FOIA Number: 2018-0764-F

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Subgroup/Office of Origin: National AIDS Policy Office

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OA/ID Number: 19403

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Folder Title:
[Issues] AIDS Vaccine [2]

Stack:	Row:	Section:	Shelf:	Position:
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May 19, 1997

President Bill Clinton
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500

Dear Mr. President:

The International AIDS Vaccine Initiative strongly supports your call for an urgent increased and time-bound effort to develop safe and effective HIV vaccines. We agree that an HIV vaccine is possible and with nearly 10,000 new infections occurring a day worldwide, time is of the essence.

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. HIV is the first large global epidemic of an emerging infectious disease in this era of global interconnectedness. How we deal with this epidemic portends how we will contend with future, yet undiscovered infectious diseases. Your leadership on this issue internationally will intensify recognition of the impact of HIV/AIDS on international health and development, and bring together the strengths and commitment of national and international agencies and organizations to address and solve the impact of HIV/AIDS on worldwide human and economic development.

We concur that the U.S. government must continue to support or even enhance the excellent basic scientific research that serves as the essential underpinning of vaccine development. In addition, we need to enhance applied vaccine development efforts. Without good animal models and without clear correlates of protection, there is no substitution for clinical testing of promising safe candidates in humans at an early stage. Results (whether positive or negative) from clinical testing will drive the basic science agenda as much as findings in basic science will inform the product development process.

We support the creation of a new vaccines effort at the NIH which will facilitate the important linkage between basic and clinical research. As you have acknowledged, however, industry is the best source of applied work. Unfortunately, as you are aware, there currently are not the market incentives for industry to invest substantial resources in HIV vaccine development. A new initiative needs to be considered. This initiative should be a directed research effort which

IAVI

Interim Secretariat • c/o The Rockefeller Foundation • 420 Fifth Avenue • New York, NY 10018-2702 • USA
phone (212) 852-8349 • fax (212) 852-8279

is goal oriented with clear benchmarks using the world's most experienced HIV/AIDS researchers and vaccinologists. Vaccines cannot be developed by researcher oriented mechanisms. Vaccines need to be developed by an experienced team of vaccinologists and other scientists that will, step by step, solve the problems encountered during the development process.

In addition, vaccines need to be designed for testing and use in international settings where the epidemic is spreading most rapidly and where testing can be efficiently accomplished. Use in international settings may require special characteristics such as simplicity, stability and cost that may require different vaccine designs than are being evaluated for the U.S. market.

The International AIDS Vaccine Initiative was established with just this purpose in mind -- to ensure the development of safe, effective, preventive HIV vaccines for use throughout the world. IAVI has established a partnership of international agencies (UNAIDS and the World Bank) to work directly with those in the private sector without the constraints of government funding mechanisms to accelerate vaccine development. We would welcome the opportunity to work with your staff to assure the completion of your noble and just target of a safe and effective HIV vaccine by the end of the decade.

With best wishes.

Sincerely yours,

Seth Berkley, M.D.
Interim President

cc: Sandra Thurman

SFB/pb

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UNAIDS
UNICEF • UNDP • UNFPA
UNESCO • WHO • WORLD BANK
Joint United Nations Programme on HIV/AIDS

The Executive Director

President William J. Clinton
The White House
Washington, D.C.

Reference: exr

20 May 1997

Mr President,

Your extraordinary leadership in setting the goal for the development of an AIDS vaccine in the next ten years merits sincere praise. For too long, the research agenda has been turned on its head, with ninety percent of research funds in AIDS going towards cures and only ten percent to vaccines. Important as the new developments in therapy are in reducing the suffering and prolonging lives of people living with HIV/AIDS in the few countries where treatment is possible and affordable, they are doing nothing to halt the relentless march of this disease in Africa, Asia, Latin America and Eastern Europe.

For a vaccine to be brought to the parts of the world where the disease is having its greatest impact, the countries of the industrialized world and the developing world will need to work closely together. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has a Vaccine Advisory Committee, which is chaired by Dr Barry Bloom of the Albert Einstein College of Medicine in New York, and includes representatives from several industrialized and developing countries. UNAIDS and its Committee have as their mission to promote and facilitate the scientific, ethical, legal, and practical involvement of developing countries in vaccine research and testing.

Mr President, we pledge UNAIDS to work with you, Secretary Shalala, the National Institutes of Health and other U.S. institutions in the forefront of this crusade against AIDS. A vaccine which effectively addresses a virus which is devastating the world, must be tested and proven in the most affected countries in accordance with the highest standards of science and ethics.

Again, Mr President, I should like to congratulate you for your bold step forward. By directing the scientific community to leap beyond the tested borders of biology in the 21st century, you do much to ensure your own place in the history of our planet.

Please accept, Mr President, the assurance of my highest consideration.

Peter Piot

UNAIDS@WHO.CH

THE WHITE HOUSE AT WORK
Monday, May 19, 1997

SUNDAY: PRESIDENT CALLS FOR COMMITMENT TO DEVELOP AIDS VACCINE

Yesterday, at Morgan State University, in his first commencement address at a historically black college, President Clinton announced new actions to harness the forces of science and technology so that they work for us, not against us, in the 21st Century:

- The President called for a national commitment to develop an AIDS vaccine within the next decade, announcing that the National Institutes of Health will establish a new AIDS vaccine research center; pledging to enlist other nations in this crusade at next month's Summit of the Eight in Denver; and challenging America's pharmaceutical industry to make the development of an AIDS vaccine part of its basic mission.

- To make sure that no insurer is able to use genetic data to underwrite or discriminate against any American seeking health insurance, the President urged Congress to pass legislation to prohibit insurance companies from using genetic screening information to determine premium rates or eligibility.

- President Clinton laid out four guideposts, rooted in our traditional principles of ethics and morals, that must guide us if we are to master the powerful forces of change in the new century: "One, science that produces a better life for all and not the few. Two, science that honors our tradition of equal treatment under the law. Three, science that respects the privacy and autonomy of the individual. Four, science that never confuses faith in technology with faith in God."

SATURDAY: PRESIDENT URGES PASSAGE OF BEST EDUCATION BILL IN A GENERATION: THE BALANCED BUDGET

In his weekly Radio Address, President Clinton hailed the balanced budget agreement's historic investment in education, including the most significant increase in education funding in 30 years, and the single largest increase in higher education since the G.I. Bill in 1945:

- It will fund the America Reads challenge, to help every 8-year-old learn to read; and the Technology Literacy Initiative, to help wire every classroom and school library to the Internet by the year 2000.

- It includes $35 billion in tax relief for higher education -- including HOPE Scholarship tuition tax credits, a $10,000 education tax deduction, and the

largest increase in Pell Grant scholarships for deserving students in two decades.

- It expands Head Start, increases job training, and preserves our commitment to school-to-work initiatives, to help give young people the tools they need to succeed.

Thurman Urges Support for Clinton's AIDS Vaccine Effort

In response to President Clinton's recent announcement of a ten year AIDS vaccine project, his top AIDS advisor has moved to correct a perception among AIDS advocates that the project might distract from ongoing efforts to find a cure for the disease.

Sandy Thurman, Director of the National AIDS Policy Office in Washington, DC, believes that the vaccine search is fundamental to HIV prevention, and points out that the $17 million budget does not take funds away from existing treatment research.

"We can all certainly agree that prevention must be utmost in our minds when dealing with this disease," said Thurman, "and a vaccine is prevention at its highest. We have never stopped an epidemic without a vaccine. When one considers the enormity of AIDS globally, there is no question that this important work must begin now."

Thurman rejects the idea that science is choosing those without HIV over those who are living with the virus. "We absolutely must have both a vaccine and an effective treatment for AIDS. In fact, by finding a vaccine for HIV we would be in an excellent position to devote even more resources to those living with AIDS, such as treatment, housing, direct services and, of course, the cure we all are looking for."

Some AIDS advocates responded nervously to Clinton's proposal because the 30 researchers Clinton promised for the project would be culled, he said, from various positions at the National Institute of Health. Advocates feared that this would mean pulling people off of work associated with AIDS treatments.

Thurman emphasizes that vaccine development will be conducted as an adjunct to current treatment research. "We are not abandoning any of our treatment research activities in favor of vaccine development," she said. "The people we are bringing to this project come from a variety of research backgrounds and their positions will be promptly replaced. What they will have in common is a commitment to ending this epidemic."

"The President's dedication to ending this disease is both personal and a matter of policy," said Thurman. "After so many years of governmental distrust in terms of this epidemic, I can understand why some people viewed the President's announcement with skepticism. But the truth is, we intend to fight this epidemic through both vaccine development and treatment research. There are no strings attached."

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facsimile
TRANSMITTAL

[redacted]

to: Daniel Montoya
fax #: (202)632-1096
re: Vaccine article in the BAR
date: May 24, 1997
pages: 3, including this cover sheet.

For your information - Helen

From the desk of...

Helen M. Miramontes, MSN, RN, FAAN
Associate Clinical Professor & Deputy Director
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BAY AREA REPORTER

Vol. 27 • No. 21 • 22 May 1997

Serving the Gay & Lesbian Community for more than 26 years

Clinton announces AIDS vaccine initiative

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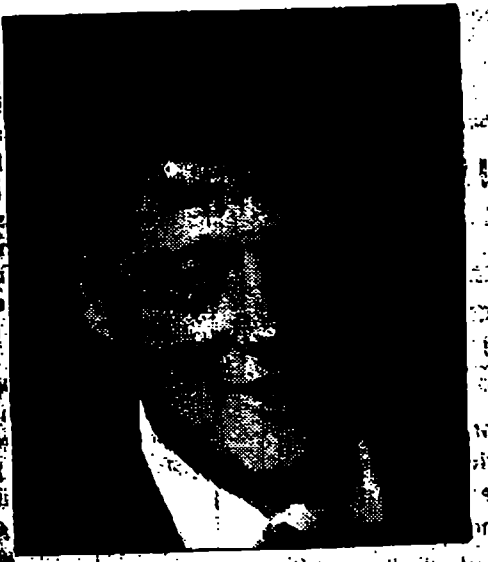
anticipated initiative was about 15 percent of
his commencement address at historically
black Morgan State University in Baltimore
on Sunday, May 18.

Most people knowledgeable of HIV applauded the president's intent but were skeptical of the outcome. Perhaps they remembered the prediction that Ronald Reagan's Secretary of Health and Human Services, Margaret Heckler, made in April 1984. She said they would have a vaccine in trial in two years. It did not happen.

Many leading scientists do not share Clinton's attitude that an HIV vaccine can be developed within that time frame, or perhaps ever. AIDS activists question whether his commitment is more than rhetoric. The President has proposed no new money. His initiative consists largely of reorganizing 30-50 existing employees at the National Institutes of Health into a vaccine research center.



Man in the moon: President Clinton wants a vaccine within a decade.

Vaccines were a high priority at a meeting of the Presidential Advisory Council on HIV/AIDS in early April. Dr. David Baltimore, chair of the AIDS Vaccine Research Committee at NIH, told them it was "not possible to put a date" on developing a vaccine, since there are "too many uncertainties." Others expressed little need for a restructuring of research. "I flinch at the concept of more coordination," said NIAID Director Anthony Fauci.

But in his most political comments of the meeting, chairman Scott Hitt told the body that the president wants to do "the man on the moon" analogy in moving this as a priority of the administration. He recommended they support the effort. The final document urged development of "a vaccine to prevent HIV/AIDS within a decade," with "a significant and sustained increase in funds... from *new* sources."

In a private conversation, Dr. William Paul, director of the Office of AIDS Research (OAR) at NIH, described the new lab as an intramural effort jointly sponsored by NIAID and NCI. They are the two major existing players in vaccine research. Each will contribute their existing resources, which will be supplemented with funding from OAR's discretionary account.

Paul called the president's challenge "a formidable undertaking...one which I am confident we can achieve, though not quite

vaccines his signature mark on the epidemic. "With new resources, NIH will now become the most powerful discovery engine for an AIDS vaccine, working with other scientists to finally end the threat of AIDS," he said in his February State of the Union Address. "We must reinforce our commitment to medical science." His subsequent budget for NIH offered an increase in funding that

Clinton

◀ page 1

in ten years." But he believes "a challenge is the right way to put it. We didn't want to trivialize it."

The science

Clinton's analogy to the moon project may be a good sound bite, but it is not an accurate comparison. In that instance we already possessed the scientific and mechanical knowledge necessary to accomplish the task. Kennedy's challenge was to summon the political and economic will of the nation to do so.

Developing an AIDS vaccine is quite different, for we are taking a leap of discovery, not one of implementation. The uncertainty is apparent in the handful of radically different approaches researchers are taking as to where and how to intervene to prevent infection. It indicates how little consensus there is, and how much basic study of HIV remains to be done.

There are six known strains of HIV, and the highly unstable virus is constantly mutating, creating variations within each strain. This is the varied, evolving foe a vaccine must protect against. Right now we simply don't know how a vaccine can work under those conditions. It has led some scientists to fear it is impossible. It has led many pharmaceutical companies to drop their efforts towards developing a vaccine, as they see foresee no profit coming from their investment.

Then there is the slippery slope of definition: How does one define "success?" The model most Americans know is that of the polio vaccine, where children are inoculated, protection is 99.9 percent effective, and side effects are minuscule.

Some researchers believe that vaccines currently in development may offer 30 percent protection for HIV. That is clearly not acceptable in the United States, where the prevalence of the virus is relative low (1 million people in a population of 270 million), the ability to reduce new infections is relatively easy and inexpensive, and the current standard of protection for vaccines is very high.

But a vaccine of such limited effectiveness might be acceptable in Third World countries where HIV infects close to half the population and sheer poverty precludes massive spending on healthcare. From a strictly public health perspective, such a vaccine might save literally thousands of lives and begin to limit the spread of the epidemic.

talk ... It's an easy promise. He's just switching NIH funds from Column A to Column B – what I call Chinese restaurant accounting."

"Show me the money," said Steve Michael with ACT UP/Washington. He echoed the sentiment expressed more diplomatically by every other AIDS organization. There is an underlying fear that increased funding for vaccine research might come at the expense of funding for research on treatment and for care for those already infected.

The Human Rights Campaign (HRC) applauded the initiative and called on the president to support a supplemental appropriation now before Congress that would add $68 million for AIDS Drug Assistance Programs (ADAP). The White House has not publicly indicated its support of that effort.

Long-term consequences include the possibility that a vaccine could result in infection with HIV, not protection from it.

There is also the dilemma of not knowing the long-term consequences of such a vaccine. They include the very real possibility that it could result in the infection of individuals with HIV, not their protection from it.

Researchers and the Advisory Council suggested creation of a body to look at the moral, ethical, and legal questions embedded in a possible vaccine for HIV. The President has yet to move on that aspect.

Reactions

Well-known AIDS researcher Dr. Robert Gallo questioned the extent of Clinton's commitment. He told *USA Today*, "If you really wanted a crash program, you'd have to have five or six centers focusing on nothing else."

The always acerbic playwright/activist Larry Kramer told the *Washington Post* that the president's speech was "more cheap

Meanwhile, Clinton continues to refuse to do things that can be done right now to prevent new infections in this country. They include lifting the federal funding ban on needle exchange programs and more effective prevention efforts.

It is statistically likely that some of the graduating seniors and their family members in the audience listening to his speech could have been spared their HIV infection had the president implemented those changes at the start of his administration. Instead, four years later, we have a vaccine initiative that may have an impact, in other countries, many years from now. ▼

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05/29/97 01:33:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: FW: SidAlerte Internationale service de presse : "Bravo Bill"

Forwarded, FYI. [Accented letters and international characters lost in this e-mail transmission.]

Date: Thu, 29 May 1997 15:14:57 +0100
From: GrUgory Haastrup <ghaastr@mail1.asi.fr>
Organization: SidAlerte
To: kamuraga@noc1.net.gn, michelyne.belleau@gre.ulaval.ca,
mdumais@courrier.usherb.ca, robert.beaudry@ccisd.bf,
raphael.bitera@syfed.bj.refer.org, sida2@scc.malinet.ml,
waly.diop@ccisd.bf, PZERBO@SYFED.REFER.SN,
francois.dery@ccisd.ulaval.ca,
mireille.trudelle@ccisd.ulaval.ca, pierre.champagne@ccisd.ulaval.ca,
campeaud@ere.umontreal.ca, sida2ci@AfricaOnline.Co.Ci,
fkintin@pase.pase.bf, francois.sobela@ccisd.bf, JCATRAYE@BASP96.BF,
j.pepin@courrier.usherb.ca, waptcas2@ncs.com.gh,
michel.alary@gre.ulaval.ca, Pierre.Viens@ccisd.ulaval.ca,
oxfamocs@web.apc.org, canews@cpha.ca, gnvrevdr@med.uovs.ac.za,
UNAIDS@WHO.CH, Esparzaj.@WHO.CH,
procaare-digest-owner@usa.healthnet.org,
nkoita@usaid.gov, BigBob411@aol.com, bgw2@CDC.GOV, canews@cpha.ca,
ben@QueerNet.org, alinde.rogatien@bow.intnet.bj,
SidAlerte@Cam.HealthNet.org, sidalert@AfricaOnline.Co.Ci, lawj@USIA.gov
Subject: SidAlerte Internationale service de presse : "Bravo Bill"

--

Reseau d'ONG en Afrique : Bravo Bill !

Le 28 mai 1997 - IRAP - L'avenement d'un vaccin represente la seule alternative pour le contole du VIH-SIDA dans les pays en voie de developpement, a declare le docteur Mamoudou Diallo, coordinateur d'un important reseau d'associations africaines de lutte contre le SIDA, present dans 13 pays d'Afrique, SIDALERTE INTERNATIONALE, a l'occasion de la visite en France du President des Etats Unis, je me rejouis que le President Bill Clinton ait percu cette necessite et s'en fasse l'avocat.

Il est heureux qu'il ait repris l'image de Kennedy quand il decida de mettre un homme sur la lune, pour proposer un nouvel ideal a realiser dans les dix ans a venir : l'Elaboration d'un vaccin contre le SIDA pour proteger l'humanite toute entiere.

Ul est essentiel que l'administration americaine s'engage a etablir le cadre propice a un partenariat entre l'Etat et les industries qui travaillent ou desirent travailler a ce vaccin, afin de retourner la situation actuelle marquee par un desinteret pour cette recherche.
En meme temps, je souhaite vivement que tout soit fait afin que les chercheurs en Afrique soient etroitement impliques dans cette recherche.

De plus, la recherche vaccinale tant sur les maladies emergentes que sur les parasitoses (paludisme, leishmanioses) beneficierait de cet elan, et justifierait l'etablissement d'un fonds mondial vaccin finance par les pays industrialises.

J'espoire que l'occasion du G8 (USA, France, Canada, Allemagne, Grande Bretagne, Italie Russie, Japon) a Denver le mois prochain, cette initiative ira encore plus avant dans la voie ouverte par le president americain.

African spokesman for AIDS NGOs supports Clinton's call for anti-HIV vaccine development

May 28th 1997 - IRAP-
"It is my deepest conviction that the only alternative to control HIV-AIDS in developing countries lies in the development of a vaccine" - declared doctor Mamoudou Diallo, coordinator of an important network of African AIDS organizations, acting in 13 francophone African countries, AIDSIDALERTE INTERNATIONAL, on the occasion of
Bill Clinton's visit to France

"I am very happy that president Clinton has understood this necessity and has become committed to vaccine development. It is fortunate that he has used the memory of Kennedy when he pledged to put a man on the moon, to put forth the new, magnificent goal for the coming ten years: the elaboration of a vaccine to protect humanity as a whole. It is essential that the US Administration commit itself to establish a framework conducive to a true partnership between States and the high tech companies working or desiring to work on vaccine development so as to transform the present situation marked by a lack of interest in this domain."

"At the same time, it is my most profound concern that African researchers be closely implicated in this research. Moroever, vaccinal research on emerging diseases as well as on parasitical diseases (such as malaria and leishmanioses) would benefit from such a vaccine drive, and today's emerging threats would justify the establishment of a world vaccine fund by industrialized countries."

"I hope that on the occasion of the G8 meeting in Denver, USA, next month, this initiative will move forward on the direction set forth by the American president."

"Last but not least, I am comforted in the American president's pledge that the highest ethical standards will be the rule in the agreements which will be prepared with African governments, to prepare for clinical trials."

bgw2 @ NIP1.EM.CDC.GOV
05/29/97 11:28:00 AM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: FORWARDED: Message from Africa re: Vaccine call

Forwarded message from Africa, FYI.
Bruce

Date: Thu, 29 May 1997 14:59:41 +0100
From: GrUgory Haastrup <ghaastr@mail1.asi.fr>
Organization: SidAlerte
To: BigBob411@aol.com, bgw2@cdc.gov, ben@QueerNet.org,
lawj@USIA.gov, nkoita@usaid.gov
Subject: Vaccine call

--

BRAVO BILL FOR YOUR AIDS VACCINE CALL !

Message to the President of the United States

from Doctor Mamoudou Diallo,
African coordinator of AIDSidAlerte International.

I am very, very happy about your call to commit your great nation to the realization of an AIDS vaccine. As coordinator over 13 countries of the largest French speaking network of AIDS organizations in Africa, as a field physician, and public health & epidemiology expert, I have been witness to the catastrophe which AIDS represents for my country, Mali, as well as for all the countries I have been to in my capacity, notably the Democratic Republic of Congo ex-Zaire last year.

I am convinced of the necessity of vaccine development, not only because I am a fighter in the struggle against AIDS, but also as a citizen committed to the future of my nation, and to the well being of future generations in Africa.

I have heard Nelson Mandela's appeal at the Davos summit, February 3rd, on the threat which AIDS represents for all the African economies and the future of democracy itself in Africa. It has long been my deepest conviction that only vaccine

development could stop our sliding into the hell which AIDS represents. Yet, on the occasion of my many visits to your country, I have been told that since vaccine trials were stopped in the US a few years ago, most industries had pulled out of vaccine research.

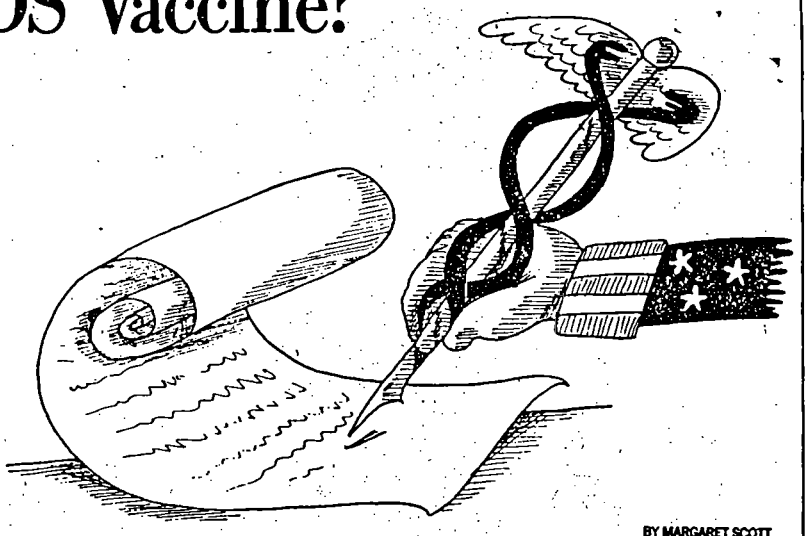
The founder and chairman of Chiron corporation William Rutter, one of the investors in HIV vaccine research has stated to my collaborators that only prevention, through vaccinations, was a viable solution for humankind in the face of HIV-AIDS, as well as most other epidemics, during an interview at the Pasteur Merieux Connaught Vaccine 2000 conference last fall in Toronto.

Bob Fogel, chairman of the International Committee of the presidential advisory group on HIV-AIDS, whom I have had the pleasure of inviting to Abidjan last March, has told me of your personal commitment to the fight against AIDS.

I am very moved by your appeal, and you may be assured of all our support. The IRAP (Information Research and Action Program) media program of AIDSidAlerte International whose purpose is to disseminate appropriate information on HIV AIDS/ STDs and tuberculosis will send out news on your initiative daily to the African media, and our publications SIDALERTE, the first medical periodical in French on HIV/AIDS as well as the medical quarterlies "AB TB & HIV" (English) and "AB TB et VIH" (French) will give ample coverage to your vaccine initiative.

Dr Mamoudou Diallo
Africa coordinator
AIDS-SIDALERTE INTERNATIONAL
Lyon, France, May 29th, 1997

Why an AIDS Vaccine?



BY MARGARET SCOTT

The reviews are in on President Clinton's dramatic declaration pledging the United States to finding an AIDS vaccine, moonshot-like, within 10 years. Apart from AIDS activists who complain that the president did not commit serious moonshot money to the enterprise ("cheap talk"—Larry Kramer), the reaction was mostly favorable. Who, after all, can be against a vaccine against anything?

No one seems to want to raise the obvious, if indelicate, question: Why embark on a huge national venture to create a vaccine for a disease that is already extraordinarily preventable?

Unlike most communicable diseases, AIDS is not contracted casually. Unlike TB, it is not contracted by being coughed on in the subway. Unlike dysentery, it is not contracted by drinking the wrong water. To get AIDS you must, in all but the rarest cases, engage in very complicated consensual social behavior, namely unsafe sex or intravenous drug abuse.

It would be nice to live in a world where one could engage in such behaviors while enjoying vaccine-induced immunity. But is that really a top national priority? Would any president propose as a top national priority an anti-lung-cancer vaccine so that people who smoke—48 million Americans do—could do so with immunity?

Nor do presidents call for a 10-year campaign to produce a vaccine against cirrhosis of the liver. Why? Not because we want to stigmatize people who drink or smoke. But for a very practical reason: These behaviors being voluntary and preventable, it makes a lot more sense to spend the scarce intellectual, scientific and financial resources of the country trying to give people immunity from diseases that they cannot otherwise protect themselves against.

The classic case is polio. When FDR contracted it in 1921, we had not a clue how people got it. By the '50s, frightened parents kept their children away from swimming pools and movie theaters and even crowds. They lived in terror not knowing what they might be doing that was contributing to their kids' chances of getting polio.

With no obvious behavioral cause, polio was the classic case of a disease crying out for a vaccine. Meningitis, cervical cancer and multiple sclerosis occupy a similar position today. But AIDS?

We abandoned public-health measures against AIDS because of political pressure. Now Clinton seeks an expensive magic wand instead.

Moreover, Clinton is calling for a huge technological innovation (which many in the field doubt is a reasonable prospect anyway) to prevent the spread of AIDS. Yet at the same time, the traditional way of controlling the spread of communicable diseases has been largely abandoned in the case of AIDS. And uniquely in the case of AIDS.

We fight just about every epidemic—tuberculosis, syphilis, gonorrhea—by identifying carriers and warning their contacts. The usual epidemiological tracing has not been done for AIDS. Gay activists and civil libertarians have vociferously opposed it. And the politicians have caved.

The story of this travesty—"the effective suspension of traditional public health procedures for AIDS"—is laid out in damning detail by Chandler Burr in the current Atlantic Monthly ("The AIDS Exception: Privacy vs. Public Health").

"AIDS has been so thoroughly exempted from traditional public health approaches," writes Burr, "that civil libertarians have defeated in court attempts by health authorities to notify the spouses of people who have died of AIDS that their husbands or wives were HIV-infected."

In 1985, in fact, gay activists brought suit to prevent the use of the first test for HIV, unless assured the tests would not be used for widespread screening of gays. Even today they oppose mandatory HIV screening for pregnant women, even though we know that early treatment of the mothers would reduce by 50 to 75 percent the number of kids who are born with HIV.

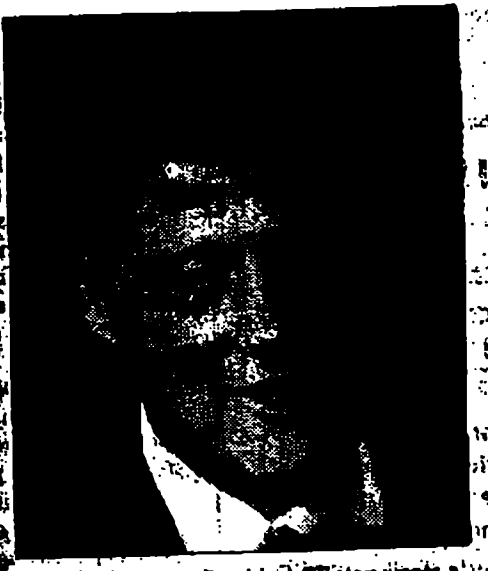
"Traditional public health is absolutely effective at controlling infectious disease," says Dr. Lee Reichman, who works with tuberculosis and AIDS patients. "It should have been applied to AIDS from the start, and it wasn't. Long before there was AIDS, there were other sexually transmitted diseases, and you had partner notification and testing and reporting. This was routine public health at its finest and this is the way STDs were controlled."

Marcia Angell, executive editor of the New England Journal of Medicine, is blunter than most: "I have no doubt . . . that if, for example, we screened all expectant mothers, we could prevent AIDS in many cases. And if we traced partners, we would prevent AIDS in many cases. And if we routinely tested in hospitals, we would prevent AIDS in many cases."

And if we had a president with guts, he would be demanding these elementary measures to save people from getting AIDS today—instead of waving a wand and telling scientists to produce for him a magic vaccine 10 years from now.

BAY AREA REPORTER
Vol. 27 • No. 21 • 22 May 1997
Serving the Gay & Lesbian Community for more than 26 years

Clinton announces AIDS vaccine initiative



Man in the moon: President Clinton wants a vaccine within a decade.

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Most people knowledgeable of HIV applauded the president's intent but were skeptical of the outcome. Perhaps they remembered the prediction that Ronald Reagan's Secretary of Health and Human Services, Margaret Heckler, made in April 1984. She said they would have a vaccine in trial in two years. It did not happen.

Many leading scientists do not share Clinton's attitude that an HIV vaccine can be developed within that time frame, or perhaps ever. AIDS activists question whether his commitment is more than rhetoric. The President has proposed no new money. His initiative consists largely of reorganizing 30-50 existing employees at the National Institutes of Health into a vaccine research center.

Vaccines were a high priority at a meeting of the Presidential Advisory Council on HIV/AIDS in early April. Dr. David Baltimore, chair of the AIDS Vaccine Research Committee at NIH, told them it was "not possible to put a date" on developing a vaccine, since there are "too many uncertainties." Others expressed little need for a restructuring of research. "I flinch at the concept of more coordination," said NIAID Director Anthony Fauci.

But in his most political comments of the meeting, chairman Scott Hitt told the body that the president wants to do "the man on the moon" analogy in moving this as a priority of the administration. He recommended they support the effort. The final document urged development of "a vaccine to prevent HIV/AIDS within a decade," with "a significant and sustained increase in funds... from *new* sources."

In a private conversation, Dr. William Paul, director of the Office of AIDS Research (OAR) at NIH, described the new lab as an intramural effort jointly sponsored by NIAID and NCI. They are the two major existing players in vaccine research. Each will contribute their existing resources, which will be supplemented with funding from OAR's discretionary account.

Paul called the president's challenge "a formidable undertaking...one which I am confident we can achieve, though not quite

vaccines his signature mark on the epidemic. "With new resources, NIH will now become the most powerful discovery engine for an AIDS vaccine, working with other scientists to finally end the threat of AIDS," he said in his February State of the Union Address. "We must reinforce our commitment to medical science." His subsequent budget for NIH offered an increase in funding that

Clinton

◀ page 1

in ten years." But he believes "a challenge is the right way to put it. We didn't want to trivialize it."

The science

Clinton's analogy to the moon project may be a good sound bite, but it is not an accurate comparison. In that instance we already possessed the scientific and mechanical knowledge necessary to accomplish the task. Kennedy's challenge was to summon the political and economic will of the nation to do so.

Developing an AIDS vaccine is quite different, for we are taking a leap of discovery, not one of implementation. The uncertainty is apparent in the handful of radically different approaches researchers are taking as to where and how to intervene to prevent infection. It indicates how little consensus there is, and how much basic study of HIV remains to be done.

There are six known strains of HIV, and the highly unstable virus is constantly mutating, creating variations within each strain. This is the varied, evolving foe a vaccine must protect against. Right now we simply don't know how a vaccine can work under those conditions. It has led some scientists to fear it is impossible. It has led many pharmaceutical companies to drop their efforts towards developing a vaccine, as they see foresee no profit coming from their investment.

Then there is the slippery slope of definition: How does one define "success?" The model most Americans know is that of the polio vaccine, where children are inoculated, protection is 99.9 percent effective, and side effects are minuscule.

Some researchers believe that vaccines currently in development may offer 30 percent protection for HIV. That is clearly not acceptable in the United States, where the prevalence of the virus is relative low (1 million people in a population of 270 million), the ability to reduce new infections is relatively easy and inexpensive, and the current standard of protection for vaccines is very high.

But a vaccine of such limited effectiveness might be acceptable in Third World countries where HIV infects close to half the population and sheer poverty precludes massive spending on healthcare. From a strictly public health perspective, such a vaccine might save literally thousands of lives and begin to limit the spread of the epidemic.

Long-term consequences include the possibility that a vaccine could result in infection with HIV, not protection from it.

There is also the dilemma of not knowing the long-term consequences of such a vaccine. They include the very real possibility that it could result in the infection of individuals with HIV, not their protection from it.

Researchers and the Advisory Council suggested creation of a body to look at the moral, ethical, and legal questions embedded in a possible vaccine for HIV. The President has yet to move on that aspect.

Reactions

Well-known AIDS researcher Dr. Robert Gallo questioned the extent of Clinton's commitment. He told *USA Today*, "If you really wanted a crash program, you'd have to have five or six centers focusing on nothing else."

The always acerbic playwright/activist Larry Kramer told the *Washington Post* that the president's speech was "more cheap talk ... It's an easy promise. He's just switching NIH funds from Column A to Column B – what I call Chinese restaurant accounting."

"Show me the money," said Steve Michael with ACT UP/Washington. He echoed the sentiment expressed more diplomatically by every other AIDS organization. There is an underlying fear that increased funding for vaccine research might come at the expense of funding for research on treatment and for care for those already infected.

The Human Rights Campaign (HRC) applauded the initiative and called on the president to support a supplemental appropriation now before Congress that would add $68 million for AIDS Drug Assistance Programs (ADAP). The White House has not publicly indicated its support of that effort.

Meanwhile, Clinton continues to refuse to do things that can be done right now to prevent new infections in this country. They include lifting the federal funding ban on needle exchange programs and more effective prevention efforts.

It is statistically likely that some of the graduating seniors and their family members in the audience listening to his speech could have been spared their HIV infection had the president implemented those changes at the start of his administration. Instead, four years later, we have a vaccine initiative that may have an impact, in other countries, many years from now. ▼

Letters to the Editor

We must support the life-sustaining work of AIDS activists

I wholeheartedly agree with your May 21 editorial, "No skimping on AIDS," which advocated increased funding for HIV-related education and prevention by the City of Boston. The advances in treatment for people with HIV and AIDS over the past year have been remarkable. The success of needle exchange programs in getting addicts into treatment for substance abuse and HIV is indisputable. The result of these advances has been that organizations combating this epidemic are increasingly overloaded, and yet there is no additional city funding to support their life-sustaining work.

Unfortunately, there appears to be a disturbing pattern of disconnection between political rhetoric and reality. Mayor Tom Menino and President Clinton have shown personal compassion for people with HIV. This has not, however, been followed by a commitment of significantly increased funding where it could make a difference. President Clinton recently set a goal for the nation to develop a preventive vaccine for HIV in the next 10 years, and likened this to President Kennedy's goal of landing on the moon.

Obviously, this is a worthy goal, although it completely ignores the need for finding a cure for people who are already infected.

Apparently the president thinks this can be achieved without one additional dollar of funding and by taking 14 researchers away from other important projects. It is as if we planned a lunar landing by borrowing a few planes from the Air Force, closed our eyes and said, "I think I can. I think I can." At Community Research Initiative of New England, our mission is to increase access to treatment for people with HIV through promising research and the administration of the HIV Drug Assistance Program.

At our board of directors meeting last week, we grappled with our goals for the coming year, which include an increase of 60 percent in fund-raising from private sources. It was not without irony that we noted after the meeting that President Clinton's "historic" announcement was not mentioned once.

DAVID M. ARONSTEIN
President
Community Research Initiative
Board of Directors
Brookline

AIDS Vaccine Using Nasal Spray Shows Promise

Inoculated Chimps Resist Infection a Year Later, but Costs May Stall Additional Testing

By Rick Weiss
Washington Post Staff Writer

Chimpanzees inoculated with an experimental AIDS vaccine have successfully fought off repeated exposures to the AIDS virus up to a year after they were vaccinated, a research team reported yesterday.

The novel vaccine, which consists of a series of nasal sprays followed weeks later by a booster shot in the arm, is the latest addition to a small but growing arsenal of experimental AIDS vaccines showing early signs of promise after many years of mostly disappointing results.

Scientists cautioned that other vaccines have looked similarly effective in chimpanzees, only to fail in human clinical trials. But researchers said they were encouraged by the strength of the immune response triggered by this vaccine, and especially impressed with its ability to confer protection so long after vaccination.

In previous tests of AIDS vaccines, chimps or monkeys have been exposed to the AIDS virus, HIV, soon after they were vaccinated—an unrealistic scenario. The new vaccine worked even when chimps were challenged with a big HIV dose 50 weeks after they were vaccinated—longer than has worked in any other study.

Unfortunately, several researchers said, the company that helped develop the vaccine—Wyeth-Ayerst Research of Radnor, Penn.—has, like other vaccine developers, been questioning the cost-effectiveness of ushering its vaccine through the expensive and time-consuming labyrinth of clinical trials and regulatory approval. Key Wyeth scientists who spearheaded the work have been removed from the project, leaving its future uncertain.

Given the latest chimpanzee results and President Clinton's recent call for a renewed national commitment to developing an AIDS vaccine within the next decade, however, scientists said they hoped the company would reconsider financing the necessary work that could lead to early safety tests in human volunteers.

"There is no doubt that a good percent of the pharmaceutical industry, for reasons that are in part understandable and obvious, have become in recent years less interested in financing development of an AIDS vaccine," said Robert C. Gallo of the Institute of Human Virology in Baltimore, who co-discovered HIV and was involved in the latest chimpanzee studies. "It's possible, and we hope it's true, that these and other recent promising findings will renew their interest."

Representatives for Wyeth-Ayerst did not return phone calls this weekend. But study leader Marjorie Robert-Guroff, of the National Cancer Institute, said the possibility of working toward a small safety trial in people was "under discussion."

The new vaccine was made from an adenovirus—a kind of virus that can cause colds in people—that was genetically engineered to contain an extra gene called gp160, normally found only in HIV. When sprayed into the nasal passages of chimps, the modified virus settled into the animals' upper respiratory tracts and intestines.

During the next week or so, the viruses multiplied in the chimps' mucous membranes and spewed out gp160 proteins. As predicted, the chimps' immune systems responded to the HIV proteins by making antibodies and white blood cells programmed to attack HIV.

The researchers boosted that protective immune response by giving the chimps a shot in the arm containing laboratory-made versions of a different HIV protein, gp120. More than 11 months later, they subjected the chimps to intravenous infusions of HIV.

Robert-Guroff and her colleagues reported in the June issue of Nature Medicine, released yesterday, that unvaccinated chimps became infected with the deadly virus within a month, but vaccinated chimps remained healthy and apparently uninfected until the study ended, almost a year later.

Adenovirus-based vaccines have a potential advantage over other kinds of AIDS vaccines because adenoviruses can stimulate a potent immune system response in mucous membranes, including the urinary tract, and vaginal and rectal tissues. "We'd like to induce mucosal immunity," Robert-Guroff said, "because worldwide transmission of HIV is predominantly across mucosal barriers" through intercourse rather than by intravenous infection.

The new report does not specifically reveal whether mucosal antibodies were generated in the chimps, but the U.S. military has given soldiers oral adenovirus vaccines for years to protect against upper respiratory tract infections, generating mucosal immunity and very few complications, he said. Nonetheless, researchers warned, any AIDS vaccine made from a live virus that is capable of causing disease in people, as adenoviruses can, will have to be tested carefully for safety. Several said they hoped that will happen soon.

"Eight thousand people a day and 3 million a year are being infected with HIV despite all the education and counseling, so most experts believe that to get control worldwide we are going to need a safe, affordable and effective vaccine," said Mark Mulligan, director of the HIV vaccine evaluation unit at the University of Alabama at Birmingham. "This vaccine is an encouraging step in the pathway to getting there," Mulligan said. "My feeling is that adeno-vaccines should be given serious review for advancing into small, Phase 1 human trials where their safety and human immune response can be evaluated."

San Francisco Chronicle; 5-20-97

A Vaccine For AIDS — New Goal For Science

PRESIDENT CLINTON'S call for the development of an AIDS vaccine within the next 10 years was a dramatic gesture from the bully pulpit, and a positive step forward in the campaign against the deadly disease.

In a commencement address at Morgan State University in Baltimore on Sunday, Clinton likened the quest for an AIDS vaccine to President Kennedy's stirring, 1961 challenge to put an American on the moon by the end of the decade.

Clinton's bully-pulpit cheerleading for an AIDS vaccine encourages scientific research

"With the strides of recent years, it is no longer a question of whether we can develop an AIDS vaccine," Clinton said, "it is simply a question of when."

Such rosy optimism is not yet warranted at a time when researchers are barely scratching the surface of the diabolical HIV — the mutating virus that causes AIDS — which has defied medical science and spread like wildfire since it was recognized in the early 1980s. Some respected researchers say a vaccine may never be discovered.

Clinton offered no additional money for AIDS research, yet merely by championing the cause he reminded the public of the desperate need for a vaccine, perhaps the only way to fight the disease on a global scale. And by challenging scientists and pharmaceutical companies, the president is asserting that such a vaccine is possible.

"What he has done is a major cheerleading effort, which is important," said Geert Kersten, Chief Executive Officer of Cel-Sci Corp. which is testing a vaccine. "It clearly helps because it changes perception" and could lead to greater investor confidence in vaccine research.

An estimated 29 million people around the globe are living with HIV, and 3 million are newly infected every year. In the United States about one million people carry the virus, with 40,000 new cases a year.

While Clinton's call for a vaccine fell short of his 1992 campaign promise to make AIDS research into a Manhattan Project, it was a forceful advancement of his administration's strategy to fight AIDS.

That strategy is to develop both a cure and a vaccine; reduce new infections; guarantee access to quality care for AIDS patients; fight AIDS-related discrimination; translate scientific advances into treatment and provide U.S. leadership in international efforts against the disease.

We are moving in the right direction. There is reason for hope.

The Boston Globe: 5-21-97

No skimping on AIDS

The 4,200 people with AIDS in Boston can look forward to new drug treatments that promise them longer, more productive lives. Ironically, because fewer people are dying from AIDS, more support is needed for people living with AIDS. This is no time for the Menino administration to slacken its commitment to AIDS-related services in the budget proposed for next year.

Since 1991, annual city outlays for AIDS prevention and education have nearly doubled, but the much larger budget for care and services – home-delivered meals, rides to treatment, and some housing support – has been reduced 25 percent. Overall, the budget for AIDS programs through the city's public health commission has risen less than 10 percent since Menino took office, while the population of AIDS sufferers has increased 50 percent.

Besides aiding a larger population with existing services, more can be done to integrate AIDS prevention and treatment programs with similar efforts in drug abuse. The two are often linked: The needle-exchange pilot program in Boston, for example, has been credited with easing hundreds of addicts into treatment and slowing the spread of AIDS through this vulnerable population. The cost of preventing each new AIDS case is but a fraction of the costs for those who do become infected.

Menino has long been a champion of people living with AIDS. In his 1994 inaugural address he spoke movingly about those he pledged not to shut out of his administration. "I promise to dedicate my time as mayor to combating this disease with everything in my power," he said.

Unfortunately, the mayor's time is not enough, nor are his good words. Support for people with AIDS takes money. In the last fiscal year Menino promised the first of several incremental budget increases to catch up with the demand, and indeed, $250,000 was added to education efforts. But in this year's proposal, both accounts are frozen at the current levels.

Well into the second decade of the epidemic, there is no lack of innovative uses for funds in the multifront battle against AIDS. Menino should dig a little deeper.

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Comments: For the Fact Sheet
It just came through

FACTS ABOUT THE VACCINE RESEARCH CENTER AT THE NATIONAL INSTITUTES OF HEALTH

As announced by President Clinton on May 18, 1997*, the National Institutes of Health (NIH), has begun development of a Vaccine Research Center (VRC) to focus on AIDS vaccines, as a part of the NIH intramural research program**. In his announcement, President Clinton also challenged the NIH and the scientific community to develop an AIDS vaccine within 10 years.

In accepting this challenge, NIH Director Dr. Harold Varmus, said, "the President has set a difficult goal for the research community, but NIH is ready to bring its scientific expertise and resources into play. Creating a vaccine that will block the AIDS virus is a formidable scientific task. There is no guarantee that we can produce a vaccine within 10 years, but recent advances in immunology and virology have increased optimism that it can be done. NIH's new Vaccine Research Center (VRC) will be a vital part of the effort."

- The Vaccine Research Center, which will be a joint venture of the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID), will begin by incorporating into the VRC a core of NIH scientists with interest and expertise in immunology, virology, and HIV vaccine research.

- The primary focus for the VRC will be to stimulate multidisciplinary research from basic and clinical immunology and virology through to vaccine design and production. It will integrate modern immunological science with detailed understanding of the pathogenesis of HIV infection, development of immunogens and vectors, and new approaches to vaccination.

- Physical, financial, and human resources for the VRC will be provided by the NCI and the NIAID. Funds for AIDS research are allocated according to the plans developed by the Office of AIDS Research (OAR) in consultation with the NIH Institutes. In fiscal year 1998, the OAR has proposed $10 million for the Vaccine Research Center. (The total fiscal year 1998 proposal for AIDS vaccine research is $150 million, an increase of nearly 33 percent over the past two years.)

- A search committee will be named before the end of May to seek a scientist with specific expertise in vaccine development to be Director of the new VRC. There will be a broad, nationwide search.

- At first, the VRC will be a "laboratory without walls", while laboratory space is sought in the vicinity of the NIH campus to bring the scientists together. Later, as scientists are recruited from outside the NIH ranks, NIH will consider constructing a building on the campus to house the VRC.

Background

- A 1996 landmark review of the NIH AIDS program by a panel of experts recommended that NIH restructure and reinvigorate its AIDS vaccine research program, with leadership from non-government scientists. As a result of the so-called "Levine Report", named after its chairman, Dr. Arnold Levine of Princeton, NIH has increased its budget for AIDS vaccine research and established the AIDS Vaccine Research Committee (AVRC), a panel of distinguished scientists, chaired by Dr. David Baltimore. The AVRC will serve as a scientific advisory group for the new Vaccine Research Center (VRC).

- The new VRC is only a part of the vaccine development challenge. Another NIH effort is a new grant program administered by the NIAID to encourage new and novel approaches to AIDS vaccine research. Grant awards, totaling approximately $6 million, will be made later this year. In addition, NIH and other Administration officials are working with industry to find ways to overcome the formidable obstacles that have discouraged industry from continuing its investment in the development of AIDS vaccine. Further, President Clinton has said that at the summit of industrialized nations in Denver in June he will enlist other nations to join the U.S. in a worldwide effort to develop an AIDS vaccine.

- A safe and effective AIDS vaccine is a global public health imperative. More than 29 million men, women, and children around the world have been infected with HIV. More than 3 million of these infections occurred in just the past year, with nearly 95 percent in the poorest parts of the world. Without an effective vaccine, AIDS will soon overtake tuberculosis, malaria, and measles as the leading infectious cause of death in the world.

* Commencement Address, Morgan State University, Baltimore, MD, May 18, 1997.
** The NIH intramural program is the in-house NIH research effort, staffed with government scientists, primarily located on the 300 acre NIH campus in Bethesda, Maryland.

May 23, 997

A Deadline for an AIDS Vaccine

After months of quiet debate among officials and researchers, President Clinton last week called for a vaccine within a decade. But many scientists are reacting with caution rather than euphoria

Researchers regularly woo politicians for funding, but they get nervous when those same politicians respond too amorously. They worry that political and scientific goals don't always make a happy marriage. That is why many senior scientists in the past few months have pushed for additional funding for AIDS vaccine research while arguing that the president should not set a public deadline for a vaccine. Instead, they got President Bill Clinton's 18 May clarion call for a vaccine within a decade—and no specific commitment of increased funding.

At a commencement speech at Morgan State University in Baltimore, Clinton proclaimed the vaccine "a new national goal for science in the age of biology," and compared it to President John Kennedy's challenge 36 years ago to land a man on the moon. Clinton pledged to create an AIDS vaccine research center at the National Institutes of Health (NIH) to spearhead the initiative, promised to enlist other countries in the endeavor, and challenged the U.S. pharmaceutical industry to make the vaccine "part of its basic mission." Leading AIDS vaccine researchers worry about the price that science might pay if it can't deliver. Yet, they also think the high profile Clinton has given their field—which has been struggling to come up with new approaches to the challenges facing it (see p. 1196)—may help them in future funding battles.

The vaccine push gathered strength at a 3 December meeting on AIDS research, in which Clinton, Vice President Al Gore, and then–Chief of Staff Leon Panetta gathered in the Oval Office with NIH director Harold Varmus; Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID); and Office of AIDS Research chief William Paul, among others. "One of the issues most strongly raised was the desperate need for a vaccine," Paul recalls. "There was a general recognition that this was really a goal worth pursuing."

During the spring, the Presidential Advisory Council on HIV/AIDS—a 33-member group made up of government, industry, aca-

Clinton Calls for 'Human Values' in Science

President Clinton's announcement of an AIDS vaccine initiative drew most of the attention in his commencement address last week at Morgan State University in Baltimore (see main text). But the speech as a whole presented a broad view of the promise of science and the dangers of misapplying it.

Speaking on 18 May, Clinton told graduates of the historically black university that "we must do nothing to stifle our basic quest for knowledge." But he added, "As we consider how to use the fruits of discovery, we must also never retreat from our basic human commitment to human values, the good of society, and our basic sense of right and wrong." Those issues, he said, are acute now because of the potential for abuse of new genetic technologies and cloning. Clinton's call for greater ethical sensitivity in applying research results irritated some scientists, however.

WILFREDO LEE/AP

Sensitive to science. Clinton at Morgan State commencement.

Administration officials say that the White House, motivated by the breakthroughs in biology, the new views of the universe coming from the Hubble Space Telescope, and the discovery of possible life on Mars, has long wanted to articulate a clear view of the pitfalls and promises of science. The president suggested the topic as one of the themes for his three commencement addresses, and Clinton's domestic-policy adviser Bruce Reed and John Podesta, deputy chief of staff, both strongly supported the idea, according to White House sources. The Office of Science and Technology Policy, led by Jack Gibbons, weighed in with a massive briefing book, and a large team of White House officials hashed out the details of the speech over the previous 2 weeks.

As examples of science gone wrong, Clinton cited the infamous Tuskegee syphilis experiments, in which African Americans with the disease were left untreated for decades, and Cold War research in the same era that subjected individuals to doses of radiation. "We must never go back to those awful days in modern disguise," said Clinton.

The leaps in biomedicine pose new risks, he said, calling for bipartisan legislation that would prevent insurance companies from using genetic data to deny coverage or set premium rates for some individuals. He also said, "We should resist the temptation to clone ourselves," although he stopped short of proposing legislation banning human cloning. "This is a decision no president should make alone. No president is qualified to understand all of the implications," Clinton added. A panel of bioethicists will offer their recommendations on cloning to the president in a few weeks (see p. 1185).

The gap between the research community and the public also was on the president's mind. "Science can serve the values and interests of all Americans, but only if all Americans are given a chance to participate." He cited past discrimination in academia, and called for the "voices and talents of everyone in this stadium—especially those of you who are going on to pursue a career in science and technology." And he cautioned against the hubris that can accompany the search for knowledge. "Science is not God," the president said, adding, "our deepest truths remain outside the realm of science."

Some of these admonitions irked Carl Feldbaum, president of the Biotechnology Industry Organization. He said the president "has gone too far if he means to imply that scientists ... aren't deeply concerned or actively involved in addressing the ethical and moral issues associated with their work." –A.L.

demic, and advocacy representatives—pondered possible next steps in HIV vaccine development as part of a broader examination of AIDS research. The council's nine-member research committee solicited opinion about AIDS vaccine R&D from a wide variety of researchers at an April panel discussion. While the researchers heartily agreed on the need for more financial support, they had little collective enthusiasm for some of the specific recommendations the council had floated.

A draft that was widely circulated prior to the meeting raised many eyebrows by recommending that the U.S. government spend $400 million on AIDS vaccine research and development each year—roughly three times the total now spent on the effort. It also called for steps that would force NIH to share more of the responsibility for AIDS vaccine R&D with the Centers for Disease Control and Prevention and other federal agencies.

But it was the draft's recommendation that Clinton set a national goal of developing an AIDS vaccine by a certain date that drew the most fire. "It's folly to give a date," Fauci told the council at the April meeting. Added Paul: "Promising a vaccine within a specific period of time, within a decade, is not a wise thing. ... It could lead to disappointment." But Yichen Lu of the Virus Research Institute in Cambridge, Massachusetts, disagreed. "We need a date ... to generate a sense of urgency," said Lu.

Lu's point of view won out in the council, which in April called for Clinton to "declare an urgent goal of developing a vaccine to prevent HIV/AIDS within a decade." The goal "is clearly feasible and should be considered of the highest priority for our government," the group stated. But the council rejected the proposal to triple vaccine funding, urging only "a significant and sustained increase in funds." And specific proposals for greater coordination among agencies and additional White House oversight were watered down.

The president accepted the council's advice, but he tempered his vaccine pledge by saying that "there are no guarantees. It will take energy and focus and demand great effort from our greatest minds." He added, however, that "with the strides of recent years, it is no longer a question of whether we can develop an AIDS vaccine; it is simply a question of when. And it cannot come a day too soon."

After Clinton's announcement, Fauci said that "most of us were uncomfortable with saying we'll have a vaccine by this date," but he added, "I don't have an inherent fundamental problem with a goal ... as long as it's made clear that this is not a guarantee." Paul echoes that: "I would have had trouble [if Clinton had said] 'We will have a vaccine in a decade.' "

The most immediate outcome of the announcement will be an AIDS vaccine center, which NIH will establish at Clinton's direction. The details of such a center are being hashed out now by the NIH AIDS Vaccine Research Committee led by Nobel Prize–winning virologist David Baltimore, which met on 9 May to discuss the project. It will start off as a "virtual center" jointly administered by NIAID and the National Cancer Institute (NCI), says Paul, before finding a physical home. Its major thrust, he says, will be to bring more immunology to the AIDS vaccine field, which has been dominated by virologists. The center also aims to attract vaccine developers from other fields. Paul adds that the center—formally called the NIAID/NCI AIDS Vaccine Center—may manufacture pilot lots of vaccines, a task now left to industry. That should help researchers test their ideas more quickly.

"The size is not fixed," he says. "In the early phase, it will be relatively small ... and obviously we will need to recruit senior people from outside." NIH officials will soon set up a search committee to select a director and other senior staff. Meanwhile, the Administration has requested up to $10 million for such a center in the 1998 budget, although it's not clear what its total cost would be. Money for the center, says Paul, will not come at the expense of extramural research funds.

There is little question that Clinton's initiative will create a more favorable environment in Congress and within the Administration for AIDS vaccine funding. "Think of what [the announcement] might mean next year when we're asking for money," says Fauci. "When the president of the United States starts putting that out, it can't hurt." So, while Clinton's embrace may be too close for comfort, researchers likely will cling to their newfound admirer.

–Andrew Lawler with Jon Cohen

Additional reporting by Eliot Marshall.

BIOETHICS

Panel Weighs a Law Against Cloning

When a Scottish research team startled the world by revealing 3 months ago that it had cloned an adult sheep, President Clinton moved swiftly. Declaring that he was opposed to using this exotic animal husbandry technique to clone humans, he ordered that federal funds not be used for such an experiment—although no one had proposed to do so—and asked an independent panel of experts chaired by Princeton President Harold Shapiro to report back to the White House in 90 days with recommendations for a national policy on human cloning. That group—the National Bioethics Advisory Commission (NBAC)—has been working feverishly to put its wisdom on paper, and at a meeting on 17 May, members endorsed a near-final draft of their recommendations.

NBAC will ask that Clinton's 90-day ban on federal funds for human cloning be extended indefinitely, and possibly that it be made law. But NBAC members are planning to word the recommendation narrowly to avoid new restrictions on research that involves the cloning of human DNA or cells—routine in molecular biology. The panel has not yet reached agreement on a crucial question, however: whether to recommend legislation that would make it a crime for private funding to be used for human cloning.

In a draft preface to the recommendations, discussed at the 17 May meeting, Shapiro suggested that the panel had found a broad consensus that it would be "morally unacceptable to attempt to create a human child by adult nuclear cloning." Shapiro explained during the meeting that the moral qualms stem mainly from fears about the risk to the health of the child. The panel then informally accepted several general conclusions, although some details have not been settled.

NBAC plans to call for a continued moratorium on federal government funding for any attempt to clone somatic cell nuclei to create a child. Because current federal law already forbids the use of federal funds to create embryos for research or to knowingly endanger an embryo's life, NBAC will remain silent on embryo research.

NBAC members also indicated that they will appeal to privately funded researchers and clinics to refrain from trying to clone humans by somatic cell nuclear transfer. But they were divided on whether to go further by calling for a federal law that would impose a complete ban on human cloning. Shapiro and most members favored an appeal for such legislation, but in a phone interview, he said this issue was still "up in the air."

DENISE APPLEWHITE/PRINCETON UNIVERSITY

Moral stand. Commission chair Harold Shapiro.

Many NBAC members wanted to recommend that no regulations be adopted that would interfere with the cloning of animals, cells, or DNA. Others preferred a more muted approach, on

als have rested on optically active organic molecules known as chromophores. Chemists can easily tailor these molecules and incorporate them into transparent host polymers. In 1989, Garito and his colleagues proposed a strategy for developing chromophores that have strong third-order NLO properties: create molecules that can sustain large separations of electric charge.

These researchers knew that many chromophores can essentially shuttle negative charges to one end of the molecule, leaving the other end positively charged, and that this separation increases in response to light. They calculated that the greater this light-driven charge separation, the greater the material's light-changing NLO properties would be. As Marder's collaborator George Stegeman, a physicist at the University of Central Florida in Orlando, explains, the charge separation alters the electronic structure of the molecule, making it easier for trios of photons to interact in the material.

In 1993, Marder and his colleagues improved a class of small chromophores to more than double their NLO properties. In the current experiment, the team turned to longer molecules whose charges could separate even farther. The researchers started with a batch of β-carotene, a well-known third-order NLO chromophore consisting of a long, narrow chain of carbon atoms capped on either end by ring-shaped groups. One of the rings is an electron-hungry "acceptor" group that snags an electron from the other end of the molecule, giving β-carotene its NLO properties, among the strongest yet observed.

To enhance these properties, Marder and his colleagues replaced the β-carotene's acceptor with successively stronger electron grabbers. When Stegeman and his colleagues at Central Florida added these chromophores to a polymer known as poly (methyl methacrylate) and spun it into films, they found that the films made with chromophores that had the strongest electron grabbers produced an NLO effect 35 times stronger than the starting molecule. For many applications, says Garito, that is "very close" to what's needed for commercial success.

The chromophores break down when they are exposed to light and heat, ruling out their use in light-based communication devices, says Nasser Peyghambarian, an NLO expert at the University of Arizona, Tucson. But he and others believe that the same charge-separation strategy could improve the NLO properties of other types of molecules, among them more robust chromophores made from chains of linked rings or compounds containing stable metal complexes. "It's fairly wide open," says Garito. If so, more and more communications visionaries are likely to see the light.

–Robert F. Service

AIDS VACCINE

Looking for Leads in HIV's Battle With Immune System

BETHESDA, MARYLAND—When officials at the National Institutes of Health (NIH) tapped Nobel laureate David Baltimore last December to head its newly formed AIDS Vaccine Research Committee, they hoped he would give a much-needed boost to a floundering field. It is too early to tell whether Baltimore's committee will live up to those expectations. But a 4-day meeting* on AIDS vaccine development held here at the NIH last week suggests that it will have plenty of new leads to follow.

AIDS vaccine development has been limping along since 1994, when NIH decided not to push ahead with large-scale tests of the leading vaccine candidates because they didn't look promising enough (see sidebar). The organizers of last week's meeting—the ninth in a series of these annual gatherings—tried to give the field a booster shot by adding reports of cutting-edge basic research on how HIV causes disease to the standard AIDS vaccine fare. This strategy seemed to pay off. Several reports—including one by Baltimore—on the protective role played by the immune system's killer cells, called cytotoxic T lymphocytes (CTLs), sparked much discussion. A presentation on the possible capture of a long-sought factor that provides some protection against HIV sent a ripple through the meeting, as did a suggestion that a goat virus might provide the basis for an HIV vaccine.

> **"I'm convinced that we will have a vaccine ... in a reasonable period of time."**
> **—Anthony Fauci**

Although the 550 attendees heard no headline-grabbing talks, veterans in the field came away moderately encouraged. "Pessimism is destructive," said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID). "I'm convinced that we will have a vaccine and that we'll have it in a reasonable period of time."

For many AIDS vaccine researchers, the most troubling roadblock has been teasing out which immune responses a vaccine should trigger to protect a person from HIV. Most viral vaccines work by stimulating the immune system to produce antibodies that bind to a virus, preventing it from infecting cells. But it's not clear that antibodies offer much protection against HIV. "As I try to understand the role of antibodies, ... I keep coming up with a blank," said Baltimore, hence the focus on CTLs.

Like smart bombs, CTLs search out and destroy cells that a virus has infected. They play a key role in the body's natural defenses, and many traditional vaccines stimulate their production along with antibodies. "Cytotoxic T lymphocytes are at least very important, if not the most important, thing [for protection from HIV]," said Baltimore.

However, an AIDS vaccine that stimulates CTLs would face hurdles too, as Baltimore's own work shows. When a cell is infected by HIV, it typically puts a piece of the virus on its surface. CTLs are trained to pulverize any cells that display these viral peptides. Baltimore and his Massachusetts Institute of Technology colleague Kathleen Collins, collaborating with HIV CTL guru Bruce Walker of the Massachusetts General Hospital, have new evidence that HIV escapes the deathblows of CTLs by preventing cells from displaying viral peptides.

Building on work first published in the March 1996 *Nature Medicine* by the Pasteur Institute's Olivier Schwartz and co-workers, the Baltimore group focused on the HIV protein Nef. As the Schwartz group showed, Nef can prompt cells to yank down from their surfaces a molecule known as the major histocompatibility complex (MHC), which displays viral peptides to the immune system. The group predicted that this "down-regulation" of MHC would make HIV-infected cells resistant to CTL killing—just what the Baltimore group's new data now show. Baltimore says these findings imply that if researchers hope to base a vaccine on stimulating CTLs, the timing is critical: Unless CTLs flood the bloodstream shortly after an infection occurs, HIV may undermine their utility by dispatching Nef.

That may be a tall order, but one heartening talk at the meeting, by Duke University's Kent Weinhold, suggests that the down-regulation of MHC by Nef does not completely shut down CTL activity. "I don't think it's an all-or-none phenomenon," says

* Conference on Advances in AIDS Vaccine Development, 4–7 May, sponsored by NIAID, Bethesda, Maryland.

Planned Tests in Thailand Spark Debate

While researchers in the United States are looking for new approaches to developing AIDS vaccines (see main text), two first-generation vaccines are inching toward full-blown efficacy trials in Thailand. However, as plans for the trials advance, a debate is heating up. Critics within Thailand, using data supplied by U.S. researchers, contend that the vaccines are likely to prove worthless, while others worry that the furor could frustrate the best chance to determine once and for all whether these preparations can slow the epidemic.

DARROW MONTGOMERY

Front lines. AIDS patient and family in a Thai hospital. Thailand is facing a growing epidemic.

To date, more than two dozen AIDS vaccines have been tested in small-scale human studies to assess their safety and ability to trigger immune responses. None of these tests has as yet moved into an efficacy trial, which would involve several thousand people at a cost of $20 million or more. In June 1994, two vaccines, both made from genetically engineered versions of HIV's surface protein gp120, were set to take the plunge. But a panel convened by the National Institutes of Health (NIH) decided that the probability of the preparations' efficacy was too low for the government to fund these trials. The panel's decision, however, applied only to the United States; countries facing more intense epidemics might deem it worth the risk.

Indeed, researchers in Thailand, facing a serious AIDS epidemic, pressed ahead with small-scale trials of these vaccines, originally made by Genentech of South San Francisco and Chiron Corp. of Emeryville, California. Thai researchers hope to begin these efficacy tests as early as next year. David Baltimore, the Nobel laureate who heads a committee that advises NIH on AIDS vaccines, says he recently discussed Thailand's interest in testing these vaccines with Natth Bhamarapravati, who chairs a similar group in Thailand. Baltimore says he thought their thinking "was all very reasonable."

Last month, however, Praphan Phanuphak, who directs the Thai Red Cross Society's Programme on AIDS, wrote to the deputy governor of Bangkok that the gp120 vaccines are "not useful in preventing HIV infection" and that it was "not appropriate for Thailand to allow (approve) an efficacy trial of the mentioned vaccine." Praphan based his doubts on data that he requested from Steven Wolinsky of Northwestern University and David Ho of the Aaron Diamond AIDS Research Center in New York City. However, these data, on "breakthroughs"—people who became infected despite receiving the gp120 vaccine in the small-scale U.S. trials—should not be overinterpreted, according to Wolinsky: "We'd be remiss if we didn't provide the Thais with that information. But it never was intended to stop or start a trial. Our colleagues in Thailand are very intelligent, and they don't need David Ho or Steven Wolinksy to tell them what to do."

Praphan's criticisms are troubling Thai officials. William Heyward, an epidemiologist who heads the AIDS vaccine program of the Centers for Disease Control and Prevention in Atlanta—which has been helping Thailand stage AIDS vaccine trials—says the issue came up last week when a delegation visited from the Thai Ministry of Health. They were "very concerned" that Thai politicians "would not fully understand the debate and would back off [from efficacy trials]," says Heyward.

That worries the U.S. companies supplying the vaccines, as well as their academic and government collaborators. Chiron hopes to begin a 300-person study this summer that includes a new gp120 vaccine made with HIV subtype E, a strain found in Thailand. If all goes well, the company hopes to start efficacy trials around 2000. Donald Francis, who a few months ago started the company VaxGen to develop Genentech's gp120 vaccine, calls the attacks on the trials "myopic." VaxGen has raised more than $24 million during the past few months to stage efficacy trials of the Genentech vaccine, which Francis says could begin next year. –J.C.

Weinhold. In contrast to the Baltimore group's finding, Weinhold and co-workers showed that CTLs could kill 10% to 40% of HIV-infected cells in a test-tube assay.

And Weinhold had more good news about CTLs. Researchers have long worried that an HIV vaccine might only work against the particular viral strain from which it is made. But Weinhold's study of blood taken from people given experimental vaccines made from pieces of HIV showed that their CTLs could kill cells infected with a wide range of HIVs. "The extent to which he found cross-reactivity [to different HIV strains] with CTLs is surprising people," said Patricia Fast, NIAID's associate director for vaccines and prevention. Still, many questions remain about how long these CTL responses will last, and whether they pack enough wallop to fend off a real infection.

Mary Klotman of New York's Mount Sinai School of Medicine presented intriguing findings pointing to another possible criterion for a promising vaccine. Klotman's work addresses a finding by Jay Levy of the University of California, San Francisco, that some white blood cells carrying a CD8 receptor on their surface produce some kind of soluble factor that can suppress HIV. Levy called this mysterious substance the CD8+ Antiviral Factor (CAF). But despite years of trying to identify CAF, Levy has been stumped. Recently, Klotman and Arevik Mosoian of her lab isolated and characterized an "extremely small protein" that she thinks might be the elusive CAF. If so, vaccine developers may have yet another lead to analyze in their hunt for immune responses that correlate with protection.

Perhaps the meeting's most unusual talk suggested that infection with a goat virus might protect humans from HIV. Angeline Douvas of the University of Southern California in Los Angeles reported that people infected with caprine arthritis-encephalitis virus—a distant HIV relative, common in Mexico, that appears harmless to humans—make antibodies that react with HIV. Bruce Weniger, an epidemiologist at the Centers for Disease Control and Prevention in Atlanta, went to the microphone and connected the dots. "This is really a remarkable finding that raises the wild speculation that you discovered the natural accidental vaccine for HIV … [in] the way cowpox was the natural accidental vaccine that works for smallpox," said Weniger. Douvas replied that they hope to test this hypothesis by doing an epidemiologic study of people infected with the goat virus to see if they have a lower incidence of HIV infection.

Will any of these exotic findings pan out? Who knows. But this meeting proved that AIDS vaccine research is at least bubbling with ideas.

–Jon Cohen

URGENT

National Institutes of Health
National Institute on Drug Abuse
Division of Epidemiology and Prevention Research
5600 Fishers Lane Room 9A-53
Rockville, Maryland 20857

FACSIMILE MESSAGE COVER SHEET

Date: June 20, 1997

Following are 4 pages including this cover. If any part of this message is received poorly or missing please call us immediately on the number listed below.

To: Name: Ms. Sandra Thurman, Director
Organization: National Office of AIDS Policy
FAX Tel No.: (202) 632-1096
Tel No.: (202) 632-1090

From: Name: Dr. Peter Hartsock
FAX Tel No.: (301) 480-4544
Tel No.: (301) 443-6720

Please see attached re U.S.-Russian cooperation.

URGENT

URGENT

June 20, 1997

NOTE TO: SANDRA THURMAN, DIRECTOR, NATIONAL OFFICE OF AIDS POLICY
FROM: PETER HARTSOCK, NIH/NIDA

Re: Update on U.S.-Russian Cooperation in AIDS; particularly HIV Vaccine Development

I just spoke with Dr. Kozlov. He was successful in meeting with President Yeltsin's advisors and the response he got from them was positive concerning U.S.-Russian cooperation in HIV vaccine development. Dr. Kozlov also got messages to President Yeltsin through several other channels.

At this time (Friday morning), Dr. Kozlov has not received any message directly from President Yeltsin so we can't speculate beyond what I have told you. Again, however, the response from the advisors to President Yeltsin has been positive.

Dr. Kozlov said that, if you are at the Summit, it would be good to talk with President Yeltsin's advisors concerning U.S.-Russian cooperation.

Also, Dr. Kozlov sent a letter directly to President Yeltsin which parallels and reinforces the attached letter which was sent to you yesterday by Dr. Robert Gallo.

Something else of importance is the fact that the International HIV Vaccine Initiative has sent a memorandum to the Denver Summit endorsing international cooperation in vaccine development and calling for a fund to be established to help support R&D cooperation and vaccine purchase. Dr. Kozlov is a signatory of the memorandum. The International HIV Vaccine Initiative, by the way, has also endorsed and been supportive of U.S.-Russian efforts.

I'll keep you posted on further developments.

Best wishes.

NSTITU E OF HUMAN V RO OGY

MEDICAL BIOTECHNOLOGY CENTER
University of Maryland
725 West Lombard Street, Suite S307
Baltimore, Maryland 21201
(410) 706-8614; FAX: (410) 706-1952

Dr. Robert Gallo
PROFESSOR AND DIRECTOR

19 June, 1997

Ms Sandra Thurman
Director
National Office of AIDS Policy

Dear Ms Thurman,

Drs. Andrei Koslov and Peter Hartsock have suggested that I write to further emphasis to you of our effotts to create a collaborative partnership between the Institute of Human Virology at the University of Maryland in Baltimore and the Research Institute of Highly Pure Biopreparation in St. Petersburg, Russia.

Our hope is that Russia will apply for a World Bank loan to underwrite a vaccine development program that combines the considerable research strengths of both Institutions. There is considerable research talent in Russia but they have less experience regarding vaccine testing and development.

We have been serious about this program for over a year now and have already submitted our contribution to the World Bank proposal.

We feel that it is collaborative efforts like this that President Clinton had in mind when he announced his support for International Cooperation for HIV vaccine development.

I hope that you find this information helpful before the G7 (or is it now going to be the G8) summit.

Sincerely,

RC Gallo

Robert C. Gallo, MD
Professor and Director

International Call for Action on HIV Vaccine Development

Summit of the Industrialized Nations
Denver, Colorado USA

On May 18, 1997, United States President Bill Clinton asked that we "commit ourselves to developing an AIDS vaccine within the next decade."

AIDS has already taken the lives of millions of men, women and children. More than 29 million individuals have been infected with HIV. Each day, approximately 10,000 new infections occur, almost 95 percent of these in the developing world.

The investment of substantial government and private sector funds, over a sustained period of time, enabled researchers to make extraordinary progress in developing new HIV therapeutics. Tragically, these advances are far beyond the reach of most HIV-infected individuals in the world. An effort of similar magnitude is needed to develop HIV vaccines, without which AIDS will continue its relentless march of destruction.

President Clinton stated that at the Summit of the Industrialized Nations in Denver, he will seek to "enlist other nations to join in a worldwide effort to find a vaccine to stop one of the world's greatest killers."

We, the undersigned, believe that HIV disease is a global disease and requires a global response. No single country or company has the resources to go it alone. Therefore, we call upon the industrialized nations of the world to support a global effort to develop safe, effective, preventive HIV vaccines for use throughout the world by 2007. We call upon the nations participating in the Denver Summit to agree on a specific plan to meet this goal.

We also call upon the large industrialized nations to devote new resources to this vaccine development effort, including assuring that vaccines are produced for developing countries, creating incentives for maximum participation of the pharmaceutical/vaccine industry, and agreement on specific mechanisms to ensure mutual cooperation and coordination of the effort. The excruciating burden of this disease demands that funds not be diverted from research for HIV therapeutics or prevention. The creation of new financing mechanisms, such as an AIDS Vaccine Development Fund and AIDS Vaccine Purchase Fund, should be considered.

Finally, we call upon the large industrialized nations to expand this effort to other international forums, including the G-77 nations. The industrialized nations must begin working with each other and less developed countries, private industry, international agencies, and non-governmental organizations to lay the groundwork for maximizing the research effort and securing broad international access to any HIV vaccines that are developed.

All countries around the world will gain by this effort and each has a unique contribution to make, such as providing funding, scientists, testing sites, and vaccine production. A global effort of this magnitude would demonstrate how the world can come together in an era of globalization for the good of all humankind – a noble goal for the next century.

725 W. Lombard Street, 3rd Floor
Baltimore, MD 21201
(410) 706-8181
FAX (410) 706-8184

OFFICE OF THE DIRECTOR

MBC FAX COVER SHEET

FAXED:___DATE:_____TIME:_____

DATE: 19 June

TO: Ms Sandra Thurman

FROM: Dr R. Gallo

FAX #: 202 632 1096

_____ For Your Information
_____ Per Conversation
_____ Per Your Request
_____ Please Advise/Comment
_____ Please Review
_____ Please Reply
_____ Other _____

Comments:

Pages to Follow: _____

Institute of Human Virology

Department of Molecular Biology and Biophysics

faxsheet.032897

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Dr. Robert Gallo
PROFESSOR AND DIRECTOR

19 June, 1997

Ms Sandra Thurman
Director
National Office of AIDS Policy

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I hope that you find this information helpful before the G7 (or is it now going to be the G8) summit.

Sincerely,

RC Gallo

Robert C. Gallo, MD
Professor and Director

facsimile
TRANSMITTAL

to: Daniel Montoya
fax #: (202)632-1096
re: Vaccine article in the BAR
date: May 24, 1997
pages: 3, including this cover sheet.

For your information - Helen

SLT-
FYI
DCM

From the desk of...

Helen M. Miramontes, MSN, RN, FAAN
Associate Clinical Professor & Deputy Director
University of California, School of Nursing &
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BAY AREA REPORTER

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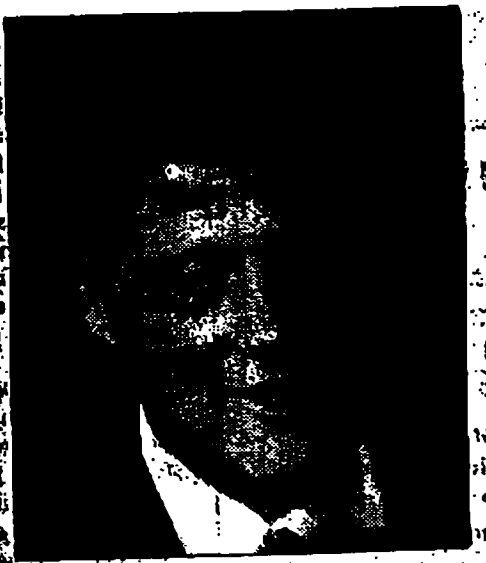
Clinton announces AIDS vaccine initiative

question of whether we AIDS vaccine, it is simply en," said President Bill ed the nation to devel- vaccine within ten years, com- John F. Kennedy's pledge to put on the moon in the 1960s. The long anticipated initiative was about 15 percent of his commencement address at historically black Morgan State University in Baltimore on Sunday, May 18.

Most people knowledgeable of HIV applauded the president's intent but were skeptical of the outcome. Perhaps they remembered the prediction that Ronald Reagan's Secretary of Health and Human Services, Margaret Heckler, made in April 1984. She said they would have a vaccine in two years. It did not happen.

Many leading scientists do not share Clinton's attitude that an HIV vaccine can be developed within that time frame, or perhaps ever. AIDS activists question whether his commitment is more than rhetoric. The President has proposed no new money. His initiative consists largely of reorganizing 30-50 existing employees at the National Institutes of Health into a vaccine research center.



Man in the moon: President Clinton wants a vaccine within a decade.

vaccines his signature mark on the epidemic. "With new resources, NIH will now become the most powerful discovery engine for an AIDS vaccine, working with other scientists to finally end the threat of AIDS," he said in his February State of the Union Address. "We must reinforce our commitment to medical science." His subsequent budget for NIH offered an increase in funding that

Vaccines were a high priority at a meeting of the Presidential Advisory Council on HIV/AIDS in early April. Dr. David Baltimore, chair of the AIDS Vaccine Research Committee at NIH, told them it was "not possible to put a date" on developing a vaccine, since there are "too many uncertainties." Others expressed little need for a restructuring of research. "I flinch at the concept of more coordination," said NIAID Director Anthony Fauci.

But in his most political comments of the meeting, chairman Scott Hitt told the body that the president wants to do "the man on the moon" analogy in moving this as a priority of the administration. He recommended they support the effort. The final document urged development of "a vaccine to prevent HIV/AIDS within a decade," with "a significant and sustained increase in funds... from *new* sources."

In a private conversation, Dr. William Paul, director of the Office of AIDS Research (OAR) at NIH, described the new lab as an intramural effort jointly sponsored by NIAID and NCI. They are the two major existing players in vaccine research. Each will contribute their existing resources, which will be supplemented with funding from OAR's discretionary account.

Paul called the president's challenge "a formidable undertaking...one which I am

Clinton

◀ page 1

in ten years." But he believes "a challenge is the right way to put it. We didn't want to trivialize it."

The science

Clinton's analogy to the moon project may be a good sound bite, but it is not an accurate comparison. In that instance we already possessed the scientific and mechanical knowledge necessary to accomplish the task. Kennedy's challenge was to summon the political and economic will of the nation to do so.

Developing an AIDS vaccine is quite different, for we are taking a leap of discovery, not one of implementation. The uncertainty is apparent in the handful of radically different approaches researchers are taking as to where and how to intervene to prevent infection. It indicates how little consensus there is, and how much basic study of HIV remains to be done.

There are six known strains of HIV, and the highly unstable virus is constantly mutating, creating variations within each strain. This is the varied, evolving foe a vaccine must protect against. Right now we simply don't know how a vaccine can work under those conditions. It has led some scientists to fear it is impossible. It has led many pharmaceutical companies to drop their efforts towards developing a vaccine, as they see foresee no profit coming from their investment.

Then there is the slippery slope of definition: How does one define "success?" The model most Americans know is that of the polio vaccine, where children are inoculated, protection is 99.9 percent effective, and side effects are minuscule.

Some researchers believe that vaccines currently in development may offer 30 percent protection for HIV. That is clearly not acceptable in the United States, where the prevalence of the virus is relative low (1 million people in a population of 270 million), the ability to reduce new infections is relatively easy and inexpensive, and the current standard of protection for vaccines is very high.

But a vaccine of such limited effectiveness might be acceptable in Third World countries where HIV infects close to half the population and sheer poverty precludes massive spending on healthcare. From a strictly public health perspective, such a vaccine might save literally thousands of lives and begin to limit the spread of the epidemic.

There is also the dilemma of not knowing the long-term consequences of such a vaccine. They include the very real possibility that it could result in the infection of individuals with HIV, not their protection from it.

Researchers and the Advisory Council suggested creation of a body to look at the moral, ethical, and legal questions embedded in a possible vaccine for HIV. The President has yet to move on that aspect.

Reactions

Well-known AIDS researcher Dr. Robert Gallo questioned the extent of Clinton's commitment. He told *USA Today*, "If you really wanted a crash program, you'd have to have five or six centers focusing on nothing else."

The always acerbic playwright/activist Larry Kramer told the *Washington Post* that the president's speech was "more cheap talk ... It's an easy promise. He's just switching NIH funds from Column A to Column B – what I call Chinese restaurant accounting."

"Show me the money," said Steve Michael with ACT UP/Washington. He echoed the sentiment expressed more diplomatically by every other AIDS organization. There is an underlying fear that increased funding for vaccine research might come at the expense of funding for research on treatment and for care for those already infected.

The Human Rights Campaign (HRC) applauded the initiative and called on the president to support a supplemental appropriation now before Congress that would add $68 million for AIDS Drug Assistance Programs (ADAP). The White House has not publicly indicated its support of that effort.

Long-term consequences include the possibility that a vaccine could result in infection with HIV, not protection from it.

Meanwhile, Clinton continues to refuse to do things that can be done right now to prevent new infections in this country. They include lifting the federal funding ban on needle exchange programs and more effective prevention efforts.

It is statistically likely that some of the graduating seniors and their family members in the audience listening to his speech could have been spared their HIV infection had the president implemented those changes at the start of his administration. Instead, four years later, we have a vaccine initiative that may have an impact, in other countries, many years from now. ▼

Daniel,
Please fax to Research Comm. members for Friday call.
Thanks,
Bill

File Vaccines

FYI.

Director, Vaccine Research Center

The National Institute of Allergy and Infectious Diseases and the National Cancer Institute, National Institutes of Health (NIH) are recruiting for the position of Director, Vaccine Research Center (VRC). The VRC's goal is the development of an effective HIV vaccine through the integration of modern immunological science with a detailed understanding of HIV and of the mechanisms of the pathogenesis of HIV infection. The VRC will develop existing and new immunogens and vectors and may undertake entirely new approaches to vaccination. The Director will have responsibility for directing a multidisciplinary research program ranging from basic and clinical immunology and virology through vaccine design and production of an HIV vaccine. Applicants must have earned an M.D. or doctorate degree in biomedicine, virology, immunology or related field and have experience with HIV/AIDS, vaccine development and outstanding stature and reputation in the scientific community in the areas of immunology and/or virology. Further qualifications include: experience as a scientific research administrator in the virological, immunological and/or clinical aspects of infectious diseases in a laboratory and/or clinical research setting and knowledge of medical research operations within the Federal Government, universities and non-profit research institutions, industry, and in an international setting. Annual salary range up to $148,400. Recruitment bonus up to 25% of base pay may be available. Persons interested in this position may call Dr. John McGowan, Deputy Director, NIAID at (301) 496-9677. For more information on the application process, please contact Lynn Hellinger at: 301-496-9686.

Applicants should submit either a curriculum vitae or resume by August 29, 1997, to:

Ms. Lynn C. Hellinger, Director
Office of Human Resources Management, NIAID
Building 31/Room 7A20
31 Center Drive
MSC-2520
Bethesda, MD 20892-2520.

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Developing Vaccines against HIV: Options for Accelerated Progress

Richard T. Mahoney

DANIEL for Rep. Comm.

INTRODUCTION

The development of a vaccine against HIV will require the successful completion of many steps including basic research, animal trials, clinical trials, regulatory agency licensure, production, and establishment of distribution systems. As Fields has persuasively argued, basic research should be the highest priority today.[1] But it is also important to ensure that the process for developing a vaccine against HIV is well managed–from start to finish. Various management systems are available, and they have different capabilities. The development of an HIV vaccine will require the participation of private industry; so far, however, private industry has accorded low priority to the development of an HIV vaccine, especially one for developing countries. A recent assessment carried out by Widdus reports that only about $25 million per year is being spent on developing vaccines against HIV.[2] The development of a single new vaccine entails investment on the order of $200 million to $300 million.

THE SPECIAL ROLE OF THE PUBLIC SECTOR

The public sector must take the lead in ensuring that there is an effective management system for the development of an HIV vaccine–especially for a vaccine to be used in developing countries. (The *public sector* is defined as governments, international multigovernmental agencies, universities, and nonprofit agencies. The *private sector* is all those companies whose primary goal is commercial gain.) Although the private sector can take initiatives (for example, forming industrial consortia) the public sector should take the most important steps. The public sector controls most of the funding for science, controls the regulatory process, sets priorities for public health interventions, cares for most of the unvaccinated who become ill, and buys and delivers the vaccines. With respect to public health and, in particular, vaccines, the public sector is best poised to facilitate the creation of market opportunities to which the private sector can and will respond.

So far, progress in developing an HIV vaccine has been slow. While it is true that lack of basic knowledge has inhibited development, it is also probably true that lack of funding and commitment by the private sector has contributed to this slow pace. The problem is not that the private sector is callous to the needs of developing countries or that it has turned its back on the need for an HIV vaccine. The private sector has been the major producer of products such as vaccines and contraceptives that have done so much to benefit developing countries. The problem is that the public sector has not properly organized itself and established the appropriate conditions to allow industry to do what it can do: manufacture high-quality, safe, effective vaccines in cost-efficient ways.

SPECIAL REQUIREMENTS FOR SUCCESS

Certain "standard" requirements must be met for successful development of vaccines: establish-

Richard T. Mahoney, *PhD, is Director of Institutional Development at the International Vaccine Institute in Seoul, Korea. This article was prepared while he was Vice President and Senior Adviser to the Office of the President at the Program for Appropriate Technology in Health, Seattle, Wash.*

ment of appropriate regulatory processes, construction of production facilities, development of appropriate clinical trial protocols, and creation of effective immunization programs for delivery of the vaccine. These are by no means simple tasks, but they have been done in the past. It is likely that no fundamentally new systems will be needed to meet these requirements for HIV vaccines. In addition to these standard requirements, there are three "special" requirements for successful development of vaccines against diseases that affect the developing world: (1) ensuring that promising laboratory discoveries enter the product-development process; (2) ensuring mobilization of the dispersed capabilities for vaccine research and development; and (3) ensuring procurement of these vaccines (that is, ensuring that a market exists). It is likely that new systems will be required to meet these special requirements. It is this need to establish new systems that distinguishes special requirements from standard requirements.

ENSURING THAT PROMISING LABORATORY DISCOVERIES ENTER THE PRODUCT-DEVELOPMENT PROCESS

A study carried out by the U.S. National Academy of Sciences Institute of Medicine (IOM) reported that the large pharmaceutical companies have reduced basic research on vaccines for both childhood and adult vaccines.[3] These companies prefer to obtain their leads from academia or from small biotechnology companies that, in turn, get their leads from academia. Many biotechnology firms are started by academicians who wish to commercialize their discoveries: their goal is to bring a product to market that will be profitable. This system is fairly efficient in bringing potentially profitable laboratory discoveries to the product-development stage. However, under this system, laboratory discoveries that relate to vaccines for use in the developing world are assigned low priority. With respect to vaccines that only the developing world will use, industry consistently says "the public sector will have to pay all the costs."

In the case of HIV, it has been found that the strains of HIV prevalent in developing countries differ from those appearing in developed countries. Different vaccines may be required for the various strains. One goal is to develop a multivalent vaccine that will be equally effective against all strains of HIV and in all people. This is a long-term goal that will be reached in incremental steps. Looking at industry's current priorities, it appears that one of the first steps will be the development of a vaccine that is effective against a strain that is not prevalent in developing countries. How does one get industry to accord higher priority to strains that are prevalent in the developing world?

A critical bottleneck in developing new vaccines is production of pilot lots of vaccine according to good manufacturing practices (GMPs). A facility must be certified by an independent regulatory authority that it is capable of producing vaccines according to certain high standards (GMPs) before pilot lots produced in that facility can be used in clinical trials. Because there are not enough facilities to do this work, a large backlog exists. As stated in the IOM report, "The end result of the shortage of vaccine pilot production facilities is considerable delay (sometimes years) in producing pilot batches of required vaccine."[4] This bottleneck even has an effect on vaccine manufacturers in the private sector. All other things being equal, companies will put the potentially most profitable vaccines first in the pilot-production waiting line.

MOBILIZING DISPERSED CAPABILITIES

Vaccine research and development is carried out in hundreds of laboratories, public and private, in more than 10 countries.[5] These laboratories have varying capabilities, priorities, financial resources, relationships with the private sector, policies for protection of intellectual property, and other conditions. Experience has shown that, although it is possible to bring most of the key players together in a single room to discuss a particular goal for vaccine development, it is very difficult to have all those players leave the room in agreement on a coordinated management strategy for reaching that goal. This dispersion of capabilities has certain advantages, such as facilitating competition. It also helps ensure that more than one approach will be taken to problem solving, thus helping to avoid "placing all the eggs in one basket." The World Health Organization (WHO) has been tirelessly addressing this issue with respect to HIV vaccines; the organization has convened a number of meetings seeking to reach agreement on the standard requirements for success–especially establishment of scientific research priorities, design of clinical

trials, development of regulatory requirements, and design of immunization programs. However, WHO cannot impose its findings on member states –much less on firms in the private sector.

Another effect of the dispersion of vaccine research, development, and manufacture is the need to assemble intellectual property rights (IPRs) before a vaccine can be sold. IPRs include patents, trademarks, copyrights, trade secrets, and knowledge. Unlike the vaccines currently used in childhood immunization programs, vaccines of the future will be controlled by an extensive web of IPRs. This requirement to assemble IPRs is one of the most daunting requirements for public vaccine research and development programs. Most agencies do not have an effective system for carrying out the required work. Commonly the agencies are staffed by scientists, who turn to lawyers who have little previous formal training in IPRs. In industry, these licenses are put together by business specialists who integrate scientific, legal, market, production, and regulatory issues into each license. The scientist-lawyer teams of the public sector are not trained to carry out this integration. One of the main problems public agencies face is that they will not be the eventual manufacturer of the product, so they cannot fully anticipate how the licenses need to be structured. The development of an HIV vaccine will likely face these same difficulties. Because of the dispersed nature of the vaccine enterprise, it will not be possible to have a single supranational agency that will hold, either directly or through license, all relevant IPRs for an HIV vaccine.

ENSURING VACCINE PROCUREMENT

Development of the market. What makes the HIV vaccine market for developing countries different from other vaccine markets (such as measles)? To create a market for HIV vaccines, two things must be done: create market demand (the desire to purchase) and create market power (the ability to purchase). In the coming years, while scientists are struggling to find the keys to unlock the secrets of an HIV vaccine, it will be necessary to ensure similar or better progress in the development of the market. If we believe there will be an acceptable HIV vaccine at some future time, we need to create a well-developed market so that the private sector will be willing to invest. Levin puts it this way: "The discovery of an effective AIDS vaccine will not be the beginning of the end. It will only be the end of the beginning."[6] Developing the market will not be easy because it involves many unexplored issues. In the case of an HIV vaccine, the total number of potential users is probably great. However, many people do not perceive the population at risk to be the general population; they see it instead as a smaller subset, of which they are not a member. Some individuals will want the vaccine, but "want" does not necessarily translate into a firm decision or ability to obtain the vaccine. These people will weigh their individual risks and benefits carefully and will give lower weight in their risk-benefit equation to the good of others. Many potential users will be affected by their ability to pay. If they cannot pay, but still want the vaccine, then someone else must pay. These issues–particularly as they relate to developing countries–need to be examined while the vaccine is being developed, and not afterwards. These issues need to be addressed in a comprehensive management plan.

The two-tier market. The public sector buys vaccines for immunization programs in developing countries at greatly reduced prices, compared to the prices at which the vaccines are sold in the private sector. For example, hepatitis B vaccine is sold in Korea for about $8 per dose, while the same manufacturers sell the vaccine to the international public sector for about $0.60 per dose. Companies sell vaccines at two levels based on several rationales: they have excess capacity, and using the excess capacity lowers their average production cost per dose so that sales in the private sector are more profitable; marketing and sales costs for the public sector are low; they believe sales in the public sector will generate goodwill; and they have a sincere concern for better public health. The most important factor is the existence of excess capacity beyond what is needed to meet the demand in the private sector. That excess capacity exists because of the relative ease of manufacturing the vaccines or increased production to meet additional orders. (This excess capacity does not counterbalance the absence of capacity for production of test lots of vaccine mentioned above. Facilities dedicated to the production of existing vaccines and flexible facilities for prototype production are two different types of production centers.)

A vaccine against HIV will probably sell for many dollars per dose in developed countries, which will be beyond the capabilities of developing countries or donor agencies. Thus, a two-tier market will be necessary for HIV vaccines, just as it is necessary for other vaccines in developing countries.

The public sector can implement certain policies to help ensure a two-tier market where it might not naturally evolve. These policies include: tax credits for investing in production capacity; widespread, favorable publicity for manufacturers that supply HIV vaccines to developing countries; and effective management of IPRs. Several public-sector organizations, including the Program for Appropriate Technology in Health (PATH),[7] that develop products and obtain patents on promising technologies, have implemented licensing policies that permit a private-sector licensee to sell a product in the private (commercial) sector at any price the licensee can; however, the price to the public sector (governments, philanthropies, public service agencies) must be lower than the private-sector price. For example, PATH has licensed a company to manufacture a single-use, prefilled syringe that PATH developed. The company is free to set the price to the private sector, but the public-sector price must be lower. This policy provides a substantial savings for the public sector–in the case of the syringe, greater than 25 percent.

MANAGEMENT SYSTEMS

In considering management systems, it is instructive to review the successful effort to develop a vaccine against polio. The following summary is based on information provided by Dr. F. Robbins, who won the Nobel Prize for his research on the polio virus. Polio vaccine research and development was sponsored principally by the National Foundation for Infantile Paralysis, which was the only major sponsor of virology research in the United States in the late 1930s and much of the 1940s. It raised funds primarily through public appeals (the March of Dimes) and also received funds from wealthy donors. At first, these funds were used to sponsor basic research. The foundation often sponsored research on virology not directly related to the polio virus. Only when clear leads had been identified did the foundation allocate funds for vaccine development. The foundation's research program was guided by an external advisory committee of outstanding scientists. When the vaccines became available for human trials, the foundation helped develop guidelines and provided the financial support for large-scale trials. The Salk vaccine, which emerged from this effort, was not patented. Nor was Robbin's technology for tissue culture. Several companies increased their scale of production from the laboratory methods developed by the researchers. One of these companies, Cutter, experienced difficulty in achieving complete viral inactivation. "As a result, new requirements were introduced for safety testing along with a filtration step. With these relatively modest changes, the problem was solved, and no untoward reactions from the inactivated vaccine have since been observed."[8]

Several observations can be made about this stupendous success:

- The foundation was the dominant force. It controlled the money and could determine the strategies and priorities for the field.
- Governmental regulation of vaccine manufacturing and clinical trials was limited. The foundation developed the regulations for clinical trials.
- Because the vaccines had no associated patents, many companies were able to establish production.
- The foundation used private funds, so it had great flexibility in spending.

The most important point is that a coordinated management plan was possible because a single agency was guiding most of the work, and other agencies (such as the U.S. Food and Drug Administration) did not have clear rules about vaccines. It seems unlikely that this exact model could be employed today. As noted above, vaccine research and development is too dispersed to be coordinated by a single agency unless that agency is endowed with very significant resources.

SYSTEMS CURRENTLY EMPLOYED

The public sector currently uses three systems for HIV vaccine development: investigator-initiated research programs, directed-contract research programs, and codevelopment agreements.

Investigator-initiated research programs. Most basic research is funded through investigator-initiated programs. The results of investigator-initiated research are translated into products through a process of licensing. Most universities have a "technology transfer" office that is responsible for licensing. This structure of collaboration between public and private sectors is probably the most common. For example, a licensing agreement for HIV vaccines has been signed by Harvard University Medical School and Therion Biologics Corporation of Cambridge, Massachusetts. They are seeking to develop a live, attenuated (genetically modified) HIV vaccine. In this case, Harvard completed early development work and applied for a patent on the prototype vaccine. Harvard licensed the patent to Therion, a relatively small biotechnology firm that plans to conduct further applied research studies leading to clinical trials.[9] Production of a prototype vaccine for clinical trials will be subcontracted. Because Therion does not have capabilities for vaccine production or marketing, it will most likely have to license its product to a larger vaccine company, if the project proves promising. Some national medical research agencies such as the U.S. National Institutes of Health (NIH) have policies controlling the nature of the licenses that can be granted. These controls may call for a favorable price and guaranteed access for the public sector.

Directed-contract research programs. There are many examples in the public sector of directed-contract programs, such as WHO's Tropical Disease Research Program and its Human Reproduction Program. These programs operate by identifying priorities for product development (such as a malaria vaccine). They hire scientists with relevant expertise and empower these scientist-administrators to design development programs.

Outside technical advisory committees, usually made up exclusively of scientists from the public sector, are assembled to help in design and oversee the programs. The scientist-administrators are provided a budget to contract with research and development agencies from both private and public sectors to carry out various components of the product-development program.

Co-development agreements. In a codevelopment agreement, a public research and development institution joins forces with a private company. They agree to share in the tasks necessary to commercialize a particular product. WHO has signed many codevelopment agreements, including agreements for the development of vaccines. NIH uses cooperative research and development agreements for vaccine development.[10]

NEW SYSTEMS THAT COULD BE EMPLOYED

There are three new types of management systems that could be employed for research and development of an HIV vaccine: finished-product procurement, not-for-profit institute, and consultative groups. The common denominator of these new systems is that they provide a way for the public sector to construct comprehensive management plans in which industry has a well-defined role. To be successful, the management plans would have to address each of the essential requirements discussed above (ensuring that promising discoveries enter the product-development process, mobilizing dispersed capabilities, and ensuring vaccine procurement).

Finished-product procurement. The finished-product procurement system is straightforward and is often employed by the military. For example, "We want 1,000 tanks that will travel up to 100 mph, over sand, in temperatures up to 60 degrees centigrade, and fire up to 2,000 rounds per minute." Such a tank may not exist, and the bids include the cost of research and development. The finished-product (or military-procurement) system has been considered for the HIV Vaccine Development Superfund.[11] Clearly, the finished-product procurement system will be less effective when the desired product is in the early stages of research, and it will be most effective when proven product prototypes have been developed. Further, this system requires a clear knowledge of the desirable specifications for the final product. Can specifications be accurately defined for an HIV vaccine today? With respect to vaccines for developing countries, implementation of this system would require sufficient funds not only to cover all research and development costs, but also to construct and maintain the production facility and to purchase the vaccine for a fixed period of time. Is it too early in the process of developing an HIV vaccine to implement this system?

Not-for-profit institutes. In this model, the public sector decides that there is a compelling public need for the development of certain products and that no single private company could or would undertake the work. The public sector establishes a mission-oriented agency. Examples are Airbus Industry and the Manhattan Project. Recently the IOM recommended establishing of a national vaccine authority to undertake, in collaboration with private industry, the development and production of new vaccines for children as a part of the new worldwide children's vaccine initiative (CVI):

> In the committee's view, the development of new and improved [children's] vaccines is unlikely to occur unless there is an entity that has the mandate to manage and oversee the process from beginning to end. Because the private sector alone cannot sustain the costs and risks associated with the development of most CVI vaccines, and because the successful development of vaccines requires an integrated process, the committee recommends that an entity, tentatively called the National Vaccine Authority (NVA), be organized to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of global public health need.[12]

A common denominator of these not-for-profit institutes is that they are designed to undertake research and development, but they rely on private industry for production and marketing. These institutes assume most of the risk of early product development. One of the strengths of these institutes is that they can manage the product-development process from start to finish, much as private industry does. Even though they may not actually execute each step of the process, they maintain a constant involvement as the product moves toward distribution. This ongoing involvement reflects their concern with the ultimate use of the product and not just with a single stage of the process. Undertaking the work under one roof, they seek to assemble the required IPRs, and they seek to protect the interests of the public sector, including ensuring that the public-sector market will be served.

Consultative groups. A consultative group is composed of multilateral agencies, bilateral donors, specialized agencies, industry, academia, and others. For example, the Consultative Group on International Agricultural Research (CGIAR) is a highly successful system for encouraging the development and dissemination of new crops, fertilizers, irrigation systems, and other technologies important for agriculture. It meets twice each year: once to review technical and strategic issues, and once to review financial requirements and to provide donors an opportunity to make pledges of support. The CGIAR coordinates support for a number of agricultural research institutes throughout the world. Each institute has a special area or areas of expertise, including rice, wheat, maize, irrigation, and so forth. The CGIAR operates through a secretariat at the World Bank. Each institute prepares budget proposals. The secretariat screens the proposals to ensure that they fit within an overall strategy approved by the consultative group. In addition, the proposals are reviewed by the Food and Agricultural Organization for technical merit. The secretariat then recommends to the consultative group the funding to be received by each institute. The CGIAR allocates over $200 million per year.

For a vaccine-development consultative group, industry would have to be directly involved in designing the management plan to be overseen by the consultative group. The new United Nations AIDS program may provide the basis for an HIV-vaccine-development consultative group.[13]

DISCUSSION

CURRENT MANAGEMENT SYSTEMS

The existing management systems (investigator-initiated research programs, directed-contract research programs, and codevelopment agreements) have their strengths, but they have weaknesses, too. These weaknesses may help explain why little progress has been made toward development of vaccines for developing countries. All of the existing systems are strong in transferring laboratory findings to industry when these findings are the basis for a product with a promising commercial market. In fact, this is the main objective of these systems. However, all of the systems have faced difficulties in transferring findings that relate to development of products to be used almost exclusively in developing countries. For example, both the Human Reproduction Program and the Tropical Disease Research Program at WHO have had

numerous arrangements with private industry for vaccine development. Some of these arrangements have faced difficulties because of the reluctance of the partners from the private sector to invest heavily in the product. The antifertility vaccine, which probably could enjoy a market among the well-to-do, serves as an example. WHO has struggled to find a partner from the private sector that will accept a product license and assume responsibility for production of pilot-scale batches, development of the vaccine into a commercial entity, and liability. In general, the public sector has lacked the resources to push development of these vaccines. For example, the budgets for these WHO programs have generally not exceeded $30 million per year. Because these budgets cover a wide range of products, no more than a few million dollars can be allocated to any one product.

Over the years, directed-contract research programs have faced many challenges. The most difficult challenge has been to take a product concept from the very early stages of research all the way through to a finished product. This has led many of these programs to focus increasingly on the later stages of product development. The Tropical Disease Research Program has recently been reorganized for just this purpose. The Human Reproduction Program established a downstream program a few years ago and gave it the largest budget of all the Human Reproduction Program's activities.

Certain aspects of these directed-contract research programs may limit their capability to develop products as rapidly as private industry can:

- One of the greatest challenges faced by these programs is inadequate funding. With much higher levels of funding, the success rate would certainly be greater.
- These programs are often administered by former academic scientists, who tend to identify the additional research that can be done on a product rather than to pass the product along to the next stage of development.
- The scientist-administrators and the members of the external advisory committees, also predominantly from academia, have limited experience in the product-development process.
- The organizations that house these programs have struggled to determine how and whether they should own patents, assume licenses, deal with liability, and so forth. Clear guidelines have yet to be identified.

These directed-contract research programs have many strengths. In particular they have been successful in substantially expanding research capacity in developing countries. They have also performed excellent multicentered studies of existing products to document their performance in a variety of settings.

The existing management systems are weak in facilitating the assembly of IPRs. A license agreement almost always deals with only one piece of intellectual property. Take, for example, a scientist who discovers an antigen that provokes neutralizing antibodies in experimental animals; if the antibody is produced most efficiently using a proprietary method owned by a third party, the licensee for the antibody will have to obtain rights from the third party. All structures are generally weak in taking account of the dispersed nature of the research and development community. The parties to an agreement often find themselves in competition with other groups, rather than helping to synthesize the work of a number of groups. They have a particular product lead to which they are committed, and they will work hard for its success. Although competition and product champions are important in the development process, the management systems described here have little capability to bring together disparate resources that might be valuable in achieving a successful project.

In summary, current public-sector systems of vaccine development have not been as successful as desired. They are best at implementing tactics, but they face difficulties in formulating and implementing a strategic plan that covers activities from product conception to product use.

POSSIBLE NEW SYSTEMS

The finished-product procurement system, the not-for-profit institute, and the consultative group all take a more strategic, comprehensive (start-to-finish) management approach to vaccine development than the models that are currently in use. Successful implementation of these systems requires a comprehensive management strategy, from basic research to vaccine program implementation.

The problem with the finished-product procurement system is that the HIV vaccine is not sufficiently developed to make it possible to "order" a finished product. There are also problems with the approach used with not-for-profit institute: first, it cannot harness a sufficiently wide range of capabilities; second it would take time to form the institute or to expand an existing institute to sufficient size and capability.

The consultative-group system seems most attractive. Its greatest asset is its ability to mobilize a wide range of capabilities. It could work with both the public and private sectors, help assemble IPRs, and make provisions for a two-tier market through licensing and other approaches. A well-designed consultative-group system would be likely to obtain the confidence of the donor community, which would make more funds available. The major problem is getting various power centers to agree to participate in a consultative group and thereby subjugate some of their decision-making authority to a higher body. A specific difficulty will be to obtain agreement on a system of effective management of IPRs. Without such a system, it is unlikely that the needs of developing countries, particularly the need for a two-tier market, can be met. A consultative-group system could be managed by WHO, the World Bank, or a new entity–perhaps affiliated with an existing agency–formed specifically for this purpose. The recently formed United Nations AIDS program may be able to fill this role.

CONCLUSION

The existing systems for developing a vaccine against HIV should continue to be employed and receive greater levels of funding. They can make important contributions. However, if the goal is to help control AIDS with an HIV vaccine as quickly and effectively as possible, it will be necessary to implement a more comprehensive management system. It is our belief that the most appropriate system to accelerate development of an HIV vaccine is the consultative-group model. The great advantage of this system is that it provides a means to develop a coherent, strategic management plan.

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7. PATH is an international, nonprofit, nongovernmental agency that is concerned with improving the health of women and children. It has an energetic research and development program, funded in large part by the U.S. Agency for International Development. The program has developed various technologies including a rapid-dip-strip diagnostic procedure for HIV-1 and HIV-2, which is now widely used in health programs in developing countries.

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Vaccines

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Subject:

COMMENTS:

Sandy:

It was good to see you and to have the chance to spend some time together. As you requested, I am sending along the following:

1. List of members of the Baltimore Committee

2. A piece we prepared regarding the "cross-over" benefits of AIDS research.

Hope it is helpful. Talk to you soon.

Wendy

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RESEARCH ON AIDS BENEFITS EFFORTS AGAINST OTHER DISEASES

Introduction

The nation's investment in HIV-related research is providing major benefits in our ability to understand and treat a wide spectrum of other infectious, malignant, neurologic, autoimmune and metabolic diseases. In addition to its direct and indirect medical applications, basic knowledge of the biology of HIV infection and the processes by which it causes AIDS benefits other areas of basic research including immunology, virology, microbiology, molecular biology, and genetics. Knowledge gained from the study of drugs to treat HIV infection and its complications also have helped establish new approaches for the design and conduct of more rapid clinical studies, as well as those that address the special recruitment requirements of women, minorities, and other underserved populations.

Effective drugs to treat other infectious diseases

The successful development of two classes of drugs that limit the replication of HIV, reverse transcriptase inhibitors and protease inhibitors, represents a landmark in drug development for the control of viral diseases. As a result of these efforts, the investment in AIDS research has provided a new paradigm for confronting viral diseases in general. Prior to the development of these potent drugs, virtually all efforts to deal with viral diseases involved prevention (using vaccines) or palliation (treating symptoms). Few effective treatments were available for most common viral infections. The impact of the AIDS drug development experience not only benefits development of treatments for other viral diseases, but also will hasten drug development efforts for bacterial, mycobacterial and fungal diseases.

- The drug lamivudine, (also known as 3TC, an inhibitor of the HIV reverse transcriptase enzyme), initially developed to treat HIV infection, now has been shown to be the most effective therapy to treat chronic hepatitis B infection. Prior to the availability of lamivudine, no effective therapies existed, and many infected persons would proceed inexorably to cirrhosis, liver failure and liver cancer. Lamivudine represents a "lead compound" that should expedite the development of even more effective therapies to treat, and perhaps even cure, chronic hepatitis B infections.

- Experience gained from the development of protease inhibitors to treat HIV infection are being utilized to develop specific inhibitors of the hepatitis C protease. At present, there are no therapies that can effectively treat hepatitis C virus infection and prevent its life-threatening consequences.

- Current therapies for cytomegalovirus (CMV) are toxic and expensive. Using techniques developed to derive inhibitors of the HIV protease, new candidate drugs have been designed that represent promising leads as agents to treat CMV infection.

- Using techniques successfully validated in the course of HIV drug development, progress has been made in targeting a number of steps in the influenza virus life cycle for inhibition.

- New animal models of viral diseases that have been developed in the course of AIDS

research will facilitate studies of other infectious agents and the diseases that result from them.

Advances in methods for drug design

AIDS therapeutic research, particularly the development of protease inhibitors, has convincingly demonstrated the importance of rational drug design and has resulted in a new generation of powerful inhibitors of HIV replication. Progress in this area depends on the identification of a promising molecular target for drug therapy, determination of the three dimensional structure of the target molecular using sophisticated X-ray crystallographic methods, and structure-based drug design aided by the techniques of structural biology and computer-based molecular modeling. HIV research has benefited from the availability of these individual methods and it also has fostered significant improvements in each of these critical technologies, including X-ray crystallographic methodologies, nuclear magnetic resonance techniques, and computational approaches to chemical processes. These advances will continue to benefit efforts to develop new drugs for other diseases.

Treatments for opportunistic infections

Individuals who receive drugs that intentionally or unintentionally suppress the function of the immune system are, like AIDS patients, at significantly increased risk of infection with organisms that generally do not pose a hazard to those with fully functioning immune systems. Many forms of modern treatment for cancer involve the use of drugs that suppress the immune system. Transplantation of solid organs as treatment for organ failure (e.g., heart, liver or kidney failure) and bone marrow transplants to treat malignant (e.g., leukemia) or hematologic diseases (e.g., immunodeficiency syndromes, or genetic disorders of hemoglobin production such as sickle cell anemia) necessarily involve the use of drugs that suppress the immune system to prevent rejection of the transplanted organs or tissues. The development of effective drugs to prevent and treat many of the microorganisms that cause such opportunistic infections promise real benefit to those undergoing cancer chemotherapy or receiving anti-transplant rejection therapy.

- Clinical research to delay or prevent life-threatening AIDS-related opportunistic diseases has helped to stimulate the development of effective drugs to treat these pathogens in immunosuppressed persons, such as *Pneumocystis carinii*, cytomegalovirus (a cause of blindness in people with AIDS and life-threatening pneumonias and serious gastrointestinal infections in bone marrow and organ transplant recipients), and a variety of serious fungal infections that cause meningitis or disseminated infections.

- Research on AIDS therapies has helped establish the concept of "prophylaxis" of certain infections in immunosuppressed persons. Providing regular, low doses of drugs that are intended to *prevent* development of disease decreases the risk of opportunistic infection. This approach is now standard practice to prevent infections caused by a variety of viruses (such as CMV), fungi and mycobacteria in immunosuppressed patients.

Understanding the origins and manifestations of malignancies

One of the cardinal manifestations of AIDS is the predisposition to develop specific types of cancer, including Kaposi's sarcoma and non-Hodgkin's lymphomas. That these cancers arise in the setting of host immunodeficiency provides strong support for the notion that the immune system can play an important role in suppressing the development of cancers. HIV infection provides a unique model to

study the role of the immune system in the emergence of cancers, and to test novel approaches by which immune responses can be modified to help treat established malignancies.

- The discovery of the likely cause of Kaposi's sarcoma, HHV8, provides a model for using novel techniques of molecular biology to search for infectious cancer-causing agents in any type of cancer. Studies involving HIV-infected persons are now serving as the model to identify potential infectious etiologies for a wide variety of common malignancies.

- HIV-infected women who are also infected with human papilloma virus (HPV) are at increased risk of developing cervical cancer, suggesting that the immune system also plays an important role in controlling this disease. A link between HPV infection and cervical cancer is also seen in women not infected with HIV. Study of HIV-associated cervical cancer has stimulated new areas of research and therapeutic strategies to treat this disease, which will likely benefit all women at risk of cervical cancer.

- Wasting, the intractable loss of weight, is a common clinical manifestation of both cancer and advanced HIV disease. New therapies developed to treat HIV-associated wasting, such as growth hormone treatment, may prove to be of benefit to persons with cancer. New anti-HIV treatments that effectively inhibit HIV replication seem to reverse the process of AIDS-associated wasting, providing an opportunity to understand how this disease manifestation arises. The results of these studies may also be of relevance to understanding the process of cancer-associated wasting.

Advances in the ability to diagnose infection and monitor the efficacy of therapy

HIV research has provided new paradigms for the diagnosis of infectious diseases, and for monitoring the efficacy of therapy. Molecular diagnostic methods use sensitive techniques to detect and quantify the pathogen in an infected patient. These methods now permit more rapid diagnosis of infectious diseases, facilitate earlier introduction of effective, potentially life-saving therapies, permit the design of faster, more informative clinical trials, and allow the individualization of optimal therapies.

- Among these new technologies is the polymerase chain reaction (PCR) test used to diagnose HIV infection or the so-called 'viral load' assays used to assess disease progression and the efficacy of anti-HIV therapies. The development of these approaches and their validation in the course of AIDS investigations have helped speed the process of clinical evaluation of candidate AIDS therapies, and similar approaches are now being employed to study treatments for other infectious diseases. PCR-based tests are now routinely used to rapidly diagnose a number of important infectious diseases including tuberculosis, chlamydia, Lyme disease and a variety of fungal infections.

- The development of tests to screen blood donations for the presence of HIV infection has stimulated advances in technologies that could be used to screen blood for the presence of other important infectious diseases, such as hepatitis C virus and the HTLV-1 and 2 viruses that are associated with the development of leukemia and serious neurologic diseases. As a result, the safety of the blood supply has been substantially improved.

Insight into the function of the human immune system in health and disease

The investment in AIDS research has enormously speeded the development of our understanding of the human immune system. Research on AIDS has led to major advances in our understanding of and ability to manipulate human immune responses. This should allow much more effective approaches to treat diseases in which dysregulated immune responses are either the actual cause of, or substantial contributing factor to, the fundamental disease process, including allergies, multiple sclerosis, juvenile diabetes, rheumatoid arthritis and systemic lupus erythematosus.

- Promising immunologic approaches currently being investigated to control cancer include the use of cytokine therapy to boost anti-tumor immune responses, the use of genetically modified tumor cells that express cytokines or other gene products intended to re-direct host immune responses to more effectively fight the resident tumor cell burden, and the expansion (in tissue culture) and transfer of immune cells that can recognize and kill tumor cells. Similar approaches have been actively pursued in the course of research on HIV therapies, and experience from studies in HIV-infected persons has helped accelerate the development and testing of these treatments in the context of cancer therapy.

New approaches to the design and conduct of drug trials

The national HIV research effort has brought about unprecedented cooperation among federal, university and pharmaceutical industry scientists in the development of potential therapeutic agents and vaccines. HIV research has resulted in new approaches for designing and conducting clinical trials, and for recruiting and enrolling patients, especially women, children and minorities in these studies. These models are now being applied to test treatments for other diseases in faster, more efficient, and more inclusive ways.

- New approaches for conducting clinical trials have been developed, including community-based trials, which capture the expertise of community physicians. AIDS clinical trials have demonstrated the importance of providing ancillary services, such as general health care, transportation, obstetrical care, day care for children, and other related services, to recruit and ensure the continued participation of women, children, adolescents, and minorities in clinical trials.

- AIDS clinical trials pioneered the development of community advisory boards to assist clinical trial sites in assuring close cooperation with community constituency groups. Such strategies will be applied in the study of treatments for other diseases in the future.

- The "parallel-track" mechanism has been shown to be consistent with the conduct of effective clinical studies of candidate therapies and will benefit persons suffering from all types of life-threatening diseases for which existing therapies are either ineffective or have failed. This mechanism permits access to promising drug treatments, prior to their formal approval by the Food and Drug Administration (FDA), for individuals who would not otherwise qualify for participation in specific clinical studies.

Advances in the study of neurologic manifestations

Research aimed at understanding how HIV enters the central nervous system (CNS) and how it results in neurologic disease has yielded important knowledge regarding the role that inflammatory

processes within the CNS can have in neuronal degeneration and impairment of cognitive and motor functions. Studies on the mechanisms involved when HIV crosses the blood/brain barrier to infect cells within the brain and how drug therapies can be delivered more effectively to the brain have led to a better understanding of the mechanisms through which this barrier functions and how it may be circumvented. The results of this research have important implications for research on Alzheimer's disease, dementia, multiple sclerosis, neuropsychological disorders, encephalitis, and meningitis.

Expansion of basic science knowledge base

The investment in AIDS and HIV research has enormously speeded our progress in many areas of basic science, including those directly impinging upon the biotechnology industry. Indeed, this effort has been a major contributor to the knowledge base upon which the biotechnology industry has been built. Biotechnology companies are capitalizing on the new basic biomedical information provided by HIV research, most notably new findings regarding chemokines and novel proteins as targets for drug and vaccine development.

Insights into the impact of human behavior on public health

Behavioral and social sciences research on HIV infection and AIDS has demonstrated the important interaction of biological, psychological, and social factors as contributors to disease prevention, transmission and progression among individuals and population groups. Lessons learned from these studies have improved our ability to study human behaviors that affect disease risk and to develop effective methods to encourage behavior change.

Progress in understanding "emerging" and re-emerging infectious diseases

The emergence of HIV infection, Ebola virus infection, and hantavirus infection within the past 15 years has demonstrated not only that new diseases can appear in human populations, but that they will likely continue to "emerge" in the future. Diseases once deemed "under control" also have re-emerged as important health problems in this country and around the world. Studies of the origin of HIV infection and the processes that contributed to its worldwide spread have significant implications for preventing or limiting similar epidemics in the future.

- HIV infection in humans appears to have originated from a virus present in certain non-human primates. Inadvertent transmission of the virus across species (so-called zoonotic infection) allowed the virus to enter human populations. Study of the origins and spread of HIV infection will provide a better understanding of how this process occurs, and how it can be prevented.

- Studies of HIV-infected individuals with clinical syndromes of previously unknown etiology have led to the discovery of a number of important new infectious agents including: human herpes virus 6 (HHV6), the cause of a number of clinical illnesses including exanthem subitum in children; human herpes virus 7 (HHV7), not yet associated with a specific clinical illness; human herpes virus 8 (HHV8 or KSHV), the likely causative agent of Kaposi's sarcoma; bacteria of the genus *Rochalimaea*, also known as Bartonella, the causative agent of bacillary angiomatosis and "cat scratch fever"; and a variety of previously uncharacterized fungi. The discovery of these agents and diagnostic methods to detect them also led to their identification in persons not infected with HIV. HHV6, for example, causes serious clinical complications in persons not infected with HIV.

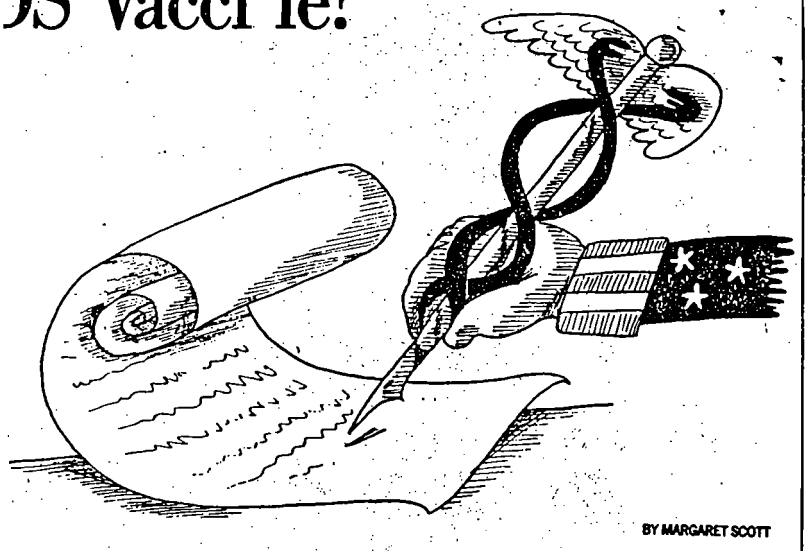
- Using molecular diagnostic techniques developed in the study of the AIDS epidemic, CDC researchers rapidly identified hantavirus as the causative virus infection of an outbreak of cases of fatal pneumonia in the Southwestern United States a few years ago. These techniques allowed the researchers to determine the origin of the virus in local populations of mice and to limit the spread of infection.

- The development of international collaborations for tracking the natural history and epidemiology of infectious diseases and for obtaining and identifying variants of infectious agents from different geographic regions helped expedite research on AIDS. This experience, and the collaborations established, will be of great value should new epidemic diseases emerge in the future.

- Computational methods and mathematical modeling developed to study HIV transmission now are being applied to track the parameters of transmission and dissemination of the bovine spongiform encephalopathy agent, and will certainly benefit the study of other infectious agents as well.

Prepared by Dr. Mark Feinberg, OAR 4/18/97

Why a ı A .)S Vacci ıe?



BY MARGARET SCOTT

The reviews are in on President Clinton's dramatic declaration pledging the United States to finding an AIDS vaccine, moonshot-like, within 10 years. Apart from AIDS activists who complain that the president did not commit serious moonshot money to the enterprise ("cheap talk"—Larry Kramer), the reaction was mostly favorable. Who, after all, can be against a vaccine against anything?

No one seems to want to raise the obvious, if indelicate, question: Why embark on a huge national venture to create a vaccine for a disease that is already extraordinarily preventable?

Unlike most communicable diseases, AIDS is not contracted casually. Unlike TB, it is not contracted by being coughed on in the subway. Unlike dysentery, it is not contracted by drinking the wrong water. To get AIDS you must, in all but the rarest cases, engage in very complicated consensual social behavior, namely unsafe sex or intravenous drug abuse.

It would be nice to live in a world where one could engage in such behaviors while enjoying vaccine-induced immunity. But is that really a top national priority? Would any president propose as a top national priority an anti-lung-cancer vaccine so that people who smoke—48 million Americans do—could do so with immunity?

Nor do presidents call for a 10-year campaign to produce a vaccine against cirrhosis of the liver. Why? Not because we want to stigmatize people who drink or smoke. But for a very practical reason: These behaviors being voluntary and preventable, it makes a lot more sense to spend the scarce intellectual, scientific and financial resources of the country trying to give people immunity from diseases that they cannot otherwise protect themselves against.

The classic case is polio. When FDR contracted it in 1921, we had not a clue how people got it. By the '50s, frightened parents kept their children away from swimming pools and movie theaters and even crowds. They lived in terror not knowing what they might be doing that was contributing to their kids' chances of getting polio.

With no obvious behavioral cause, polio was the classic case of a disease crying out for a vaccine. Meningitis, cervical cancer and multiple sclerosis occupy a similar position today. But AIDS?

We abandoned public-health measures against AIDS because of political pressure. Now Clinton seeks an expensive magic wand instead.

Moreover, Clinton is calling for a huge technological innovation (which many in the field doubt is a reasonable prospect anyway) to prevent the spread of AIDS. Yet at the same time, the traditional way of controlling the spread of communicable diseases has been largely abandoned in the case of AIDS. And uniquely in the case of AIDS.

We fight just about every epidemic—tuberculosis, syphilis, gonorrhea—by identifying carriers and warning their contacts. The usual epidemiological tracing has not been done for AIDS. Gay activists and civil libertarians have vociferously opposed it. And the politicians have caved.

The story of this travesty—"the effective suspension of traditional public health procedures for AIDS"—is laid out in damning detail by Chandler Burr in the current Atlantic Monthly ("The AIDS Exception: Privacy vs. Public Health").

"AIDS has been so thoroughly exempted from traditional public health approaches," writes Burr, "that civil libertarians have defeated in court attempts by health authorities to notify the spouses of people who have died of AIDS that their husbands or wives were HIV-infected."

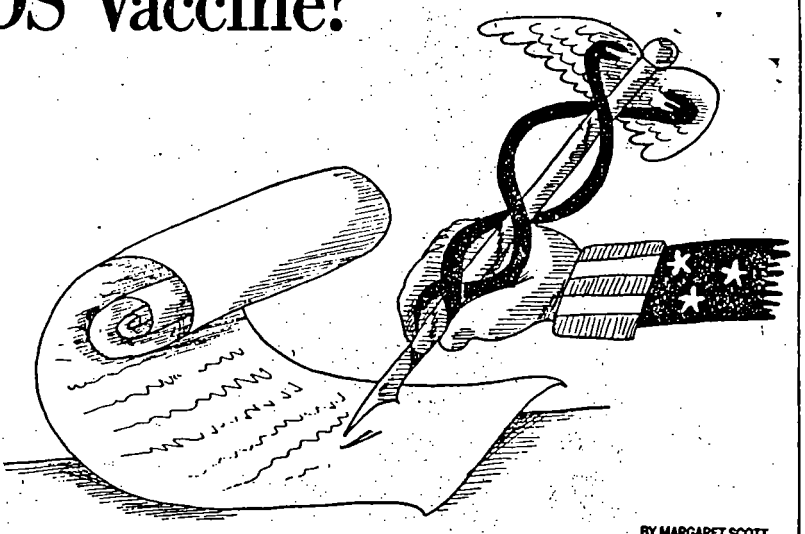
In 1985, in fact, gay activists brought suit to prevent the use of the first test for HIV, unless assured the tests would not be used for widespread screening of gays. Even today they oppose mandatory HIV screening for pregnant women, even though we know that early treatment of the mothers would reduce by 50 to 75 percent the number of kids who are born with HIV.

"Traditional public health is absolutely effective at controlling infectious disease," says Dr. Lee Reichman, who works with tuberculosis and AIDS patients. "It should have been applied to AIDS from the start, and it wasn't. Long before there was AIDS, there were other sexually transmitted diseases, and you had partner notification and testing and reporting. This was routine public health at its finest and this is the way STDs were controlled."

Marcia Angell, executive editor of the New England Journal of Medicine, is blunter than most: "I have no doubt . . . that if, for example, we screened all expectant mothers, we could prevent AIDS in many cases. And if we traced partners, we would prevent AIDS in many cases. And if we routinely tested in hospitals, we would prevent AIDS in many cases."

And if we had a president with guts, he would be demanding these elementary measures to save people from getting AIDS today—instead of waving a wand and telling scientists to produce for him a magic vaccine 10 years from now.

Why an AIDS Vaccine?



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