their family members. Men who were poor and African American, without resources and with few alternatives, they believed they had found hope when they were offered free medical care by the United States Public Health Service. They were betrayed.

Medical people are supposed to help when we need care, but even once a cure was discovered, they were denied help, and they were lied to by their government. Our government is supposed to protect the rights of its citizens; their rights were trampled upon. Forty years, hundreds of men betrayed, along with their wives and children, along with the community in Macon County, Alabama, the City of Tuskegee, the fine university there, and the larger African American community.

The United States government did something that was wrong -- deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens.

To the survivors, to the wives and family members, the children and the grandchildren, I say what you know: No power on Earth can give you back the lives lost, the pain suffered, the years of internal torment and anguish. What was done cannot be undone. But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say on behalf of the American people, what the United States government did was shameful, and I am sorry. (Applause.)

The American people are sorry -- for the loss, for the years of hurt. You did nothing wrong, but you were grievously wronged. I apologize and I am sorry that this apology has been so long in coming. (Applause.)

To Macon County, to Tuskegee, to the doctors who have been wrongly associated with the events there, you have our apology, as well. To our African American citizens, I am sorry that your federal government orchestrated a study so clearly racist. That can never be allowed to happen again. It is against everything our country stands for and what we must stand against is what it was.

So let us resolve to hold forever in our hearts and minds the memory of a time not long ago in Macon County, Alabama, so that we can always see how adrift we can become when the rights of any citizens are neglected, ignored and betrayed. And let us resolve here and now to move forward together.

The legacy of the study at Tuskegee has reached far and deep, in ways that hurt our progress and divide our nation. We cannot be one America when a whole segment of our nation has no trust in America. An apology is the first step, and we take it with a commitment to rebuild that broken trust. We can begin by making sure there is never again another episode like this one. We need to do more to ensure that medical research practices are sound and ethical, and that researchers work more closely with communities.

Today I would like to announce several steps to help us achieve these goals. First, we will help to build that lasting memorial at Tuskegee. (Applause.) The school founded by Booker T. Washington, distinguished by the renowned scientist George Washington Carver and so many others who advanced the health and well-being of African Americans and all Americans, is a fitting site. The Department of Health and Human Services will award a planning grant so the school can pursue establishing a center for bioethics in research and health care. The center will serve as a museum of the study and support efforts to address its legacy and strengthen bioethics training.

Second, we commit to increase our community involvement so that we may begin restoring lost trust. The study at Tuskegee served to sow distrust of our medical institutions, especially where research is involved. Since the study was halted, abuses have been checked by making informed consent and local review mandatory in federally-funded and mandated research.

Still, 25 years later, many medical studies have little African American participation and African American organ donors are few. This impedes efforts to conduct promising research and to provide the best health care to all our people, including African Americans. So today, I'm directing the Secretary of Health and Human Services, Donna Shalala, to issue a report in 180 days about how we

can best involve communities, especially minority communities, in research and health care. You must -- every American group must be involved in medical research in ways that are positive. We have put the curse behind us; now we must bring the benefits to all Americans. (Applause.)

Third, we commit to strengthen researchers' training in bioethics. We are constantly working on making breakthroughs in protecting the health of our people and in vanquishing diseases. But all our people must be assured that their rights and dignity will be respected as new drugs, treatments and therapies are tested and used. So I am directing Secretary Shalala to work in partnership with higher education to prepare training materials for medical researchers. They will be available in a year. They will help researchers build on core ethical principles of respect for individuals, justice and informed consent, and advise them on how to use these principles effectively in diverse populations.

Fourth, to increase and broaden our understanding of ethical issues and clinical research, we commit to providing postgraduate fellowships to train bioethicists especially among African Americans and other minority groups. HHS will offer these fellowships beginning in September of 1998 to promising students enrolled in bioethics graduate programs.

And, finally, by executive order I am also today extending the charter of the National Bioethics Advisory Commission to October of 1999. The need for this commission is clear. We must be able to call on the thoughtful, collective wisdom of experts and community representatives to find ways to further strengthen our protections for subjects in human research.

We face a challenge in our time. Science and technology are rapidly changing our lives with the promise of making us much healthier, much more productive and more prosperous. But with these changes we must work harder to see that as we advance we don't leave behind our conscience. No ground is gained and, indeed, much is lost if we lose our moral bearings in the name of progress.

The people who ran the study at Tuskegee diminished the stature of man by abandoning the most basic ethical precepts. They forgot their pledge to heal and repair. They had the power to heal the survivors and all the others and they did not. Today, all we can do is apologize. But you have the power, for only you -- Mr. Shaw, the others who are here, the family members who are with us in Tuskegee -- only you have the power to forgive. Your presence here shows us that you have chosen a better path than your government did so long ago. You have not withheld the power to forgive. I hope today and tomorrow every American will remember your lesson and live by it.

Thank you, and God bless you. (Applause.)

END 2:41 P.M. EDT

NCIH National Council for International Health

1701 K Street NW, Suite 600, Washington, DC 20006-1503 ● Tel. 202-833-5900, Fax 202-833-0075, Internet <ncih@ncih.org> <www.ncih.org>

July 8, 1997

Ms. Sandra Thurman
Office of National AIDS Policy
750 15th Street, NW
Suite 600
Washington, DC 20503

Dear Ms. Thurman:

We apologize for the misunderstanding of your acceptance to be moderator at our International Health Seminar, "AIDS Vaccine: History, Development and Ethics, the International Perspective". It was our understanding that your office had agreed to your participation and had asked for more information regarding the seminar. Please know that if needed we can make final changes to the program to accommodate you and your schedule. However, we would be delighted if you could give a brief opening presentation for the seminar.

The National Council for International Health has been in existence since 1989. Our mission is to improve global health by providing vigorous leadership and advocacy to increase private and public-sector commitment to international health issues. The NCIH Global AIDS Program, supported by USAID, is a unique alliance of more than 500 organizations from around the world, and sponsors several workshops and conferences each year relating to HIV/AIDS. The NCIH AIDS program in conjunction with the George Washington Center for International Health is proud to sponsor the seminar/discussion of AIDS vaccine development. We view this topic as vital to our mission and others who are working in the global AIDS epidemic.

Enclosed please find some **"talking points"** which may be helpful in the opening presentation. As previously stated, we would like your participation to be approximately 10 minutes and yet will understand if you would like to shorten the length of your presentation. Our original plans for calling the seminar on the AIDS Vaccine Initiative was to educate the NGO and PVO community on the development of an AIDS vaccine. Several activists and community development specialists were surprised and did not understand fully the significance or content of the President's announcement. It would be very helpful if you could describe this announcement as it relates to the international AIDS community work. It may be useful to add some background information which led up to the announcement as well as discuss future plans of the President's Office to complete the goal of developing an AIDS vaccine in ten years. For example this discussion may include:

Background Information leading up to the Announcement:

- December 3rd meeting with President Clinton, Vice President Al Gore, Chief of Staff Leon Pannetta, NIH Director Harold Varmus, Director of NIAID, Anthony Faucci, and Chief of Office of AIDS Research William Paul
- Presidential Advisory Council on HIV/AIDS recommendations in Spring of 1997

President's Announcement:

At a commencement address at Morgan State University in Baltimore on May 18, 1997, President Clinton called for the development of an AIDS Vaccine within a decade. Although we have seen new advances in the treatment of HIV/AIDS in the United States and other European Countries, we must not become complacent in searching for an AIDS vaccine. As stated by the President, "HIV is capable of mutating and becoming resistant to therapies, and could well become even more dangerous. AIDS will soon overtake tuberculosis and malaria as the leading infectious killer in the world"...