FOIA Number: 2018-0756-F

FOIA MARKER

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Subgroup/Office of Origin: National AIDS Policy Office

Series/Staff Member: Kristine Gebbie

Subseries:

OA/ID Number: 8300

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Folder Title:
National Task Force on AIDS Drug Development [3]

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Withdrawal/Redaction Sheet
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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. resume	[Personally Identifiable Information] [Partial] (1 page)	00/00/0000	b(6)
002. list	re: List of Nominees After January 13, 1994 Meeting (1 page)	01/27/1994	b(6)
003. list	re: Nominees - Female and Other (1 page)	00/00/0000	b(6)
004. memo	Terry Beswick to Kristine Gebbie; re; NTFADD [National Task Force on AIDS Drug Development] Nominees (1 page)	00/00/0000	b(6)
005. bio	re: Descriptions of Nominees - David Baltimore (1 page)	00/00/0000	b(6)
006. bio	re: Descriptions of Nominees - Martin Delaney (1 page)	00/00/0000	b(6)
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RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
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P3 Release would violate a Federal statute [(a)(3) of the PRA]
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Freedom of Information Act - [5 U.S.C. 552(b)]

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NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Tuesday, Nov. 30, 1993

Contact: Victor Zonana
(202) 690-6343

HHS Secretary Donna E. Shalala today announced the formation of a National Task Force on AIDS Drug Development to expedite the search for new therapies against AIDS and the underlying human immunodeficiency virus (HIV).

The expert panel will be highly focused, seeking new and innovative approaches to the development of AIDS drugs.

"The task force has a clear and critical mission: to identify, and remove, any barriers or obstacles to developing effective treatments," Shalala said.

The 15-member panel will be drawn from government, the pharmaceutical industry, academia, medicine and the AIDS-affected communities. "This represents unprecedented high-level collaboration among leaders in the field," Shalala said.

"It is time to refocus and re-energize our best minds for a concerted attack on this killer," Shalala said.

"None of us can guarantee success," Shalala added. "HIV is a vicious and cunning adversary. But history will judge us harshly if we fail to give it our best shot."

Shalala was joined at the announcement by Assistant Secretary for Health Dr. Philip Lee, who will chair the panel; Dr. P. Roy Vagelos, chairman and chief executive officer of Merck & Co. Inc.; Kristine M. Gebbie, national AIDS policy coordinator; and Moises

- More -

Agosto, research and treatment advocacy manager at the National Minority AIDS Council.

Also attending the National Institutes of Health press conference were Dr. David Kessler, commissioner of food and drugs; Dr. Harold Varmus, newly sworn in as director of the National Institutes of Health; and Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases.

"The FDA has made great strides in streamlining the approval process for drugs to treat life-threatening conditions, and the NIH has contributed mightily to our understanding of AIDS and HIV," Shalala said.

"In addition, the Clinton administration and Congress have raised the NIH AIDS research budget 21 percent this year, to $1.3 billion," she added.

"But the sad fact remains that not a single New Drug Application for an antiretroviral drug is currently before the FDA. No matter how much we shorten the pipeline, we cannot achieve our goal unless we start filling that pipeline with promising compounds," Shalala said.

At least one million U.S. citizens are infected with HIV. Some 340,000 have been reported to the CDC with full-blown AIDS, and over 200,000 have died.

"Unfortunately, none of the drugs we have today are curative," Dr. Lee said.

"The task force, which will be appointed by and report to the secretary, will bring together many of the top people in the field.

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"It is time to refocus and re-energize our best minds for a concerted attack on this killer," Shalala said.

"None of us can guarantee success," Shalala added. "HIV is a vicious and cunning adversary. But history will judge us harshly if we fail to give it our best shot."

Shalala was joined at the announcement by Assistant Secretary for Health Dr. Philip Lee, who will chair the panel; Dr. P. Roy Vagelos, chairman and chief executive officer of Merck & Co. Inc.; Kristine M. Gebbie, national AIDS policy coordinator; and Moises

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Agosto, research and treatment advocacy manager at the National Minority AIDS Council.

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"The FDA has made great strides in streamlining the approval process for drugs to treat life-threatening conditions, and the NIH has contributed mightily to our understanding of AIDS and HIV," Shalala said.

"In addition, the Clinton administration and Congress have raised the NIH AIDS research budget 21 percent this year, to $1.3 billion," she added.

"But the sad fact remains that not a single New Drug Application for an antiretroviral drug is currently before the FDA. No matter how much we shorten the pipeline, we cannot achieve our goal unless we start filling that pipeline with promising compounds," Shalala said.

At least one million U.S. citizens are infected with HIV. Some 340,000 have been reported to the CDC with full-blown AIDS, and over 200,000 have died.

"Unfortunately, none of the drugs we have today are curative," Dr. Lee said.

"The task force, which will be appointed by and report to the secretary, will bring together many of the top people in the field.

It will raise the level and intensity of collaboration," Dr. Lee continued.

"The group we envision will be constantly evaluating the process -- identifying obstacles, charting strategy, and asking: 'What are our options? Is anything falling through the cracks? Are we doing everything we possibly can?'" Lee said.

"We're not just talking about antivirals," Dr. Lee added. "We need an across-the-board strategy to develop drugs to treat all aspects of HIV disease. We need immune modulators, anticancer compounds, and agents to treat and prevent opportunitic infections."

"The Centers for Disease Control and Prevention inform me that AIDS and HIV, on average, kill 92 people in this country every day," Shalala said. "With so many people being held hostage by this virus, we must explore all possible options."

Shalala said she expects to begin receiving nominations for task force membership immediately.

Said Gebbie: "The mere creation of a new task force does not halt an epidemic, and if this new group were allowed to become a mere bureaucratic space-filler, it could even become counterproductive. I am confident, however, that neither of these things will occur."

Added Shalala: "This is is not just another government panel appointed to study an issue and write a report that gathers dust.

"I expect the task force to report to me personally, rapidly and regularly, and I pledge to work with all its members to eliminate any obstacles to finding effective treatments," she said.

###

FOR RELEASE UPON DELIVERY
TUESDAY, NOVEMBER 30, 1993

*REMARKS BY

DONNA E. SHALALA

SECRETARY OF HEALTH AND HUMAN SERVICES

PRESS CONFERENCE/NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

BETHESDA, MARYLAND

*THIS TEXT IS THE BASIS OF SECRETARY SHALALA'S ORAL REMARKS. IT SHOULD BE USED WITH THE UNDERSTANDING THAT SOME MATERIAL MAY BE ADDED OR OMITTED DURING PRESENTATION.

GOOD MORNING:

Last week, HHS employees gathered in the Great Hall of the Hubert Humphrey Building to unveil 32 panels from the Names Project AIDS Memorial Quilt.

Today, we gather again -- not to remember the dead, but to fight for the living.

We are here to take a major step toward one of our most important national goals -- the development of effective drugs for the epidemic known as AIDS.

For twelve years, we have lived with a disease that robs us of our future.

AIDS kills our sons and daughters; our husbands and wives; our mothers and fathers; our friends, lovers and loved ones.

The CDC maintains the grim tally: In this country, HIV and AIDS kill 92 people a day, on average. That's right: one AIDS-related death every 15 minutes.

AIDS also kills something in each of us.

It kills our belief that the future will be better than the past.

It kills our hope that our children will lead full and secure lives.

It kills our dreams that we can leave behind a better world.

But we must not despair.

AIDS <u>has not</u> killed our resolve.

AIDS <u>has not</u> killed our determination.

AIDS <u>has not</u> killed our conviction that our collective will, energy and imagination can bring forth a solution.

The Clinton Administration and the Congress have earmarked considerable new resources toward the quest for a cure. For research alone, we've increased the NIH AIDS budget 21% this year, to $1.3 billion.

It is now time to refocus and re-energize our best minds for a concerted attack on this killer. We must lock arms and move forward.

The National Task Force on AIDS Drug Development, which I am announcing today, has a clear and critical mission: to identify, and remove, any barriers or obstacles to developing effective treatment. It will make certain that all possible productive avenues are pursued with vigor.

The members of the task force will be drawn from government, the pharmaceutical industry, academia, medicine and the AIDS-affected communities.

This represents an unprecedented high-level collaboration among leaders in the field.

I'm especially pleased to be joined for this announcement by Dr. P. Roy Vagelos of Merck and Moises Agosto of the National Minority AIDS Council, who in a moment will share their perspectives on this undertaking.

The FDA, represented by its commissioner Dr. David Kessler, has made great strides in streamlining the approval mechanism for drugs against life-threatening conditions.

The NIH, represented by its new leader Dr. Harold Varmus and by N.I.A.I.D. director Dr. Tony Fauci, has contributed mightily to our understanding of HIV and AIDS.

But the sad fact today is that not a single New Drug Application for an anti-retroviral agent awaits FDA approval.

No matter how much we shorten the pipeline, we cannot achieve our goal unless we start filling that pipeline with promising compounds. That is the purpose of the new panel.

I expect to begin receiving nominations for the task force immediately and to name its members promptly.

Let me be clear: This is not just another government panel appointed to study an issue and write a report that gathers dust.

I expect the task force to report to me personally, rapidly and regularly, and I pledge to work with all its members to achieve our objectives.

None of us can guarantee success. HIV is a vicious and cunning adversary. But history will judge us harshly if we fail to give it our best shot.

Now, I'd like to introduce the person I've selected to chair this important task force.

Dr. Phil Lee, the assistant for secretary for health, is one of the greats of public health. He brings to this task force both a comprehensive knowledge of the pharmaceutical industry and a thorough understanding of the complexities of AIDS.

Before joining government, Dr. Lee served as policy coordinator for the Center for AIDS Prevention Studies at UCSF; was chair of the Policy Committee at the American Foundation for AIDS Research; and served as President of San Francisco's Health Commission during four critical years of the epidemic.

Phil will summarize the responsibilities of the task force for you:

REMARKS

PHILIP R. LEE, M.D.

ASSISTANT SECRETARY FOR HEALTH

ADMINISTRATOR OF THE U.S. PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PRESS CONFERENCE ANNOUNCING

THE TASK FORCE ON AIDS DRUG DEVELOPMENT

NOVEMBER 30, 1993

BETHESDA, MARYLAND

Attached is the text prepared for delivery; however, some material may have been added or omitted at the time of delivery.

Thank you. Over the years a number of innovative and creative approaches have been introduced to advance our progress in the search for effective drugs to treat HIV infection and HIV related diseases. However, despite the advances that have been made, it is a fact that no cure has been found and the treatments available are limited in their effect. We can and must do better in developing new drugs needed for persons who are infected with HIV and those who have AIDS and making them available to those who need them.

The Secretary has established a Task Force on AIDS Drug Development to deal both comprehensively and expeditiously with the problem. This is a creative new approach to bring the public and private sectors together to solve one of our most difficult tasks in medicine and public health. As chair of the Task Force, I will do everything possible to assure success in the effort.

The Task Force will have the responsibility of ensuring that all aspects of AIDS drug development are effectively coordinated, that all appropriate avenues of research are pursued, and that all unnecessary barriers to the development of new molecules, new compounds, and new combinations to treat and control HIV infection and HIV-related disease. Every aspect of AIDS Drug Development – from drug discovery, selection of candidates for screening, early clinical development, data-sharing, to the clinical trial process – will come under scrutiny.

The Task Force will establish subcommittees or working groups of experts to take an intensive look at key issues and to return to the task force with specific recommendations. If the recommendations are adopted by the task force, the recommendations will be forwarded to the Secretary for review and implementation.

To continually evaluate strategies and tactics and to build consensus, collaboration is required. Full participation is needed between government agencies, industry, the medical community, academia, and individuals who are HIV infected, as well as those affected by the epidemic. Too often in the past needed links have been missing or relationships have been adversarial, resulting in unnecessary duplication of efforts or potential drugs not being developed and evaluated as rapidly as they might or utilized most effectively.

While working to remove the barriers, the Task Force will not scrap innovative and creative approaches used in the past. The Task Force will build on them. It will build on the innovations that have taken place at NIH. It will build on the regulatory initiatives implemented by the FDA. It will build on community-based efforts to improve the quality and direction of clinical research. And it will build on efforts to bring together people working to find effective treatments of AIDS and HIV-related disease.

From the start, the Task Force will seek input from numerous groups including the Institute of Medicine, the Future Direction of AIDS Research Project, and the many Federal Advisory Committees that have done ground-breaking work in AIDS drug development. Open collaboration and communication are essential to move forward.

The first meeting of the Task Force will be held this winter – or at the latest – in early spring. Over the next thirty days, nominations will be sought from the public as to who should serve. Public nominations will help create a task force that is composed of people with both competence and compassion and the diversity that is reflective of the epidemic.

The Task Force represents a very important step forward and I hope it may be a model for other issues. For the first time in the fight against HIV related disease, the United States will have a systematic over-arching effort to coordinate drug development to treat HIV infection and HIV-related diseases. The Task Force will serve as an example of how government and private leadership can be used to focus national resources on national problems. By working in partnership – the pharmaceutical industry, the not-for-profit sector, private citizens and the government can and will get results.

# # # # #

SELECTED ARTICLES ON HIV INFECTION AND AIDS

PHILIP R. LEE, M.D.
Assistant Secretary for Health
Department of Health and Human Services
Washington, DC

Peter S. Arno, Ph.D.; Douglas Shenson, M.D., M.P.H.; Naomi F. Siegel, M.S.PH; Pat Franks; and Philip E. Lee, M.D., "Economic and Policy Implications of Early Intervention in HIV Disease" JAMA, September 14, 1989-Vol 262, No. 11, pp. 1493-1498.

A.E. Benjamin and Philip R. Lee, "Public Policy, Federalism, and AIDS" Institute for Health Policy Studies, University of California, San Francisco, Death Studies, 12:573-595, 1988.

A.E. Benjamin, Philip R. Lee, and Sharon N. Solkowitz "Case Management of Persons with Acquired Immunodeficiency Syndrome in San Francisco" Health Care Financing Review 1988 Annual Supplement, pp. 69-74.

Anne A. Scitovsky, M.A.; Mary Cline; and Philip R. Lee, M.D. "Medical Care Costs of Patients with AIDS in San Francisco" JAMA, December 12, 1986-Vol 256, No. 22, pp. 3103-3106.

Peter S. Arno, Ph.D. and Philip R. Lee, M.D., Institute for Health Policy Studies, School of Medicine, University of California, San Francisco, CA, "The Federal Response to the AIDS Epidemic" Health Policy, 6 (1986), pp. 259-267.

PHILIP R. LEE, M.D.

Head of the U.S. Public Health Service
and Assistant Secretary for Health
Department of Health and Human Services

Department of Health and Human Services Assistant Secretary Philip Randolph Lee, M.D., leads the U.S. Public Health Service at a time when this country's major national issue is health care reform – how to promote the health of the public through health care reform, how to ensure universal access, how to ensure quality, how to contain rapidly rising costs and how to pay for it. The programs of the Public Health Service that Dr. Lee directs contribute to virtually all those objectives.

Dr. Lee was sworn in as HHS assistant secretary for health on July 2, 1993, after being nominated by President Clinton May 14, 1993, and confirmed by the Senate July 1, 1993.

Dr. Lee brings to his new post more than four decades of involvement in health care and public health policy.

Twenty-eight years ago (November 1965), Dr. Lee was sworn in as assistant secretary for health and scientific affairs under President Johnson. In his first two years as assistant secretary, from 1965 to 1967, Congress enacted more health legislation than all the previous Congresses put together. Not since that period has the public's health and health care reform been such a huge priority on the nation's agenda.

Among his activities as assistant secretary in the 1960s, Dr. Lee helped fashion health manpower, family planning, health care, consumer protection, environmental health and biomedical research policies.

Before his first appointment to the top Public Health Service role, Dr. Lee served as director of health services in the Agency for International Development. Prior to his government service, he was a staff member at the Palo Alto Medical Clinic in California, and before that a fellow at the Mayo Clinic and Bellevue Medical Center. Dr. Lee's clinical experience enhances his commitment to public health policy and improving both care and access to care.

Dr. Lee has served with distinction as director of the Institute of Health Policy Studies, School of Medicine, at the University of California, San Francisco, for the past 21 years. In these years, he has, as a colleague recently said, worked with and influenced *hundreds* of health care policymakers and researchers, many of whom name Dr. Lee as their mentor. Since 1969, Dr. Lee has been a professor of social medicine at UCSF.

Dr. Lee has frequently advised federal and state health groups, and served on numerous advisory boards and planning committees. In 1985, then-San Francisco Mayor Dianne Feinstein named him as the first president of the city's Health Commission, which was the governing body in the city/county health department that included public health, mental health and substance abuse services, as well as the San Francisco General Hospital (the major AIDS care facility in the city), and a 1,000-bed long-term care facility.

In 1986, when Congress set up the Physician Payment Review Commission to examine reimbursement of physicians under Medicare, Dr. Lee was named to head the commission. The commission worked closely with Congress and many physician groups, consumer groups and others in shaping the physician payment reform adopted by Congress in 1989. Dr. Lee resigned from the commission early this year after being asked by President Clinton to serve as assistant secretary for health.

Until 1993 and his confirmation as assistant secretary, Dr. Lee served on the board of trustees of several California-based organizations representing a variety of public interests: the Henry J. Kaiser Foundation, Jenifer Altman Foundation, World Institute on Disability, and the Glide Foundation of the Glide Memorial United Methodist Church. Also, from 1971 to 1979, Dr. Lee served on the Board of Trustees of the Carnegie Corporation of New York.

Dr. Lee was a member of the editorial boards of the health policy journal *Milbank Quarterly* and of the *Annals of Internal Medicine* until assuming his recent Public Health Service responsibilities.

The Public Health Service includes eight agencies that lead the world in health care for the underserved, in biomedical research, in food and drug safety and in disease control. These agencies are the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Agency for Toxic Substances and Disease Registry, the Health Resources and Services Administration, the Indian Health Service, the Substance Abuse and Mental Health Services Administration, and the Agency for Health Care Policy and Research.

Also located in the Office of the Assistant Secretary are the Office of the Surgeon General, the National Immunization Program Office, the Office of Population Affairs, the Office of Minority Health, the Office of Women's Health, the Office of Disease Prevention and Health Promotion, the Office of International Health and the National AIDS Program Office.

Dr. Lee also advises and assists HHS Secretary Donna Shalala on health policy and on all health-related activities of the department. He has played an active role in the health care reform task force.

Dr. Lee received an A.B. from Stanford University in 1945, an M.D. from Stanford in 1948, an M.S. from the University of Minnesota in 1955, and an honorary Sc.D. from MacMurray College in 1967.

Dr. Lee lives in Washington, D.C. His wife, Professor Carroll Estes, also of the University of California, is a world-recognized expert in aging and long-term care policy. Dr. Lee has five children, a stepdaughter and five grandchildren.

July 1993

FOOD AND DRUG ADMINISTRATION

AIDS DRUG DEVELOPMENT INITIATIVES

I. EXPANDED ACCESS AND ACCELERATED PROCEDURES

FDA has taken significant steps toward making experimental drugs for HIV/AIDS more widely available and has initiated expedited procedures to speed the review and approval of promising therapies for HIV/AIDS.

1. Expanded Access Mechanisms

Expanded access mechanisms are designed to make promising products available as early in the drug evaluation process as possible. Expanded access mechanisms include Treatment IND protocols and parallel track protocols. In addition, the ordinary development of drugs under an IND includes a variety of open studies that also provide access to drugs. To date, tens of thousands of people have received products under expanded access mechanisms.

- o Treatment INDs

  Final regulations were issued in May of 1987 establishing conditions under which promising new drugs and biologics that have not yet been approved or licensed may be made available to persons with serious or life-threatening illnesses. Treatment INDs have generally been granted when the product is well into the clinical testing phase or when all clinical trials have been completed, after the development of some reliable evidence that the product is effective. Nine Treatment IND protocols for promising AIDS-related products have been allowed to proceed since the Treatment IND regulations became effective.

- o Parallel Track

  The final PHS policy statement on the parallel track mechanism was published in the Federal Register on April 15, 1992. The purpose of the parallel track policy is to expand the availability of promising investigational drugs to those persons with AIDS and HIV-related diseases who are without satisfactory alternative therapy and who cannot participate in controlled clinical trials. Stavudine (d4T) was the first drug submitted for consideration under the parallel track policy. The protocol was allowed to proceed on October 5, 1992.

2. Expedited Procedures

- In 1987, FDA created a "AA" priority category to classify all applications for potential AIDS therapies to ensure that these products receive the highest priority in the review process.

- In October, 1988, FDA issued interim regulations designed to expedite marketing approval of new drugs intended for life-threatening and severely-debilitating diseases, by facilitating the clinical testing and evaluation processes. Under the expedited procedures, early consultation with FDA by drug manufacturers, with agreement on the proper design of clinical trials, can lead to phase 2 studies with adequate data to support approval. In some instances, then, the need for Phase 3 testing can be virtually eliminated.

- On December 11, 1992 FDA published the final rule to accelerate the approval of new drugs for serious and life-threatening diseases when the drug provides meaningful therapeutic benefit over existing products. Under these procedures FDA may approve drugs based on surrogate endpoints that reasonably predict that a drug provides clinical benefit. This clinical benefit is then confirmed through additional human studies that will be carried out after marketing approval. The accelerated approval approach provides for removal of the drug from the market if further studies do not confirm the clinical benefit of the therapy.

II. STATUS OF AIDS PRODUCTS UNDER REVIEW

As of September 30, 1993, FDA had received over 500 IND applications for more than 150 products to be used in the treatment of HIV/AIDS. Many of the ongoing clinical trials are using combinations of two or more agents.

III. APPROVED THERAPIES FOR AIDS OR AIDS-RELATED CONDITIONS

FDA has approved 14 applications for products to treat HIV/AIDS. Three drugs are to treat HIV infection and eleven are to treat HIV/AIDS-related illnesses. There are no antiretroviral new drug applications pending review at FDA.

- **Zidovudine** (formerly AZT) - the first drug to go through the "AA" priority review designation, approved March, 1987 to treat AIDS.

- **Human Interferon alpha**, approved November, 1988 for the treatment of Kaposi's Sarcoma, a cancer affecting many

persons with AIDS.

- **Aerosolized pentamidine**, approved June, 1989, for the prevention of Pneumocystis carinii pneumonia in immunocompromised patients.

- **Ganciclovir**, approved June 1989, for the treatment of cytomegalovirus retinitis, a sight-threatening opportunistic infection from AIDS.

- **Fluconazole**, approved January, 1990, for use in the treatment of candidiasis and cryptococcal meningitis which are fungal infections.

- **Erythropoietin**, approved December, 1990, for the treatment of zidovudine-related anemia.

- **Foscarnet**, approved September, 1991, for use in the treatment of cytomegalovirus retinal infections in persons with AIDS.

- **ddI (didanosine)**, approved October 1991, for the treatment of adult and pediatric patients (over 6 months of age) with advanced HIV infection who are intolerant of zidovudine therapy or who have demonstrated significant clinical or immunologic deterioration during zidovudine therapy.

- **ddC (zalcitabine)**, approved June 1992, for use in combination with zidovudine (AZT) as a treatment option for adult patients with advanced HIV infection who show signs of clinical or immunological deterioration.

- **Itraconazole**, approved September 1992, for the treatment of blastomycosis and histoplasmosis in immunocompromised and non-immunocompromised patients.

- **Atovaquone**, approved November 1992, for the treatment of mild to moderate PCP in patients who are intolerant of trimethoprim-sulfamethoxazole, the standard therapy.

- **Dronabinol**, approved December 1992, (supplemental application) for anorexia and weight loss associated with AIDS.

- **Rifabutin**, approved December 1992, for the prophylaxis of Mycobacterium avium complex, a severe infection that often afflicts AIDS patients.

- **Megestrol acetate**, approved September 1993, (supplemental application), for anorexia, cachexia, or an unexplained weight loss in patients with AIDS.

NATIONAL INSTITUTES OF HEALTH

AIDS DRUG DEVELOPMENT AND EVALUATION INITIATIVES

Drug Development

The clinical evaluation of drugs against HIV, HIV-associated opportunistic infections (OIs), and HIV-associated malignancies requires an active preclinical drug discovery and development program. The NIH supports two major approaches in the area of drug development, including screening and rational (targeted) drug programs. The screening approach involves the testing of natural and synthetic compounds for anti-HIV activity. Rational (targeted) drug development involves characterization and delineation of the structural biology of HIV for the purpose of developing agents targeted to inhibit specific steps in the HIV life cycle. These programs have resulted in the discovery and development of AZT, ddI, ddC, d4T, and recombinant soluble CD4.

During the past year, the National Cancer Institute (NCI)-sponsored Preclinical AIDS Drug Screening Program has approved six new drugs for Phase I clinical studies. Approximately 137,000 agents have been screened for anti-HIV activity to date through this program. A new panel of screening cell lines is being developed for screening agents for activity against HIV-related malignancies, in particular HIV-related lymphomas.

The National Cooperative Drug Discovery Groups (NCDDG) and the National Cooperative Drug Discovery Groups for the Treatment of the Opportunistic Infections Associated with AIDS (NCDDG-OI) have expanded efforts to discover and develop potential treatments for HIV infection and HIV-associated OIs. The Targeted Antiviral Program provides extramural investigators with access to sophisticated techniques, while a similar program has been established for NIH intramural scientists through the Intramural AIDS Targeted Antiviral Program.

Planned programs:

- continue to screen, discover, develop, and preclinically test novel therapeutic agents that demonstrate activity against retroviruses, HIV-associated malignancies, and TB;
- bring the most promising new drugs into clinical testing;
- expand the development and validation of *in vitro* and animal model testing systems for evaluation of combination therapeutic agents;
- develop *in vitro* systems to evaluate novel combination therapies to overcome single drug resistance;

- develop therapies and interventions to prevent maternal-fetal transmission;
- perform preclinical testing of immune-based therapies in combination with traditional antiretroviral therapies; and
- delineate the crucial issues in advancing gene therapy into clinical trials.

Drug Development and Evaluation of Agents to Treat Opportunistic Infections

The NIH, through its intramural and extramural programs, has developed a multifaceted approach for the discovery, development, and preclinical and clinical evaluation of anti-OI drugs. Priority is placed on the identification of effective agents where established therapies do not exist and on the evaluation of new agents with the potential to improve efficacy or reduce toxicities of existing treatment or prophylactic regimens. OIs represent the most common cause of morbidity and mortality of HIV-infected patients. Approximately 26 percent of the current National Institute of Allergy and Infectious Diseases (NIAID)-funded AIDS Clinical Trials Group (ACTG) protocols are evaluating anti-OI therapies. There are 11 active OI protocols in the Community Programs for Clinical Research on AIDS (CPCRA). The increasing incidence of TB in HIV-infected populations is a public health priority. (A separate report has been prepared describing the NIH planned research activities on tuberculosis.)

The priority scheme for both preclinical and clinical activities associated with OIs is as follows:

Level 1 Priority	*Mycobacterium tuberculosis* *Mycobacterium avium* complex (MAC) Multiple Opportunistic Pathogens Prophylaxis Study (MOPPS) *Cryptosporidium*, Microsporidia, and other infectious causes of wasting
Level 2 Priority	Cytomegalovirus *Toxoplasma gondii* *Pneumocystis carinii*
Level 3 Priority	Pathogenic fungi (*Cryptococcus*, *Histoplasma*, and Candida)
Level 4 Priority	Other viral opportunists, other selected endemic mycoses, and serious bacterial infections.

Changes in Developing Agents for Treating Opportunistic Infections

Biomedical research on opportunistic infections (OIs) is challenged by the limited knowledge of the basic biology and natural history of these micro-organisms; the need for *in vitro* culture systems for susceptibility testing and biochemical studies; the lack of targeted screens or rational design of new agents; the need for optimization of animal models for testing treatment and prophylactic regimens; the need for evaluation of drug combinations for efficacy and safety, drug interactions, pharmacology, and immunotoxicology; and the relatively low level of interest shown by pharmaceutical manufacturers in the development of anti-OIs.

Planned activities:

- target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs;
- intensify basic biological studies on OIs;
- improve anti-OI drug evaluation methods such as rapid susceptibility testing, animal models, and outcome assessments;
- develop and standardize rapid diagnostic assays for OIs; and
- development valid animal and *in vitro* models of OIs for use in evaluating potential therapeutic agents administered singly and in combination.

Specific preclinical and clinical projects planned for each of the prioritized OIs are as follows:

MAC - discover and develop improved therapeutic modalities; determine the correlation between mycobacteremia and tissue organ burden; characterize the natural history of infection; and determine the optimal timing for treatment and prophylaxis assessing selected drug combinations.

MOPPS - including *Mycobacterium avium, Pneumocystis carinii*, the pathogenic fungi, *Cryptosporidium*) - establish the methods and procedures for evaluating the compatibility and effectiveness of agents (e.g., fluconazole, itraconazole, atovaquone, rifabutin, dapsone, TMP/SMX, ganciclovir, clarithromycin, and azithromycin) likely to be used in combination; assess drug resistance development; and initiate prophylaxis studies on multiple opportunistic pathogens.

Infectious Causes of Wasting Syndrome - identify and develop effective treatments (e.g., paromomycin, letrazuril and albendazole) for *Cryptosporidium*, Microsporidia, and other infectious causes of this syndrome; and develop *in vitro* and *in vivo* models for evaluation of drugs.

Cytomegalovirus - evaluate new, improved therapies (e.g., atovaquone, oral ganciclovir, and foscarnet) singly and in combination for the prevention and suppression of CMV infection including CMV retinitis and CMV colitis.

Toxoplasma gondii - establish an animal model for encephalitis; focus drug discovery efforts on the *Toxoplasma* bradyzoite; identify effective therapies including azithromycin + pyrimethamine, atovaquone + new macrolides for the prevention and treatment of toxoplasmosis.

Pneumocystis carinii - further define the biology and natural history of this infection; support targeted projects in drug discovery; develop new diagnostic techniques; and support prophylaxis and treatment trials with new approaches.

Pathogenic Fungi - identify diverse fungal targets for development of antifungal agents; optimize therapies for the treatment and prophylaxis regimens including evaluation of fluconazole, amphotericin B, and clotrimazole; monitor development of drug resistance; and optimize treatment strategies for cryptococcal meningitis.

Other Opportunistic Infections - Continue ongoing research efforts with other opportunistic micro-organisms; and initiate treatment and prophylaxis studies of selected opportunistic micro-organisms, such as viruses, bacteria, mycoplasma, and endemic mycoses.

Clinical Trials

The NIH has the primary responsibility for the federally supported clinical trial efforts to evaluate potential therapies for the treatment of HIV infection and its sequelae. These trials are conducted at 57 AIDS Clinical Trials Units (ACTUs) supported by the NIAID-funded ACTG (including 22 NIAID-funded Pediatric ACTUs), 17 NIAID-funded CPCRAs, 50 Division of AIDS Treatment Research Initiative (DATRI) sites, 28 NICHD-funded sites, and 3 NIH Intramural sites. Over 40,000 patients have been enrolled in these studies, which have involved the evaluation of more than 70 agents.

Accomplishments in NIH-sponsored clinical trials include demonstration of the efficacy and clinical benefits of AZT for adults and children with early and asymptomatic infection; the benefits of ddI resulting in expanded approval for patients who have been on AZT for prolonged periods of time; the benefits of interferon-alpha for reducing Kaposi's sarcoma lesions; early evidence of the benefits of nimodipine for the treatment of AIDS dementia complex; and the therapeutic benefits of ddC plus AZT combination therapy and FDA approval of the regimen. ddI and d4T have been made available through expanded access programs.

Accomplishments in combating HIV-associated OIs include demonstration of the efficacy of atovaquone (566C80) for treatment of *Pneumocystis carinii* pneumonia (PCP) in patients seriously intolerant of trimethoprim-sulfamethoxazole (TMP-SMX); TMP-SMX for prophylaxis of recurrent PCP; aerosolized pentamidine for prophylaxis and treatment of PCP; fluconazole for the treatment of cryptococcal meningitis; foscarnet for the treatment of CMV retinitis; IV gamma globulin for reducing OIs in HIV-infected children with CD4 + counts >200/mm3; early evidence on the combination of pyrimethamine and clindamycin for toxoplasmic encephalitis; and itraconazole for disseminated histoplasmosis.

Planned Clinical trials:

- evaluate multi-drug regimens, *tat* antagonists, reverse transcriptase inhibitors, protease inhibitors, potential immune-based therapies, passive immunotherapy, and chemotherapeutic agents against HIV-associated malignancies;
- evaluate interventions targeted at acute/early infection with the goal of building the infrastructure for primary infection intervention trials;
- evaluate potential therapies for treating and preventing CNS impairment and AIDS dementia complex (ADC);
- evaluate agents against the HIV-related wasting syndrome;
- evaluate novel therapies, upon their availability, to block maternal-fetal transmission; and
- identify, develop, and validate surrogate markers for demonstration of efficacy of therapeutic agents.

Participation of Under-represented Populations

The participation of specific populations in NIH-funded clinical trials reflects the changing demographics of HIV infection, an illness initially affecting homosexual and bisexual men but currently appearing with increasing incidence in women, children, adolescents, IDUs, and minority populations. Ongoing efforts within the ACTG are designed to assure participation of under-served and underrepresented populations in NIH-funded clinical trials. Other efforts to increase the participation of these populations include implementation of the CPCRA, which has dramatically increased NIAID's enrollment of underrepresented minorities and women in HIV therapeutic trials; establishment of Women's Health Committees within the ACTG and CPCRA organizations; provision of supplements to the ACTG for outreach activities toward these populations; addition of four minority institutions as fully functional ACTUs; implementation of institutional evaluations of ACTG and CPCRA sites to ensure participation of underrepresented populations; establishment of community advisory boards for each ACTG and CPCRA site. In addition, the recent recompetition of the ACTG adult and pediatric units required plans for enrollment representative of the population served by the applicant institution.

Planned initiatives:

- increase participation of urban poor, minorities, women, children, adolescents, IDUs, and rural residents in clinical trials.

THE WHITE HOUSE

WASHINGTON

Statement of
Kristine M. Gebbie, R.N., M.N.
National AIDS Policy Coordinator
at
Press Conference Announcing
National Task Force on AIDS Drug Development

As the National AIDS Policy Coordinator, I am charged with promoting the higest levels of coordination and collaboration in the nation's response to the effect of the HIV/AIDS pandemic on individuals, families, and private and government institutions. The focal point of my efforts include, research, prevention and care.

Over the past several months, representatives of the Department of Health and Human Services (DHHS) have participated in forums with academicians, AIDS advocacy groups, and the pharmaceutical industry on AIDS research improvement. Out of those sessions have come several ideas on public-private partnerships for information sharing and research that can speed the pace of discovery in our effort to find a cure for AIDS. The establishment of this new Drug Development Task Force is one example of the type of improvement anticipated by many of us.

By bringing together those conducting research on drugs to combat HIV infection from the pharmaceutical industry, the

academic community, individuals with HIV infection and those advocating on their behalf, and key agencies of the federal government, DHHS formalizes channels of communication among the partners who must be involved to successfully bring new drugs into use. Working together, these partners can identify barriers to quick action or clear communication, and can act in common to eliminate those barriers.

The mere creation of a new task force does not halt an epidemic, and if this new group were allowed to become a mere bureaucratic space-filler, it could even become counter-productive. I am confident, however, that neither of those things will occur. Instead, the steadily strengthening collaboration among all parties concerned about AIDS gives me great confidence that this is one more important step toward our collective goal of stopping AIDS.

HARVARD AIDS INSTITUTE

Chairman
M. Essex, DVM, PhD

Executive Director
Richard Marlink, MD

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December 20, 1993

DEC 21

TO Terry

Ms. Kristine Gebbie
National AIDS Policy Coordinator
750 17th Street, NW, Suite 1060
Washington, DC 20503

Dear Kristine:

It was great to see you in Marrakech last week! Those AIDS in Africa meetings are always very interesting and full of their own politics. I hope you got back okay.

I'm enclosing a blind copy of a letter Max Essex sent to Donna Shalala concerning his recommendation that I serve as a member of the newly-formed task force. I hope this is something you approve of, especially in view of my being a person on the task force with a non-governmental link to the FDAR process.

All the best for the upcoming holidays.

Sincerely,

Ric

Ric Marlink

RM:lc
enclosures

HARVARD SCHOOL OF PUBLIC HEALTH
Chairman, Department of Cancer Biology

HARVARD AIDS INSTITUTE
Chairman

M. Essex, D.V.M., Ph.D.
Mary Woodard Lasker Professor of Health Sciences

December 16, 1993

The Honorable Secretary Dr. Donna Shalala
Department of Health & Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Shalala:

I am writing to nominate an academic physician to serve on the newly formed Task Force on AIDS and Drug Development. I strongly recommend Dr. Richard Marlink, as he has perhaps the broadest experience with AIDS research and clinical issues of any individual I know in the fight against this epidemic.

Dr. Marlink has been involved in the clinical care of people with AIDS since the beginning of the epidemic. After training in New York City, he became instrumental in the initial clinical effort here in Boston. He also became involved in collaborative research with IVDU populations in Massachusetts and continues to coordinate a clinical AIDS research program in Senegal. In these collaborations he has helped to bring solutions from the laboratory bench to actual field applications through development of new assays and diagnostics suitable for clinical field testing. His experience in identifying gaps and overcoming obstacles in translating laboratory findings into clinical products would seem to be an important asset for the task force.

Dr. Marlink also has extensive experience in conducting virological research of HIV. In addition, he is a hematologist/oncologist and has worked in the clinical trial networks established for both AIDS and medical oncology.

Perhaps the most important reason for my recommending Dr. Marlink for membership on the task force, however, is his leadership role at the Harvard AIDS Institute. As executive director of the Harvard AIDS Institute for the past two years, Dr. Marlink has led the Institute in creating real solutions for those affected by the epidemic by capitalizing on the vast amount of basic and clinical research on AIDS at Harvard. His skill at working behind the scenes to make things happen has been unparalleled. Over a year ago, for example, he initiated a national evaluation of our research priorities. He was motivated by two central concerns: (1) the past presidential AIDS commissions and other venues have discussed primarily clinical care, prevention, and social issues, yet have not included a "national discussion" about how we can do better in basic science and how we can develop better AIDS treatments; and (2) it had become obvious that existing AIDS treatments were sub-optimal, and promising treatments were not coming to fruition. Dr. Marlink therefore developed a program—now known as the Future

Telephone: 617-432-1 23 Facsimile: 617

Directions in AIDS Research—and collaborated with the University of Wisconsin and Project Inform to develop a unique set of meetings, of which you have been aware since the first meeting in Madison. I remember discussing the concept last year in my conversations with Al Carnesdale (dean of the Kennedy School here) and Dr. Marlink; but it was really Dr. Marlink who formulated the concept and ensured that it became a reality.

I hope that you and Dr. Lee will seriously consider Dr. Marlink for membership on the National Task Force on AIDS and Drug Development. With his background, experience, and ability to act as a bridge between the Future Directions in AIDS Research group and the task force, he would be an ideal candidate. He not only possesses the high level of energy that would be required to help forge the solutions and agreements needed in developing effective AIDS treatments, but he is also very personable. He is one of those rare colleagues who gets along well with everyone and is skilled at ensuring that consensus is achieved. I have enclosed his curriculum vitae; please do not hesitate to call me if you have any questions.

Sincerely,

Max Essex

Max Essex, PhD, DVM

ME:lc
enclosure
cc: Dr. Philip Lee
Dr. Randolph Wykoff

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CURRICULUM VITAE

PERSONAL DATA

Name: **RICHARD GEORGE MARLINK**

Address: 18 Falmouth St., Belmont, Massachusetts 02178

Born: (b)(6)

EDUCATION

Date	Discipline	Degree	Institution
1976	Human Biology	B.A.	Brown University Providence, Rhode Island
1980	Medicine	M.D.	University of New Mexico Albuquerque, New Mexico

EXPERIENCE

[001]

Date	Field of Activity	Place	Title
1991 - present	AIDS Research & Education	Harvard AIDS Institute Cambridge, Massachusetts	Executive Director
1989 - present	Cancer Biology	Harvard School of Public Health, Boston, Massachusetts	Senior Research Director/ Lecturer
1987 - 1988	Cancer Biology	Harvard School of Public Health, Boston, Massachusetts	Research Associate
1984 - 1985	Hematology & Oncology	Harvard Medical School, New England Deaconess Hospital, Boston, Massachusetts	Clinical Fellow
1981-83	Primary Care Track	University of New Mexico, Albuquerque, New Mexico	Internal Medicine Residency
1980-81	Medicine	St. Vincent's Hospital New York, New York	Rotating Internship

HONORS AND AWARDS

1976 B.A. *magna cum laude*, Brown University; Phi Beta Kappa, Brown University Chapter; Sigma Psi, Honorary Scientific Society, Brown University Chapter.

PROFESSIONAL CERTIFICATIONS

1989 Diplomate, American Board of Medical Oncology
1988 Eligible, American Board of Hematology
1988 Instructor, Advanced Trauma Life Support
1986 Instructor, Advanced Cardiac Life Support
1984 Diplomate, American Board of Internal Medicine
1983 Medical Licensure, Massachusetts
1981 Diplomat, National Board of Medical Examiners
1976 Emergency Medical Technician

PROFESSIONAL ACTIVITIES

Associate Staff, New England Baptist Hospital
Associate, American College of Physicians
Reviewer for *AIDS*, *AIDS and Human Retroviruses*, *Cancer*, *Journal of AIDS*
Member, Organizing Committee for VIII International Conference on AIDS
Member, Organizing Committee for VI International Symposium on AIDS in Africa
Curriculum Committee, Brown University, 2 years
Curriculum Committee, University of New Mexico School of Medicine, 3 years

MEMBERSHIPS

American Association for the Advancement of Science; American Society of Clinical Oncology; Physicians for Social Responsibility; American College of Physicians; International AIDS Society

CLINICAL RESEARCH

Alpha interferon phase II trials for Kaposi's sarcoma, melanoma and renal cell carcinoma. Co-investigator; Deaconess Hospital, Boston, MA, 1985.

AZT and Suramin in phase I/II trials. Co-investigator; Deaconess Hospital, Boston, MA, 1986-1988.

West African clinical studies concerning HIV-1 and HIV-2. Senior Research Project Director: Harvard School of Public Health, Boston, MA, and Dakar, Senegal, 1989-present.

TEACHING

1987-93	Directed tutorial research of four post-doctoral fellows; Teaching responsibilities—Harvard School of Public Health, AIDS curriculum faculty.
1985-92	Grand Rounds at Beth Israel Hospital; Beverly Hospital; Cambridge Hospital; Goddard Hospital; Joslin Clinic; Joint Centers for Radiation Therapy, Harvard University; New England Deaconess Hospital; Therapeutic Radiology Department, Tufts, N.E.M.C.; Winchester Hospital; Shadduck Hospital.
1981-86	Teaching responsibilities of Medical Residency and Hematology/Oncology Fellowship, U.N.M. Hospital and New England Deaconess Hospital.

1975-76 Teaching Associate—"Experimental Embryology," graduate level. Brown University.

1975-76 Teaching Associate—"Comparative Anatomy," graduate level. Brown University.

1977-79 "Alternative Systems of Health Care Delivery," initiated and developed this elective course, U.N.M. School of Medicine.

1977-79 Organizer—"Medical Ethics Seminar," initiated and organized series. U.N.M. School of Medicine.

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INVITED SEMINARS AND SCIENTIFIC MEETINGS

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February 3-5, 1986; Kuwait, Kuwait; First International WHO Conference on AIDS in the Middle East, "Structure and Pathogenesis of HTLV-III/LAV."

February 3-5, 1986; Kuwait, Kuwait; First International WHO Conference on AIDS in the Middle East, "Diagnosis and Treatment of Hematologic and Oncologic Complications of HTLV-III/LAV."

June 5, 1986; Boston, MA; National Tumor Registrars Assoc., 12th Annual Meeting, "AIDS—A Clinical Update."

November 14, 1986; Birmingham, AL; American Society for Microbiology, "Biology of Simian T-Lymphotropic Viruses and Related Human Retroviruses."

February 11-12, 1987; Geneva, Switzerland; WHO Meeting on Newly Identified HIV-Relative Retroviruses, "HIV-2 in West Africa - The Clinical and Immunological Manifestations."

June 4, 1987; Washington, DC; III Int. Conf. on AIDS, "High Rate of HIV Exposure in IVDA's from a Small-Sized City and the Use of a Specialized Methadone Maintenance Program to Educate and Reduce High Risk Behavior."

December 11-12, 1987; Dakar, Senegal; Inter-University Convention on Prevention of AIDS and Other Viral Diseases, "Clinical Update on AIDS: HIV-1 and HIV-2."

February 15-17, 1988; Woods Hole, Massachusetts; International Health Programs of Harvard School of Public Health, Workshop on "AIDS and Reproductive Health: Research Priorities of an International Scientific Network."

February 26, 1988; Durham, New Hampshire; University of New Hampshire Center for International Perspectives, "New Human Retrovirus in West Africa: A New AIDS Epidemic?"

May 9-11, 1988; Milford, Massachusetts; Massachusetts Association of Blood Banks-16th Annual Seminar, "Human Retroviruses: An Overview of the Alphabet Soup."

April 23, 1989; Lubumbashi, Zaire; Second Symposium and Workshop on AIDS and other Retroviral Diseases, "Adult AIDS in the United States."

May 4, 1989; Boston, Massachusetts; Massachusetts General Hospital Ether Dome Seminars, "Epidemiology of AIDS in Developing Countries."

May 22-24, 1989; Geneva, Switzerland; WHO Working Group on HIV-2.

August 20-26, 1989; Bethesda, Maryland; Annual Meeting of the Laboratory of Tumor Cell Biology, National Cancer Institute, "Is HIV-2 Less Pathogenic Than HIV-1?"

August 20-26, 1989; Bethesda, Maryland; Annual Meeting of the Laboratory of Tumor Cell Biology, National Cancer Institute, "Epidemiology of HIV-2 in Prostitutes in Senegal."

November 30, 1989; Washington, D.C.; Walter Reed Army Institute of Research Workshop, "Epidemiology of HIV-2 in West Africa."

September 20-22, 1990; Taipei, Taiwan; Human Retrovirology Conference: HIV and HTLV, "HIV-Related Malignancies and Their Treatment."

September 27-29, 1990; Mexico City, Mexico; National Institutes of Health Program on AIDS and Cancer, "Epidemiology, Etiology and Treatment of Kaposi's Sarcoma."

October 9, 1990; Kinshasa, Zaire; WHO Workshop on WHO Staging System of HIV Infection in an African Context, "How to Develop a Staging System Adapted to the Needs of Developing Countries."

December 10, 1990; Boston, Massachusetts; Boston University School of Public Health Program on AIDS: Medical, Economic Psychosocial and Legal Issues; "International Perspective of AIDS."

June 6, 1991; Atlanta, Georgia; CDC International Seminar Series, "Immunologic and Clinical Outcome of HIV-2 versus HIV-1 Infection."

May 15-17, 1992; Taipei, Taiwan; II International Formosa AIDS Conference 1992, "AIDS Therapy 1992: Lessons from Medical Oncology."

July 19-24, 1992, Amsterdam, The Netherlands; VIIIth International Conference on AIDS/IIIrd STD World Congress.

June 6-11, 1993, Berlin Germany, IXth International Conference on AIDS/IVth STD World Congress.

December 12-16, 1993, Marrakech, Morocco; VIIIth International Conference on AIDS in Africa/VIIIth African Conference on Sexually Transmitted Diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

ASSISTANT SECRETARY
FOR PUBLIC AFFAIRS

July 27, 1993

NOTE TO: Christine Gebbie
AIDS Coordinator

RE: AIDS Drug Development Task Force

This proposal has been signed off on by all parties. I wanted you to have a look at it and offer your thoughts before we set up a press conference to make the announcement.

Avis LaVelle

Avis LaVelle

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

June 4, 1993

MEMORANDUM

TO: The Secretary
Through: DS_____
COS_____
ES_____
Acting ASH_____

FROM: David A. Kessler, M.D., FDA
Anthony S. Fauci, M.D., NIH

SUBJECT: National Task Force on AIDS Drug Development--ACTION

ISSUE

The purpose of this memorandum is to request your review and approval of a proposal to create a National Task Force on AIDS Drug Development by the Department of Health and Human Services in conjunction with the President's Domestic Policy Advisor for AIDS. The objective of the task force is to ensure continuity, enhance cooperation, eliminate barriers, and establish a national strategy in all aspects of the development of treatments for AIDS and HIV-related diseases.

BACKGROUND

A number of innovative and creative approaches have been developed and implemented in the effort to find effective treatments and preventatives for HIV-related diseases. These have included a broad range of efforts on the parts of the Public Health Service, private industry and community advocacy organizations, as well as a number of important reviews of critical aspects of drug development conducted by both governmental and non-governmental bodies. There has not, however, been a systematic over-arching effort to ensure that all aspects of drug development--from initial drug discovery to the use of the product in the clinical setting --are rapidly taking place in a coordinated manner, free of unnecessary barriers.

PROPOSAL

The proposal calls for the creation of a Task Force on AIDS Drug Development that would be created, and charged, by the Secretary of the Department of Health and Human Services and the President's Domestic Policy Advisor for AIDS. The chairperson of this task force would be the Assistant Secretary for Health while the vice chairs of the task force would be

Dr. David A. Kessler, Food and Drug Administration, and Dr. Anthony S. Fauci, National Institutes of Health. The task force would be composed of a cross section of those involved in AIDS drug development, including representatives of the pharmaceutical industry, clinical researchers, practicing physicians, and community-based advocacy (see proposed list at Tab A). Additionally, the membership of the task force may be periodically supplemented to meet the needs of a particular topic area. The task force would meet frequently and would provide for both broad public testimony and public deliberation. Immediately after announcement of the task force, the chairperson and vice chairs will meet to finalize organization and establish administrative mechanisms for accomplishing goals.

It would be the responsibility of the task force to ensure that all aspects of AIDS drug development are effectively coordinated, that all appropriate avenues of research are pursued, and that all unnecessary barriers to effective development and utilization of treatments for AIDS are eliminated. Suggested topics for consideration by the task force are provided at Tab B.

We recognize that this task force would constitute an advisory committee and, as such, would be subject to all requirements and restrictions applying to advisory committees, including the recent Executive Order to reduce their number. However, because the White House has expressed interest in being involved in this task force, we believe that its formation could be justified. If you agree with this proposal, we will assemble a full committee management package with a proposed slate of candidates as well as a memorandum for your signature to the Office of Management and Budget requesting concurrence for a new advisory committee.

RECOMMENDATION

I recommend that you approve the formation of the National Task Force on AIDS Drug Development.

DECISION

Approved_____ Disapproved_____ Date_____

Anthony S. Fauci, M.D. David A. Kessler, M.D.

2 Attachments:
Tab A - Task Force Proposed Membership
Tab B - Suggested Topics for Consideration

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

PROPOSED MEMBERSHIP

PANEL CHAIR: The Assistant Secretary for Health

CO-CHAIRS: Anthony S. Fauci, M.D., NIH
David A. Kessler, M.D., FDA

MEMBERSHIP:
- Five leading AIDS researchers/Chief Executive Officers from the Pharmaceutical Industry
- Five leading AIDS researchers from academia, AIDS Clinical Trials Groups, and community-based research sites
- Five leading experts in AIDS drug development from the NIH, FDA, and other governmental bodies
- Five community-based AIDS advocates

Additional membership would include AIDS-experienced clinicians, representatives from third party payers, and representatives from trade associations/professional organizations.

PROPOSED TOPICS FOR CONSIDERATION

Barriers to drug development
- use of effective animal models
- the use of surrogate end-points in early clinical trials
- use of observational data bases
- prophylactic treatments for opportunistic infections
- studies involving pregnant women
- including minorities and women in clinical trials

Barriers to novel medical intervention
- immunomodulators
- preventative vaccines
- combination products and treatment regimens
- products to prevent perinatal transmission
- products for treating HIV in childhood
- clinical trials in patients with early disease

Accelerated Review and Approval Procedures
- predicting clinical relevance from pre-clinical data
- selection of products for entry into clinical trials
- correlation of in-vivo and in-vitro product effects
- improved use of pharmacokinetic data
- innovative models for clinical trial design

Access for People with Missing or Inadequate Health Care
- to clinical trials
- to products on expanded access

Health Policy Issues
- early distribution of the results of clinical trials
- definition and distribution of standards of care
- educating physicians in the standards of care
- problems with reimbursement for non-approved standards of care
- prevention of AIDS Health fraud
- international aspects of drug development

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
002. list	re: List of Nominees After January 13, 1994 Meeting (1 page)	01/27/1994	b(6)

COLLECTION:
Clinton Presidential Records
National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
National Task Force on AIDS Drug Development [3]

2018-0756-F
jp4863

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
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C. Closed in accordance with restrictions contained in donor's deed of gift.
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RR. Document will be reviewed upon request.

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b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
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003. list	re: Nominees - Female and Other (1 page)	00/00/0000	b(6)

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National Task Force on AIDS Drug Development [3]

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RESTRICTION CODES

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004. memo	Terry Beswick to Kristine Gebbie; re; NTFADD [National Task Force on AIDS Drug Development] Nominees (1 page)	00/00/0000	b(6)

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National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
National Task Force on AIDS Drug Development [3]

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b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Descriptions of Nominees

Name	Agosto, Moises
Degree	B.A.
Title	Research and Treatment Advocacy Manager
Organization	National Minority AIDS Council
City	Washington
State	DC
Nominated By	Paul Kawata; National Minority AIDS Council
Nominated By	Ann Donnelly; Project Inform
Nominated By	Daniel Bross; AIDS Action Council
Nominated By	ACT UP/Golden Gate
Description	Mr. Agosto, a Latino, is the Research and Issues Manager for the National Minority AIDS Council. Mr. Agosto has a broad background in community outreach, education, and advocacy. He is a member of the NIH AIDS Clinical Trials Group Community Constituency Group, the Pharmacology Core Committee, and the Community Advisory Board of the Howard University AIDS Clinical Trials Unit. Mr. Agosto is also a member of the National HIV Community Advisory Board at Burroughs Wellcome, the Treatment Action Group (TAG), and is a founding member of the Latino/a AIDS Treatment Issues Group.

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
005. bio	re: Descriptions of Nominees - David Baltimore (1 page)	00/00/0000	b(6)

COLLECTION:
Clinton Presidential Records
National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
National Task Force on AIDS Drug Development [3]

2018-0756-F
jp4863

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
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P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
006. bio	re: Descriptions of Nominees - Martin Delaney (1 page)	00/00/0000	b(6)

COLLECTION:
Clinton Presidential Records
National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
007. bio	re: Descriptions of Nominees - Carmen Feliciano (1 page)	00/00/0000	b(6)

COLLECTION:
Clinton Presidential Records
National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
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2018-0756-F
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Descriptions of Nominees

Name	Fullilove, Mindy
Degree	M.D.
Title	Research Psychiatrist, HIV Center
Organization	New York State Psychiatric Institute
City	New York
State	NY
Nominated By	Internal Planning Group
Description	Dr. Fullilove, an African-American, is a research psychiatrist at the HIV Center of the New York State Psychiatric Institute. She has been involved in AIDS-related activities over the past several years. Her research has covered topics ranging from substance abuse in multi-ethnic populations as well as HIV/AIDS in the African-American community.

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
008. bio	re: Descriptions of Nominees - Richard Gelb (1 page)	00/00/0000	b(6)

COLLECTION:
Clinton Presidential Records
National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
National Task Force on AIDS Drug Development [3]

2018-0756-F
jp4863

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Descriptions of Nominees

Name	Ho, David
Degree	M.D.
Title	Director
Organization	Aaron Diamond AIDS Research Center
City	New York
State	NY
Nominated By	Gregg Gonsalves; Treatment Action Group (TAG)
Description	Dr. Ho, a physician/scientist, is the director of the Aaron Diamond AIDS Research Center in New York City and Professor of Medicine and Microbiology at the New York University School of Medicine. Dr. Ho's recent research has focused on the pathogenesis of HIV and the host's immune response to the virus.

Withdrawal/Redaction Marker
Clinton Library

DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
009. bio	re: Descriptions of Nominees - Derek Hodel (1 page)	00/00/0000	b(6)

COLLECTION:
Clinton Presidential Records
National AIDS Policy Office
Kristine Gebbie
OA/Box Number: 8300

FOLDER TITLE:
National Task Force on AIDS Drug Development [3]

2018-0756-F
jp4863

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Descriptions of Nominees

Name	Hoth, Daniel
Degree	M.D.
Title	Senior Vice President
Organization	Cell Genesys
City	Foster City
State	CA
Nominated By	Carl Feldbaum; Biotechnology Industry Organization
Description	Dr. Hoth is senior vice president and director of the clinical development program at Cell Genesys, a biotech company located in California. Prior to joining Cell Genesys, Dr. Hoth was the Director, Division of AIDS, in the National Institute of Allergy and Infectious Diseases, NIH.

Descriptions of Nominees

Name	McGovern, Theresa
Degree	JD
Title	Director
Organization	HIV Law Project
City	New York
State	NY
Nominated By	Mercedes Kuilan; Katrina Haslip Law TAP
Nominated By	Michelle Allen; New York Univesity
References	Carola Marte; Beth Israel Medical Center
References	Mardge Cohen; Women and Children's AIDS Project, Cook County
References	Donna Futterman; Adolescent AIDS Program, Montefiore
References	Helen Rodriguez-Trias
References	Rebecca Denison; WORLD
Description	Ms. McGovern is the founder and director of the HIV Law Project, which is based in New York City. The HIV Law Project provides legal representation for low-income HIV positive persons. Ms. McGovern's work for the Project has included lead counsel representation on SP v. Sullivan, a class action suit challenging Social Security Administration standards for disbursement of disability benefits to HIV-infected individuals as discriminatory towards women and the poor, and counsel on legal action challenging FDA guidelines barring women from early phases of clinical trials.

Descriptions of Nominees

Name	Nelson, Charles
Degree	B.S.
Title	Laboratory Technician
Organization	Morehouse School of Medicine
City	Atlanta
State	GA
Nominated By	Thomas Gleaton; Inner City AIDS Network (ICAN)
Description	Mr. Nelson, an African-American, is a laboratory technician in the Department of Biochemistry at the Morehouse School of Medicine. Mr. Nelson is an active community participant in HIV/AIDS issues as a member of a variety of national and local committees, including the NIH AIDS Clinical Trials Group Community Constituency Group and the Community Advisory Board of the AIDS Research Consortium of Atlanta.

Descriptions of Nominees

Name	Raab, G. Kirk
Degree	BA
Title	CEO
Organization	Genentech
City	South San Francisco
State	CA
Nominated By	David Barr, GMHC
Description	Mr. Raab has been Chief Executive Officer of Genentech since 1985. Genentech, a biotech company located in California, has been active in the development of immune-based therapies and vaccines for HIV/AIDS.

Descriptions of Nominees

Name	Schooley, Robert (Chip)
Degree	M.D.
Title	Director, Colorado ACTU
Title	Professor of Medicine
Organization	University of Colorado
City	Denver
State	CO
Nominated By	ACT UP/Golden Gate
Description	Dr. Schooley is the director of the NIH-sponsored AIDS Clinical Trials Unit at the University of Colorado, and Professor of Medicine and Head of the Infectious Diseases Division at the University of Colorado Health Sciences Center in Denver. Dr. Schooley is involved in clinical research on HIV/AIDS, particulary in the areas of immunology and the development of immune-based therapies, with extensive participation in the NIH AIDS Clinical Trials Group.

Descriptions of Nominees

Name	Staley, Peter
Title	Founding Director
Organization	Treatment Action Group
City	New York
State	NY
Nominated By	Charles Franchino; TAG
Nominated By	David Barry; Burroughs Wellcome
Nominated By	Mathilde Krim; AmFAR
Nominated By	David Barr; GMHC
Description	Mr. Staley is the Founding Director of the Treatment Action Group (TAG), and has also been a member of ACT UP/New York. Through his work with TAG and ACT UP, he has focused on AIDS research policy, working with government officials, pharmaceutical companies, and advocacy organizations on issues related to AIDS research. Mr. Staley is also working with the Inter-Company Collaboration for AIDS Drug Development, providing community advice for this important initiative.

Descriptions of Nominees

Name	Scolnick, Edward
Degree	M.D.
Title	President
Organization	Merck Research Laboratories
City	Rahway
State	NJ
Nominated By	Roy Vagelos; Merck & Co.
Nominated By	John James; AIDS Treatment News
Nominated By	Gregg Gonsalves; Treatment Action Group (TAG)
Nominated By	ACT UP/Golden Gate
Nominated By	David Barr; GMHC
Description	Dr. Scolnick, a physician/scientist, is pesident of Merck Research Laboratories. Early in 1993, Dr. Scolnick spearheaded the formation of the Inter-Company Collaboration for AIDS Drug Development. This collaboration represents a unique organization of 15 pharmaceutical companies who have agreed to work together to facilitate, through sharing of information and drug supplies, early human effectiveness trials of combination drug therapies to fight HIV/AIDS.

Descriptions of Nominees

Name	Wong-Staal, Flossie
Degree	PhD.
Title	Professor of Medicine and Biology
Organization	University of California
City	San Diego
State	CA
Nominated By	Lynda Dee; ACTG/CCG
Nominated By	Gregg Gonsalves; Treatment Action Group (TAG)
Description	Dr. Wong-Staal is a molecular biologist who currently holds the Florence Riford Chair in AIDS Research, and is a Professor of Medicine and Biology at the University of California, San Diego. Her research interests include the molecular biology of human pathogenic viruses, cancer, and AIDS; mechanisms of gene regulation; novel approaches to gene therapy; and, molecular vaccines.

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Friday, Feb. 4, 1994

Contact: HHS Press Office
(202) 690-6343

SHALALA NAMES MEMBERS OF AIDS DRUG DEVELOPMENT TASK FORCE

HHS Secretary Donna E. Shalala today named the members of the expert panel she has charged with expediting the search for new therapies for AIDS and the underlying human immunodeficiency virus.

The new, highly focused National Task Force on AIDS Drug Development will be headed by Philip R. Lee, M.D., assistant secretary for health and director of the Public Health Service.

The panel, whose creation was announced Nov. 30, includes representatives of government, academia, the pharmaceutical industry, medicine and the AIDS-affected communities.

"AIDS now kills an average of 92 Americans a day. It is urgent that we expedite the development and use of better drugs. I've asked this panel to identify new approaches in research and to remove any barriers or obstacles to developing effective treatments," Shalala said.

"We had hundreds of qualified nominees," Shalala commented. "The people we've selected represent a superb mix of the top people in the field."

Shalala added: "As I said when I announced the creation of this panel, none of us can guarantee success. HIV is a vicious and cunning adversary. But history will judge us harshly if we fail to give it our best shot."

- More -

Kristine Gebbie, National AIDS Policy Coordinator, said the task force members "bring great diversity of expertise and perspective" to their mission.

"I am confident the entire federal government, as well as the private sector, will be diligent in urgently responding to their requests for information and their recommendations for action. No stone should be left unturned in the task force's work," Gebbie added.

The members of the panel are:

Moises Agosto Research and Treatment Advocacy Manager	National Minority AIDS Council Washington, D.C.
Arthur Ammann, M.D. Director, Ariel Project	Pediatric AIDS Foundation Novato, Calif.
Stephen K. Carter, M.D. Senior Vice President Worldwide Clinical Research and Development	Bristol-Myers Squibb Princeton, N.J.
Ben Cheng Information and Advocacy Associate	Project Inform San Francisco, Calif.
Deborah J. Cotton, M.D., M.P.H. Assistant Professor of Medicine	Harvard Medical School Boston, Mass.
Mindy Fullilove, Ph.D. Research Psychiatrist, HIV Center	New York State Psychiatric Institute New York, N.Y.
David Ho, M.D. Director	Aaron Diamond AIDS Research Center New York, N.Y.
Daniel Hoth, M.D. Senior Vice President	Cell Genesys Foster City, Calif.
David A. Kessler, M.D. Commissioner	Food and Drug Administration

Philip R. Lee, M.D., Assistant Secretary for Health	Department of Health and Human Services
Theresa McGovern Director	HIV Law Project New York, N.Y.
Charles Nelson Laboratory Technician III	Morehouse School of Medicine Atlanta, Ga.
G. Kirk Raab CEO	Genentech San Francisco, Calif.
Robert Schooley, M.D. Director, Colorado ACTU	University of Colorado Denver, Colo.
Edward Scolnick, M.D. President	Merck Research Laboratories Rahway, N.J.
Peter Staley Founding Director	Treatment Action Group New York, N.Y.
Harold Varmus, M.D. Director	National Institutes of Health
Flossie Wong-Staal, Ph.D. Professor of Medicine and Biology	University of California San Diego, Calif.

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NEW YORK NEWSDAY, FRIDAY, FEBRUARY 4, 1994

New AIDS Task Force Named

By Laurie Garrett
STAFF WRITER

A surprisingly fresh, high-powered list of names for a new federal task force on AIDS drug development will be announced today, Washington sources said.

The announcement comes on the heels of several setbacks in the Clinton administration's attempts to formulate a vital new set of policies for controlling the epidemic. And the mandate of the task force — to completely revamp the national search for a viable AIDS treatment — will be sweeping.

It's a move, experts said yesterday, that undoubtedly will please activists who claim the research effort has grown stale, dominated by what they see as an old-guard elite who have been highly influential since the disease was first discovered in the early 1980s.

"Some new blood — that's great!" said one of the new task force members, who asked not to be identified.

Sources said the 18-member task force will be named today by Health and Human Services Secretary Donna Shalala, and that it would represent a spectrum from the pharmaceutical industry to behavioral scientists.

One of the relatively new faces to be named to the task force is Dr. Mindy Fullilove of the New York Psychiatric Institute's HIV center. Fullilove, a noted expert on drug use, sexual behavior and the social demographics of AIDS, is among five New York City residents named to the task force, sources said.

The other New Yorkers include Stephen Carter, senior vice president, Bristol-Myers Squibb Co. and Dr. David Ho of the Aaron Diamond AIDS Research Laboratory.

THE WHITE HOUSE

WASHINGTON

DEC 23 1993

A. Arthur Gottlieb, M.D.
Imreg, Inc.
144 Elk Place, Suite 1400
New Orleans, Louisiana 70112

Dear Dr. Gottlieb:

Thank you for your letter of December 2 concerning the National Task Force on AIDS Drug Development. I am also hopeful that the formation of this committee will help expedite the discovery of better therapies for HIV/AIDS.

I would also like to endorse your view that it is important to remember the many different perspectives of individuals, researchers and companies involved in AIDS drug development. While large and small drug manufacturers have many similar regulatory and scientific concerns relating to drug development, many small companies may have a different set of obstacles from the larger companies. We will keep this, and your own nomination, in mind as the Task Force is assembled.

I am enclosing a copy of the Federal Register notice of December 2, 1993 announcing the formation of the Task Force. I would like to suggest that you also send your CV directly to Randy Wykoff, Director of the FDA Office of AIDS and Special Health Issues, at the address noted in the Register.

Thank you again for your support for these efforts, and your own work to find better therapies for HIV/AIDS.

Sincerely,

Kristine M. Gebbie, RN, MN
National AIDS Policy Coordinator

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC - 8 1993

Dear Colleague:

On November 30, 1993, Dr. Donna Shalala, Secretary for Health and Human Services (HHS) announced the creation of the National Task Force on AIDS Drug Development. The Task Force will be composed of 15 members of the government, pharmaceutical industry, academia, medicine and the AIDS-affected communities, and will seek to remove barriers and to recommend new and innovative approaches to AIDS drug development.

For your information, I have enclosed the HHS Press Release and the Federal Register Notice of December 2, 1993, announcing the creation of the Task Force and the request for nominations. I hope you will share this information with your constituents and consider nominating individuals for the Task Force.

Please do not hesitate to call my staff at (301) 443-0104 if additional information is needed.

Sincerely,

Randolph F. Wykoff, MD, MPH & TM
Director
Office of AIDS and
Special Health Issues

Enclosures

Major mitigation proposals related to the proposed Calexico East POE are identified below.

Water quality impacts in the United States due to growth which might occur in Mexicali are being addressed by various federal government agencies in Mexico and the United States. This growth is occurring and would occur with or without the new POE. While GSA understands that opening a new border crossing may accelerate development which would likely result in increased pollutant emissions that could affect the U.S., it also believes that the mitigation of these types of impacts should be coordinated on a large scale between the two countries rather than on a case by case basis.

To this end, various U.S. and Mexican federal agencies, including the U.S. State Department, U.S. Section of the International Boundary and Water Commission (USIBWC) and Environmental Protection Agency (EPA), have been working together to insure that future impacts to the Alamo and New Rivers are mitigated. USIBWC Minute 288 provides a conceptual plan for the long term solution to border sanitation problems in the Calexico-Mexicali area. This plan has been integrated into the *Intergrated Environmental Plan for the U.S.-Mexico Border* under EPA leadership in which a total of approximately $384 million has been allocated by the United States for environmental protection along the border including approximately up to $20 million for construction of a wastewater treatment facility at the New River in Calexico.

Mexico has committed $460 million for urban infrastructure projects along the border, of which $197 million has already been obligated, and of which $17 million is specifically targeted for improvements in the Mexicali area.

There are several potential areas of impact to air quality. During construction, on-site activities would increase the levels of PM–10 (airborne particulate matter measuring greater than 10 microns). Mitigation to reduce wind entrainment of dust will include watering unpaved, exposed surfaces twice daily, keeping vehicle speeds on site to below 15 miles per hours, and guaranteeing that loaded trucks be tarped.

Potential impacts associated with the operation of the POE include emissions generated as the result of the operation of the incinerator. GSA will adhere to the regulations for operation set by the Imperial County Air Pollution Control District (APCD) to mitigate any potential impacts.

Another potentially significant air quality occurs as the result of idling vehicles waiting to be inspected. GSA believes that, regionally, the increased throughput potential at the new POE, combined with the capacity at the downtown facility, will result in shorter waiting times for trucks and automobiles crossing into the U.S. and thus *improved* air quality. However, at the request of the EPA and the Imperial Valley APCD, source receptor modeling for carbon monoxide (CO) was preformed as a part of the EIS. The modeling, which measured potential ground level concentrations ("at the tailpipe") at the fenceline and within the queuing area, was done using conservative emission factors at the request of EPA Region 9 to approximate the combination of Mexican and American vehicles which will cross into the U.S. at the new POE. The modeling found that, as is the case with all places where automobiles sit idling, there are times when this area may become a local "hot spot" for CO concentrations (thresholds are exceeded).

To protect susceptible populations (those likely to spend at least an hour in the queue or at the fenceline, such as vendors and Customs and INS inspectors), mitigation will include denying vendors and pedestrian access to the vehicle queue and discouraging them from congregating at the fenceline, and pressurizing the inspection booths so that exhaust air and fumes do not enter the booths. Also, a vehicle exhaust dilution system will be installed in the work areas in the vicinity of the queuing area to assist in dispersing CO.

Further, GSA will install ambient air monitoring equipment at the POE in consultation with the U.S. Department of Public Health and Imperial County Air Pollution Control District. If pollutant readings exceed acceptable levels established by the Occupational Safety and Health Administration (OSHA), measures will be taken to alleviate the impacted area.

Other significant environmental mitigation associated with this project include the following:

A pre-construction survey for burrowing owl presence will be conducted by a qualified biologist no more than 90 days prior to grading activities. Each burrow will be hand excavated, any birds found within the burrows will be allowed to escape, and the burrow will be collapsed and destroyed prior to construction. No burrows will be excavated during the owl's nesting period, from March 15 to June 15. If burrows remain on site after March 15, construction and grading activities will not be allowed within 100 feet of the burrow site(s) until at least June 15.

Because commercial vehicles carrying hazardous materials will be allowed to cross to the POE, a Hazardous Materials Response Plan will be developed to outline procedures to be followed in the unlikely event of a breach. The plan will be developed by GSA and FIS agencies in consultation with the EPA, U.S. Fish and Wildlife Service, California Office of Emergency Services, California EPA, California Highway Patrol, California Department of Fish and Game, Regional Water Quality Control Board, Imperial County, Imperial Irrigation District, and the Calexico Fire Department.

Emergency services response (fire, medical) will be coordinated with the appropriate County and Calexico City agencies.

The General Services Administration believes that there are no outstanding issues to be resolved with respect to the prospect project. Requests for a comprehensive copy of mitigation measures associated with the Calexico East Port of Entry and State Route 7 may be directed to Mr. Alan Campbell, Planning Staff (9PL), U.S. General Services Administration, 525 Market Street, San Francisco, CA 94105, (415) 744–5252.

Dated: November 12, 1993.

Aki K. Nakao,

Acting Regional Administrator (9A).

[FR Doc. 93–29493 Filed 12–1–93; 8:45 am]

BILLING CODE 6820-23-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Request for Nominations for Members on Public Advisory Committees; National Task Force on Acquired Immune Deficiency Syndrome (AIDS) Drug Development

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: The Office of the Secretary, Department of Health and Human Services, in conjunction with the National AIDS Policy Coordinator, is requesting nominations for 14 members to serve on the National Task Force on Acquired Immune Deficiency Syndrome (AIDS) Drug Development. Elsewhere in this issue of the Federal Register, the Secretary of Health and Human Services (the Secretary) is publishing a notice announcing the establishment of this Task Force.

The Secretary and the National AIDS Policy Coordinator has special interest

in ensuring that women, minority groups, and the physically handicapped are adequately represented on advisory committees and, therefore, extends particular encouragement to nominations for appropriately qualified female, minority, or physically handicapped candidates.

DATES: Nominations should be received on or before January 3, 1994.

ADDRESSES: All nominations for membership should be sent to the contact person (address below).

FOR FURTHER INFORMATION CONTACT: Regarding all nominations: Randolph F. Wykoff, Director, Office of AIDS and Special Health Issues (HF–12), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–0104.

SUPPLEMENTARY INFORMATION: The Office of the Secretary, Department of Health and Human Services, in conjunction with the National AIDS Policy Coordinator, is requesting nominations for 14 members to serve on the National Task Force on AIDS Drug Development. The function of the Task Force is to identify any barriers and provide creative options for the rapid development and evaluation of treatments of HIV infection and its sequelae. It shall advise the Secretary, and, as needed, other parts of the Administration, on issues related to such barriers, and provide options for the elimination of such barriers. The Task Force will provide its recommendations through the use of subcommittees, public testimony, and Task Force deliberations.

Persons nominated for membership should be from among authorities knowledgeable about AIDS and treatment development issues. Members shall represent the drug development industry, academic and medical research centers, clinical medicine, Federal government, and the HIV-infected and affected communities.

Members shall be invited to serve for overlapping four-year terms: terms of more than two years are contingent upon the renewal of the Task Force by appropriate action prior to its expiration. Of the first members appointed: four shall serve for a term of two years, five for a term of three years, and five for a term of four years, as designated at the time of appointment.

A member may serve after the expiration of a member's term until a successor has taken office.

Nominations Procedures

Interested persons may nominate one or more qualified persons for membership on the Task Force. Nominations shall state that the nominee is willing to serve as a member of the Task Force and appears to have no conflict of interest that would preclude Task Force membership. The Secretary, in conjunction with the National AIDS Policy Coordinator, will ask the potential candidates to provide detailed information concerning such matters as financial holdings, consultancies, and research grants or contracts to permit evaluation of possible sources of conflict of interest.

This notice is issued under the Federal Advisory Committee Act (5 U.S.C. app. 2), relating to advisory committees.

Dated: November 22, 1993.

Donna E. Shalala,

Secretary.

[FR Doc. 93–29478 Filed 11–30–93; 8:45 am]

BILLING CODE 4110–60–P

Advisory Committees; National Task Force on Acquired Immune Deficiency Syndrome (AIDS) Drug Development; Establishment

AGENCY: Office of the Secretary, HHS.

ACTION: Notice of establishment.

SUMMARY: The Office of the Secretary, Department of Health and Human Services, in conjunction with the National AIDS Policy Coordinator, is announcing the establishment by the Secretary of Health and Human Services (the Secretary), of the National Task Force on Acquired Immune Deficiency Syndrome (AIDS) Drug Development. Elsewhere in this issue of the Federal Register, the Secretary is also publishing a notice requesting nominations for membership on this Task Force.

DATES: Authorization for the Task Force being established will end on November 22, 1995, unless the Secretary formally determines that renewal is in the public interest.

FOR FURTHER INFORMATION CONTACT: Donna M. Combs, Committee Management Office (HFA–306), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–2765.

SUPPLEMENTARY INFORMATION: Under the Federal Advisory Committee Act of October 6, 1972, Public Law 92–463, as amended (5 U.S.C. app. 2), and 21 CFR 14.40(b), the Office of the Secretary, Department of Health and Human Services, in conjunction with the National AIDS Policy Coordinator, is announcing the establishment by the Secretary of Health and Human Services (the Secretary) of the National Task Force on AIDS Drug Development.

The Task Force shall advise the Secretary and, as needed, other parts of the Administration, on how best to proceed in developing therapies to treat AIDS, a major pubic health problem in the United States today. The Task Force will assist the Administration, including the agencies of the Public Health Service, other agencies within HHS, the Department of Defense, and other Departments as appropriate, in the establishment of a national strategy in all aspects of the development of treatments for human immunodeficiency virus (HIV) infection and HIV-related diseases. It will be charged with first identifying any barriers that may be preventing the rapid development and evaluation of such treatments, and to then identify steps that can be taken to remove such barriers. Additionally, the Task Force will be charged with identifying creative options to enhance the development and evaluation of useful treatments for treating HIV infection and HIV-related diseases.

Dated: November 22, 1993.

Donna E. Shalala,

Secretary.

[FR Doc. 93–29479 Filed 11–30–93; 8:45 am]

BILLING CODE 4110–60–P

Public Health Service

[GN# 2149]

Public Health Service Award for Exceptional Achievement in Orphan Product Development

AGENCY: Office of the Assistant Secretary for Health, DHHS.

ACTION: Solicitation of nominations for the PHS Award for Exceptional Achievement in Orphan Products Development.

SUMMARY: The Office of the Assistant Secretary for Health and the Orphan Products Board are soliciting nominations for the PHS Award for Exceptional Achievement in Orphan Products Development. This award, which is presented by the Assistant Secretary for Health, is intended to encourage and give recognition to individual groups in the public and private sectors who engage in research or aid significantly the development of orphan products for rare diseases or conditions.

ADDRESSES: Nominations should be sent to Dr. Richard J. Bertin, Executive Secretary, Orphan Products Board, Office of Orphan Products Development

NAPO Document Control Slip

NAPO Number : 7398 PHS Number : OS Number : Document Type : Action Letter

Document Date: 12/02/93 Refer'd Date : 12/10/93 Int Due Date : 12/17/93 Ext Due Date : 12/17/93
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Purge Date : 12/10/95 Disposition : EVALUATE Final Date : Document Loc : -CHRON

********** Correspondent Information **********

From : A. ARTHUR GOTTLIEB Title : PRESIDENT Organization : IMERG
Address : 144 Elk Place, Suite 144 City : New Orleans State : LA Zip :
On Behalf Of : To : KG

********** Subject or Title **********

National Task Force on AIDS Drug Development

********** Keywords **********

********** Special Instructions **********

Send CV to HHS (Dr. Lee's Office)

********** Assignment/Action History **********

Process Type : Kristine Gebbie Correspondence

Assignee	Initials	Action	Status	Due Date	Completed	Comments TO assignee
Terry Beswick	TB	PF	ASGN	12/17/93	12/21	Response attached → D. Speigl ltr
Steve Lee		CLER	ASGN	12/17/93		
Steve Lee		SFP	ASGN	12/17/93		

HSP 12/21

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Related WordPerfect Filenames: _____ _____ _____

Comments FROM assignees:

IMREG

Suite 1400
144 Elk Place
New Orleans, LA 70112
(504) 523-2875
Telecopier: (504) 523-6201

2 December 1993

Dr. Jack Killen
Acting Director, Division of AIDS
National Institute of Allergy
and Infectious Diseases
6003 Executive Blvd., Room 2A-18
Rockville, MD 20892

Dear Dr. Killen:

I am writing at the suggestion of Ms. Christine Gebbie, the National AIDS Policy Coordinator with whom I met recently.

As you perhaps know, I am the developer of the IMREG®-1 biopharmaceutical an investigational immunomodulator which has been through a placebo controlled clinical trial in patients with advanced HIV disease. The important results of that trial were published in the Annals of Internal Medicine, and a follow-up study was reported in the International Journal of Immunopharmacology - I enclose copies of these articles for your files. The data from the controlled clinical trial was thoroughly reviewed by the FDA's Vaccines and Related Biological Products Advisory Committee which reached a consensus that IMREG®-1 may have an effect in HIV disease, and recommended that a second controlled clinical trial should be carried out to confirm efficacy. Protocols for this second clinical trial have been approved by FDA.

We are seeking the funds required to carry out this clinical trial and, in particular, would like to explore the possibility of a sole source contract for this purpose. I might say that we have to date received no governmental support for any of our work. I would appreciate it very much if we could exchange views on these matters. As there is urgency in respect of our situation, it would be greatly appreciated if we could speak by phone at your earliest convenience.

I look forward to speaking with you.

Cordially,

A. Arthur Gottlieb, M.D.
President and Scientific Director

AAG/jn
enclosures
bcc: Kristine M. Gebbie, RN, MN

IMREG

Suite 1400
144 Elk Place
New Orleans, LA 70112
(504) 523-2875
Telecopier: (504) 523-6201

2 December 1993

Kristine M. Gebbie, RN, MN
National AIDS Policy Coordinator
Executive Office of the President
200 Independence Avenue, SW, Room 738G
Washington, D.C. 20201

Dear Ms. Gebbie:

I certainly am impressed by the apparent commitment of the Administration to move aggressively in respect of finding appropriate therapies for HIV/AIDS. The construction of a National Task Force on AIDS Drug Development appears to be a useful step - I note that it is contemplated that this Task Force will be comprised of members from the governmental, academic, pharmaceutical and activist communities.

May I suggest that the Administration may wish to consider appointing Task Force members from small as well as large companies that are developing AIDS therapeutics. In this context, assuming that mechanisms would be provided to avoid conflict of interest, it occurs to me that I could make an important contribution as a member of this Task Force and I would be willing to serve in this capacity, if asked to do so.

As you may recall from our meeting in your office in August, I have been a leading advocate for several years of the concept that it is essential to develop drugs or biologics that have the ability to correct or modify the state of immune dysregulation that is seen in HIV disease. In my view, HIV disease/AIDS is as much an "immune problem" as a "viral problem" and the national effort to develop drugs for HIV/AIDS has been much too focused, until recently, on antiviral drug development. As we now appreciate, the overall results in the antiviral drug arena have been disappointing. I might also suggest that because of my more than ten years experience at the academic-industrial interface, I have a rather unique perspective to bring to the Task Force in this regard.

As a matter of record, it may be of further interest to note that:

(1) I played an important role in documentation of the 1968 case of HIV disease which was reported in the media (1987) and subsequently in JAMA 260 2085 (1988).

(2) To the best of my knowledge, I was the first one to demonstrate that the state of immunologic nonresponsiveness to antigen seen in advanced HIV infection could be reversed. I accomplished this in 1984 by treating the patient with a cruder form of what is now the IMREG®-1 biopharmaceutical. This and other findings led, of course, to the larger studies of IMREG®-1 in HIV disease and the important results obtained therein (Annals of Internal Medicine, July 1991).

I do appreciate your consideration.

Yours sincerely,

A. Arthur Gottlieb, M.D.
President and Scientific Director

AAG/jn
enclosures

December 2, 1993

CURRICULUM VITAE

A. ARTHUR GOTTLIEB

Born:	December 14, 1937
Citizenship:	United States of America
Marital Status:	Married (Dr. Marise S., 1958): Two children (Mindy and Joanne)
1957:	A. B. Columbia College (summa cum laude) Distinction in Chemistry
1961:	M.D. New York University School of Medicine
1961-1962:	Medical House Officer, Peter Bent Brigham Hospital, Boston, Massachusetts
1962-1963:	Assistant Resident Physician (Medicine) Peter Bent Brigham Hospital, Boston, Massachusetts
1963-1965:	Commissioned Officer, United States Public Health Service Clinical Associate, National Heart Institute, National Institutes of Health
1965-1967:	Research Fellow in Chemistry, Harvard University (laboratory of Professor Paul Doty) Tutor in Chemistry, Harvard University Assistant in Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts
1968:	Associate in Medicine, Harvard Medical School Associate in Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts Tutor in Biochemical Sciences, Harvard University
Jan. 1969-Nov. 1969:	Assistant Professor of Medicine Harvard Medical School
Dec. 1969-June 1972:	Associate Professor of Microbiology, Institute of Microbiology, Rutgers University, New Brunswick, New Jersey
July 1972-May 1975:	Professor of Microbiology, Institute of Microbiology, Rutgers University, New Brunswick, New Jersey
Present Position:	Professor and Chairman, Department of Microbiology and Immunology, Tulane University School of Medicine, New Orleans, Louisiana

Concurrent Positions:	Professor of Medicine, Tulane University School of Medicine
	President, Chief Executive Officer and Scientific Director, IMREG, INC, New Orleans, Louisiana, a publicly held biotechnology company in the area of immunoregulation.
Editorial:	Member, Advisory Board, J. Reticuloendothelial Society (1978-1979)
	Member, Editorial Advisory Board, Immunological Communications
	Member, Editorial Advisory Board, IRCS Journal of Medical Sciences
	Member, Publications Committee, Reticuloendothelial Society (1976-1977)
	Chairman, Publications Committee, Reticuloendothelial Society (1977-1978)
Licensure:	New York, New Jersey, Massachusetts, Louisiana (3569)
Government Consultations:	Member, Breast Cancer Task Force, Breast Cancer Treatment Committee, National Cancer Institute (1976-1980)
	Consultant Immunologist, FDA, National Center for Toxicological Research, Jefferson, Arkansas (1976-1978)
Medical School Committees:	Executive Faculty Personnel and Honors (appointments) Chairman, Basic Science Council (1976-present) Curriculum Committee (1975-1976) Institutional Biohazard Committee (Recombinant DNA) Search Committee for Chairman of Surgery (1975) Search Committee for Chairman of Tropical Medicine (1975) Planning Committee for Louisiana Cancer Center (1975-1978) Chairman, Dean's ad hoc Committee on Medical School Finances Member, Dean's Committee on Ethics in Research

University Committees: Committee on Educational Policy (1977-1978)

General Research Interests:
(1) Immunology, Immunotherapy,
(2) Lymphoid Cell Biology and Biochemistry

Specific topics of current research interest:

(1) Structure and Function of Immunoregulatory Molecules in Man
(2) Development of new approaches to immunotherapy
(3) Studies of Unique DNA Sequences in Malignant Human and Murine Lymphoid Cells
(4) Eukaryotic DNA polymerases, especially those associated with Murine Myeloma
(5) Macrophage Function, particularly in regard to antigen presentation

Memberships:
American Association for the Advancement of Science
American Association for Cancer Research
American Association of Immunologists
American Chemical Society
American Society of Biological Chemists
American Society for Cell Biology
American Society for Clinical Investigation
American Society for Microbiology
International Association for Comparative Research on Leukemia and Related Diseases
New York Academy of Sciences
Reticuloendothelial Society
Society for Experimental Biology and Medicine
Association of Medical School Microbiology Chairman - Councilor

Honors: Collegiate: Phi Beta Kappa (1956)

Honors: Professional:
Alpha Omega Alpha (1960)
Alpha Omega Alpha first prize for highest scholastic standing over four year medical school course
Sigma Xi (1972)
Research Career Development Awardee of the National Institute of General Medical Sciences (1968-1969)
Recipient of the Frances Stone Burns Award of the American Cancer Society, Massachusetts Division (1968)
Travelling Fellow, Royal Society of Medicine
Fellow, American College of Physicians

Fellow, American Academy of Microbiology
Visiting Professor,
Walter and Eliza Hall Institute for Medical Research,
Melbourne, Australia (June-Aug. 1979)
(sponsored by NSF U.S.-Australia Cooperative Science Program)
Visiting Professor, Wakayama Medical College and Gunma Medical College, Wakayama and Maebashi, Japan (May 1980)
Keynote Lecturer, 33rd Annual Meeting of the Japanese Hematology Society
May 1980
Visiting Professor of Medicine and Pharmacology
Shanghai Medical University
Shanghai, China, June 1991
Listed in "Who's Who in America", 41st and subsequent editions

Honors: Civic:

Mayor's Certificate of Merit, City of New Orleans, May 9, 1985

Other Committees and Panels:

1. Science and Public Policy
   (a) Member, Public Policy Committee of the Association of Medical School Microbiology Chairmen
   (b) Invited testimony before U.S. House Appropriations Committee in 1974 and 1978
   (c) Invited testimony before the Presidential Commission on the Human Immunodeficiency Virus Epidemic, February 1988

2. Member, Scientific Advisory Board
Cancer Association of Greater New Orleans
(1979-1984)

3. Member, Immunology Test Committee
Microbiology-Immunology Test Item (MITI)
Bank sponsored by Association of Medical School Microbiology Chairmen (1980-present)

4. Member, Review Panel on Special Aspects of Human Genetics, Louisiana Board of Regents Research and Development Program (1983, 1984)

5. Ad hoc Study Section - Small Business Innovation Research Program. NIH June, 1984.

6. Member, University of New Orleans Technology Review Board (1984-present)

7. Councillor, Association of Medical School Microbiology Chairmen (1987-1990)

PUBLICATIONS

(Abstracts not included)

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2. Gottlieb, A. A., Peterkofsky, B., and Udenfriend, S., "Use of Collagenase to Identify Enzymatically Formed Collagen and a Hydroxyproline Deficient Intermediate," J. Biol. Chem., 240, 3009 (1965).

3. Tyler, H.R. and Gottlieb, A.A., "Peripheral Neuropathy in Uremia," Proc. of 8th International Congress of Neurology (Vienna), pp. 351-356 (1956).

4. Gottlieb, A.A., Kaplan, A., and Udenfriend, S., "Further Evidence for a Hydroxyproline-Deficient Intermediate in collagen Biosynthesis," J. Biol. Chem., 241, 1551 (1966).

5. Fujita, Y., Gottlieb, A.A., Udenfriend, S. and Witkop, B., "The Preparation of cis and trans-4-H^3-L-Prolines and Their Use In Studying the Mechanism of Enzymatic Hydroxylation in Chick Embryos," J. Amer. Chem. Soc., 86, 4709.

6. Gottlieb, A.A., Fujita, Y., Udenfriend, S., and Witkop, B., "Incorporation of cis and trans-4-fluoro-L-Prolines into Proteins and Hydroxylation of the trans isomer during Collagen Biosynthesis," Biochemistry, 4, 2507 (1965).

7. Gottlieb, A.A., "Assay of Neutralizing Antibody: Increased Sensitivity of Assay by Plating on Salt-Deficient Agar," Nature, 212, 513 (1966).

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11. Gottlieb, A.A., and Straus, D., "Physical Studies on the Ribonucleoprotein Fraction of Macrophage Cells," J. Biol. Chem., 244, 3324 (1969).

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14. Bishop, D.C., and Gottlieb, A.A., "Macrophages, RNAs and the Immune Response" Current Topics in Microbiology and Immunology, 51 1, Springer-Verlag, New York (1970).

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16. Bishop, D.C. and Gottlieb, A.A., "Distribution of Antigen-RNP Complexes within Rat Peritoneal Exudate Cells," J. Immunology, 107, 269 (1970).

17. Gottlieb, A.A., "Antigen Capture by a Unique Ribonucleoprotein of Macrophage Cells," in "Biological Effects of Polynucleotides," R. Beers and W. Braun, Eds., pp. 293-301, Springer-Verlag, New York (1971).

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23. Gottlieb, A.A., and Waldman, S.R., "The Multiple Functions of Macrophages in Immunity," Critical Reviews in Microbiology, 1, 321-353 (1972).

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32. Gottlieb, A.A., Smith, A.H., Plescia, O.J. Persico, F.J. and Nicholson, D.E., "Inhibitor of DNA Polymerase Found in the Sera of Tumor-Bearing Mice," J. International Research Communications, I, (6), 36 (1973).

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52. Brennessel, B., Buhrer, P., and Gottlieb, A.A., "The Use of Insoluble Heparin for Isolation of DNA Polymerase Enzymes from Murine Myeloma," Analytical Biochemistry, 87, 411 (1978).

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Response to Treatment with the Leukocyte-derived Immunomodulator IMREG-1 in Immunocompromised Patients with AIDS-related Complex

A Multicenter, Double-Blind, Placebo-Controlled Trial

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■ *Objective:* To determine if a 6-month course of therapy with IMREG-1, a leukocyte-derived immunomodulator, slows disease progression in patients with AIDS-related complex.

■ *Design:* Randomized, double-blind trial.

■ *Setting:* Five academic- and three community-based clinics.

■ *Patients:* Immunocompromised patients (143) with HIV.

■ *Interventions:* IMREG-1 or placebo every 2 weeks (13 doses).

■ *Main Results:* Twelve of forty-eight patients on placebo and 5 of 95 patients on IMREG-1 experienced adverse events (AIDS-defining opportunistic infection or neoplasm, wasting syndrome, HIV-associated encephalopathy, or peripheral sensory neuropathy). Based on an intention-to-treat analysis, Kaplan-Meier event probabilities were 26% for the placebo group and 6% for the IMREG-1 group ($P < 0.001$); based on the Cox proportional hazards model, the relative risk for patients on placebo compared with patients on IMREG-1 was 5.1 (95% CI, 1.8 to 14.8). The frequency of symptoms significantly increased from baseline in patients receiving placebo. The mean decrease in CD4+ cells from baseline was 80×10^6 cells/L in the placebo group and 29×10^6 cells/L in patients on IMREG-1, with 20% (8) and 38% (32) of patients, respectively, showing a trend toward an increase ($P = 0.04$). In patients receiving IMREG-1, the size and rate of delayed hypersensitivity responses were larger than in the placebo group.

■ *Conclusions:* Patients with AIDS-related complex experienced fewer adverse events and constitutional symptoms after IMREG-1 treatment. The slower loss of CD4+ cells and increased size and rate of delayed hypersensitivity responses most likely reflect the effect of IMREG-1 on the immune system. No toxicity related to IMREG-1 administration was observed.

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Infection with human immunodeficiency virus (HIV) leads to progressive impairment in cell-mediated immunity, depletion of CD4+ lymphocytes, increased incidence and severity of constitutional symptoms, risk for developing opportunistic infections and malignancies, and death (1). Among patients with AIDS-related complex, immunodeficiency is progressive and the risk for developing an opportunistic infection increases.

IMREG-1 is an endogenous immunomodulator recovered from the leukocytes of healthy persons (2-5). In preliminary studies, its administration to patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex was associated with measurable recovery of delayed hypersensitivity and apparent stabilization of disease course (6-9). Therefore, a double-blind, randomized, placebo-controlled, multicenter trial was initiated to evaluate the ability of IMREG-1 to interrupt the progression to AIDS in a well-defined group of immunocompromised patients with AIDS-related complex. End points for the trial included the first occurrence of an AIDS-defining opportunistic infection or neoplasm, wasting syndrome, HIV-associated encephalopathy, or peripheral sensory neuropathy. In addition, possible toxicities and the effect of IMREG-1 on constitutional symptoms, CD4+ lymphocyte count, and delayed hypersensitivity response to recall antigens were evaluated.

Methods

Setting and Participants

Patients who were seropositive for HIV, had AIDS-related complex, and were at risk for developing an AIDS-defining condition within 6 months were enrolled at eight U.S. clinical centers; five of these were based at academic medical centers and three were based at or associated with major community medical centers. Patient enrollment began in November 1986. The study was terminated in March 1988.

Eligibility criteria included immune dysfunction as manifested by complete or partial anergy *and* either a CD4+ (help-

er) cell count of 100 to 400 × 10^6/L *or* a helper/suppressor cell ratio of less than 0.7, *and* at least one of the following: night sweats and chills (twice a week for at least 2 weeks); an intermittent or continuous oral temperature of greater than 38.0 °C in the preceding month; diarrhea (three or more episodes per day for 2 or more weeks); involuntary weight loss of 10% or greater of body weight in the preceding 3 months; persistent debilitating fatigue in the preceding month; a history of oropharyngeal candidiasis; or a history of herpes zoster. Complete anergy was defined as the failure to respond to intradermal administration of 0.1 mL of undiluted fluid tetanus toxoid, purified protein derivative, candida, and mumps or histoplasmin. Partial anergy was defined as induration of less than 5 mm in diameter at 48 hours in response to an antigen to which the patient had known sensitivity. Patients were required to have a CD4+ cell count of at least 100 × 10^6/L, because a minimal number of these cells appears to be necessary to demonstrate an effect of the drug. Patients had to be 18 to 60 years of age, have a Karnofsky performance status of 70% or greater, and, if female, could not be using oral contraceptives and had to agree not to become pregnant for the duration of the trial. The study was approved by the institutional review board at each participating center, and all subjects gave written informed consent.

Exclusion criteria included previous or current AIDS-defining opportunistic infection; miliary tuberculosis; neoplasms; HIV-associated encephalopathy; collagen vascular or granulomatous disease; other immunosuppressive disease; concurrent disease or therapy that could interfere with the evaluation of IMREG-1; significant renal, hepatic, cardiac, or other visceral dysfunction; a serum creatinine level of greater than 180 μmol/L; a serum bilirubin level of greater than 34 μmol/L; a serum transaminase value three times normal; myocardial infarction in the preceding 6 months; a platelet count of less than 50 × 10^9/L; a leukocyte count of less than 3.0 × 10^9/L; a hematocrit less than 0.30; recent therapy with immunomodulators, corticosteroids, nonsteroidal anti-inflammatory drugs, antiviral medication (except acyclovir), H_2-receptor antagonists, sulfadoxine with pyrimethamine, dapsone, pentamidine, amphotericin B, rifampin, or ansamycin; chronic methadone hydrochloride treatment; current intravenous drug use; recent blood transfusions; cancer chemotherapy; radiation therapy; or a positive pregnancy test. Prophylaxis for *Pneumocystis carinii* pneumonia was not permitted within 4 weeks of enrollment or during the trial.

Research Design

A 2:1 treatment-to-placebo allocation was implemented to encourage patient enrollment and compliance in a placebo-controlled trial. A random code was prepared for each of the clinical centers so that of every 9 patients, six would receive IMREG-1 and three would receive placebo. Vial codes were unique for each site. Treatment assignment was issued sequentially from the coordinating center from prerandomized assignments. Each patient was randomly assigned to receive IMREG-1 or placebo every 2 weeks for 26 weeks (13 treatments). The coordinating center, the clinical investigators, and the patients remained blinded to the code until the termination of the study. Treatment was to be discontinued after the occurrence of an adverse experience or an AIDS-defining event that could endanger the welfare of the patient if he or she continued on the protocol.

All data were recorded on structured case-report forms; two parts of the three-part carbonless paper form went to Imreg, Inc., Cambridge, Massachusetts, for review and statistical analysis, and the other part remained at the test center.

Interventions

IMREG-1 was prepared by sequential dialysis and high pressure liquid chromatography (HPLC) fractionation of leukocyte extracts (2-4, 10). The dose of IMREG-1, as determined from previous dose-escalation studies, was the product derived from approximately 1.25 × 10^5 buffy-coat leukocytes obtained from a healthy donor. Each dose contained 4.2 fmol of tyrosine-glycine and 0.2 fmol of tyrosine-glycine-glycine, as measured by a radioiodination technique (10), and 30 pmol of phenylalanine, plus a third immunologically active component that is recoverable by specifically defined HPLC procedures but whose structure has not been determined. Tyrosine-glycine, tyrosine-glycine-glycine, and the third component are capable of enhancing delayed hypersensitivity to recall antigens (10). Five doses were placed in coded vials, stored between − 4 °C and − 70 °C and were reconstituted with 0.5 mL sterile saline before administration. Before use of IMREG-1 in the trial, representative vials were shown to be sterile and free of endotoxin, nucleic acid, and hepatitis B surface antigen. Dilutions made from randomly selected drug vials enhanced delayed hypersensitivity to tetanus toxoid in three normal subjects. IMREG-1 and an identical-appearing placebo were provided by Imreg, Inc. (New Orleans, Louisiana), and both were given by intradermal injection, 0.1 mL every 2 weeks for 26 weeks (13 doses).

Outcomes

Subjects were screened for eligibility and evaluated before enrollment; the evaluation included repeated testing for delayed hypersensitivity response to skin-test antigens; a baseline medical history; a physical examination; a chest radiograph; urinalysis; a complete blood count with differential and platelet counts; and determinations of serum electrolytes, glucose, blood urea nitrogen, creatinine, uric acid, total bilirubin, total protein, albumin, serum aspartate and alanine aminotransferase, alkaline phosphatase, creatine phosphokinase, and lactate dehydrogenase. Immunologic assessment included CD4 and CD8 cell counts and quantitative evaluation of serum immunoglobulins (IgA, IgM, IgG). An interval history and physical examination were repeated every 2 weeks; a laboratory evaluation, including immunologic studies, was done at weeks 9, 17, and 25; additional chemistries were done at week 2; and additional hematologic studies were done at weeks 2 and 12. A chest radiograph and urinalysis were repeated at week 28.

Local certified laboratories were used by each clinical site for the duration of the trial for chemistries and hematologic assessments. All sites were required to use the same method for CD4+ cell measurements.

Diagnostic criteria for end points included histologic confirmation for *P. carinii* pneumonia, candida infection, and lymphoma; Centers for Disease Control (CDC) clinical criteria for wasting syndrome (≥ 10% weight loss, fever, and weakness) and HIV-associated encephalopathy (disabling cognitive function but normal brain imaging and cerebrospinal fluid); and an appropriate clinical history and examination for peripheral sensory neuropathy (11, 12).

Constitutional symptoms (diarrhea, night sweats and chills, cough, and fever) were ascertained by direct questioning and individually recorded for their frequency at 2-week intervals and scaled as follows: 0 = never; 1 = less than 1 day per week; 2 = 1 to 2 days per week; 3 = greater than 2 days per week; and 0.5 = "yes, but frequency unknown." The total symptom score is the sum of the scores of all four symptoms.

Skin testing with four recall antigens (0.1 mL intradermal tetanus toxoid, purified protein derivative, candida, and histoplasmin or mumps) was done twice for baseline and at week 25, and skin testing with tetanus toxoid alone was done at weeks 9 and 19. These skin-test sites were scored for erythema and induration by reading a vertical and longitudinal diameter at 7, 24, and 48 hours after injection.

Statistical Analysis

Study investigators participated in the design of the protocol, particularly with respect to criteria for patient enrollment and selection of outcome measures. To ensure consistency in diagnoses, a group of the investigators who were blinded to treatment assignments met to review the clinical status of all trial patients. They confirmed that patients who left the study before completing the protocol did not leave because of an unreported end-point event. By reviewing the case-report forms and supportive documents, they also confirmed that the end points designated by individual investigators consistently

met the diagnostic criteria. These prospectively defined end points were used in the analysis of the trial.

A group of scientists with no other formal relationship to the trial or to the sponsor, having relevant experience in biostatistics, epidemiology, immunology, and infectious diseases, were requested by the sponsor to review the trial and advise the sponsor on its outcome (Appendix). This independent review group met while patients were being enrolled to review the trial's progress and defined, a priori, several clinically relevant prognostic variables. Representatives of the independent group directed and later confirmed the data analysis.

To test the effectiveness of randomization, the distribution of all continuous variables and dichotomous variables with frequencies of more than 10% was compared by treatment group. Comparisons of dichotomous variables were done using the Yates corrected chi-square or the Fisher exact test as appropriate; continuous variables were compared using the Mann-Whitney rank-sum test.

Event probability distributions were estimated using the Kaplan-Meier product-limit method. Distributions were compared between treatment groups using the Breslow generalized Wilcoxon test. Because of their documented clinical importance, the number of CD4+ cells were included in all multivariate models. Additional potential prognostic variables were selected in a forward stepwise manner in accordance with the Cox proportional hazards model by the maximum partial likelihood ratio method. Covariate effects were adjusted for in the Cox model and the effect of treatment was evaluated by a score test based on the first derivatives of the partial likelihood function. Ninety-five percent confidence intervals (CI) are given when appropriate.

Results were obtained for both an intention-to-treat analysis, which included all appropriately randomized patients who completed 6 months on study and patients who were lost to follow-up or were withdrawn from the study before completion, and a subset analysis in which only time on study medication was used for patients who met the criteria for protocol compliance for a period of up to 6 months. Some laboratory studies and interval histories are not available for patients who left the study before completing the protocol. Therefore, the intention-to-treat method cannot be directly used for the analyses of change in symptom scores and CD4+ cell numbers from baseline to study termination. In these analyses, a last-observation-carried-forward method was used in which the last valid measurement of the variable of interest was "carried forward" for each patient for 26 weeks or until the termination of the study (ten patients were still on protocol and six patients who had reached an end point or left the study would have still been on protocol at the time of study termination). The use of the last available result, although it does not account for potential continued decline in patients no longer on protocol, serves to reduce the bias introduced by the selective removal of the sickest patients.

Symptoms were evaluated using eight time points: baseline, the average of six pairs of biweekly examinations, and the final examination. The 93 patients who had a subsequent value for comparison were included at baseline. Differences between treatment groups were evaluated by the Mann-Whitney rank-sum test; variables tested for such differences included mean symptom scores for each time point; mean CD4+ cell numbers at baseline and for the last available measurement; and the trend of these measurements. Comparisons within treatment groups were tested using the Wilcoxon signed-rank test; variables tested included mean change from baseline for symptom scores; CD4+ cells (both for number and percent of baseline); and the trend of these changes. Trends of the symptom score per time point were calculated as the linear regression averaged over all patients per treatment group. Trends are expressed as change per time point. Trend analysis was carried out on unprojected data. Changes in CD4+ cell numbers of a magnitude equal to or greater than 30% from baseline to the last available measurement and the direction of the trend of any change from baseline were evaluated by the Fisher exact test.

Skin test results were evaluated for an increase in the mean area of induration from baseline to the last available measurement, removing the highest and lowest value so that markedly outlying values could not influence the mean. Comparisons between and within treatment groups were done using rank-sum tests and include all values.

Hematologic and blood chemistry values from the various sites were adjusted for differences in laboratory ranges to control for any interlaboratory variation. Changes from baseline for individual patients were calculated and compared.

Results

Between 26 November 1986 and 25 November 1987, 147 patients were entered into the study. Ninety-nine patients were assigned to receive IMREG-1 and 48 to receive placebo. Four patients on IMREG-1 were disqualified based on protocol-specified entry criteria: One patient developed an opportunistic infection within the first 4 weeks, 2 used disqualifying medications, and 1 never started treatment. The study group therefore consisted of 95 patients randomly assigned to IMREG-1 and 48 patients randomly assigned to placebo.

The treatment groups were similar regarding demographic variables (11 patients were female, 39 were non-Caucasian, 121 were male homosexuals, and 11 had used intravenous drugs). They were also similar regarding baseline prognostic variables ($P > 0.05$; Table 1).

When the trial was terminated, ten patients had not completed the 26-week protocol. Their baseline values for prognostic variables were similar to those of the whole trial population, and their mean duration on trial was 150 days. Based on the frequency of AIDS-defining events occurring during the trial, it was unlikely that such events would occur in the ten patients during the time it would take each to complete the study, and, in fact, none did. These patients are included in the analysis only until the termination of the study.

There were 12 AIDS-defining and AIDS-related events in the 48 patients who received placebo and 5 such events in the 95 patients treated with IMREG-1 (Table 2). All seven episodes of *P. carinii* pneumonia occurring while patients were on study medication (five on placebo, two on IMREG-1) were confirmed by histologic examination of a bronchial lavage or biopsy specimen. An additional patient in the IMREG-1 group, who had begun treatment with zidovudine after leaving the study, developed *P. carinii* pneumonia 38 days after his last IMREG-1 treatment but within 6 months of his first treatment. Disseminated cryptococcosis was diag-

Table 1. Preselected Clinically Relevant Prognostic Variables of Patients Enrolled in the IMREG-1 Trial*

Variable	IMREG-1 (n = 95)	Placebo (n = 48)	P Value†
Age, y	35 ± 7.6	37 ± 8.4	0.2
Hematocrit	0.44 ± 0.03	0.43 ± 0.03	0.2
Leukocyte count, $10^9/L$	5.2 ± 1.7	4.7 ± 1.2	0.1
Total lymphocytes, $10^9/L$	1.7 ± 0.6	1.7 ± 0.6	> 0.2
CD4+ cells, $10^6/L$	357 ± 146	329 ± 164	0.2
Serum albumin, g/L	45 ± 3	44 ± 3	> 0.2
Percent of ideal body weight	1.01 ± 0.1	1.03 ± 0.2	> 0.2

* All values are expressed as means ± SD.
† These P values correspond to the Mann-Whitney (stratified Wilcoxon rank-sum) test statistic.

... End Points and Days to Diagnosis, by Treatment, in the IMREG-1 Trial Patients

Variable	IMREG-1		Placebo	
	Patients (n = 95)	Days on Study*	Patients (n = 48)	Days on Study*
Opportunistic infections				
Pneumocystis carinii pneumonia	3	98, 121, 149†	5	41, 69‡, 83, 113, 166
Candidiasis				
Bronchial			1	84
Esophageal	1	154		
Neoplasms			2	32, 139
Wasting syndrome			1	140
Encephalopathy (dementia)			1	141
Peripheral sensory neuropathy	1	121	2	139, 139
Total	5		12	

* Each number represents the duration of treatment for one patient.
† Patient left the trial at 127 days, included in intention-to-treat analysis.
‡ Also diagnosed with cryptococcal fungemia.

nosed serologically (serum antigen titer exceeding 1:16 000) in a patient who also had *P. carinii* pneumonia. Bronchial and esophageal candidiasis were diagnosed by endoscopy and confirmed histologically. Kaposi sarcoma and lymphoma were confirmed histologically. Peripheral sensory neuropathy and encephalopathy were diagnosed clinically.

Identified as significant predictors of end points in the Cox model ($P < 0.001$) were allocation to placebo (relative risk, 5.1; CI, 1.8 to 14.8), lower hematocrit (relative risk, 1.4/0.1 fall; CI, 1.2 to 1.7), and lower absolute lymphocyte count (relative risk, $1.2/100 \times 10^6$ cells/L fall; CI, 1.02 to 1.3).

Based on an intention-to-treat analysis, the Kaplan-Meier estimates of the probability of experiencing an end event were 26% (12 events in 48 patients) for placebo and 6% (5 events in 95 patients) for patients on IMREG-1 therapy ($P < 0.001$, Figure 1). The Cox relative risk of an end point occurring in a patient on placebo compared with a patient treated with IMREG-1 was 5.1 (CI, 1.8 to 14.8). Excluding the three cases of peripheral sensory neuropathy (two in the placebo group, one in the IMREG-1 group) designated and confirmed by the investigators but not specified as AIDS-defining in the CDC criteria, Kaplan-Meier estimates of the probability of an event were 21% (10 events in 48 patients) for the placebo group and 5% (4 events in 95 patients) for the IMREG-1 group ($P = 0.001$). The Cox relative risk for an event occurring in patients on placebo compared with patients on IMREG-1 was 6.1 (CI, 1.8 to 20.6).

One hundred and three patients completed the protocol. Thirty left the study before completing or reaching an end point (9 in the placebo group and 21 in the IMREG-1 group, numbers consistent with the 2:1 drug to placebo allocation ratio, $P > 0.05$), and their mean time on trial was 97 days. Two of these patients, both on IMREG-1, completed less than 4 weeks on study and were not included in the compliers analysis, as dictated by the protocol. Data on the other 28 patients were included through the period of compliance. These patients included 6 who completed 26 weeks on study and had multiple protocol violations and 8 who withdrew to begin zidovudine therapy (2 in the placebo group, 6 in the IMREG-1 group). As previously discussed, the data on the additional 10 patients who were actively on protocol at the time of study termination were included up to that time.

In patients who complied with the study protocol and were included in the analysis for the period of compliance, the Kaplan-Meier estimates of the probability of an AIDS-defining or AIDS-related event were 28% (12 events in 48 patients) for patients on placebo and 5% (4 events in 93 patients) for patients on IMREG-1 ($P < 0.001$). The Cox relative risk of reaching an end point for a placebo recipient compared with a patient on IMREG-1 was 6.9 (CI, 2.1 to 22.2).

Although the frequency of symptoms at baseline was higher in the IMREG-1 group than in the placebo group, the difference was not significant for individual symptoms or for all symptoms combined ($P = 0.16$). In accordance with the concept of last-observation-carried-forward analysis, in the placebo group, the frequency of individual symptoms increased from baseline after week 10 (by week 22, $P < 0.05$; Figure 2), and by week 22 the combined symptoms were more frequent than at baseline ($P < 0.001$; Table 3). By week 22, each symptom had also become more frequent in the placebo group compared with the IMREG-1 group ($P < 0.05$; Figure 2). This was also true for the combined group of

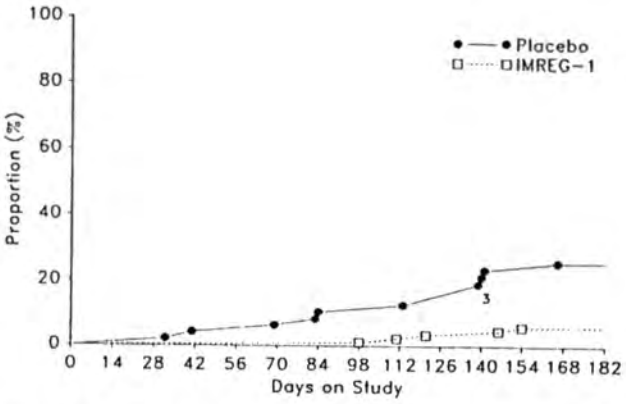

Figure 1. Kaplan-Meier probability of reaching AIDS-defining or AIDS-related (peripheral sensory neuropathy) events within 26 weeks in patients with AIDS-related complex. The probability was 6% (5 of 95) in treated patients and 26% (12 of 48) in placebo recipients ($P < 0.001$). The relative risk for placebo recipients was 5.1 (95% CI, 1.8 to 14.8).

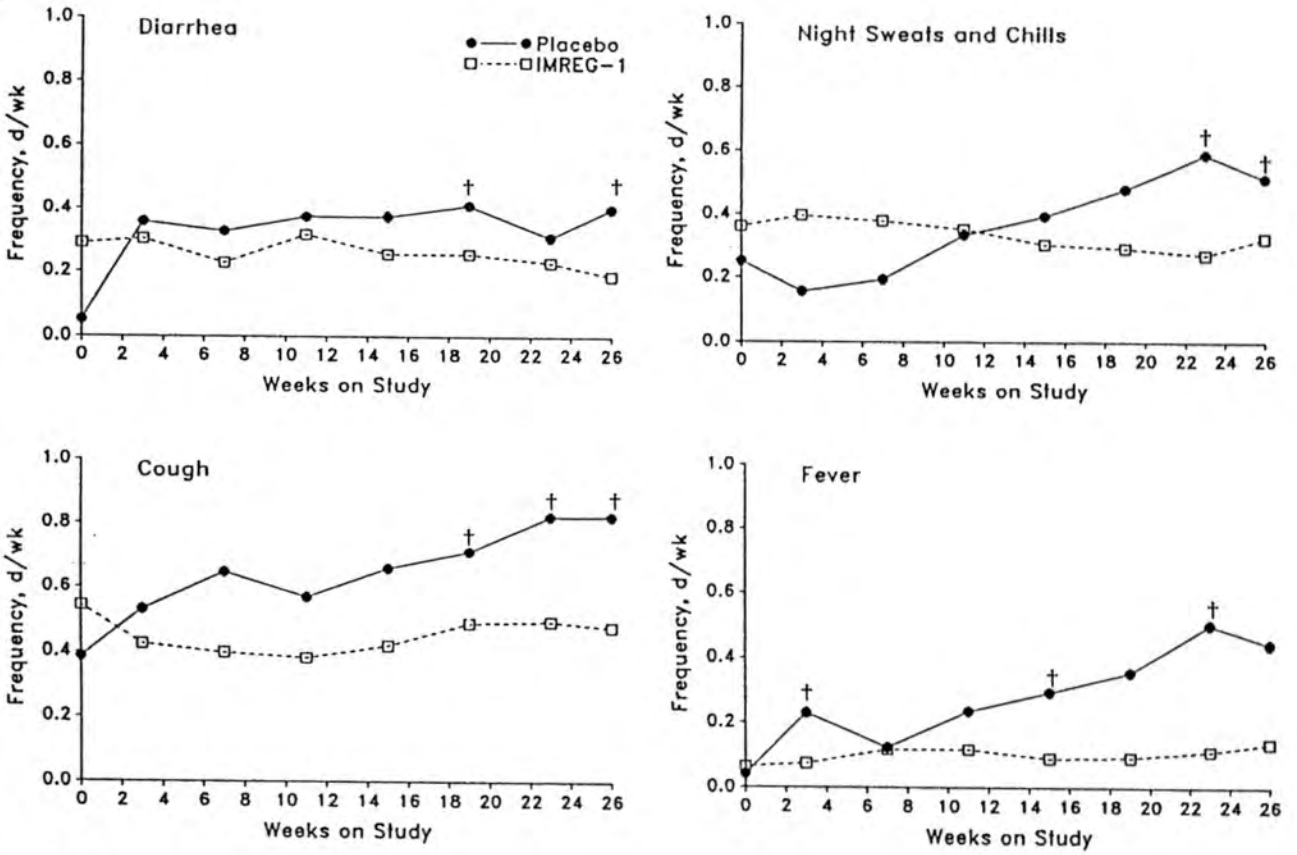

Figure 2. Frequency scores for various constitutional symptoms occurring in patients with AIDS-related complex who received either placebo or IMREG-1. Frequency score: 0 = never; 1 = less than 1 day per week; 2 = 1 to 2 days per week; 3 = greater than 2 days per week; and 0.5 = yes, but frequency unknown. † $P < 0.05$ for the difference between the placebo and IMREG-1-treated groups. (● = placebo recipients; □ = IMREG-1 recipients.)

symptoms ($P = 0.003$; Table 3). The total symptom score increased 1.96 days per week in the patients receiving placebo, as indicated by the trend, and decreased 0.07 days per week in patients receiving IMREG-1.

The treatment groups had similar mean CD4+ cell numbers at baseline (placebo group, 329 ± 164; IMREG-1 group, 357 ± 146). Although patients were not stratified according to CD4+ cell number at enrollment, there were no differences in treatment-to-placebo patient allocation by stratum ($P > 0.05$), and in each stratum the proportion of patients reaching end points was higher in the placebo group than in the IMREG-1 group. Decreases in the mean CD4+ cell numbers from baseline to all time points were larger in actual numbers and as a percent of baseline in the placebo group. The mean decrease from baseline to the last available measurement in the placebo group ($n = 41$) was 80×10^6 cells/L and 29×10^6 cells/L in the patients on IMREG-1 ($n = 84$); the last available CD4 cell counts were lower in the placebo group ($P = 0.06$). The mean percent decrease was 20% in the placebo group and 8% in the IMREG-1 group. The trends show a mean decrease of 111×10^6 cells/L for the placebo recipients and of 21 cells $\times 10^6$/L for the patients receiving IMREG-1. Over the course of the study, the CD4+ cell numbers increased by at least 30% in 5% (2 of 41) of the patients on placebo and in 19% (16 of 84) of the patients on IMREG-1 ($P = 0.05$). (A trend for an increase in CD4+ cell numbers was apparent in 20% [8 of 41] of the placebo recipients and in 38% [32 of 84] of the patients on IMREG-1 [$P = 0.04$].)

The increase in the mean area of induration in response to intradermal tetanus toxoid from baseline to the last available value and the increase based on the trend appear to occur earlier and to be larger at each time of evaluation in patients on IMREG-1 compared with patients on placebo. The greatest response in the patients on IMREG-1 ($n = 60$) was 65 mm^2, which was seen at 7 hours ($P < 0.001$); the response at 7 hours in the placebo patients ($n = 30$) was 15 mm^2. After antigenic challenge, the greatest response in the placebo group ($n = 31$) was 29 mm^2 and was observed at 24 hours ($P < 0.01$); the response in patients treated with IMREG-1 ($n = 65$) was 57 mm^2 at 24 hours. Nineteen of seventy-four patients (26%) on IMREG-1 and 6 of 40 patients (15%) on placebo responded to tetanus toxoid at 48 hours with induration of 5 mm or more in diameter.

Toxicity

Four patients on placebo (8%) and five patients on IMREG-1 (5%) developed transaminase elevations that were more than three times the upper limit of normal. Myalgia was reported in four patients on placebo (8%) and in eight patients on IMREG-1 (8%). Only two patients had sustained myalgia, leading to withdrawal of the drug. The myalgias and the transaminase elevations

did not resolve. No neutropenia or remarkable changes or differences in hematocrit or hemoglobin between the treatment groups were seen during the trial.

Discussion

Patients with AIDS-related complex and immunodeficiency characterized by reduced CD4+ cell numbers and impaired delayed hypersensitivity responses to recall antigens who were treated with IMREG-1 for up to 6 months had a lower incidence of opportunistic infections, including *P. carinii* pneumonia, and of other serious complications of HIV infection.

The various AIDS-defining and AIDS-related events that occurred in the placebo group and their relative frequency represent the natural history of the disease and demonstrate the appropriateness of our study sample. The behavior of the placebo group is the appropriate comparison against which the treated group should be evaluated. Further, because 11 female (7%) and 39 non-Caucasian (27%) patients were evenly distributed by treatment category, the results of the trial may be generalizable beyond the white male population.

The similarity of the treatment groups regarding demographic and baseline prognostic variables engenders confidence that there was no systematic bias in the randomization procedure. This absence of systematic bias implies that the observed result is not likely to be due to confounding by an imbalance in unknown variables.

Zidovudine was approved for distribution while this trial was in progress (13). Six of eight patients who left the trial to take zidovudine were in the active drug treatment category. The other 20 patients who withdrew from the study followed the 2:1 drug/placebo allocation ratio (13/7).

In an intention-to-treat analysis, adverse events occurring in noncompliers are included that may lessen the drug's apparent benefit; also, patients who withdraw early from treatment continue to have follow-up and are included in the analysis. In the intention-to-treat analysis, IMREG-1 delayed disease progression, as shown by the Cox relative risk of 5.1 for patients receiving the placebo compared with patients receiving IMREG-1. Furthermore, the increase in the frequency of constitutional symptoms in the placebo group, which may reflect subclinical infections, is consistent with the observed risk for progression to an end event in this group.

The primary action of IMREG-1 is believed to be as an immunomodulatory agent. Clinical effects are corroborated by changes in variables used to measure cell-mediated immunity (such as delayed hypersensitivity to recall antigens and CD4+ cell numbers). Given that progressive deterioration in these variables is expected in HIV infection and that one of our entry criteria was anergy to recall antigens, the observation that more patients on IMREG-1 showed increased CD4+ cell numbers and the greater rate of return of delayed hypersensitivity response to recall antigens support the view that an improvement in immunologic response is associated with a delay in the progression of HIV infection for at least 6 months (the duration of our trial).

Although there was a smaller than predicted rate of return of delayed hypersensitivity in our trial (26%) in patients receiving IMREG-1 than had been seen in the earlier uncontrolled clinical studies (50%) (6-9), it should be noted that skin testing was done less frequently in our trial (five times in 6 months compared with eight times in 3 months). It is possible that before a response to a recall antigen can be elicited, "formerly anergic" patients may need to be resensitized by repeated exposure to the antigen after their capacity to mount an antigen-specific response has been restored as a result of therapy with IMREG-1. Although less frequent skin testing permitted masking to be maintained, some patients who were anergic at entry may not have been sufficiently resensitized to antigen to be able to respond during the 6-month study period. Continued treatment of patients with IMREG-1 after completion of the trial was associated with a 41% rate of returned delayed hypersensitivity in one group of patients (14).

A principal criterion for enrollment of patients in our

Table 3. Change in Combined Symptom Score from Baseline in the IMREG-1 Trial Patients

Variable	IMREG-1		Placebo		*P* Value
	Patients	Symptom Score*	Patients	Symptom Score*	
	n		*n*		
Baseline†	93	1.26 ± 0.22	48	0.73 ± 0.22	
Weeks 2 to 4	93	− 0.06 ± 0.19	48	0.55 ± 0.27‡	0.04
Weeks 6 to 8	93	− 0.14 ± 0.22	48	0.56 ± 0.24§	0.02
Weeks 10 to 12	93	− 0.09 ± 0.22	48	0.78 ± 0.31§	0.05
Weeks 14 to 16	93	− 0.19 ± 0.22	48	0.99 ± 0.35§	0.006
Weeks 18 to 20	91	− 0.10 ± 0.23	48	1.22 ± 0.44§	0.008
Weeks 22 to 24	87	− 0.16 ± 0.24	46	1.51 ± 0.47‖	0.003
Week 26	82	− 0.04 ± 0.26	43	1.63 ± 0.46‖	0.01
Last available score	93	− 0.06 ± 0.24	48	1.24 ± 0.46§	0.05
Trend	93	− 0.01 ± 0.05	48	0.28 ± 0.11‡	0.09

* Symptom scores are given as means ± SE.
† Baseline is actual score at baseline; values for subsequent time points are changes from baseline.
‡ $P < 0.05$ for within-group comparison.
§ $P < 0.01$ for within-group comparison.
‖ $P < 0.001$ for within-group comparison.

trial was a high risk for occurrence of an AIDS-defining event in a 6-month period. The enrollees were a subset of patients with AIDS-related complex who had also lost the capacity to respond to recall antigens and were symptomatic or had oral candidiasis. In our study, the selection of patients based on several criteria was effective (as judged by the frequency of end-point events in the placebo group) in defining a sample of immunocompromised patients at high risk for progression of disease (15, 16).

IMREG-1 was first identified as a possible therapy because of its ability to augment and accelerate delayed hypersensitivity responses to recall antigens in normal test subjects in an antigen-dependent but antigen-nonspecific fashion (2, 3). In vitro, IMREG-1 enhances the production of leukocyte migration inhibition factor by antigen-stimulated lymphocytes of the CD4+ cell phenotype, the antigen-induced production of interferon-gamma, and the expression of interleukin-2 receptors by human CD4+ helper cells (5, 10, 17).

In earlier uncontrolled clinical trials, administration of IMREG-1 to patients with AIDS and AIDS-related complex was associated with the enhanced ability of patients' lymphocytes to produce interleukin-2 and interferon-gamma (8), the reconstitution of delayed hypersensitivity responses to recall antigens (6, 8, 9), and a relative preservation of circulating CD4+ cells (7, 9). The mechanism underlying the protective effect of IMREG-1 in AIDS-related complex is unknown, and the precise contributions of tyrosine-glycine and tyrosine-glycine-glycine have not been specified. Recipients of IMREG-1 had relatively preserved CD4+ cell counts during our trial. This effect may be a consequence of IMREG-1-mediated augmentation of lymphokine release, as has been demonstrated in vitro (5, 10).

Serum p24 antigen was not systematically measured in our study, but previous studies have shown that IMREG-1 does not increase the expression of HIV p24 core antigen by HIV-infected lymphocytes exposed to recall antigen in vitro (18). Viral cultures were not done.

The results of our placebo-controlled study show that the administration of IMREG-1 resulted in a lower incidence of AIDS-defining and AIDS-related events in patients with HIV infection, particularly among patients with AIDS-related complex who had a CD4+ cell count of 100×10^6/L or more before treatment. The relation between depressed immunologic function and clinical outbreaks of latent viral or mycotic infections has long been recognized; among HIV-infected persons there is an increased frequency of cytomegalovirus, herpes zoster, and herpes simplex infections; candidiasis; and tuberculosis. An immunomodulatory agent, such as IMREG-1, could be a very useful therapy in cases where antiviral therapy is inappropriate or unavailable or where toxicity or development of viral resistance may limit the usefulness of such therapy. It may also be a useful adjunct to effective antiviral therapy, provided that potential bone marrow toxicity of some antiretroviral therapy does not interfere with the action of IMREG-1. Our trial was conducted before prophylactic therapy with aerosolized pentamidine for *P. carinii* pneumonia became widespread. Therefore, it is not known whether aerosol pentamidine and IMREG-1 would interact. However, IMREG-1 would probably have its greatest applicability before the stage of HIV infection for which aerosolized pentamidine is approved. The limited experience with patients receiving IMREG-1 and zidovudine does not show any interference of zidovudine with the action of IMREG-1 (19).

We have presented the results of the first placebo-controlled trial of a new experimental therapy for AIDS-related complex. IMREG-1 is derived from human leukocytes and appears to modulate several immune parameters both in vitro and in vivo. The complete chemical characterization of this immunomodulator, its mechanisms of action in patients with HIV infection, and its role in normal immune function have not been fully defined. Although identifiable as sequences within β-endorphin and the *N*-terminal end of the enkephalins, the tripeptide tyrosine-glycine-glycine and the dipeptide tyrosine-glycine are devoid of opioid activity and may represent molecular links between the neuroendocrine and immune systems. Much additional work is required to determine the effects of IMREG-1 on mortality and over the wide range of HIV infection as well as in other clinical conditions in which altered immune function contributes or is integral to the disease state.

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Documentation of an AIDS Virus Infection in the United States in 1968

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The acquired immunodeficiency syndrome was first recognized as a clinical entity in the United States in the early 1980s; however, the issue of when human immunodeficiency virus, the causative agent of the acquired immunodeficiency syndrome, was introduced into at-risk populations in the United States is unresolved. Previously, we reported the case study of a 15-year-old black male who was admitted to St Louis City Hospital in 1968 for extensive lymphedema of the genitalia and lower extremities. Chlamydial organisms were widely disseminated and isolated from numerous body fluids and organs. Over a 16-month clinical course his condition progressively deteriorated, and at autopsy there was widespread Kaposi's sarcoma of the aggressive, disseminated type. Recently performed Western blot and antigen capture assays on serum and autopsy tissue specimens frozen since 1969 have disclosed that this sexually active teenager was infected with a virus closely related or identical to human immunodeficiency virus type 1. The clinical and immunologic findings together suggest that an immunosuppressive retrovirus existed in the United States before the late 1970s.

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THE ACQUIRED immunodeficiency syndrome (AIDS) is characterized by lymphadenopathy (nonspecific reactive hyperplasia), peripheral lymphocytopenia, and greatly increased risk for opportunistic infections and otherwise rare forms of cancer, including Kaposi's sarcoma.[1] Associated symptoms include weight loss, diarrhea, fever, night sweats, and central nervous system dysfunctions. The causative agent of AIDS is a cytolytic retrovirus that has been designated *human immunodeficiency virus* (HIV). Human immunodeficiency virus is capable of replicating in cells that express the CD4 cell surface protein, including T4 lymphocytes (helper T-cells), monocytes, and certain cells of the central nervous system.[2] Progressive depletion of T4 lymphocytes characteristically occurs in AIDS, but accounts for only some, not all, of the effects on the immune system resulting from HIV infection. Human immunodeficiency virus–induced cytopathic effects on CD4-positive brain cells may also be involved in the neuropathological features of AIDS.[3]

Acquired immunodeficiency syndrome was first recognized and defined as a clinical entity in the United States in the early 1980s.[4-8] The earliest diagnosed AIDS cases in the United States comprised homosexual or bisexual males, intravenous drug abusers, hemophiliacs, prostitutes, and recent immigrants from Haiti.[4,8] It has been suggested that HIV originated in Africa rather than the United States and that the current epidemic strain of HIV was imported from Africa to the Caribbean, and from there to the United States in the late 1970s.[9,10] However, the issue of when HIV was introduced into "at-risk" populations in the United States is unresolved, yet important for understanding transmission of this virus and for modeling the AIDS epidemic.[5,11]

A patient whose case history bears on the origin of AIDS in the United States was reported previously.[12,13] In brief, a 15-year-old black male was admitted to St Louis City Hospital in 1968 for extensive lymphedema of the penis, scrotum, and lower extremities. He had no history of travel outside of the Midwest, intravenous drug abuse, or blood transfusion. Chlamydial organisms were isolated from thoracic duct lymph, peripheral edema fluid, prostatic secretions, conjunctival scrapings, pleural fluid, and serum. The patient also had seropositive reactions for herpes simplex virus, cytomegalovirus, and Epstein-Barr virus, although active infections were not documented. Immunologic manifestations included peripheral lymphocytopenia and lymphoid tissue depletion along with negative tuberculin, histoplasmin, and Frei antigen skin tests. Over the ensuing 16 months his clinical course progressively deteriorated, and at the time of death the patient was severely wasted. Autopsy revealed a solitary cutaneous nodule of Kaposi's sarcoma on the medial aspect of the right thigh, and much of the soft tissue of the body, including the anorectum, was infiltrated with Kaposi's sarcoma. Reexamination of the tissue sections prepared at autopsy indicated that the Kaposi's sarcoma was indistinguishable from the aggressive, disseminated type characteristic of that of contemporary AIDS patients (M.H.W., unpublished data, 1988). Involvement of the anorectum with obliterative lymphangitis, prominent hemorrhoids, and Kaposi's sarcoma raised the possibility that the patient, who admitted to being sexually active, engaged in anal intercourse. Indeed, as is commonly the case in homosexuals, the rectum may have been the portal of entry for the chlamydial infection as well as HIV.

Recently, sensitive and specific tests for the presence of antibodies specific for HIV and for HIV antigens have been developed. Accordingly, we opted to reexamine the serum and autopsy specimens, which had been frozen since 1969, of the patient to determine whether he was infected with HIV or a similar virus. The findings raise important implications about the evolution of the AIDS epidemic in the United States.

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EDITORIAL

Development of Immunosupportive Drugs for Patients with AIDS/ARC

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The emergence of AIDS as a major world health problem is at once a challenge to the immunologic community, as well as a vindication of the investment which has been made in basic immunologic research over the last two decades, for without that information, our ability to understand and deal with this disease would be nil. The characteristics of this devastating disease are widely known, but it is well to emphasize that a principal feature is a defect in the capacity of the patient to mount immune reactions to specific antigenic challenges, as a result of selective progressive destruction of $CD4^+$ helper cells. Associated with failure of immune reactivity against specific antigens, part of the immune system appears to be excessively overactive, producing a variety of antibody-like proteins which are nonspecific and have no protective value. Concomitant features include the development of antilymphocyte and antiplatelet antibodies indicative of an autoimmune process. In a very real sense, this condition should be viewed as an acquired dysregulation of the immune system, the most prominent feature of which is a deficiency in the ability to mount specific immune responses. Reversal of these serious and complex immune dysfunctions does not occur spontaneously, and the disease in its advanced form has a high degree of fatality. The emergence of AIDS as a world public health problem of major dimensions poses a need for intense and comprehensive attention to all possible approaches to the treatment of this infection.

It is essential to recognize that the original definition of AIDS, as promulgated by the Centers for Disease Control, is very narrow and reflects only a minor fraction of this very serious public health problem. It is more logical to regard infection with human immunodeficiency virus as being able to cause a deficiency of the immune system to a variable degree in each patient who is infected. That is, some individuals who have been infected with the human immunodeficiency virus (HIV) (previously referred to as the LAV/HTLV) will have little compromise of immune function, while others will have a severe deficiency, and many will fall in between. In general, the more severe the immunodeficiency, the more likely the patient will experience the serious clinical complications of opportunistic infections and malignancies.

It should also be noted that although substantial information has been developed about the human immunodeficiency virus, and the fine structure of its ge-

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netics, relatively little is known about the way in which this virus damages cells of the immune system and thereby leads to disease.

Some basic questions about the pathogenic processes involved are:

(1) Are all $CD4^+$ (T helper) cells destroyed, after infection with HIV, or are there particularly critical subclasses which are most affected? It is well to remember that only 1 in 10,000 to 1 in 100,000 $CD4^+$ cells contain virus (1).

(2) What is the basis for the elevation in T8 ($CD8^+$) cells, in the aggregate, or in respect of specific subclasses of these cells, some of which may exert cell-mediated immunity against this virus?

(3) What is the basis for overactivity of the B-cell lymphocyte population, as reflected in the production of nonspecific immunoglobulins and follicular hyperplasia in the lymph nodes, in the face of an inability to produce antibody to specific antigen?

(4) What is the role of infectious agents, in the body and/or the environment, in activating lymphocytes for viral production?

(5) What are the effects of latent HIV infection in host cells for long periods of time? Does this affect the ability of the immune system to reconstitute and/or repopulate itself?

(6) What is the nature of circulating immunosuppressive molecules seen in these patients? What role do these play in the pathogenesis of the disease?

Moreover, we have little information about the cells that are needed to trigger immunity against this virus, and we remain puzzled as to why initial infection leads to circulating antibody which is not protective.

In thinking about approaches to treatment and control of HIV infection, three initiatives come to mind:

(1) Development of antiviral drugs that will suppress production of new HIV, or prevent infection of healthy lymphocytes by that virus, it being recognized that no technological means for eliminating the virus from the host DNA is possible, at the present time, or seems likely to be developed in the next decade.

(2) Development of vaccine(s) to confer protective immunity upon uninfected individuals. Apart from the fact that patients are infected with different strains of HIV, thereby creating a need for several types of vaccine(s), there is a great deal of fundamental information that needs to be developed, in order to provide the groundwork for development of vaccines against HIV strains.

(3) The development of biologics and/or drugs that ameliorate or modify the state of immune dysregulation with predominant immunodeficiency that is the hallmark of this disease. There is developing evidence (2–5) including a paper in the current issue of this Journal (6) that support of the immune system is possible in these patients. In our view, too little attention is being paid to this critical aspect of the problem. It is surprising that the repair of the immune deficiency in AIDS/ARC has, to date, been considered the least important aspect of treatment and control of this infection.

We submit that while extensive efforts have been undertaken in the area of development of antiviral agents, there is too little effort being directed toward a comprehensive understanding of the pathogenesis of this disease and the effects of HIV on the immune system. Such information would, of course, also be critical to

development of vaccines. Moreover, in our judgment, there has been a lack of appropriate emphasis on the development of drugs and/or biologics which can modify or repair the immune deficiency.

A consideration of importance as regards the development of immunosupportive or immunoreconstructive drugs is the apparent ability of the immune system of patients with HIV to undergo a process of immunologic compensation. For example, we have noted that some patients with HIV infection manifest normal functional immune responses, as reflected in response of their lymphocytes to mitogens, and/or in the ability to respond to skin test antigens, notwithstanding an absolute reduction in numbers of their $CD4^+$ (T helper) cells. What appears to happen in these instances in that the remaining cells work harder to "take up the slack." While the remaining cells are capable of doing this, the immune system maintains a normal or near normal level of function. However, as more $CD4^+$ cells are destroyed, the compensatory capacity of the remaining cells becomes compromised, and immunological function declines. If a drug or biologic could stabilize a compensated immune system or prevent decompensation, that would likely be beneficial for the patient.

In this context, the development of drugs/biologics capable of moving a patient's immune system from a state of immune deficiency to one of more normal function would likely have an impact on this disease. Such a drug/biologic would not be a cure, since it would not eliminate the virus, but it could control some of the manifestations and course of the disease.

The specific rationale for an immunosupportive drug in HIV disease is as follows:

(1) A principal feature of the disease is an immune deficiency.

(2) Although it is possible to design a program for the development of an antiviral drug(s) for widescale application, such a drug(s) is not available at present. The anticipated timetable for such a drug(s) is a minimum of 5 years, with time frames out to 15 years.

(3) It is clear that correction of the immune defect in these patients is a desirable objective, and it is reasonable to anticipate that improving immune function would reduce the frequency of opportunistic infections, and possibly malignancies in HIV-infected patients.

While it is claimed in some quarters that an "effective" antiviral would eliminate the necessity for an immunosupportive drug, since the immune system would regenerate on its own, this assumption is not based on any known evidence. It is well to point out that the ability and/or the period of time required for the $CD4^+$ cell population (or progenitors thereof) to be reconstituted in adequate numbers and function, once viral production is suppressed, is unknown. In this respect, attention should be paid to the possibility that bone marrow progenitor cells may be latently infected with HIV, and that such latent infection may well affect the ability of such lymphocytes to adequately reconstitute the immune system.

A further important consideration is the prospect that a drug having supportive effects on the immune system might enhance immune reactivity against strains of HIV which infect particular patients. That is, this might provide a means for enhancing the ability of the patient's immune system to react against the particular

viral strains which have infected the patient. This concept of postinfection vaccination, which is possible owing to the long latent period seen in this disease, has been advanced by several researchers and is an initiative that should be vigorously addressed, since:

(a) it might provide a means for possible protection of patients who have already been infected with HIV;

(b) it would be an extremely useful ancillary to a vaccine, if a vaccine were developed;

(c) it would reduce the need to come up with effective vaccines against multiple viral strains.

The development of immunosupportive drugs or biologics should be viewed as complementary to the development of antiviral drugs for widescale application to HIV-infected individuals. As developments proceed to find drugs which suppress production of new HIV particles and/or prevent infection of healthy $CD4^+$ cells by new viral particles, it is important to keep in mind the requirement that such drugs must be free of significant toxicity either for bone marrow precursors of immune cells or for effector cells of the immune system. To date, we believe that there has been too great a concentration of effort on developing antiviral therapy, and too little emphasis on learning about and correcting the disorders in immune function which are manifested in variable degrees in HIV-infected patients.

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FAX TO: Steve Lee

Office of National AIDS Policy Coordinator

FAX NO: (202) 632-1096

From: Jan McKay

Message: Letter requesting Mrs Gelbier give remarks at the meeting of the National Task Force on AIDS Drug Development.

Note: This transmission is from a dex Express 6300 telecopier. If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the number listed above.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 8, 1994

Kristine M. Gebbie, RN, MN, FAAN
National AIDS Policy Coordinator
750 17th Street, NW
Suite 1060
Washington, DC 20503

Dear Ms. Gebbie:

I am pleased to inform you that the first meeting of the National Task Force on AIDS Drug Development has been scheduled for April 14 and 15, at the Sheraton National Hotel, in Arlington, Va.

In discussions with Mr. Lee, a member of your staff, it was suggested you may wish to address the Task Force during their meeting. Therefore, I am pleased to invite you to present your remarks on the first day of the meeting, April 14, following Secretary Shalala. It is anticipated that these remarks would require approximately 15 - 20 minutes. While the public comment period is scheduled for later in the afternoon, please let us know if you would like to address questions from the members or the audience.

We appreciate your consideration of this invitation and look forward to a favorable reply.

Sincerely,

Randolph F. Wykoff, MD, MPH & TM
Associate Commissioner for AIDS
and Special Health Issues

THE WHITE HOUSE

WASHINGTON

November 24, 1993

MEMORANDUM

TO: Nancy-Ann Min, Associate Director for Health
Office of Management and Budget

FROM: Kristine M. Gebbie, R.N., M.N.
National AIDS Policy Coordinator

SUBJECT: National Task Force on Drug Development

There is a request before Mr. Panetta to fund the National Task Force on Drug Development in the Department of Health and Human Services. I strongly urge prompt approval. I would appreciate you carrying this message forward to Mr. Panetta.

If I can provide additional information, please let me know. My number is 632-1090.