DAY: THURSDAY
DATE: APRIL 14, 1994
TIME: 8:00A
LOCATION: SHERATON - ARLINGTON
EVENT: NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

PHOTOCOPY
PRESERVATION

Put in folder or something for mtg

RECEIVED

APR 11 1994

APR 12 1994

NOTE TO: KRISTINE GEBBIE

FROM: JEAN MCKAY

I have provided you with copies of all information sent to the members of the National Task Force on AIDS Drug Development. If you have any questions or concerns, please do not hesitate to call me at (301) 443-0104.

4/6/94

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT
April 14 - 15, 1994
Sheraton National Hotel
Arlington, VA

DRAFT AGENDA

Thursday, April 14, 1994

7:30 - 8:30	Registration	
8:30 - 8:45	Opening Remarks	Secretary Shalala
8:45 - 9:00	Remarks	Ms. Gebbie
9:00 - 9:30	Overview of meeting	Dr. Lee
9:30 - 10:30	Introduction/Remarks	Task Force
10:30 - 10:45	Break	
10:45 - 12:00	Introduction/Remarks	Task Force
12:00 - 1:30	Lunch	
1:30 - 4:30	Broad View of Barriers to AIDS Drug Development	

1. Intercompany Collaboration on AIDS Drug Development (Jurgen Drews, MD - Hoffman-LaRoche)
2. Treatment Action Group (Mark Harrington)
3. Project Inform/Future Directions in AIDS Research/Immune Restoration (Martin Delaney)
4. Pediatric AIDS Foundation

3:00 - 3:15 Break

5. Institute of Medicine (Gerald Friedland, MD)
6. Keystone Center - (David Barr, JD)
7. Government Internal Planning Group
   - A. Discovery - Robert Yarchoan, MD
   - B. Development - Steven Schnittman, MD
   - C. Collaborations - Jack Killen, MD

4:30 - 5:30 Open Public Comment

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DRAFT AGENDA

Friday, April 15, 1994

8:30 - 10:00	Discussion	Task Force
10:00 - 10:15	Break	
10:15 - 11:30	Formation/Charge Subcommittees	Dr. Lee
11:30	Adjourn	

2/4/94

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

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_____ Number of Pages (including coversheet) Date: 2-17-94

FAX TO: Steve Lee
Office of National AIDS Policy

FAX NO: (202) 632-1096

From: Jean McKay

Message: per your request - attached are the addresses for the members 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.

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4/6/94

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Kristine -

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Discussed the Manhattan Project concept with him briefly, he said good, but be careful. These be treacherous waters. However, I think it may be better to be bold than middlin' right now.

By the way, the speaker in the afternoon from Hoffman LaRoche will announce on behalf of the InterCompany Collaboration on AIDS Drug Development that they will be initiating within two months a number of "master protocols" combining various antiviral drugs, such as AZT, ddI, ddC, Nevarapine, protease inhibitor, etc. Will start with several 100 person studies for people between 200 and 500 CD4 cells, and will be conducted at universities, coordinated by contract research organization. "Complementary to ACTG", says Linda Distlerath of Merck.

Terry

draft "Talking Points" for NAPC for Kick-off of the National Task Force on AIDS Drug Development on April 15, 1994.

Introduction:
I want to congratulate the Secretary, as well as Dr. Lee and all the other government representatives who got this Task Force off the ground in record time. It shows a real commitment to the urgency of this issue.

As members of the National Task Force on AIDS Drug Development, you have accepted a heavy responsibility. I hope that each of you has considered very carefully the potential impact of your work on this Task Force for the millions of people around the globe infected with HIV. Your charge is to change the course of this epidemic - to change the course of human history - nothing less.

The wonderful thing about this Task Force is its unique blend of government, industry, academia and community representatives. Each brings an equally valuable perspective to the table.

As you develop your recommendations and send them to Secretary Shalala, I know they will be responded to as a top priority, particularly as she has appointed the top leadership in her department on this issue to the Task Force itself. By naming Dr. Lee as chair, and including Drs. Varmus and Kessler, the Task Force will be able to reach mutual agreement between government and the private sector on what steps should be taken, without need of additional time-consuming study.

Many of the issues you will be addressing may involve agencies and departments throughout the federal government, and potentially Congress as well. Working together, we will use all the powers of the executive branch to respond to your recommendations.

The conclusions you reach will carry far more weight than anything that I or the president or anyone else in this administration could come up with on our own - your combined wisdom and expertise will bring authority to your recommendations, and will give necessary momentum to any necessary reforms.

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The Task:
All members of the Task Force have a responsibility to each other, to be candid in providing information and opinion.

Do not shy away from any topic that could potentially bear fruit. The subject matter is too important to allow political ideologies or conventional wisdom to get in the way. There should be no sacred cows here.

Though it may sound simple to some, your job is extremely daunting:

to identify the barriers and the opportunities in AIDS drug development, and to recommend as quickly as possible how those barriers can best be removed, and how those opportunities can best be taken advantage of.

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The Manhattan Project:

One question that is sure to come up for you, at least as often as it has for me, is: what is the Manhattan Project for AIDS?

Over the last several months, I have sought to bring some definition to what people call the "Manhattan Project" for AIDS research.

As uncomfortable as the term makes me personally, I believe we cannot shy away from evaluating the different interpretations of this abstract concept as it applies to AIDS. The President himself has thrown us all into this debate, promising a "Manhattan Project for AIDS", knowing of course that a few details would need to be worked out on this. I take this seriously, and I think we have a responsibility to respond.

I have listened to many diverse points of view on this subject, and while there is still wide disagreement, largely because of the fact that there is so much still to be done in basic research, I have reached some conclusions on this subject.

I believe that we must begin to regard the entire Federal and private AIDS research enterprise, not only in the United States but internationally, as a developing "Manhattan Project" for AIDS research. Then, we have to go about the business of making this huge enterprise work to its maximum potential.

If our goal is to find effective therapies and vaccines for HIV/AIDS, all our energies need to be focused on taking a hard look at this big picture.

This is what makes the formation of this Task Force so brilliant and so critically important: you are uniquely positioned to answer the most pressing questions: What are the real obstacles and opportunities in the whole AIDS research enterprise, and what can and should be done about them? What can we do to make the whole thing work better, leaner, meaner, and faster?

Several significant steps have been taken on this path in the last 16 months. In addition to the formation of this Task Force,

- the revitalized NIH Office of AIDS Research with its expanded planning and budgeting authorities, now under the leadership of Dr. William Paul;
- significant increases to the NIH AIDS research budget;
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which I understand will be making important announcements later today;

- the Madison Project, which has many interesting recommendations which will be discussed later today;
- a new working group convened by the State Department to develop mechanisms for international coordination; and many other initiatives of the administration and the private sector.

These are additional steps along the way to turning the whole international AIDS research effort into a more efficient, working "Manhattan Project" for AIDS research.

I don't know that we need to turn the whole thing on its head, as some have suggested, or that we should try to remove what somebody decides is good or most important from the whole and put it in one physical place or under new management.

We need to fix what we have by enhancing communication, coordination, and collaboration, in a way that fosters new ideas and ensures that we don't miss the boat altogether.

I think we need many focused, complementary AIDS research initiatives, not just one. And indeed, many focused projects are already going on in government and in the private sector. However, I think it's obvious that any new projects must be closely coordinated with existing programs.

****

Funding:

On the issue of funding, I encourage the Task Force not dwell too long on it. Of course, more money could probably be effectively spent for research, as well as for many other programs.

But I think the most important thing we can do is to make sure that the money we do spend is well spent, and that it is managed efficiently.

I believe that this process of evaluation is well underway at the NIH, and we are working to broaden this to research programs throughout the Federal government.

Our ultimate goal for AIDS research funding should be to eliminate all inefficiency and unnecessary duplication, while taking advantage of all promising scientific opportunities.

I hope that all private sector efforts can be brought into close coordination with each other and with the Federal government to accomplish this goal.

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Conclusion:

Again, on behalf of the President, I hope and pray that this National Task Force on AIDS Drug Development comes up with some answers for all of us. We desperately need your help, and I thank you from the bottom of my heart for taking on this task.

Though to many people the horizon still looks pretty bleak for new effective therapies and vaccines, I am optimistic that your efforts, and all the renewed energy of the last year, and new efforts still to come, will reap some truly great rewards down the road, and will bring that day when the world can be free of this terrible plague that much closer.

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God speed.

[20] From: Terry Beswick 4/13/94 3:39PM (10684 bytes: 25 ln, 1 fl)
To: Kristine Gebbie
cc: Steve Lee, John Gurrola, Andrew Barrer, Paul Tran, Arthur Lawrence, Carlos Velez
Subject: Talking Points
---------- Message Contents ----------

Text item 1:

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Director, Division of Retrovirology

Douglas Mayers, M.D.
Chief, Drugs and Gene Therapy

Office of National AIDS Policy Advisor

Terry Beswick

Health Care Financing Administration

Helen Smits, M.D.
Deputy Director
(TFMEMFAX.11)

4/6/94

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT
April 14 - 15, 1994
Sheraton National Hotel
Arlington, VA

DRAFT AGENDA

Thursday, April 14, 1994

7:30 - 8:30	Registration	
8:30 - 8:45	Opening Remarks	Secretary Shalala
8:45 - 9:00	Remarks	Ms. Gebbie
9:00 - 9:30	Overview of meeting	Dr. Lee
9:30 - 10:30	Introduction/Remarks	Task Force
10:30 - 10:45	Break	
10:45 - 12:00	Introduction/Remarks	Task Force
12:00 - 1:30	Lunch	
1:30 - 4:30	Broad view of barriers to AIDS drug development	

1. Intercompany Collaboration on AIDS Drug Development (Jurgen Drews, MD - Hoffman-LaRoche)
2. Treatment Action Group (Mark Harrington)
3. Project Inform/Future Directions in AIDS Research/Immune Restoration (Martin Delaney)
4. Pediatric AIDS Foundation

3:00 - 3:15 Break

5. Institute of Medicine (Gerald Friedland, MD)
6. Keystone Center - (David Barr, JD)
7. Government Internal Planning Group
   - A. Discovery - Robert Yarchoan, MD
   - B. Development - Steven Schnittman, MD
   - C. Collaborations - Jack Killen, MD

4:30 - 5:30 Open Public Comment

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT
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DRAFT AGENDA

Friday, April 15, 1994

8:30 - 10:00	Discussion	Task Force
10:00 - 10:15	Break	
10:15 - 11:30	Strategies to address issues	Dr. Lee
11:30	Adjourn	

EFFECT OF SPECIAL GOVERNMENT EMPLOYEE STATUS ON APPLICABILITY OF CRIMINAL CONFLICT OF INTEREST STATUTES AND OTHER ETHICS RELATED PROVISIONS

Definition

As defined by 18 U.S.C. § 202(a), a "special government employee" (SGE) in the executive branch is an officer or employee who is retained, designated, appointed, or employed to perform temporary duties, with or without compensation, for a period not to exceed 130 days during any period of 365 days, either on a full-time or intermittent basis.

Financial Disclosure

An SGE is subject to the financial disclosure provisions of the Ethics in Government Act and 5 C.F.R. Part 2634. If an SGE is reasonably expected to serve more than 60 days in any calendar year; and the SGE is paid at an hourly rate equal to or greater than $38.30 per hour, or at a daily rate equal to or greater than $306.40 per day; the Public Financial Disclosure Report (SF 278) must be filed. 5 C.F.R. §§ 2634.202(c) and 2635.204. If the salary rate is less than $38.30 per hour or $306.40 per day; or if the SGE, regardless of pay rate, is expected to work 60 days or less; submission of the Confidential Financial Disclosure Report (SF 450) is required. 5 C.F.R. § 2634.904(b).

Substantive Restrictions

With certain significant exceptions outlined below, the criminal conflict of interest statutes, the seminal ethics executive order (E.O. 12674, as amended by E.O. 12731), and the executive branch standards of ethical conduct (5 C.F.R. Part 2635) are applicable to SGEs. Other ethics related statutes and regulations dealing with outside earned income and employment, the honoraria ban, and political activities, are either wholly or partially inapplicable. The principal distinctions between the rules applicable to regular government employees and those governing SGEs are as follows:

I. Criminal Conflict of Interest Statutes

18 U.S.C. § 203 -- Prohibition of Compensated Representational Activities By Federal Employees Directed Towards the United States

Regular Employee: Section 203 prohibits an employee from seeking, accepting, or agreeing to receive or accept compensation for any representational services, rendered personally or by another, in relation to any particular matter in which the United States is a party or has a direct and substantial interest.

Special Government Employee: The scope of the restriction is limited significantly for SGEs. The bar applies only in relation to a particular matter involving a specific party or parties --

(1) in which the SGE has at any time, participated personally and substantially as a Government employee; or

(2) if the SGE has served in excess of 60 days during the immediately preceding 365 days, such matter is pending in the department or agency in which such employee is serving.

18 U.S.C. § 205 -- Prohibition of Uncompensated or Gratuitous Representational Activities By Federal Employees Directed Towards the United States

Regular Employee: Section 205 prohibits an employee, whether or not for compensation, from acting as agent or attorney for anyone in a claim against the United States or from acting as agent or attorney for anyone, before any department, agency, or other specified entity, in any particular matter in which the United States is a party or has a direct and substantial interest. It also prohibits receipt of any gratuity, or any share of or interest in a claim against the United States, in consideration for assisting in the prosecution of such claim.

Special Government Employee: The broad prohibition is narrowed in the same manner as noted above for section 203.

18 U.S.C. § 207 -- Post-Employment Restrictions

Regular Employee: Section 207 imposes bans of varying durations to prevent communications by former employees made with the intent to influence the Government. The lifetime ban covers particular matters involving specific parties in which the former employee was personally and substantially involved. A similar two-year ban deals with such matters that were merely pending under the employee's official responsibility during the final year of government service. A one-year ban applies to employees involved in trade or treaty negotiations. Other rules apply to senior personnel paid at an annual rate in excess of $108,200; such senior employees are subject to a one-year "cooling-off" period precluding any contacts with their former agency on any matter for which official action is sought.

(Note: For senior Clinton Administration appointees, the duration of the "cooling-off" period has been increased to five years. The 5-year "cooling-off" period prescribed by E.O. 12834 of January 22, 1993, is applicable only to full-time, non-career senior appointees who personally have executed a pledge of compliance as a condition of their appointment.)

Special Government Employee: The one-year "cooling-off" period for senior employees is not applicable to an SGE who served less than 60 days in the one-year period prior to termination. Inasmuch as SGEs are not full-time appointees, the 5-year ban is not applicable. All other prohibitions are applicable to SGEs.

18 U.S.C. § 208 -- Conflict of Interest Provision

Regular Employee: Section 208 proscribes personal and substantial participation in any particular matter which will have a direct and predictable effect on an employee's own or imputed financial interests. A waiver under section 208(b)(1) permitting official action in such matters may be obtained from an employee's appointing authority, if the financial interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such employee.

Special Government Employee: The same conflict of interest rules apply to SGEs. However, the standard for obtaining a waiver for certain SGEs is reduced (and thus easier to justify) by focusing on the need for the services, rather than the value of the financial interest. Specifically, a waiver under section 208(b)(3) for SGEs serving on an advisory committee within the meaning of the Federal Advisory Committee Act is available where the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

18 U.S.C. § 209 -- Ban on Supplementation of Salary

Regular Employee: Section 209 prohibits an employee from receiving any salary or any contribution to or supplementation of salary from any source other than the United States as compensation for services as a government employee.

Special Government Employee: This provision is not applicable.

II. Other Ethics Related Statutes

5 U.S.C. App. 7, § 501(a) -- Outside Earned Income Limitation

Regular Employee: Section 501(a), and implementing regulations at 5 C.F.R. §§ 2636.301 through 2636.304, provide that a non-career employee paid at a rate in excess of a GS-15 may not, in any calendar year, receive outside earned income attributable to that calendar year which exceeds 15 percent of the annual rate of basic pay for level II of the Executive Schedule under 5 U.S.C. 5313, as in effect on January 1 of such calendar year (15% of 129,500 for calendar year 1993 = $19,425).

Special Government Employee: This provision is not applicable.

5 U.S.C. App. 7, § 501(b) -- Honoraria Ban

Regular Employee: Section 501(b), and implementing regulations at 5 C.F.R. §§ 2636.201 through 2636.205, prohibit an employee from receiving any compensation for an appearance, speech or article, even though the subject may be unrelated to the employee's official duties.

Special Government Employee: This provision is not applicable. Refer to 5 C.F.R. § 2635.807 for teaching, speaking, and writing provisions that do apply to SGEs.

5 U.S.C. App. 7, § 502(a) -- Limitations on Outside Professional Employment and Teaching

Regular Employee: Section 502(a), and implementing regulations at 5 C.F.R. §§ 2636.305 through 2636.307, prohibit a non-career employee paid at a rate in excess of a GS-15 from receiving any compensation for: practicing a profession which involves a fiduciary relationship; affiliating with or being employed by a firm or other entity which provides professional services involving a fiduciary relationship; serving as an officer or member of the board of any association, corporation or other entity; or teaching without prior approval.

Special Government Employee: This provision is not applicable.

5 U.S.C. §§ 7321 - 7328 -- Hatch Act Political Activity Restrictions

Regular Employee: The Hatch Act, and implementing regulations at 5 C.F.R. Part 733, prohibit most employees from engaging in certain partisan political activities and prohibit all employees from interfering with elections and conducting political activities in the Federal workplace.

Special Government Employee: SGEs are covered by the Act only during the 24-hour period of any day in which they are actually performing government business.

III. Executive Branch Standards of Ethical Conduct

The government-wide Standards of Ethical Conduct promulgated by the Office of Government Ethics, 5 C.F.R. Part 2635, are fully applicable to both regular and special government employees. Notably, an SGE is covered by the standards even though the individual does not perform official duties on a given day.

Those portions of the standards that restate the statutory rules noted previously in this discussion are not set out below. The following text notes the only other areas where the standards differ based on SGE status.

5 C.F.R. § 2635.805 -- Service as an Expert Witness

Regular Employee: An employee shall not serve, other than on behalf of the United States, as an expert witness, with or without compensation, in <u>any proceeding</u> before a court or agency of the United States <u>in which the United States is a party or has a direct and substantial interest</u>, unless the employee's participation is authorized by the designated agency ethics official (DAEO).

Special Government Employee: For SGEs, the bar against expert testimony applies only if the individual has participated while a Federal employee in the particular proceeding or in the particular matter that is the subject of the proceeding.

If an SGE has been appointed by the President; serves on a commission established by statute; or has served or is expected to serve for more than 60 days in a period of 365 consecutive

days, an additional restriction applies. These SGEs cannot serve, other than on behalf of the United States, as an expert witness, with or without compensation, in any proceeding before a court or agency of the United States in which the individual's employing agency is a party or has a direct and substantial interest, unless the employee's participation is authorized by the DAEO.

5 C.F.R. § 2635.807 -- Teaching, Speaking, and Writing

Regular Employee: Except for certain teaching activities, an employee shall not receive compensation from any source other than the Government for teaching, speaking, and writing that relates to the employee's official duties. The "relatedness" test is met if: (A) the activity is undertaken as an official government duty; (B) the circumstances indicate that the invitation to engage in the activity was extended to the employee primarily because of the employee's official position rather than the employee's expertise on the particular subject matter; (C) the invitation to engage in the activity or the offer of compensation for the activity was extended to the employee, directly or indirectly, by a person who has interests that may be affected substantially by performance or nonperformance of the employee's official duties; (D) the information conveyed through the activity draws substantially on ideas or official data that are nonpublic information; or (E) the subject of the activity deals in significant part with:

(1) Any matter to which the employee presently is assigned or to which the employee had been assigned during the previous one-year period;

(2) Any ongoing or announced policy, program or operation of the agency; or

(3) In the case of certain noncareer employees, the general subject matter area, industry, or economic sector primarily affected by the programs and operations of the employee's agency.

Special Government Employee: The restrictions in paragraphs (2) and (3) do not apply to an SGE. The restriction in paragraph (1) applies only during the current appointment of an SGE; except that if the SGE has not served or is not expected to serve for more than 60 days during the first year or any subsequent one year period of that appointment, the restriction applies only to particular matters involving specific parties in which the SGE has participated or is participating personally and substantially.

5 C.F.R. § 2635.808 -- Fundraising Activities

Regular Employee: An employee may engage in fundraising in a personal capacity provided that the individual does not personally solicit funds or other support from a subordinate, or from any person known to the employee to be one of the five types of prohibited sources specified in section 2635.203(d).

Special Government Employee: An SGE may engage in fundraising in a personal capacity provided that the individual does not personally solicit funds or other support from a subordinate, or from any person known to the employee to be a prohibited source within the meaning of section 2635.203(d)(4), i.e., a person whose interests may be substantially affected by the performance or nonperformance of the employee's official duties.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the General Counsel
Washington, D.C. 20201

MAR 25 1993

MEMORANDUM

TO : Special Government Employees Serving as Advisory Committee Members

FROM : Jack M. Kress
Special Counsel for Ethics

SUBJECT: Post-Employment Restrictions Applicable to "Special Government Employees"; Rules for Seeking Concurrent and Subsequent Employment; and Teaching, Speaking, and Writing

This memorandum summarizes the post-employment restrictions that apply when your service as a special government employee (SGE)/advisory committee member is completed, as well as rules applicable to you when seeking concurrent or subsequent employment and when you teach, speak, or write. These restrictions and rules apply throughout the term of your appointment, not just on the days you attend committee meetings or otherwise perform advisory committee member functions.

Post-Employment Restrictions

There are basically three restrictions in a criminal statute (18 U.S.C. § 207), that are relevant to you as an SGE:

The **lifetime ban** prohibits any former government employee from representing another person or entity before any Federal agency or court on any particular matter, if the matter is one in which the former employee participated personally and substantially as a government employee, the matter involved specific parties at the time of the participation, and in which the United States has an interest. 18 U.S.C. § 207(a)(1).

The **2-year ban** on representational contacts applies to those particular matters involving specific parties in which you were not personally involved, but were simply pending under your official responsibility during your last year of government service. 18 U.S.C. § 207(a)(2).

> The **1-year "cooling-off" period** prohibits former <u>senior</u> employees from representing anyone to the agency (or component) in which they served for a period of one year after termination from government employment. 18 U.S.C. § 207(c)[1]

As a practical matter, the first two provisions are less likely to affect the post-employment activities of many SGEs significantly because the focus of each ban is on "particular matters involving specific parties." This phrase refers to discrete matters associated with an identified individual or entity, such as a contract, a grant, litigation, a new drug application, a waiver application, or a claim. If you are involved in such matters (as you would be, for example, on an FDA Advisory Committee reviewing a new drug application), you are probably very aware of the confidential nature of your involvement, as well as the impact any representation may have on specific parties. You should be aware that your duties often do concern particular matters involving specific parties.

In contrast, however, broad rulemaking, legislation, the formulation of general policy, standards, or objectives (or other actions of general application) are not covered. If your activities generally fall in the latter category (as would be the case, for example, with such advisory committees as the President's Council on Mental Retardation), the lifetime and 2-year bans rarely would be applicable.

The 1-year "cooling-off" period will be applicable only to those <u>senior</u> SGEs who serve 60 days or more in the year immediately preceding termination. (Keep in mind that this provision applies to any matter and does not require any personal participation or official responsibility.) "Senior employees" are defined as those who are paid at a rate greater or equivalent to Executive Level V. For calendar year 1993, <u>senior</u> SGEs are those individuals whose hourly pay rate equals or exceeds $51.84 per hour, or whose equivalent daily rate equals or exceeds $414.72 per day. If your salary rate is lower, then the "cooling-off" period will not concern you.

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[1] The five year "cooling-off" period prescribed by President Clinton's Executive Order 12834, of January 22, 1993, is applicable only to full-time, non-career senior appointees who have executed a pledge.

Moreover, for the purpose of applying the 1-year "cooling-off" period, the Department is divided into a parent organization and five separate components. The parent is comprised of the Office of the Secretary and its constituent staff divisions. The five designated components are the Public Health Service (PHS), the Health Care Financing Administration (HCFA), the Social Security Administration (SSA), the Administration for Children and Families (ACF), and the Food and Drug Administration (FDA). Former senior SGEs are restricted from representational contacts only with that segment of the Department in which they served.

If you are appointed as an SGE with HCFA, for example, you may contact the parent department, i.e., the Office of the Secretary, or any other component, provided that no other restriction, such as the lifetime or 2-year ban, applies. If you serve in the parent organization, the bar prohibits post-employment contacts with other employees of the parent organization, but contact with current employees of designated components would be permitted.

There are also exceptions to the 1-year "cooling-off" period for representations made on behalf of the United States, State or local governments, colleges and universities, non-profit hospitals and medical research institutions, and international organizations; and for certain scientific and technological information and testimony under oath.[2]

The three basic post-employment rules focus only on appearances or communications made with the intent to influence official action. None of these restrictions applies to "behind the scenes" advice, i.e., where another individual whom you have briefed is the one making the representation. In addition, purely social contacts, requests for publicly available documents, or requests for purely factual information are all allowed. Post-employment appearances before or communications to Members of Congress and legislative staff are permitted as well.

As this is intended to be a brief summary, additional and not widely applicable one-year restrictions on those involved in trade or treaty negotiations or who work for foreign governments or foreign political parties have not been addressed. See 18 U.S.C. §§ 207(b) and (f). Further, there are Procurement Integrity Act provisions applicable to those individuals involved in government contracting. See 41 U.S.C. § 423.

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[2] For the applicability of various exceptions to the lifetime and 2-year bans, please consult committee management staff. For example, the exception for certain scientific and technological information and testimony under oath applies to the lifetime ban under 18 U.S.C. § 207(a).

Rules for Seeking Concurrent and Subsequent Employment

You should be aware that the government-wide Standards of Ethical Conduct regulations (5 C.F.R. Part 2635, Subpart F) prohibit all present government employees (including SGEs) from participating in particular matters affecting the financial interest of any potential employer with whom they are seeking employment or a business relationship, whether as a concurrent outside activity or as a subsequent position following Federal service. Unless an appropriate official authorizes the activity, an SGE must effect a disqualification by not acting with respect to the problematic interest. This rule can come into play with a situation as ostensibly innocuous as arranging a speaking engagement.

Note, in addition, that the criminal conflict of interest statute (18 U.S.C. § 208), prohibits employees, including SGEs, from participating in particular matters affecting the financial interests of a person with whom they are negotiating prospective employment. Unless an appropriate official formally waives the conflict, an SGE must effect a disqualification with respect to the problematic interest.

Teaching, Speaking, and Writing

Finally, while SGEs are not covered by the honoraria ban (5 U.S.C. App. 7, § 501(b)), there are some restrictions on SGEs with respect to teaching, speaking, and writing for compensation. Under 5 C.F.R. § 2635.807, an employee (including SGEs) cannot receive non-Federal compensation (including transportation, lodging, and meals) for teaching (except a course at an accredited educational institution), speaking or writing that **relates to the employee's official duties.**

For SGEs, an activity relates to the employee's official duties if: (A) the activity is undertaken as an official government duty; (B) the circumstances indicate that the invitation to engage in the activity was extended to the employee primarily because of the employee's official position rather than the employee's expertise on the particular subject matter; (C) the invitation to engage in the activity or the offer of compensation for the activity was extended to the employee, directly or indirectly, by a person who has interests that may be affected substantially by performance or nonperformance of the employee's official duties; (D) the information conveyed through the activity draws substantially on ideas or official data that are nonpublic information; **or** (E) the subject of the activity deals in significant part with any matter to which the SGE presently is assigned or to which the SGE had been assigned during the previous one-year period. (If the SGE has not served or is not

expected to serve for more than 60 actual days of Federal employment during the first year or any subsequent one year period of that appointment, then the last indicator of "relatedness" focuses not on assigned matters, but only on particular matters involving specific parties in which the SGE has participated or is participating personally and substantially.)

Section 2635.807 does not preclude an SGE from receiving compensation for teaching, speaking or writing on a subject within the employee's discipline or inherent area of expertise based on the employee's educational background or experience even though the teaching, speaking or writing deals generally with a subject within the agency's areas of responsibility. Remember as well that this provision is only applicable during the period in which you are a Federal employee; this is not a post-employment restriction.

If you have any specific questions about these restrictions or the application of these rules to particular fact situations, please do not hesitate to contact committee management staff or the Office of the Special Counsel for Ethics at (202) 690-7258.

CHARTER AMENDMENT

National Task Force on Acquired Immunodeficiency Syndrome (AIDS) Drug Development

Structure

The Task Force shall consist of the Assistant Secretary for Health as Chair and 17 members selected by the Secretary from among authorities knowledgeable about AIDS and treatment development issues. Members shall be drawn from the drug development industry, academic and medical research centers, clinical medicine, Federal government, and HIV-infected and affected communities. Members representing the drug development industry shall serve as industry representatives and shall not be appointed as special Government employees. All other members shall be appointed as special Government employees of the Department of Health and Human Services.

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 members first appointed: six shall serve for a term of two years, six 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 his/her term until a successor has taken office.

Subcommittees composed of members of the parent Task Force shall be established to perform specific functions within the Task Force's jurisdiction. The Department Committee Management Officer shall be notified upon establishment of each subcommittee, and shall be provided information on its name, membership, function, and estimated frequency of meetings.

Management and support services will be provided by the Office of AIDS and Special Health Issues, Food and Drug Administration, and the Office of AIDS Research, National Institutes of Health.

Compensation

Members who are not full-time Federal employees, but who are special Government employees, shall be compensated at the rate of $150.00 per day for the time spent at meetings, plus per diem and

travel expenses in accordance with Standard Government Travel Regulations. Members who serve as industry representatives shall not be compensated by the Department, but may receive per diem and travel expenses.

APPROVED:

_____ _____

Date Secretary

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER AMENDMENT

National Task Force on Acquired Immune Deficiency Syndrome(AIDS) Drug Development

Structure

The Task Force shall consist of the Assistant Secretary for Health as Chair and 17 members selected by the Secretary 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 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 members first appointed: six shall serve for a term of two years, six 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 his/her term until a successor has taken office.

Subcommittees composed of members of the parent Task Force shall be established to perform specific functions within the Task Force's jurisdiction. The Department Committee Management Officer shall be notified upon establishment of each subcommittee, and shall be provided information on its name, membership, function, and estimated frequency of meetings.

Management and support services will be provided by the Office of AIDS and Special Health Issues, Food and Drug Administration, and the Office of AIDS Research, National Institutes of Health.

APPROVED:

2/28/94
Date

Secretary

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

C H A R T E R

National Task Force on Acquired Immune Deficiency Syndrome (AIDS) Drug Development

Purpose

The Secretary of the Department of Health and Human Services is charged with the administration of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. The National Task Force on AIDS Drug Development will advise the Secretary and, as needed, other parts of the Administration, on how best to proceed in developing drugs to treat AIDS, a major public 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 the Department of Health and Human Services, the Department of Defense, and other Departments, as appropriate, in conjunction with the National AIDS Policy Coordinator, 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. The Task Force 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.

Authority

42 USC 217a; Section 222 of the Public Health Service Act, as amended. The Task Force is governed by the provisions of Public Law 92-463, as amended (5 U.S.C. app. 2), which sets forth standards for the formation and use of advisory committees.

Function

The Task Force shall identify any barriers and provide creative options for the rapid development and evaluation of treatments for 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.

Structure

The Task Force shall consist of the Assistant Secretary for Health as Chair and 14 members selected by the Secretary 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 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 members first 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 his/her term until a successor has taken office.

Subcommittees composed of members of the parent Task Force shall be established to perform specific functions within the Task Force's jurisdiction. The Department Committee Management Officer shall be notified upon establishment of each subcommittee, and shall be provided information on its name, membership, function, and estimated frequency of meetings.

Management and support services will be provided by the Office of AIDS and Special Health Issues, Food and Drug Administration, and the Office of AIDS Research, National Institutes of Health.

Meetings

Meetings shall be held approximately four times a year at the call of the Chair, who shall also approve the agenda. A Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings of the Task Force shall be conducted and records of the proceedings kept as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time Federal employees shall be paid at the rate of $150.00 per day for the time spent at meetings, plus per diem and travel expenses in accordance with Standard Government Travel Regulations.

Annual Cost Estimate

The estimated annual cost for operating the Task Force and its subcommittees and working groups, including compensation and travel expenses for members, but excluding staff support is $ 122,550. The estimated personyears of staff support is 3.0, at an estimated annual cost of $ 175,104.

Reports

An annual report shall be submitted to the Secretary no later than November 1 of each year which shall contain as a minimum the function of the Task Force, a list of members and their business addresses, the dates and places of meetings, and a summary of the Task Force's activities and recommendations during the preceding year. A copy of the report shall be provided to the Department Committee Management Officer.

Termination Date

Unless renewed by appropriation action prior to its expiration, the National Task Force on Acquired Immune Deficiency Syndrome (AIDS) Drug Development will terminate two years from the date this charter is approved.

APPROVED:

MAY 22 1993
Date

Secretary

Executive Summary

Date: April 6, 1994

To: Members of the AIDS Task Force

From: Steven Gitterman, M.D., Ph.D., CDER, FDA
Kazem Kazempour, Ph.D., CDER, FDA
Ilana Fogelman, M.D., CBER, FDA
Douglas Mayers, M.D., Department of Defense
Jeffrey Murray, M.D., CDER, FDA
David Wilde, M.D., CBER, FDA

Proposal: Initiation of a focused effort to assess the value of newer surrogate markers in the treatment of HIV.

Summary: Identifying and validating virological surrogate markers of HIV activity has great potential for advancing the care of HIV-infected patients in the immediate future. Newer techniques that can directly quantitate viral replication have a potential not realized by earlier surrogate measures. We propose that a coordinated effort be directed toward the specific goal of validating newer measures with the cooperation of government, academia, and industry. The AIDS Task Force can be of great assistance in facilitating such an effort.

Statement of The Problem:

There is an urgent need for better validated markers of *in vivo* viral activity as a means to:

(1) Reduce the size and duration of clinical trials of therapy for HIV-infected persons and thereby expedite the overall development of anti-HIV therapy, including drugs, vaccines, and immune modulators.

(2) Reduce the substantial direct and indirect costs associated with therapy of uncertain or unknown benefit.

(3) Individualize treatment so that drug therapy can be more appropriately selected for a given patient.

Proposal: It is specifically proposed that either a separate panel or subcommittee of the Task Force be chosen and charged with the following tasks:

(1) Review published and unpublished studies (and available datasets) of tests that hold promise as surrogate markers in the treatment of HIV-disease, including polymerase chain reaction (PCR), branched chain DNA assay, SI versus NSI isolates, and certain genotypic mutations. These assays should be considered both for sensitivity/specificity and potential cost-effectiveness.

(2) Identify specimen banks from experimental and observational studies that could be used to address the validity of surrogate markers; a mechanism should be provided for assaying samples if necessary. There should also be establishment of a centralized specimen bank to hold clinical samples and HIV isolates from prior clinical studies; this resource should also solicit samples from patients with well-documented clinical outcomes and interventions as well as from a prospective cohort.

(3) Support a series of focused joint meetings of the companies commercially developing these methods with representatives of PHS, DOD, the pharmaceutical industry, the major clinical trials groups, and expert consultants. The specific goal of these meetings would be to explore the means of validating these virological and immunological measures for use in both clinical trials and patient management, and how each group can contribute to this effort.

Introduction:

Although the contribution of direct HIV-induced pathology to that mediated by immune mechanisms is under study, there is undeniably a major role for HIV replication in the pathogenesis of disease. This has led to the screening of compounds for the treatment of HIV by the demonstration of *in vitro* viral suppression. Compounds that demonstrate viral suppression and favorable results in preclinical studies (e.g., animal toxicity, pharmacokinetics) are then investigated in clinical studies. For the three approved antiretroviral agents, zidovudine, zalcitabine, and didanosine (AZT, ddC, and ddI), both *in vitro* and *in vivo* viral suppression have been demonstrated, and all have been shown to have clinical efficacy, although limited.

HIV-infected patients' long median survival time from infection until AIDS (averaging over 10 years) poses substantial difficulties for the conduct of clinical trials of investigational drugs. Because there is less clearly demarcated severe illness at earlier stages of HIV disease, clinical trials have been forced to focus almost exclusively on the use of opportunistic infections, malignancies, and death as endpoints in studies of anti-HIV therapy. Consequently, most clinical trials are either too prolonged for practical study, or are forced to enroll patients with advanced disease who are at greater risk of clinical events. For the latter patients, therapy is likely to be less efficacious than for patients at earlier stages of disease, and may be associated with a greater incidence of adverse effects. In addition, results from studies with patients at later stages of disease may not always generalize to less ill patient cohorts.

The search for surrogate markers of HIV disease progression that could be used as substitutes for clinical markers of disease progression has been vigorous. CD4 cell count has been the most widely accepted surrogate marker for monitoring the course of HIV disease: it has been used by physicians and patients for making therapeutic decisions, and effect on CD4 cell count has been an important endpoint in almost every study of antiretroviral therapy. Provisional approval of both ddI and ddC was based on therapy-associated increases in CD4 cell count. However, the utility of CD4 cell counts for treatment and regulatory decisions is limited by inherent variability in measurement and by analyses from earlier AZT trials where it has been shown that change in CD4 cell count explains only a small part of drug effect on disease progression.

Existing virological markers of anti-HIV activity such as suppression of serum p24 antigen or reduction of plasma viremia titers have validity as indicators of *in vivo* viral suppression after the administration of certain drugs. However, these measures are of limited value in assessing an individual's response to therapy because of low sensitivity and inherent biological problems associated with measurement; in general, low sensitivity also restricts their use to patients with relatively advanced disease. A more reliable measure of direct *in vivo* viral suppression, if correlated with clinical outcome, would be a major advance in the management of individual patients. This could allow physicians to discontinue or modify antiretroviral therapy by direct assessment of a drug's suppressive activity in vivo; it would also likely result in substantial clinical benefit by improving the risk/benefit of therapy, e.g., by discontinuing inactive therapy or stopping therapy where the antiviral activity is outweighed by adverse effects. There could be tremendous cost savings from reducing the

direct cost of medication and associated direct and indirect costs of drug toxicity (including monitoring for drug toxicity); however, even greater overall benefit may result by having the means to permit drugs currently under development to be introduced into clinical practice with scientifically guided principles for use. In addition to individualization of therapy, a direct measurement of viral activity that was validated as a surrogate marker of clinical outcome would have a substantial effect on the conduct of clinical trials, allowing for shorter and smaller trials and resulting in an overall improvement in the drug development process.

Recently developed assays that directly quantitate the amount of virus present in patient samples such as the branched chain DNA assay (or b-DNA) and quantitative polymerase chain reaction (PCR) have the potential to dramatically affect the ability to measure viral replication *in vivo* for patient monitoring. These methods represent a substantial improvement for measuring viral activity compared to older methods of direct culture (e.g., plasma viremia) or antigen detection (serum p24 antigen). The relatively high sensitivity permits their use over a broader spectrum of HIV disease than previously possible. The diagnostic and therapeutic application of these assays are readily apparent.

The perceived need by the authors to expedite and coordinate the effort of validating these newer "surrogate markers" of disease activity is the sole purpose for this document.

Statement of The Problem:

There is an urgent need for better validated markers of *in vivo* viral activity as a means to:

(1) Reduce the size and duration of clinical trials of therapy for HIV-infected persons and thereby expedite the overall development of anti-HIV therapy, including drugs, vaccines, and immune modulators.

(2) Reduce the substantial direct and indirect costs associated with therapy of uncertain or unknown benefit.

(3) Individualize treatment so that drug therapy can be more appropriately selected for a given patient.

Proposal: It is specifically proposed that either a separate panel or subcommittee of the Task Force be chosen and charged with the following tasks:

(1) Review published and unpublished studies (and datasets) of recently developed tests that hold promise as surrogate markers in the treatment of HIV-disease. This should be limited to those tests that could be made available for widespread clinical use, i.e., the branched chain DNA assay, quantitative PCR, screening for SI vs. NSI isolates, and the presence of certain genotypic mutations (e.g., Codons 215 and 74). These assays should be considered both for sensitivity/specificity and potential

cost-effectiveness (the latter by decision analytic models).[1] Where critical data exist but have not been analyzed appropriately, the panel should request that such data be submitted for expeditious review by FDA or a group identified by the panel. This would also include insuring that there was appropriate analysis of several markers considered simultaneously (including known measures of immune activation [e.g., serum neopterin and/or beta-2 microglobulin]) to ascertain whether increased predictability could be achieved by a multivariate approach (as is likely).

(2) Identify specimen banks from experimental and observational studies that could be used to address the validity of surrogate markers; a mechanism should be provided for assaying samples if necessary. There should also be establishment of a centralized specimen bank to hold clinical samples and HIV isolates from prior clinical studies; this resource should also solicit samples from patients with well-documented clinical outcomes and interventions as well as from a prospective cohort. This facility would offer an invaluable repository and resource for validating current and future proposed surrogate markers.

(3) Support a series of focused joint meetings of the companies commercially developing these methods with representatives of PHS, DOD, the pharmaceutical industry, the major clinical trials groups, and expert consultants. The specific goal of these meetings would be to explore the means of validating these virological and immunological measures for use in both clinical trials and patient management, and how each group can contribute to this effort.

It is expected that the results of this process would include:

(1) A clear statement of the types of studies (or data) that would be necessary for adoption of these measures in clinical studies (or for patient management), as well as the criteria by which these would be evaluated.

(2) Confirmation that all available sources of data have been identified and adequately analyzed. This would include a mechanism to support the analysis of data that remains inadequately evaluated, and would specifically include analysis of any frozen/banked samples that can contribute to answering these questions.

(3) A mechanism to insure that virological and immunological data from ongoing studies are analyzed as quickly as possible and evaluated for clinical utility once other information from the study is available.

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[1]Since the original draft of this document, the recent PNAS paper by Saksela et al. on mRNA expression has added another marker that appears to warrant study.

Although seemingly a daunting task, we believe this could be accomplished expeditiously and to the substantial benefit of AIDS drug development. There are academicians who have devoted their scientific careers to the analysis of surrogate markers in clinical studies, and even individuals solely dedicated to analyzing the use of surrogate markers in clinical studies of HIV. FDA has made a substantial commitment and devoted significant manpower toward the statistical analysis of surrogate markers in HIV trials, as has NIAID through the Division of AIDS and the AIDS Clinical Trials Group, and similarly the Department of Defense; approval of both didanosine and zalcitabine by FDA was based on changes observed in surrogate markers during clinical studies. A working group with detailed responsibility for this specific task could be arranged with collaboration between PHS, DOD, and industry.

The substantial data already available regarding the interindividual variability from the newer measures of viral burden (e.g., b-DNA and PCR) and genotypic analysis (e.g., Codon 215) clearly indicate that the formation of such a committee is not premature. The results of such an effort may find that under close scrutiny the measures are not as promising as is hoped or anticipated, yet this should not deter initiation of this urgently needed effort. This should be performed as expeditiously as possible given the tremendous public health benefits that could ensue. We cannot emphasize more forcibly the importance of the immediate formation of a committee or task force to address these issues as rapidly as possibly.

Appendix: Brief Overview of current assays[2]

The motivation for this proposal is the recent development of direct measures of "viral burden" and/or viral sensitivity to drugs that could be marketed and applied on a commercial scale. It is postulated that the use of these newer markers of antiviral activity could directly address the problems stated above.

Although the potential advantages of validated surrogate marker use are obvious, it needs to be delineated why this proposal is necessary considering the poor predictive value of CD4 cell counts and serum p24 antigen in earlier studies of HIV therapy. This can be reconciled by several points. The first, and most obvious, is that changes in CD4 cell count have generally predicted outcomes of clinical studies well although not necessarily for individuals (similar to p24 antigen). For each of the major nucleoside trials, e.g., zidovudine (AZT) vs. placebo, AZT vs. ddC, and AZT vs. didanosine (ddI), the study arm with the greater rise in CD4 cell count has performed better clinically over the initial phase of therapy.[3] However, problems in assessing the clinical value of surrogate markers are apparent when one considers the multiple effects of these compounds. All of these drugs are anti-metabolites with significant clinical toxicity; the anti-HIV effects of these compounds are based on relative selectivity for virus-infected versus non-infected host cells, not on unique activity in viral-infected cells alone (e.g., as opposed to a specific inhibitor such as acyclovir). Fatal or severe adverse effects from any of these drugs would mask a relationship between outcome and antiviral effect, as would noncompliance because of less severe adverse effects. Even more problematic is the issue of viral resistance: it is clearly apparent that HIV mutates to forms resistant *(in vitro)* to existing nucleoside analogues. If the model of virtually every other antibiotic or antiviral currently in clinical use is applied to HIV chemotherapy, it is likely that individuals with resistant virus should obtain little, if any benefit, from nucleoside analogues in the face of viral resistance.[4] Data from several cohorts demonstrates this effect.

A major problem with analysis of CD4 cell count changes in clinical studies has been the parabolic response curve to nucleoside analog therapy, i.e., an increase and then return to baseline. The interpretation of this response has been problematic: this may reflect a measure of immunological reserve (the "AZT stress test") more than a direct correlate of viral suppression. However, group curves manifesting this response have been contrasted by several researchers with individual responses that differ from the "average" pattern when consideration of viral sensitivity is accounted for. The relationship between viral sensitivity, changes in viral replication, and CD4 count mandates immediate review and further analysis. If a measure of viral replication (or sensitivity) can serve to predict CD4

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[2]This discussion is necessarily abridged and for supplementary purposes only. We would be glad to comment on this further if asked.

[3]This is not strictly accurate, but for conciseness is not discussed further.

[4]We do not wish to purposefully ignore the potential of virulence of different viral strains, i.e., there may be benefit by drug selection of less-virulent resistant strains, but there has been no evidence for this to date.

response to therapy (or maintenance of CD4 cell count), this may significantly contribute to the analysis of these curves from clinical trials and, more specifically, the individualization of therapy. This may also provide substantial insight into the mechanism of drug-induced CD4 cell counts increases that have been observed in clinical trials.

Proposed newer surrogate markers, e.g., branched chain DNA assays or quantitative polymerase chain reaction differ substantially from CD4 and p24 antigen in several respects. Most apparent is that they likely to be more direct measures of drug activity. If it is believed that CD4 cell count rises after initiating nucleoside therapy are pathophysiologically linked to viral suppression, then the degree of direct viral suppression should predict an increase in CD4 cells. (Obviously modeling would be necessary since CD4 cell count increases greater than those observed from nucleoside therapy may not occur since these responses may be asymptotes reflecting immunological reserve despite greater viral suppression; similarly, viral suppression may not predict individual rises in CD4 counts, but group changes may be predictable by differences in antiviral potency.) The drugs that have been developed since the original nucleosides (e.g., non-nucleoside reverse transcriptase inhibitors [NNRTI's] and especially the newer protease inhibitors) may show greater utility for primary virological markers when compared to the approved nucleoside analogues since they are far less likely to have secondary immunosuppressive or toxic effects. (It is certainly conceivable that the loss of benefit from nucleoside therapy is due to secondary antimetabolite effects of drug that over time outweigh the initial viral suppression, especially if the development of viral resistance limits drug activity over time.) Further, if patients are studied at the time of initiation of drug (for initial response to therapy) and serially over time (i.e., for persistence of viral suppression), an assessment of the utility of drug can be derived that is currently lacking in clinical practice.[5] The relationship between degree of viral suppression and clinical outcome urgently needs analysis; although likely to be more complex than a simple relationship, demonstration of this relationship would allow assessment of the potential therapeutic impact of a new class of drug as well as the effect of different therapies on a given individual.[6] Although it may evolve that CD4 may be a better predictor of outcome and clinical response than viral suppression (by perhaps being closer in the pathophysiological chain to direct immune suppression), viral suppression may still have greater utility for treating patients and assessing response to therapy[7]. The lack of this form of analysis for combination therapy is

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[5] Although the principle that viral suppression may not prevent clinical progression is possible and needs to be studied, the converse that lack of viral suppression may prevent clinical progression is almost certainly fallacious.

[6]This is obviously a simplified scenario since different drugs may have different distributional properties or effects in different cell lines that may be of clinical value despite less overall activity. However, it is striking that although certain drugs may be immediately removed from further study because of demonstrated resistance (and concomitant rises in viral burden), other drugs continue to be used clinically despite a similar level of resistance in certain individuals (e.g., resistance to zidovudine).

[7]There are likely to be circumstances where a compound may result in enhanced viral replication but still be clinically efficacious, e.g., certain cytokines or proposed immune modulators. Although this proposal has been framed in the context of drugs presumed to act as antiviral agents, the absence

especially troublesome, given that virological analysis may predict which patients truly have a synergistic or additive effect of additional therapies versus those for whom the additional drug increases activity as the sole active agent.[8,9]

Serum p24 antigen analysis suffers from several methodological problems. The test is insensitive in that most patients are serum antigen negative at earlier stages of disease. The test is further complicated since antigen-antibody reactions may interfere with measurement, and an increased antibody response as a drug effect may persist even after the antiviral effects of drug are no longer present (i.e., maintaining p24 suppression after the antiviral effect of drug is lost). However, p24 antigen has not been shown to be of any value for predicting individual response to treatment, and since virological suppression may correlate well with p24 antigen response, this may portend a lack of value of primary virological measures.[10]

At present, the only available means to individualize therapy is broadly following CD4 cell counts or clinical signs and symptoms which for a given individual is often problematic for assessing clinical benefit from a particular therapy. The only therapy demonstrably effective against HIV to date have been drugs that almost certainly act by the direct suppression of viral replication *in vivo*, i.e., nucleoside therapy (such as zidovudine, didanosine, and zalcitabine). However, none of the antiretroviral compounds currently approved for therapy by FDA are curative agents for HIV, and all are associated with significant toxicity. We hope that this proposed effort will aid in the more scientifically guided use of these and other agents.

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of an antiviral effect (or even enhancement of replication) does not necessarily exclude the possibility that the agent has clinical benefit. Different classes of drugs or biologics will need need to be considered separately from primary antiviral agents.

[8]One goal of the committee should be to insure that studies have been conducted, are ongoing, or are planned that address whether these measures can be useful for individualizing therapies by studies where drugs are added or subtracted as the result of their impact on viral burden. To our knowledge this has not been done in a systematic manner.

[9]Although not specifically mentioned, obvious advantages of the use of virological measures are the greater dynamic range of measurement of these markers, and their applicability over a much wider spectrum of stages of HIV disease.

[10]It is also possible that the correlation of direct viral measurements with clinical outcome may be different for different classes of drugs, e.g., nucleoside analogues may show a greater decrease in viral burden by direct inhibition of viral replication than drugs which act by formation of RNA-containing replication-defective viruses. We also clearly recognize that for some therapies (e.g., certain cytokines), mixed effects may occur that will need to be considered (e.g., improved CD4 responses but also increased viral burden). We believe this proposal will aid evaluation of therapies with mixed effects, but obviously those compounds raise different evaluation considerations.

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April 3, 1994

Jean H. McKay
Contact person for April 1994 meeting of the
National Task Force on AIDS Drug Development
Office of AIDS and Special Health Issues (HF-12)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

via FAX and Post

RE: April 1994 meeting of the National Task Force on AIDS Drug Development

Dear Ms. McKay:

Would you please forward these comments to the Task Force?

As a clinical drug researcher who concentrates on HIV therapeutics, I would like to share my observations on how to speed up the testing of drugs for HIV. There are several general problems which are impeding the rapid development of new drugs.

1. **The NIH needs to test drugs which are not likely to be tested quickly by pharmaceutical companies.** The ACTG system has spent an extraordinary amount of money testing nucleoside analogs which would be tested anyway by pharmaceutical companies because they stand to profit enormously. It does make sense that the NIH handled the original AZT research; however, once AZT was shown to be beneficial, NIAID efforts should have gone into drugs for which a new composition of matter patent cannot be granted. Examples of this are: Tagamet, warfarin, aspirin, Hoffmann LaRoche's tat gene inhibitor combined with pentoxyfylline, glycyrrhizin, michellamine A & B, not to mention vitamin E and beta-carotene. **The literature is full of compounds which show in vitro activity, but have no corporate sponsor.**

2. **There should be a time limit for restrictions on access to Drug Master Files at the FDA.** It is currently not possible to access Drug Master Files unless the company which has filed the DMF gives its permission. While this has obvious benefits, in the case of AIDS, it can become a significant impediment when a company is moving slowly or not pursuing a promising drug and another group wishes to pursue testing. Hypericin is a reasonably good example of this problem. The company involved, Vimrx, has not finished Phase I testing in the more than four years it has been pursuing the drug. Most of this delay has been due to the stupidity of the company. The actual researchers, led by Dr. Fred Valentine at New York University, have been diligent in their work. A community group attempted to start another trial, more expeditious. Vimrx of course refused to collaborate, even though a very favorable arrangement was offered to them. The community group was unable to access any of Vimrx's DMF. The result was that the IND require-

ments were prohibitively expensive for a community group, and the project did not proceed.

3. **Any regulatory or grant agencies, including most importantly, Institutional Review Boards, need to insist that protocols are designed to be easily recruitable.** Often protocol developers are so removed from the real world that they let their enthusiasm for perfect data interfere with the reality of getting drugs tested. There is a new protocol out (Hoffmann LaRoche's protease inhibitor, I believe) which requires 600 people with CD4 < 300 who have never taken an antiviral! In the trial of N-acetylcysteine which I am running, I have found only a tiny fraction of patients under CD4 300 who have not taken an antiviral.

4. **A climate of extreme urgency needs to be fostered and continuously nurtured. The Task Force has an excellent opportunity to do this.**

Thank you for this opportunity to express these thoughts. Good luck in your debates.

Sincerely,

Greg Dubs

Greg Dubs, Ph.D.
Research Associate

cc: John James, AIDS Treatment News

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April 6, 1994

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Jean H. McKay, FDA
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Rockville, MD 20857

Dear Members of the AIDS Task Force:

I wish to identify a barrier to the development of new approaches for HIV infecton. This barrier is the failure of the NIH to adequately fund and to encourage research on long terminal repeat (LTR) inhibitors as a new kind of potential AIDS treatment.

As you are aware, the LTR is the "on-off" switch of the HIV virus. Using a screening assay for LTR inhibition, we have identified at least six compounds with anti-HIV properties. Three of these compounds, pentoxifylline (an inhibitor of tumor necrosis factor and of the transcription factor NF-kappaB), tenidap (an inhibitor of IL-6), and curcumin (an ingredient of the spice turmeric) are currrently in clinical trials. The pentoxifylline study is being conducted by the AIDS Clinical Trial Group. The LTR is activated by different transcription factors of cellular (e.g., NF-kappaB) and of viral (e.g.,Tat) origin. We recently showed that a combination of drugs which inhibits both NF-kappaB (e.g., pentoxifylline) and Tat (e.g., Tat inhibitor Ro 24-7429) is synergistic.

We have done the LTR work under difficult and wastefully distracting financial circumstances. We have been unsuccessful in getting funding for AIDS research from the NIH. We have submitted a grant on the LTR twice and will be submitting it a third time on May 1, 1994. The scores on the first two submissions were around 150-160 (i.e. in the excellent to outstanding range). The reviewers picked on minor and potential problems which by the exploratory nature of an original proposal are unavoidable.

I am therefore convinced that to make progress against AIDS, we must adequately fund **innovative** research. I hereby request that the National Task Force on AIDS Drug Development underscore the LTR as a target for novel therapeutics and pave the way for funding research on the subject.

I am enclosing the February 4, 1994 issue of **AIDS Treatment News** which demonstrates the interest of the AIDS community in this approach and states "clearly this line or work should be pursued rapidly".

I thank you for your time and attention.

Sincerely yours,

Bruce Dezube

Bruce Dezube, MD
Assistant Professor of Medicine

AIDS TREATMENT NEWS

Enclosure to Letter by Bruce Dezube, MD

Issue Number 192
February 4, 1994

Published twice monthly by
John S. James
P.O. Box 411256
San Francisco, CA 94141
415/ 255-0588
Internet: aidsnews@igc.apc.org

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LTR Inhibitors, a New Kind of Potential AIDS Treatment: Interview with Arthur B. Pardee, Ph.D.

by Charles Davidson and John S. James

In a paper published in March 1993, Chiang J. Li and others at Dana Farber Cancer Institute and Harvard Medical School reported results of laboratory tests which identified three substances which should be investigated as potential treatments for AIDS or HIV.[1] The three are curcumin (an antioxidant and anti-inflammatory agent found in turmeric, the mild spice used in curry), topotecan (an experimental treatment now in phase II/III trials for cancer, but never tested in patients as a treatment for HIV), and beta-lapachone, a plant derivative which has not been tested in humans. The researchers found these three by screening selected substances for activity against the LTR (long terminal repeat), which is the "on-off switch" of the HIV virus; when the "switch" is off, the virus is not being stimulated to reproduce. After these tests, all three substances were tested against live HIV, and all showed activity in both acutely and chronically infected cells. In short, this new approach to finding AIDS treatments has quickly found three attractive potential candidates — substances which are available, already in human use in two cases, active against both acute and chronic HIV infection in cell cultures, and which work by a completely different mechanism than standard treatments.

To help the AIDS community understand LTR inhibitors as an approach to drug development, *AIDS Treatment News* interviewed Arthur B. Pardee, Ph.D., who is head of the group which initiated the research cited above. Dr. Pardee is Professor of Biological Chemistry and Molecular Pharmacology at Dana-Farber Cancer Institute and Harvard Medical School, and Chief of the Division of Cell Growth and Regulation at Dana-Farber. He is a member of the National Academy of Sciences, and has co-authored 400 technical papers and other publications. He is a molecular biologist; two other researchers on the project, Clyde S. Crumpacker, M.D., and Bruce J. Dezube, M.D., have run AIDS clinical trials for years.

The laboratory test for LTR inhibitors is well established in basic research. (The particular version of the test used by Pardee's group was donated by the Herzenberg's laboratory at Stanford University — which has studied NAC, an experimental HIV treatment which may reduce LTR activation indirectly.) Dr. Pardee's team has used this test to study anti-HIV properties of available, known, nontoxic compounds — to look for a new class of potential drugs which target the on-off switch of the virus. And they have used the same test to show that these kinds of HIV inhibitors may work far better together, in certain combinations which block different paths involved in LTR activation.[2] (This recent paper, on combining a Tat inhibitor with pentoxifylline in laboratory tests, was described in *AIDS Treatment News* #188, December 3, 1993).

Clearly this line of work should be pursued rapidly — especially since other approaches have had only limited success. But much of this research is not funded; only the fact that the laboratory tests are inexpensive enabled it to be done at all. The

AIDS Treatment News

Published twice monthly

Subscription and Editorial Office:

P.O. Box 411256
San Francisco, CA 94141
800/TREAT-1-2 toll-free U.S. and Canada
415/255-0588 regular office number
fax: 415/255-4659
Internet: aidsnews@igc.apc.org

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ISSN # 1052-4207

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problem seems to be that searching for AIDS treatments by screening for LTR inhibitors has not yet become an influential part of the mainstream thinking, which has focused on other kinds of drugs — mostly AZT, etc., or high-tech approaches which may not be ready for years.

One great barrier stopping new AIDS drugs today is the lack of funding and other support for preclinical work needed to move promising ideas from the laboratory into early human tests. This barrier is now impeding the practical development of LTR inhibitors, slowing or preventing the fairly obvious research steps that are needed next.

Background for Non-Technical Readers

After HIV infects a cell, its genetic information becomes part of the DNA (the genetic inheritance) of the cell. Each cell contains a complete copy of all the person's DNA — the information needed to construct all the organs of the body. Of course not all of this DNA is active in any particular cell. Instead, complex regulatory mechanisms determine which genes are expressed, and when. (Each *gene* is a part of the DNA which codes the information for creating one protein.)

When a cell has been infected and contains the HIV DNA, that DNA is often inactive, not making new virus or doing any other harm. Only when the HIV is activated is it harmful. Various different substances can increase or decrease this activation, and many of them have their effect through the LTR (the long terminal repeat of the AIDS virus).

An LTR inhibitor is a compound which prevents or reduces this activation, and thereby blocks viral replication and other viral functions.

There is a rapid, inexpensive test which can be used to screen substances to identify the ones which show promise as LTR inhibitors. This test, created by genetic engineering, uses living cells which have additional, artificially added DNA. This additional DNA includes the LTR of HIV (or of another virus being studied), together with a "reporter" gene. A reporter gene is a gene which produces a protein (usually an enzyme) that can easily be detected in the laboratory (for example by causing a color change in a test tube). In the test cells, the reporter gene is controlled by the HIV LTR, so that it produces its protein only when the LTR is activated.

To run the test, the cells are treated with a chemical (such as tumor necrosis factor) which is known to activate the LTR, and the resulting activity of the reporter gene is observed. A substance being tested can be added; if it inhibits the LTR, it will turn off or reduce the activity of the reporter gene. This test is easy to do, and it does not require live HIV, so it does not require the elaborate safety precautions needed to work with HIV itself. It can be done in most laboratories, and could quickly screen many substances to look for potential LTR inhibitors. Positive results must be confirmed using laboratory tests with the live virus, but this only needs to be done for the much smaller number of substances which show good results from the initial screening. (These screening programs often test hundreds, or even thousands, of random chemicals to find one which may have value. Pardee's group had better success looking for LTR

inhibitors — three found out of a dozen chemicals tested — because they were not funded for mass screening, and instead used intelligent guesses about what was likely to work.)

Of various factors which increase HIV activity by activating the LTR, the most powerful is the protein produced by the Tat gene of HIV. Another important cause of viral activation is excessive levels of a different protein, NF-κB (NF-kappa B) — which (unlike Tat) is normally present in the body. Each of these binds to the LTR (at different sites), activating HIV. NF-κB can be induced by a variety of stimulants, including T-cell activation, inflammation, bacterial products, and oxidative stress.

Other research groups had found that HIV is much more active when *both* the Tat protein, and also high levels of NF-κB, are present.[3] It appears that the two together act in concert in a way that is far more than additive; in one experiment, NF-κB alone upregulated the virus by 16 times, Tat alone by 80 times, and both together 388 to 760 times, depending on the concentration of Tat used.

Dr. Pardee and his colleagues have built on basic research to find potential LTR inhibitors, and especially synergistic combinations of these compounds. Recently Debajit K. Biswas, Ph.D., and others showed that a combination of drugs that inhibit both NF-κB and Tat worked much better than either one alone — so much better that the concentrations of both drugs (pentoxifylline, and the Roche Tat inhibitor Ro 24-7429) could be reduced ten times, and still give the same inhibition as the larger concentration of either one alone.[2]

This paper gives some insights as to why the Hoffmann-La Roche trials of its Tat inhibitor failed to reduce viral activity in humans. Since NF-κB activity is likely to be excessive in people with HIV, due to oxidative stress caused by infections, it may be necessary to combine a Tat inhibitor with another treatment (such as pentoxifylline) to reduce NF-κB activity. Further improvements may be made by adding other LTR inhibitors with different mechanisms of action.

The scientific search for LTR inhibitors also led Dr. Pardee's lab to investigate topotecan, which inhibits a DNA-unwinding enzyme which upregulates many genes (in other words, makes them more active), including those governed by the HIV LTR. This inhibitor, now in use in cancer trials but never tested in persons with HIV, can be tolerated in patients at a concentration that is 200 times that which inhibits 80 percent of viral production in laboratory tests.[1]

Dr. Pardee's lab is also considering a number of substances to modify levels of pro-inflammatory cytokines, secreted by certain immune cells, which upregulate the LTR. (In addition to pentoxifylline to decrease TNF, another example is tenidap, to inhibit IL-6 production). Also, as certain enzyme systems become upregulated in people with AIDS, inhibitors of these pathways might also be targets for inhibiting the LTR.

The synergistic inhibition of viral production, using novel combinations of drugs at tolerable doses, is a here-and-now approach. In view of the urgent need for better treatments for AIDS, we must not overlook a potentially effective antiviral strategy that is possibly within reach today.

Interview

Dr. Pardee was interviewed by John S. James of *AIDS Treatment News*, and by Charles Davidson, a graduate student with a strong interest in Tat and LTR inhibitors, who brought much of this information to our attention.

James: Could you summarize the rationale for your work?

Pardee: Our approach is a simple one. We look at the LTR of HIV-1, and see what substances respond. It's a quick, easy test, and you don't need special safety precautions [which would be required for working with the live virus]. We're pretty much limited to that test [because of lack of funding to do the live-virus tests]. But we've come up with pentoxifylline, and the other three compounds we reported a year ago. We've done other work on tenidap, which looks interesting, and we have more potential drugs in the pipeline. This approach has been productive. We have shown an effect on the LTR system; now it's pretty much up to someone else to carry it forward. Bruce [Dr. Bruce Dezube] can carry it into the clinic if it looks good, but you need somebody in between [to do the preclinical development], and we do not have funds for that.

Davidson: You found the topoisomerase inhibitor was quite effective?

Pardee: Topotecan, the one we used in that work of a year ago, was by far the most potent drug. We think it has some promise. It was tested with the virus system very extensively, as we reported in our paper.[1] For reasons that aren't too clear to me, Smith-Kline Beecham does not seem very interested in pursuing it further. It's the company's decision at this point; it's pretty much out of our hands.

We have largely shifted to some other camptothecin analogs; they look pretty effective, too. We are working mostly with camptothecin itself; there are analogs that are clinically preferable, but there are no patents on camptothecin; you run into problems when you work with companies.

There are several ways a drug can inhibit the LTR, which is quite complicated. There are NF-κB motifs, and Tat-TAR motifs, and some others, SP-1 motifs, etc. The questions are what is the target for a particular compound, and how can we set up better assays for finding new compounds, by taking advantage of what we've learned with the first generation.

And of course curcumin [first discovered to have anti-HIV activity by Pardee's group, using the test for LTR inhibitors] is another one which needs to be investigated. I understand there will be a clinical trial in the Boston area, also [to be conducted by the Community Research Initiative of New England — in addition to the trial by SEARCH Alliance, in Los Angeles]. I have no further information on it. We are starting further work on curcumin. We hear stories about India, where they eat a lot of turmeric; some people say there's lots of AIDS in India. I understand there is a lot of HIV infection, but not very much AIDS, so it may slow down the disease. Dr. Biswas, my Indian colleague, is currently in India; he is in close contact with top leaders in their infectious-disease work, and they are interested. There are also some other Indian plant products which may be quite interesting; we're hoping to look at them. Concerning

curcumin, I have been told by another Indian scientist that there are other compounds in that plant which are more active than curcumin. There is much we can do if we get the time and resources.

James: Two callers told me that they didn't know where to get the more concentrated curcumin, so they used turmeric from a grocery store. Both said they had substantial improvement in blood work. This should be studied.

Davidson: Curcumin is classified as an antioxidant?

Pardee: Yes, but we don't know what its real mechanism of action is against HIV. Somebody published an abstract at a recent meeting saying it may inhibit the HIV protease. They did a computer study of what the structure should be to block the specific HIV protease, and came up with a curcumin structure.

Davidson: If you have several different mechanisms, and there is synergism, one should be able to use smaller doses of the drugs?

Pardee: Right, you should be able to get more effectiveness with less side effects, we hope. But people are very complicated organisms; just because it works on some simple system in the laboratory does not mean there will be no toxicity or other problem.

Pardee: I wish that what might be called the AIDS establishment was a little more open to innovative approaches. I have not been able to get a penny from the NIH to do any of our work, and we have come up with several new compounds [with potential use for AIDS], and we have several more in the pipeline. We will soon report on another class of compounds which is effective against the HIV LTR. But we can't go on working without funds. We have to pay researchers to eat and pay rent.

James: What study groups at NIH review your proposals?

Pardee: It goes into some AIDS study groups. I must say that one of the reviews, on attempts to follow up on the topoisomerase inhibitors, was erroneous. It claimed that we did the work before we submitted the grant, which is absolutely untrue. We did all this work in the two years of the grant; we published two good papers, and they said we didn't accomplish anything. And they also said we should be working on HIV-2 as well as HIV-1. Well, we are not a factory. If we discover something active against the HIV-1 LTR, it could be pursued with HIV-2 by someone else. It's pretty discouraging.

James: Over the years I have seen that this is not a new problem.

Pardee: The AIDS establishment has to produce something with all the money they are spending. They give us no encouragement or help at all [for innovative approaches]; and we get the same story from colleagues. The whole AIDS granting process has been dominated by the AZT types, and a few other interest areas. It's like molasses to get funded. This new panel [the National Task Force on Drug Development] is likely to have people who don't rock the boat.

A carefully worded article about how we need innovative approaches against AIDS, and need to support these innovative approaches, would hopefully do some good if it gets to the right people.

We need to find out more about the mechanism of action, why these work. We are likely to find some new targets. When we know what the target is, and we get an assay for that target, we can test for other substances that work better. We published on several potential drugs already. Nobody has clinically tried topoisomerase I inhibitors on AIDS, and yet these compounds are pretty powerful, as we reported.

We think we have a fairly clear understanding of pentoxifylline, how it blocks the LTR. It's through NF-κB, but there are additional details. It's part of another very interesting class of inhibitors of the LTR. It's not too hard to come up with possibilities. Hopefully some of them will work.

Our approach is to use the LTR as a target, just like others use the protease as a target. I think it's a very promising target.

Davidson: How much do you think has been spent so far on LTR inhibitors?

Pardee: I don't know how much companies such as Roche spend. We get a small amount to do our work on pentoxifylline, from Hoechst-Roussel Pharmaceuticals, Inc. We luckily got an NIH grant to work on topoisomerase inhibitors, which I used to work on the AIDS problem; but that is terminating and won't be renewed, so this work will stop rather fast. We have never been funded to work on this project specifically; we haven't gotten one cent. And very few people elsewhere are working on this approach. Virtually nothing has been spent on it. We'll eke out what little we can.

Davidson: Do you have any idea how the Roche Tat drug [Ro 24-7429] works?

Pardee: There are accessory proteins involved in the Tat-TAR interaction. We're trying to take these apart as fast as we can.

[Editor's note: Obstacles to the research on the Ro 24-7429, the Hoffmann-La Roche Tat inhibitor, have included not only lack of funding, but difficulty getting the drug to test, and lack of access to results from other researchers. Even though this substance failed to reduce viral activity in humans in a single-drug trial, it may be important because of the possibility that it might work in combination — for example, with pentoxifylline, since that combination works very well in the laboratory. Also, it is worth investigating *why* Ro 24-7429 did not work by itself in people; there are many possible reasons that a particular drug will not work in the body, and the failure of one compound does not invalidate the whole approach. (A recent paper suggests that Ro 24-7429 alone does not inhibit the Tat protein itself, but another protein which works with Tat.[4] This might help to explain the disappointing results of human tests.)

While there are a number of ways to inhibit the LTR through the NF-κB mechanism, Tat inhibitors are still scarce. A very different Tat drug is being developed in Canada, by Allelix Biopharmaceuticals, but it is just beginning human tests (see *AIDS Treatment News* #187, November 19, 1993). A prescription drug, d-penicillamine, was tested as a Tat inhibitor in Europe several years ago; it did not help patients in trials, but perhaps should be re-examined as a possible part of a combination.

We believe that the most important work at this time is human trials of topotecan, curcumin, some other LTR inhibitors being tested by Pardee's group, and the combination of Ro 24-7429 with pentoxifylline. Equally important is the laboratory search for new LTR inhibitors, and especially for better combinations of LTR inhibitors, and combinations of these with other classes of AIDS treatments. This area could move quite rapidly, if it had support instead of roadblocks from corporations and from government research agencies.]

References

1. Li CJ, Zhang LJ, Dezube BJ, Crumpacker CS, and Pardee AB. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proceedings of the National Academy of Sciences, USA.* March 1993; volume 90, pages 1839-1842.

2. Biswas DK, Ahlers CM, Dezube BJ, and Pardee AB. Cooperative inhibition of NF-κB and Tat-induced superactivation of human immunodeficiency virus type 1 long terminal repeat. *Proceedings of the National Academy of Sciences, USA.* December 1, 1993; volume 90, pages 11044-11048.

3. Liu J, Perkins ND, Schmid RM, and Nabel GJ. Specific NF-κB subunits act in concert with Tat to stimulate human Immunodeficiency virus type 1 transcription. *Journal of Virology.* June 1992; volume 66, number 6, pages 3883-3887.

4. Braddock M, Cannon P, Muckenthaler M, Kingsman AJ, and Kingsman SM. Inhibition of human immunodeficiency virus type 1 Tat-dependent activation of translation in *Xenopus* oocytes by the benzodiazepine Ro 24-7429 requires *trans*-activation response element loop sequences. *Journal of Virology.* January 1994; volume 68, number 1, pages 25-33.

AIDS Research Databases Now Free to Community Organizations, Public Libraries, and Individuals

by Tadd Tobias

The world's largest library of health sciences, the National Library of Medicine (NLM, a unit of the National Institutes of Health), will no longer charge access fees for three AIDS-related research databases and an online directory of information sources. This means that AIDS organizations and public libraries can now offer their clients the ability to do a computer search of the medical literature to find extensive background information on almost any drug, condition, or other medical topic related to AIDS. Results are available immediately, allowing users to refine their searches again and again in order to get the information they need.

AIDSLINE, the most important of these databases, includes 90,000 references (many with abstracts) to AIDS-related journal articles, conference presentations, government reports, books, and audiovisuals. It focuses on biomedical, epidemiological, health-care administration, and social and behavioral science AIDS literature. For example, AIDSLINE includes the several thousand abstracts from each year's International Conference on AIDS, as well as abstracts from other conferences, which otherwise are not readily available for computer searching.

Arranging to Use the System

Current users of AIDSLINE (and the other AIDS databases which have now been made free) will no longer be charged if they are accessed directly through the NLM (either by the "Grateful Med" software recommended by NLM, or by direct connection). *New* users must establish an account with the NLM to begin using the databases. There are two ways of doing this. Those organizations interested in using only the free databases may request a special password and user identification allowing free access. This option is good for libraries and service organizations which may want to let their clients use the databases without close supervision, since there is no danger that the client will accidentally get into a costly database and run up a bill. But organizations which also want to use other NLM databases (such as MEDLINE) must go through the standard registration process. They will have access to all the NLM databases, but will not be billed for using the AIDS-related ones. [Note: individuals are not eligible for the special free accounts, which are for community organizations and libraries. But individuals can get still get free access, by opening a regular account, and then using the AIDS databases, which will not be charged for.]

In either case, users must have a computer and modem (or direct Internet access, usually through a local-area network at a university or other institution). The Grateful Med software, which makes the system easier to use, is available in IBM and Macintosh formats for $29.95. To order this software, contact

NEWS RELEASE

FIFTEEN PHARMACEUTICAL COMPANIES FORM AN AIDS DRUG DEVELOPMENT COLLABORATION

CONTACTS: SEE PAGE 3 **EMBARGOED UNTIL 4/20/93**

APRIL 19, 1993 – Fifteen pharmaceutical companies from the United States and Europe have agreed to work together to facilitate -- through the sharing of information and drug supplies – early human effectiveness trials of combination drug therapies to fight AIDS and HIV infection, the companies announced today.

The companies have formed the Inter-Company Collaboration for AIDS Drug Development to better enable each of them to independently conduct early-stage combination studies of their respective investigational antiviral AIDS compounds. Specifically, the companies hope that this endeavor will expedite combination and comparative studies – through sharing of information and drug supplies, as well as collaborating on certain aspects of drug development such as the standardization of assay testing. The companies agree to share with each other pertinent data through at least the early human effectiveness phase of investigation.

Increasingly, AIDS researchers have been focusing on the use of combinations of drugs because the virus develops resistance to individual ones.

The names of the participating companies are: AB Astra, Boehringer Ingelheim, Bristol-Myers Squibb, Burroughs Wellcome, Du Pont Merck, Glaxo, Hoechst AG, Hoffmann-La Roche, Eli Lilly, Merck, Pfizer, Miles (on behalf of its German parent company), Sigma-Tau, SmithKline Beecham and Syntex.*

*[Aji Pharma joined March 18, 1994]

All pharmaceutical companies actively involved in HIV antiviral development are eligible to join the Collaboration. Researchers from universities and government, as well as representatives from the HIV community, will be consulted and kept informed on a regular basis.

The companies stress that the chances against successful drug discovery and development remain daunting. The odds against getting a compound to market are about 10,000 to 1. This means that for every 10,000 substances examined, only 10 enter clinical (human) trials -- and only one gains U.S. Food and Drug Administration approval.

The idea of an inter-company cooperative program has been discussed for years. Two new factors recently converged to make it a plausible idea:

- The realization that the virus will likely develop resistance to every HIV antiviral compound, and
- The availability of more compounds for possible use in combination therapies that may mitigate the resistance problem.

The Collaboration evolved as a way of maintaining the competitiveness, which results in innovation, while engendering the sharing of data and compounds at a stage where it might make a difference.

The announcement of the formation of the Inter-Company Collaboration for AIDS Drug Development marks the culmination of formal discussions that have been ongoing for more than one year. The Collaboration has a narrow but ambitious focus -- cooperation by participating companies to facilitate the conduct of early human effectiveness trials of antiviral AIDS drugs.

# # #

FOR INFORMATION:

For general information about the Collaboration, contact:

Mr. John Doorley (Merck) – (908) 423-4081 (office) or (908) 232-2052 (home)
Dr. Linda Distlerath (Merck) – (908) 423-4165 (office)

Alternate for Europe: Mr. Martin Sutton (Glaxo Holdings) at 011-44-71-966-8256

For information on company-specific inquiries regarding their research, products or participation in the Collaboration, contact:

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Merck	Dr. Linda Distlerath (908) 423-4165 Mr. John Doorley (908) 423-4081

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SUMMARY OF PRINCIPLES
INTER-COMPANY COLLABORATION FOR AIDS DRUG DEVELOPMENT
4/19/93

BACKGROUND

Since the mid-1980s, research-based pharmaceutical companies have aggressively but independently pursued the development of drugs to treat or prevent HIV infection and AIDS -- with mixed results. While the Pharmaceutical Manufacturers Association reports 91 medicines and vaccines for AIDS or AIDS-related conditions in development, only a few have been approved for use in patients. Conversely, HIV infection is a mounting public health crisis worldwide.

In the United States and Europe, research-based pharmaceutical companies are continuing research with non-nucleoside reverse transcriptase inhibitors, protease inhibitors, tat inhibitors, and nucleoside reverse transcriptase inhibitors. However, development of many potential HIV antiviral compounds has been hindered by toxicity, viral resistance, low bioavailability (inadequate dispersal in the blood stream), and complexities of drug synthesis.

For the foreseeable future, HIV antiviral therapy will probably require multiple-drug treatment. Many companies in the industry believe that a new synergy is necessary to increase efficiency, avoid duplication of effort, and ultimately to produce truly effective HIV drugs, whether they are developed separately or in concert with other companies or agencies. By sharing knowledge as well as HIV antiviral compounds at the early stages of development, and by standardizing assay methodologies, pharmaceutical companies might well accelerate the clinical evaluation of the most promising HIV antiviral combinations.

ABOUT THE COLLABORATION

Inter-Company Collaboration: The research-based pharmaceutical industry has been strongly committed to developing novel drugs to treat or prevent HIV infection and AIDS. To hasten the development of new HIV antivirals, 15 pharmaceutical companies engaged in ongoing HIV antiviral research have elected to form a Collaboration. The Collaboration will develop fair and reasonable practices and procedures to facilitate sharing of data and compounds in line with antitrust and other regulatory considerations.
Participating companies are: *

AB Astra
Boehringer Ingelheim
Bristol-Myers Squibb
Burroughs Wellcome
Du Pont Merck
Eli Lilly
Glaxo
Hoechst AG
Hoffmann-La Roche
Merck
Miles[1]
Pfizer
Sigma-Tau
SmithKline Beecham
Syntex

[1]on behalf of its German parent company

*[Aji Pharma joined March 18, 1994]

Goals: The intent of the Collaboration is to encourage the sharing of information on concomitant and/or comparative research in HIV antiviral investigations, and supplies of developmental and marketed antiviral compounds where appropriate and feasible. This cooperation will enable each company to independently evaluate more rapidly the potential of antiviral drugs in early clinical studies and to facilitate future clinical development in comparative or combination studies with other investigational or approved drugs.

Focus: The Collaboration will focus primarily on early clinical development (i.e., Phase II) of HIV antiviral drugs which have already demonstrated potential clinical safety and efficacy. Activities and results of the Inter-Company Collaboration will not preclude existing or envisioned shared projects with the National Institutes of Health (NIH), universities or other investigatory bodies. On the contrary, participating companies are hopeful that this new synergy will facilitate new approaches to combination studies with various HIV antiviral compounds in order to prevent or delay the onset of resistance to individual compounds.

Objectives:

- Facilitate clinical testing of HIV antiviral compounds in combination which may delay or eliminate development of individual drug resistance.
- Share relevant information gained from preclinical and clinical testing of HIV antiviral compounds so that the most appropriate combinations of HIV antivirals can be clinically evaluated.
- Develop more effective standardized preclinical testing procedures, such as assay systems, which will enable researchers to evaluate antiviral compound data more rapidly and effectively.
- Facilitate the sharing of compounds among participants to conduct appropriate clinical investigations on a concomitant or comparative basis.

Limits: The Collaboration will not be involved in non-HIV antiviral development or in any commercial activities. No legal entity will be formed, and all participants will continue to conduct research and development activities on an independent basis.

Membership: Any pharmaceutical company *actively* involved in AIDS antiviral research that accepts the Principles of the Collaboration is eligible to join.

INTER-COMPANY COLLABORATION FOR AIDS DRUG DEVELOPMENT
Summary of July 1, 1993 Meeting

The Inter-Company Collaboration for AIDS Drugs Development held its first formal meeting on July 1. Each of the 15 member companies sent its head of research or another senior researcher to begin the sharing of HIV drug development data. In April 1993 the companies agreed to work together to facilitate – through the sharing of information and drug supplies -- early human effectiveness trials of combination drug therapies to fight AIDS and HIV infection.

Dr. Edward Scolnick, President of Merck Research Laboratories, was elected Chair of the Board of Participants, the oversight body with general responsibilities for implementing the principles guiding the Collaboration.

Professor Juergen Drews, President of International Research and Development at Hoffmann-La Roche, was elected Chair of the Scientific Panel, the committee that will coordinate the exchange of scientific information, access to investigational agents and other scientific activities.

Scientific disclosures on HIV antivirals in development were made by three companies: Hoffmann-La Roche presented on its proteinase inhibitor Ro 31-8959 and TAT antagonist Ro 24-7429*; Bristol-Myers Squibb on its nucleoside analog, d4T; and Merck on its non-nucleoside reverse transcriptase inhibitor L-697,661, and protease inhibitor L-735,524.

A subcommittee of the Scientific Panel was appointed to evaluate potential collaborative projects in the areas of assay validation, methods standardization and antiviral resistance databases. Dr. Emilio Emini of Merck will lead that subcommittee.

The next meeting of the Collaboration will be held in the fall, when the remaining companies with HIV antivirals in Phase II development will make scientific disclosures.

Contact individual companies for more information about their specific HIV antivirals in development. For general information about the Collaboration, contact Linda Distlerath (908-423-4165) or John Doorley (908-423-4081) at Merck.

**Post-meeting note: On August 2, 1993, Hoffmann-La Roche announced that development of the TAT antagonist had been discontinued.*

INTER-COMPANY COLLABORATION FOR AIDS DRUG DEVELOPMENT
Summary of October 8, 1993 Meeting

The Inter-Company Collaboration for AIDS Drug Development held its second formal meeting on October 8. Each of the 15 member companies* was represented by its head of pharmaceutical R&D (or authorized delegate) and senior scientists and clinicians responsible for HIV antiviral research. The formation of the Collaboration was announced in April 1993 as a means to facilitate early clinical evaluation of various HIV antivirals in combination through the sharing of information and drug supplies.

Dr. Edward Scolnick, President of the Merck Research Laboratories, chaired the meeting of the Board of Participants, the oversight body with general responsibilities for implementing the activities of the Collaboration. The Board appointed subcommittees to facilitate interactions with various third-party groups and organizations--including NIH (subcommittee to be chaired by Dr. Scolnick), FDA (chaired by Dr. Leon Rosenberg, Bristol-Myers Squibb), HIV community (chaired by Dr. David Barry, Burroughs Wellcome), and the "Future Directions in AIDS Research" group (chaired by Dr. John Niblack, Pfizer).

Professor Juergen Drews, President of International Research and Development at Hoffmann-La Roche, chaired the meeting of the Scientific Panel, which coordinates the exchange of scientific information and other scientific activities related to HIV antiviral evaluation. Six companies made scientific disclosures on HIV antivirals and related compounds: Glaxo presented on the nucleoside analog 3TC®; Astra on Foscavir® as a broad spectrum antiviral; Boehringer-Ingelheim on the non-nucleoside analog nevirapine; Burroughs Wellcome on the nucleoside analog 935U; Hoechst on pentoxifylline; and Eli Lilly on the non-nucleoside analog LY300046.

Dr. Emilio Emini, Senior Director of HIV Virology at the Merck Research Laboratories and chair of the Scientific Panel's subcommittee on assay validation, reported that a consensus protocol was established for determining cell culture antiviral activities of novel anti-HIV therapeutic agents. The assay will be tested in several laboratories using standardized reagents supplied by various member companies. Data from such an assay will permit direct comparisons of different therapeutic agents and will facilitate the consideration of possible combinations.

The next meeting of the Collaboration will take place in early 1994.

Contact individual companies for more information about their specific HIV antivirals in development. For general information about the Collaboration, contact Dr. Linda Distlerath (908-423-4165) or Mr. John Daly, (908-423-4001) at Merck.

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**Member companies: AB Astra, Boehringer-Ingelheim, Bristol-Myers Squibb, Burroughs Wellcome, DuPont Merck, Glaxo, Hoechst AG, Hoffmann-La Roche, Eli Lilly, Merck, Pfizer, Miles (on behalf of its German parent company), Sigma Tau, SmithKline Beecham and Syntex.* [Note: Aji Pharma joined March 18, 1994]

PROJECT INFORM
An Overview

1/1/93

Project Inform was founded in San Francisco in 1985 to address a unique problem arising out of the AIDS epidemic: people had early news of promising treatments and frequently some form of access to them well before researchers began to test them. Most physicians soon found themselves monitoring patients who were using unproven and unapproved medications. Since no proven or even tested AIDS therapies existed at the time, many patients had some involvement with the unproven variety, leaving three possibilities about what they were doing:

- it might be helping them,
- it might be hurting them, or
- it might just be wasting their money.

PROJECT INFORM was originally meant to be a short-term project, a proposal to create a community-based research study of the effects of the treatments that were in common use, for better or for worse. As such, it was one of the nation's first calls for community-based research, a process which sought to unite the patient community, researchers, and practicing physicians. The concept of community-based research was ahead of its time in 1985 and PROJECT INFORM had considerable difficulty getting off the ground. While the patient community was quick to appreciate the value of the proposal, the medical community was at best lukewarm. Some feared that such research would further legitimize the unproven drugs. Although most physicians were quietly monitoring use of such drugs, they didn't like it. This lack of support, perhaps aided by our own inexperience, made it all but impossible to raise funds to complete the original mission. Variations on the concept of community-based research, however, were taken up and successfully implemented by others beginning in 1987. PI shifted gears and attempted to address the same problems through use of educational materials. This lead to the creation of printed materials, a hotline service, and regular public "town" meetings.

The Hotline Program

A key PROJECT INFORM program which grew out of our education work is the toll-free Treatment Hotline, the only nationwide hotline service devoted exclusively to a broad range of treatment issues. Fielding several thousand callers monthly, the Treatment Hotline is a widely known and widely respected method of updating people on the latest in treatment news, as well as debunking the latest in treatment hype. Government offices and national hotline services, such as the National AIDS Hotline, regularly refer treatment questions to the PROJECT INFORM Treatment Hotline for reliable and up-to-date treatment information.

PI Publications

To update the over 70,000 people who have requested information from us, a periodical journal - *PI Perspective* - was created in 1987. Published 3 times yearly, *PI Perspective* quickly became one of the most widely respected and widely circulated AIDS publications. It is noted both for the quality and accuracy of its information as well as its activist stance on issues which affect funding, research and access to treatment. The journal provides an in-depth analysis of the state of the art in AIDS treatment and research, as well as the political, scientific, and regulatory issues which affect the lives of people with HIV.

The *PI Briefing Paper* is a newsletter, published 3 times yearly, which augments the *PI Perspective*. The *PI Briefing Paper* contains legislative updates, reports on late-breaking news and developments, and updates on current drugs in development and standards of care. Because of funding issues, the *PI Briefing Paper* is regularly mailed only to donors making contributions to PROJECT INFORM -although it is made available, by request, to persons calling the PROJECT INFORM Treatment Hotline.

In order to provide the thousands of people calling the PROJECT INFORM Treatment Hotline with the most up-to-date information on new treatments developments in standards of care for HIV and its associated opportunistic diseases, PROJECT INFORM produces "Fact Sheets" and "Discussion Papers". A "Fact Sheet" provides specific information on treatments and standards of care, including the latest in research findings. "Discussion Papers" give perspectives on a variety of issues ranging from approaches to developing a comprehensive treatment strategy for managing HIV-disease, to commentary and discussion on misinformation on AIDS in the media.

The Outreach Program

PROJECT INFORM's role as an educator has always included an extensive public speaking program in the form of "Town Meetings" held twice monthly in San Francisco and by request throughout the nation. The Outreach Program has expanded and currently regular "Town Meetings" take place in several major cities throughout the United States. These meetings educate the HIV-positive community on the latest in treatment news. Through this vehicle, PROJECT INFORM was the first major AIDS organization to advocate for anonymous HIV antibody testing, a position held since our inception in 1985 and made into a public campaign beginning in 1987. PROJECT INFORM's treatment message has led the nation in urging testing, monitoring, early intervention, prevention for opportunistic infections, lower-dose use of existing therapies, and combination therapy.

The Advocacy Program

Working in the field of treatment information brought PROJECT INFORM in contact with government authorities and the regulations which govern research and access to treatment. In 1986, PROJECT INFORM became the first activist organization to initiate constructive relations with the Food and Drug Administration (FDA) over a wide variety of regulatory issues. Ever pragmatic, PI's relationship with the FDA today ranges from that of educated critic to co-presenter at medical conferences, depending on the situation. Over the years, our activist posture has expanded to include extensive work with the National Institute of

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Allergies and Infectious Diseases (NIAID), the National Cancer Institute, the Laboratory of Tumor Cell Biology, the AIDS Clinical Trials Group, the Department of Health and Human Services, Congress and private industry. Along with ACT UP/New York, PROJECT INFORM was one of the two key developers of the "Parallel Track" program and helped write the regulations to implement it. PROJECT INFORM also played a key role in developing policy recommendations for regulatory reform which the FDA implemented in 1992, including the expedited approval of drugs for the treatment of life-threatening illness.

PI Treatment Action Network -1991 brought the development of several advocacy projects, including the PI Treatment Action Network (TAN). The group will serve to coordinate and unite people throughout the country, bringing together their collective will and efforts to bear on issues which affect research, access to treatment, and health care. Currently TAN has hundreds of members from over 40 states.

Project Opportunistic Infections -Project Opportunistic Infections was developed to track and expedite the development of preventions and treatments for the many opportunistic infections associated with HIV-disease. Through Project OI, PROJECT INFORM played an influential role in obtaining an expanded access program for the experimental MAC drug, Clarithromycin.

Project Immune Restoration -A volunteer initiated project, this project was established to follow and advance the "lost child" of AIDS research, immune-based therapies designed to restore the immune system of persons in later stage disease. Project Immune Restoration coordinated an Immune Restoration Think Tank which brought together the world's top scientists and researchers in the field of immunology and immune-based therapy. Results of the Think Tank included constructive and creative dialog around new approaches to this field of research, the creation of new collaborations between research groups working in different fields of immune-based therapies and the formation of the Think Tank as a standing body which holds meetings biannually.

The Research Program

In a final about-face, 1989 saw the return to our roots in the conduct of the controversial and now famous Compound Q studies. In this program, PROJECT INFORM acted upon its original mission of seeking safety information on a new treatment which had come into community use before researchers had begun to test it. The Compound Q study highlighted for all the need to speed the research of new treatments which had completed the laboratory phase of their development. It also renewed the founding spirit of community-based research, which some felt had become moribund in its own brand of red tape since the first active groups were formed in 1987.

To facilitate research, the previously independent Community Research Alliance of San Francisco was invited to become a funded program of PROJECT INFORM in early 1990. Within a month, PROJECT INFORM was granted an independent license to study GLQ223 (Compound Q). In December of 1990, PROJECT INFORM became the second community-based research group to have a study published in a major medical journal (AIDS, 12/18/90).

The Research Program has since expanded and now includes a wide range of activities. On a limited basis, it is involved in the conduct of community-based clinical trials, sometimes as a sponsor, sometimes as a funding source. The PROJECT INFORM Institutional Review Board conducts ethical reviews of community-based research projects, including Project Inform studies and those of the independent San Francisco-based Community Consortium, one of the nation's largest and most successful community research groups (the Community Consortium is not affiliated with Project Inform). The Research Program also reviews protocols for pharmaceutical companies, research groups and government programs which seek the input of community voices who are knowledgeable about clinical study design. Similarly, the Research Department attempts to provide cursory reviews of the many research and treatment programs promoted by individuals outside the mainstream of medical research.

PROJECT INFORM Today

There remain three key aspects to our work:

- to inform the HIV-infected (and all those at risk) of life-saving strategies like early diagnosis and early intervention;
- to give people and their physicians the means to make informed choices about the most promising treatment options;
- to change research and regulatory policies which delay or prevent access to treatment.

PROJECT INFORM has stayed true to its founding as a grass-roots community organization. We do not seek growth for its own sake, nor are we concerned with our posture relative to other non-profit organizations. We are and will remain committed to the work of ending this epidemic with as little loss of life as possible. We have been permitted the honor of doing this work only through the generous contributions of our supporters, to whom we are indebted.

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More Hope For People With AIDS

The goal of Project Immune Restoration (PIR) is to create a centralized office for assisting the research aimed at making immune reconstitution possible. PIR plans to enable HIV positive people to better understand the technical issues and to speed the development of such therapies by providing input for prioritizing and implementing these studies to agencies that set HIV research policy in the United States and world wide.

PIR will monitor information in immune system research and development, especially those directly related to AIDS and other diseases involving dysfunctional or suppressed immunity. This information will facilitate access to treatments by making them available faster and by informing the affected community of their existence, whether in a trial setting, through expanded access or through "underground sources". A primary goal will be to identify obstacles to the development and/or availability of treatments and develop specific action plans to remove these obstacles. The information will also be used to develop an agenda for clinical and basic research. PIR will also help organize conferences like the successful Institute of Medicine meeting on Immune Restoration in HIV in December 1990, the April 1992 Immune Restoration Think Tank held in Washington, D. C., and the February 1993 Immune Restoration Think Tank held in Rutherford, CA.

While there are existing organizations for some of these activities, we feel that PIR has features that make it a distinctly useful addition. Key features include:

- **Focus**
  PIR is designed to look exclusively at improving the immune function in the HIV infected. PIR has as one of its main goals to form an informal, but effective, "think tank" to solve this critical problem. As new, more effective antivirals are developed, those with already devastated immune systems may not be able to greatly benefit without therapies for enhanced immunity.

- **Reputation**
  PIR intends to build on the highly respected reputation of Project Inform within the HIV and scientific communities as an aggressive and effective advocate of new therapies for people with HIV and source of information

regarding these therapies. Our reputation has earned us influence with groups like the AIDS Clinical Trial Group at NIAID, the U. S. FDA, the Clinton Administration and the University of California, all of which in very different ways influence basic and clinical HIV research.

- **Independence**
  As an organization representing the patient community, PIR is outside the academic and federal research establishments. We, therefore, can advocate the investigation of more radical approaches to restored immunity without the concern for professional criticism while legitimately articulating the risk/benefit from the perspective of the patient.

- **Motivation**
  A large percentage of our volunteers and supporters are the HIV positive or their friends, and many of these people have severely suppressed immunity. Without significant improvements in therapy, we will certainly lose these cherished friends and crucial members of our community.

IMMUNE RESTORATION THINK TANK 3

Abstracts

A Model for Community Interaction with HIV Research

Dobson, J.C.*, Lein, B., Delaney, M.
Project Inform, San Francisco, CA USA

Despite progress in antiviral and opportunistic infection research, community activists have recently recognized that one of the necessary components of a "cure" for late-stage HIV infection would require restoration of some or all of the immunity lost due to attack by HIV. In response, Project Immune Restoration (PIR) was created to be a focal point of facilitating the research aimed at making this possible. PIR strives to enable better understanding of the technical issues involved and speed the development of therapies by providing input for prioritization and implementation. We also inform the community about their progress.

While there are existing fora for some of these activities, PIR offers a focus and independence from academic and government bureaucracies. PIR has already had some impact. For example, we have held two meetings of the Immune Restoration Think Tank, a gathering of top AIDS researchers and clinicians resulting in a research plan for immune restoration. This and other activities have led to an increased emphasis and funding of immune based therapy projects worldwide. The strategies of PIR will be presented with an analysis of past mistakes and successes and future plans. Applying this model to other areas of HIV research will be discussed.

Conclusions

1. Project Immune Restoration has created an effective model for organized, supportive interaction between people with HIV and their advocates and those doing basic and clinical research on therapies for HIV.

2. This interaction has lead to targeted plans that could speed the development of new therapies and their introduction to the clinical setting.

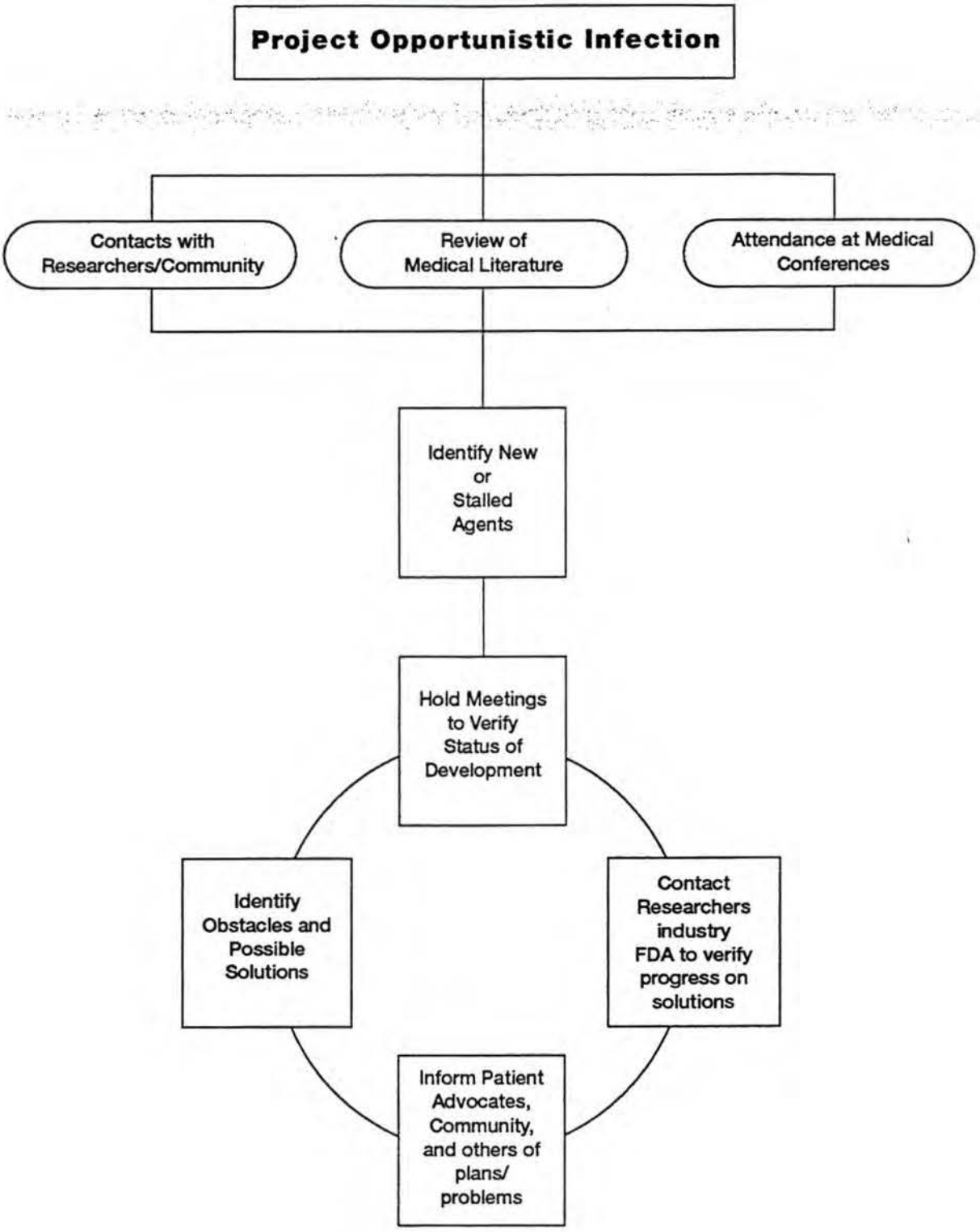
3. Project Immune Restoration has been successful in shifting the emphasis of HIV therapeutic research to be more inclusive of immune-based therapies.

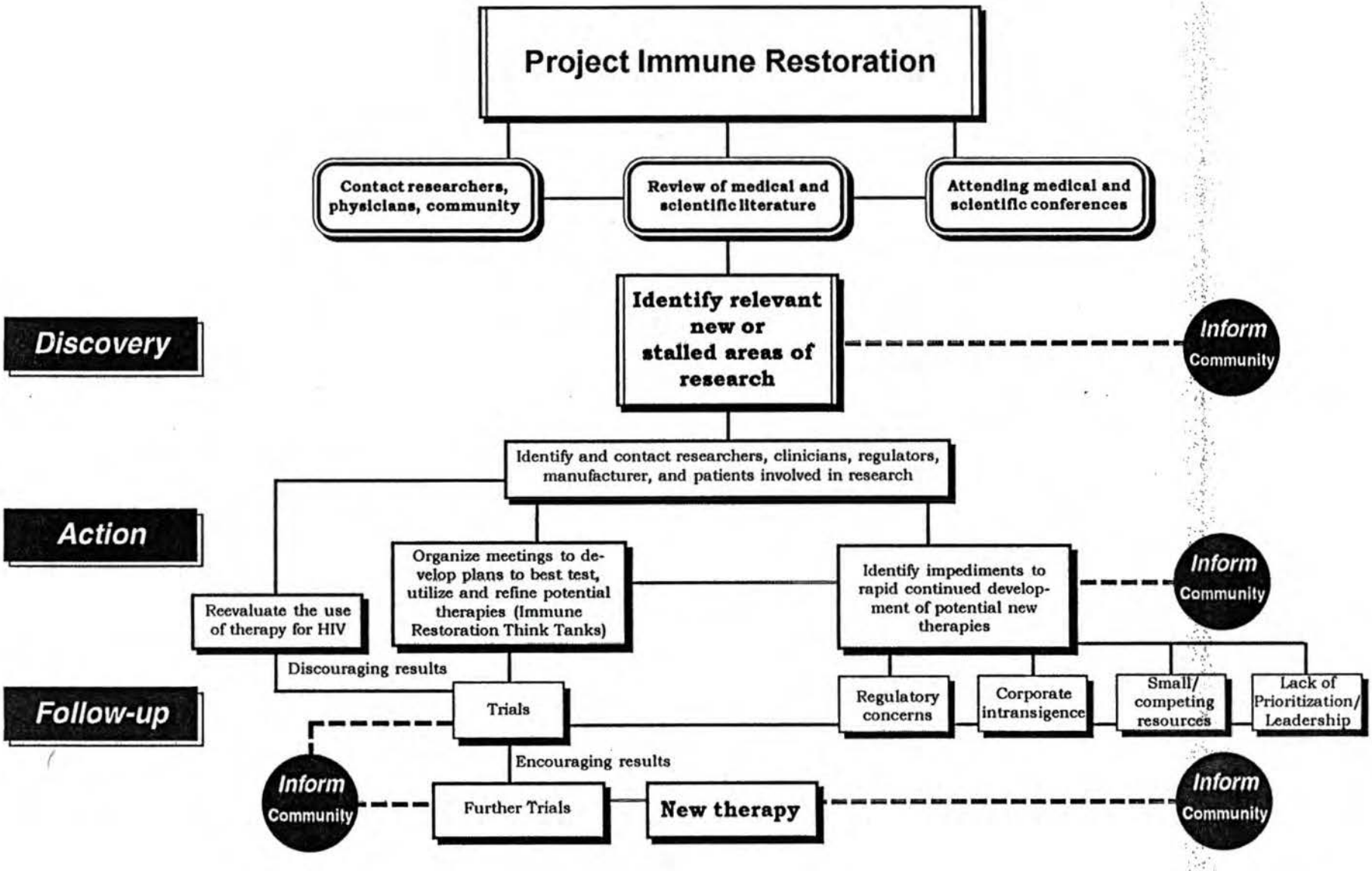
4. Project Immune Restoration provides a structure for efficient involvement of community activists in influencing the direction of therapeutic research

5. The model can easily by modified to apply to other areas of HIV therapy, *e.g.* antivirals, neurological involvements, Kaposi's Sarcoma, wasting, opportunistic infections, etc.

You Can Make A Difference!!!

For more information about Project Immune Restoration, for more detailed outlines of the Immune Restoration Think Tank Plans, or to become involved in the project, please leave a mailing address and/or business card in the envelope attached to this poster with a few details regarding the additional information you would like sent.


Project Opportunistic Infection
Contacts with Researchers/Community
Review of Medical Literature
Attendance at Medical Conferences
Identify New or Stalled Agents
Hold Meetings to Verify Status of Development
Contact Researchers industry FDA to verify progress on solutions
Inform Patient Advocates, Community, and others of plans/ problems
Identify Obstacles and Possible Solutions


Project Immune Restoration
Contact researchers, physicians, community
Review of medical and scientific literature
Attending medical and scientific conferences
Discovery
Identify relevant new or stalled areas of research
Inform Community
Action
Identify and contact researchers, clinicians, regulators, manufacturer, and patients involved in research
Reevaluate the use of therapy for HIV
Organize meetings to develop plans to best test, utilize and refine potential therapies (Immune Restoration Think Tanks)
Identify impediments to rapid continued development of potential new therapies
Inform Community
Discouraging results
Follow-up
Trials
Regulatory concerns
Corporate intransigence
Small/ competing resources
Lack of Prioritization/ Leadership
Encouraging results
Inform Community
Further Trials
New therapy
Inform Community

Think Tank Helping to Get HIV Immune-Restoration Trials Off the Ground

DURING THE NEXT 6 months, a change in emphasis in research on HIV disease should begin to take hold.

Work that focuses more on repairing the damaged immune system than on directly killing the human immunodeficiency virus (HIV) shifts into high gear.

The necessity of both treatment approaches has been evident since the early days of the AIDS epidemic. But research on immune restoration languished after the approval of the antiretroviral drug zidovudine (Retrovir, commonly called AZT, Burroughs Wellcome, Research Triangle Park, NC). What trials were done had disappointing or equivocal results.

The pace is picking up now, in large part due to a unique think tank called Project Immune Restoration. It is made up of a broad array of researchers, government officials, and activists who, for the past 18 months, have focused intensively on finding out what can be done in the clinic now and what needs to be done in the laboratory for further progress to take place. The unique effort was shepherded by Jesse Dobson of Project Inform, who died of AIDS-related disease in September, just as concrete evidence of its success was beginning to emerge.



Ron Zuckerman

Jesse Dobson is credited by researchers involved with Project Immune Restoration for its success. He died of AIDS-related disease in September.

Rave Reviews

Participants raved after the think tank's latest meeting last month in Baltimore, Md, about the rare opportunity it is providing to translate ideas into action much more quickly than they otherwise could. Immune-cell–based therapies in particular are leapfrogging from the laboratory into the clinic.

In this next year "there are going to be many cell-therapy trials started for the first time" in HIV disease, says Thomas Merigan, MD, professor of medicine at Stanford University, Palo Alto, Calif.

"This field is moving fast. We all heard things we have not heard before," says Robert (Chip) Schooley, MD, chief of infectious diseases at the University of Colorado School of Medicine, Denver, and chair of the immunology committee for the National Institute of Allergy and Infectious Disease's AIDS Clinical Trials Group.

The think tank meetings differ from most medical conferences. "Instead of talking about things we have done, we talk about things we would like to see done. And with so many people here brought together specifically because of their different areas of expertise, you can build together a team that can actually do these things," says Schooley.

Controversial concepts get a more constructive airing as well, says Stella Knight, PhD, head of the Division of Antigen Presentation Research at Great Britain's Clinical Research Center, Harrow, Middlesex.

Knight's work suggests an important role for dendritic-cell depletion, which precedes the better known depletion in T cells in HIV pathogenesis. She believes this is important because dendritic cells "teach" naive T cells how to respond to antigen; but she acknowledges that her theory is "still questioned by many."

However, at the Project Immune Restoration meeting, "instead of spending energy questioning the concept, you go with the concept, discuss how it might integrate into a greater picture, and see whether it is useful. We can be open without fear of immediate contradiction or condemnation before we've had a chance to look at where the ideas lead, and devise strategies for those working in areas that may be controverial but still need to be worked on," she says.

Integrated Picture

"You get an integrated picture without the nitpicking," says Knight, adding that she now has a much clearer sense of where her work, if confirmed, would fit in with the overall picture of other cell-population irregularities in HIV disease.

"People don't learn very well when they're on the defensive," says Martin Delaney, director of Project Inform. "A lot of science puts people on the defensive rather than opening their minds to each other's work. We're trying to get these people from all disciplines who work on these different pieces in different ways to come together and look at it as a whole," says Delaney.

There is still a great need to "more precisely define what's broken in the immune response in AIDS," says Delaney. While that may seem obvious, "it is much more complicated than a loss of CD4 cells. We're looking on one hand at sustaining what's there and prevent-

ing more damage, and then on rebuilding what's broken."

Jonas Salk, MD, who developed the first polio vaccine and is working on HIV therapeutic vaccines, says participating in the Project Immune Restoration think tank "reminds me of the days when the National Foundation for Infantile Paralysis focused its attention on resolving that problem."

Concrete Proposals

Schooley says Project Immune Restoration provides not only a "renewed sense of hope" for understanding how HIV causes immunodeficiency, and a wider view of things that might reverse the immunodeficiency in late-stage HIV disease, but "concrete proposals that will actually lead to things that otherwise would not have been done."

"There are 15 million people infected with the virus around the world, and many are reaching the stage where even if we had a magic tablet that would get rid of the AIDS virus, many would still not be able to survive simply because too much damage has been done to this vital [immune] system," says John Dwyer, MD, PhD, head of the Department of Medicine at Prince of Wales Hospital, Sydney, Australia.

"As a result of our deliberations, we have a half dozen or so very practical strategies that can be worked on in the next year to see if we can't correct some of those deficiencies, extending life and the quality of life considerably," says Dwyer.

Mark Harrington, an activist with the Treatment Action Group in New York, NY, concurs that "there is consensus that we can get protocols up and start this process of shoring up the immune system while we're waiting for the perfect antiviral."

Expanding Cell Expansion

What can be expanded right away are cell-expansion studies, in which immune cells are taken from patients while they are still healthy, grown in culture, perhaps augmented in a variety of ways, stored, and then reinfused in the late stages of disease.

Dwyer's laboratory has harvested cells from 50 patients at various stages of infection and is "sitting back and waiting for the time when it would be appropriate to give the cells back, and trying in the meantime to work out the best strategies for when to give them."

Participants in Project Immune Restoration "deliberately kept our thinking to things that modern-day knowledge and technology will allow us to do." With investigators from the United States and elsewhere likely to "pick up on our protocol and do the same sort of things, we'll all get the answers we want that much faster."

Dwyer is not separating the different components of the harvested blood cells, because "we're not sure which cells are most important, and we thought it seemed a good strategy as a starting point to say that since the patients we're taking cells from are perfectly well, their cells are in balanced proportion, so we will try to give them all back and see what happens." If it works, then storing cells early in infection will be like "an insurance policy" for patients, he says.

Dwyer also wants to try immunizing patients with Salk's vaccine to boost anti-HIV activity before harvesting cells.

There are many variations on the cell-expansion approach. Expansion and reinfusion of CD8 cells has been under way for 2 years.

A clinical protocol for expansion of CD4 cells is in review now at The Johns Hopkins University School of Medicine, Baltimore, Md. Researchers at Stanford University are working on getting support for a protocol using expansion of CD4, CD8, and dendritic cells.

Investigators at Tufts University School of Medicine, Boston, Mass, are separating out only cells that are specifically active against individual patients' own strain of HIV. Judy Lieberman, MD, PhD, is mapping the small number of short (eight to 10 amino acid) peptides on the virus that T cells actually recognize, which varies from patient to patient. She then cultures only the T cells with receptors for those peptides, multiplies them in vitro, and reinfuses them, so far into nine patients. Similar work that uses cloning to get large numbers of virus-specific T cells is set to begin soon at the University of Washington in Seattle.

There are also several proposals for somehow beefing up cells while they are in culture, either with cytokines or genetic alterations, though these approaches are not as near to clinical testing.

Ethics and Logistics

The logistics and ethics of cell-expansion therapy are going to be addressed at a meeting being planned for early next year by John Kagan, PhD, chief of the clinical science section, Division of AIDS at the National Institute of Allergy and Infectious Disease.

Repositories will be needed to store frozen cells, and "since we would probably not have the capacity to offer this to as many patients as would potentially want it, the ball starts rolling on ethical issues of access and a whole bunch of reasons for which there could be difficult questions arising," says Kagan. He adds that there is "probably no shortage of folks out there already ready to prey on the wishful thinking of AIDS patients, and take their money to store their cells with some promise of a treatment" that may not come.

Kagan is also hoping to schedule two other meetings on cell therapy. One, which he says he may hold yet this year, will be to discuss whether evidence from about a half dozen anecdotal reports of allogeneic blood lymphocyte transfer between half-matched (sibling) donors is enough to warrant a formal trial.

Second, Kagan is working on a 2-day meeting for early 1994 to discuss stem-cell transplant possibilities, including bone marrow and peripheral blood stem cells. The goal would be to determine the best direction for basic research on such things as whether stem-cell maturation is dependent on the thymus, which is severely damaged in patients with AIDS.

There is great heterogeneity of opinion about whether patients with HIV have all the things necessary for the development of cells, and whether that might explain why bone marrow transplant trials in HIV disease have been so disappointing, says Kagan.

Laboratory groundwork for trying thymus transplants again is being laid, says Dwyer. Experiments by him and others in the mid 1980s in 18 patients were "tried and failed and put aside. Any immune cells that were generated were soon killed; the virus more or less said thanks very much, here are more T cells to destroy," he recalls.

But while there are still a number of technical problems to work out, there have been enough advances in knowledge that investigators now think they may be able to get new cells in transplanted thymus tissue to fight the virus in a new host, says Dwyer. "It's now at the stage where it is worth researching again."

Also, looking at the long-term picture, there is a surprising amount of interest in the possibility of xenogenic transplants.

Kagan says many at the Baltimore meeting have responded to a request for applications from his institute for new research programs that combine innovative basic research with preclinical work "so as to hasten the development of novel therapies into clinical trials."

"Maybe a lot of these protocols initially will not save patients," says Delaney, "but we will learn something that will make it possible to save the next patient."—by Paul Cotton

Future Directions in AIDS Research
Toward a Cure . . .

On July 30 and 31, 1993 a historic meeting was convened at the University of Wisconsin, Madison, to address the current state of AIDS Research and to look at potential improvements in the direction of research efforts for the future. The 40 attendees included leading American AIDS researchers, from both the government and academia; representatives of community AIDS groups nationwide; industry and regulatory representatives; and representatives of the US government who would have a role in implementing recommended policy changes. Kristine Gebbie, the National AIDS Policy Coordinator, made one of her first public appearances in her new position to attend the meeting.

The meeting was prompted by Project Inform founder Martin Delaney's call for an assessment of the state of AIDS research and suggestion for a targeted research effort. Many attendees were invited to participate because they had also called for either an assessment or a directed research effort; some participants had proposals for change in hand, while others expressed caution yet were willing to put the issues on the table. With such a diverse group, the discussion was lively, intense, and often surprisingly in agreement.

The first day of the "think tank" focused on identifying critical research questions necessary to answer in order to advance the current state of AIDS research. Issues included the need to intensify research in the areas of gene therapy, immune reconstitution, specific questions of pathogenesis and the development and standardization of sensitive assays to measure viral load.

The second day turned towards examining various obstacles to hastening the pace of AIDS research and developing constructive solutions. Among a number of recommendations was the need for a more collaborative effort and a higher level of information exchange among all parties involved in AIDS research. Participants developed consensus on a number of issues, including the need for incentives to develop more creative approaches to AIDS research and an increase in budgets for both biomedical research in general and AIDS research in particular.

The meeting, chaired by June Osborn, former Chair of the National Commission on AIDS, was highly successful. It was agreed at the end of the two days that the discussion was not finished, that much work remained to be done, and that the group should reconvene in November to create a concrete list of scientific and policy suggestions for new directions in AIDS research.

Project Inform participants and/or assistants included Martin Delaney, Brenda Lein, Joel Thomas, Jesse Dobson, Anne Donnelly, and David Lewis.

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Future Directions in AIDS Research
Toward a Cure . . .

CONSENSUS STATEMENTS
JULY 30-31, 1993

Premise: We believe that effective treatments will be discovered for this disease. We are committed to the belief that it is possible to develop new therapies within a reasonable time capable of providing long-term survival without clinical disease.

1. Insufficient resources inhibit the pace of both general biomedical research and AIDS-specific research. More resources will shorten the time to develop effective treatments

2. There is an unmet need to identify gaps or discontinuities in programs of research and in the implementation of clinically relevant findings.

3. Targeted special programs should be considered for emerging, gap-filling, or risky innovative research areas. Mechanisms for prioritization are possible and should be utilized.

4. There is a need to improve communication pathways and coordination among investigators. One example is the need to develop high quality repositories for defined clinical samples.

5. The urgent challenge of AIDS highlights the problem of constituting complex drug trials using multiple proprietary compounds from distinct public and private sources. A rational and comprehensive strategy should be implemented to overcome barriers at all levels that mitigate against these novel therapeutic trials. This point addresses the crucial problem of initiating therapeutic studies with multiple, simultaneous agents owned by different entities.

6. There is a need for the further stimulation and support of creative thinking in the AIDS research community. This should include an assessment of different management styles and structures and an emphasis on the training of new investigators.

7. There is need to expand and create AIDS research programs by infusion of money and talent from outside the current NIH structure.

8. The government should work with industry to create a mechanism to attract the pharmaceutical industry to participate in these efforts.

9. The President, his Administration and Congress must take a leadership role in educating the American public and world community on why these initiatives are important and urgent.

No amount of structural review or proposals for change will work without first defining the mechanism for implementation and then finding the will and courage to carry them out.

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Participant List

July 30-31,1993 meeting

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Dr. Sam Broder -*National Cancer Institute, National Institutes of Health, Bethesda, MD*
Dr. Irvin Chen -*UCLA School of Medicine*
Dr. Tom Coates -*Center for AIDS Prevention Studies, University of California San Francisco, CA*
Dr. Max Essex -*Harvard AIDS Institute and Harvard School of Public Health, Cambridge, MA*
Dr. Anthony Fauci -*National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD*
Dr. Robert Gallo -*National Cancer Institute, National Institutes of Health, Bethesda, MD*
Dr. William Haseltine -*Human Genome Sciences, Inc., Rockville, MD*
Dr. Maurice Hilleman -*Merck Institute for Therapeutic Research, West Point, PA*
Dr. Norman Letvin -*Harvard University and the New England Regional Primate Research Center, Southborough, MA*
Dr. Richard Marlink -*Harvard AIDS Institute and Harvard School of Public Health, Cambridge, MA*
Dr. Gary Nabel -*Howard Hughes Medical Institute, University of Michigan, Ann Arbor*
Dr. John Niblack -*Intercompany Collaboration for AIDS Drug Development and Pfizer, Inc., Groton, CT*
Dr. June Osborn -*School of Public Health, University of Michigan, Ann Arbor, MI*
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Mr. Steve Morin -*House Committee on Appropriations, Washington, DC*
Ms. Kristine Gebbie -*National AIDS Policy Coordinator, Washington, DC*
Mr. Moises Agosto -*National Minority AIDS Council, Washington, DC*
Mr. Terry Beswick -*Human Rights Campaign Fund, Washington, DC*
Mr. Dan Cusick -*ACT UP Golden Gate, San Francisco, CA*
Ms. Lynda Dee -*AIDS Action, Baltimore, MD*
Mr. Martin Delaney -*Project Inform, San Francisco, CA*
Mr. Jesse Dobson -*Project Inform, San Francisco, CA*
Mr. Greg Gonzalves -*Treatment Action Group, New York, NY*
Mr. Greg Haas -*Committee of 10,000, Minneapolis, MN*
Mr. Mark Harrington -*Treatment Action Group, New York, NY*
Mr. Derek Hodel -*AIDS Action Council, Washington, DC*
Mr. Larry Kramer -*Playwright and AIDS activist, New York, NY*
Mr. Mark Milano -*ACT UP New York, NY*
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Cooperative research

New projects targeted to fill gaps in AIDS knowledge

By Sari Staver
AMNEWS CORRESPONDENT

SAN FRANCISCO — Last summer, 50 leading HIV experts held an unusual two-day "think tank" in Madison, Wis., to study ways to improve AIDS research. The participants ranged from T-shirted activists to button-down drug industry executives and government officials.

A second gathering is planned for next month, after which the group says it will present the Clinton administration with a set of recommendations.

The meeting, called historic by organizers, reflects a growing spirit of cooperation and collaboration among AIDS experts, long united in their dedication to battling the decade-old epidemic but frequently at odds over strategy and style.

Fueling this trend is the view among some authorities that the pace of research has been unacceptably slow, said Derek Hoedel, treatment issues director for the AIDS Action Council, an advocacy group based in Washington, D.C. Frustration only increased during this year's international AIDS conference in Berlin, where report after report noted the limited efficacy of current treatments.

"Scientists and regulators are now willing to consider any option that offers a chance for progress," Hoedel said.

The efforts, aimed largely at identifying and addressing gaps in research, have created some scenarios unimaginable in years past: government scientists and policymakers setting research agendas in partnership with anti-establishment activists, and rival pharmaceutical manufacturers collaborating to conduct clinical trials.

Jeffrey Laurence, MD, senior scientific adviser to the American Foundation for AIDS Research, says the time is right, scientifically, for such efforts. Until now, "we didn't know what we didn't know" about the human immunodeficiency virus, he explained. "Now we seem ready to target the questions that need to be answered."

> **'It is ironic that it took a community-based organization to bring together such a group to do what we've needed to do all along — talk to each other in a cooperative, constructive manner.'**
>
> **ROBERT SCHOOLEY, MD**

Building bridges

Among the cooperative efforts:

■ Fifteen pharmaceutical companies have formed the Inter-Company Collaboration for AIDS Drug Development to facilitate trials of combination drug therapies against HIV. The manufacturers will share information and supplies so that each individually can conduct early-stage combination studies.

Consortium coordinator Linda Distelrath, PhD, senior director of public policy management at Merck & Co., traced the unprecedented industry collaboration to three factors: the recognition that HIV apparently develops resistance over time to all antivirals; the increase in the number of potential treatment compounds; and the evidence that multidrug combinations might mitigate the resistance problem.

■ More than 40 physician networks are conducting AIDS clinical trials with government or private-sector funding.

One of the largest is the 10-year-old County-Community Consortium of AIDS Physicians in San Francisco, created originally to inform private physicians about the clinical trials available to their patients at San Francisco General Hospital. Over time, however, it became clear that some trials might be done more effectively in doctors' offices, said Donald I. Abrams, MD, who heads the effort.

For example, "more and more, we realize that one of the missing pieces of information is data on longer-term outcomes, including survival" of patients taking antivirals, he said. Community-based primary care physicians are most likely to stay with patients long enough to provide such longitudinal data.

"Studies now under way on the treatment and prevention of common opportunistic illnesses could greatly improve the quality of life of our patients. I think we will find our greatest impact in helping practitioners learn to better manage this disease."

■ Since the late 1980s, the National Institutes of Health, the Food and Drug Administration and dozens of pharmaceutical companies have included AIDS activists on advisory panels that help guide trials.

Their presence has led to improved clinical trials, said Jack Killen, MD, acting director of the Office of AIDS at the National Institute of Allergy and Infectious Diseases. For example, input from activists enabled federal investigators to enroll more women in a major antiviral drug trial, ACTG 175. The activists pointed out that the eligibility criteria did not account for the physiological differences between men and women, and thus inadvertently excluded women. The criteria were then altered, Dr. Killen said.

■ The Ariel Project, a three-year, $15-million research effort sponsored by the Pediatric AIDS Foundation, is studying 150 HIV-infected, pregnant women at seven sites nationwide. The goal is to determine the virologic and immunologic factors influencing mother-to-child HIV transmission. The project was developed by a multidisciplinary board of physicians and scientists representing government, academia and the drug industry, who identified this area as one that

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AIDS

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had been insufficiently addressed in previous research.

■ Project Immune Restoration, a 2-year-old initiative by the San Francisco-based advocacy group Project Inform, has held two think-tank-style gatherings to set research priorities for treatment of late-stage HIV-disease, another area in which they say not enough research has been focused. Participants called for studies of the role of thymic transplantation, gene therapy, *ex vivo* cell expansions and xenogenic tissue transfer. They are seeking interest from public and private sector investigators. A third meeting, scheduled for November, will address regulatory, funding and other implementation concerns.

"Meetings like these should have been held throughout the first 12 years of the epidemic," said Robert Schooley, MD, head of infectious diseases at the University of Colorado School of Medicine and a member of the initiative's expert panel. "It is ironic that it took a community-based organization to bring together such a group to do what we've needed to do all along — talk to each other in a cooperative, constructive manner."

Model for change

But perhaps the most promise for change is seen in the meeting held in Madison, which was organized by the University of Wisconsin Medical School, the Harvard AIDS Institute and Project Inform. Participants ranged from Larry Kramer, founder of the radical advocacy group ACT-UP, to federal AIDS policy coordinator Kristine Gebbie; Commissioner David A. Kessler, MD, of the Food and Drug Administration; and Anthony M. Fauci, MD, director of the National Institute for Allergy and Infectious Diseases.

Gebbie described the meeting as "very significant, because it was the first time such an intriguing mix of people met together in a productive atmosphere."

Said organizer David Pauza, PhD, associate professor of medicine at the University of Wisconsin, Madison, "It is not unfair to characterize this as an historic meeting that begins a new process to reinvigorate our fight."

In broad-based discussions, the group reached consensus on several points. Chief among those was that insufficient resources are the primary obstacle to research progress, said Richard Marlink, MD, executive director of the Harvard AIDS Institute. A variety of approaches were suggested for boosting financial support, from marshaling a more organized private response, like the March of Dimes and American Cancer Society have done, to forming a public-private consortium, or "Manhattan Project," that would collect, prioritize and disperse all resources to fight the disease.

The group also noted the need for a mechanism to encourage drug companies to assume the risk for developing a larger number of basic scientific findings, many of which now languish in academic or government research laboratories.

Martin Delaney, founding director of Project Inform, said projects such as the Madison meeting reflect the growing role of AIDS advocates. "A few years ago, we begged to attend other people's meetings, and when we were allowed in, we were often greeted with skepticism and hostility. Now we call the meetings, and those same people are anxious to attend, usually at their own expense." Delaney cited two other recent activist-sponsored conferences that were well received: one on clinical trial design sponsored by ACT-UP Boston and one on vaccines sponsored by New York's Gay Men's Health Crisis.

The think-tank model is highly suitable for collaborations between scientists and activists, Delaney said. "We want them to buy into a project that they are creating, as opposed to some suggestions that are being made to them." Gebbie also praised the model: "I think there are lots of places in our HIV-related programs where we can apply this kind of gathering."

Dr. Fauci, however, was less enthusiastic. He said the Madison meeting offered nothing new scientifically, and was useful only "in clarifying perceptions about what is being done" for people "who hadn't heard parts of the story before."

Delaney is optimistic, nonetheless, that the effort's ultimate impact on research progress will be significant. "Our challenge now is keeping our nose to the grindstone so that we can reach a consensus on programmatic proposals we can present to the administration."

FEBRUARY 1994

Project Inform

The Second Front Update

Future Directions In AIDS Research

by Martin Delaney

In November of 1993, Project Inform co-sponsored the second meeting of *Future Directions in AIDS Research* (FDAR). The historic meeting concluded in Boston, where heads of national institutes, policy-makers, industry and regulatory representatives, researchers and a number of community activists met to discuss developing proposals aimed at accelerating the pace of AIDS research. These proposals, once fully developed, should compliment reforms to strengthen the Office of AIDS Research (OAR)[1] at the National Institutes of Health (NIH). Clearly, AIDS research can be better managed, information flow can be enhanced and greater collaboration will lead to meaningful advances. While most areas of discussion received full consensus, others were more controversial. A few voices, some seeking greater detail, others overly invested in the *status quo,* were leery of a 'Second Front' approach, which would pilot test a coordinated multidisciplinary team approach to managing AIDS research. What is certain, however, is that it's time for a change and no amount of change will happen without first finding the will and courage to make it happen. Outlined below are the primary recommendations which have received intensified focus in FDAR working groups over the past several months.

It's time for a change and no amount of change will happen without first finding the will and courage to make it happen.

1. Create a Free-standing, Ad Hoc Task Force

AIDS research is afflicted by an incestuous assessment process which often lacks objectivity and is clouded by self-interest. The FDAR group endorsed the creation of an independent, multidisciplinary Task Force to oversee, assess and provide non-binding guidance to AIDS research. To assure the utmost degree of objectivity, it was suggested that the Task Force not be a part of, or convened by, the government.

2. Encourage and Support the Inter-Company Collaboration (ICC) on AIDS Research

The ICC is a group of major pharmaceutical companies formed to increase industry collaboration in AIDS drug development, specifically combination approaches. The FDAR group recommended that the ICC be designated as the principal conduit for transmitting information and policy concerns into and out of the pharmaceutical industry. The ICC would be expected to supply periodic progress reports of its activities.

3. Enhance the Use of Information Technology in AIDS

Surprisingly, in the age of computer technology and the dawning of the information super highway, there is no centralized communication network linking information on AIDS research, nor linking information on AIDS with research in other diseases. Information flow is haphazard, resulting in a large amount of duplicative effort and impeding the ability to apply discovery in other diseases to AIDS. The FDAR group called for funding advanced user-friendly communication technology in AIDS research. The working group proposed using the existing InterNet system and developing an AIDS-specific "gopher" system to provide immediate access to information. An AIDS-specific Unified Language System and a Unified "Metathesaurus" should be constructed. A "Metathesaurus" would enable the linkage of general scientific concepts, providing easy access to related work in other diseases. The FDAR group recommended that the National Library of Medicine work with governmental and non-governmental groups in this endeavor, to best serve the large and diverse basic and clinical science constituencies.

Continued...

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4. Create a National Specimen Repository

Thousands of blood, serum and tissue samples are stored from experiments conducted over the past 11 years. Much can be learned about HIV disease and the effects of various drugs from these existing specimens. Accessing samples and information is random and highly dependent on professional networking. Time and money could be saved by having a National Registry of existing specimens and a defined system for access. The FDAR group endorsed the creation and funding of a central NIH repository and a centralized, updated and available inventory of repositories. A Task Force should be established to monitor the process of accessing samples.

5. Expand Training and Grant Programs

The objectives of the intended programs would include:

a. Expanding college and training programs to nurture a multidisciplinary approach to AIDS, drawing together disciplines such as: cancer biology, molecular biology, immunology, *et al* in a common environment to foster the exchange of ideas and information.

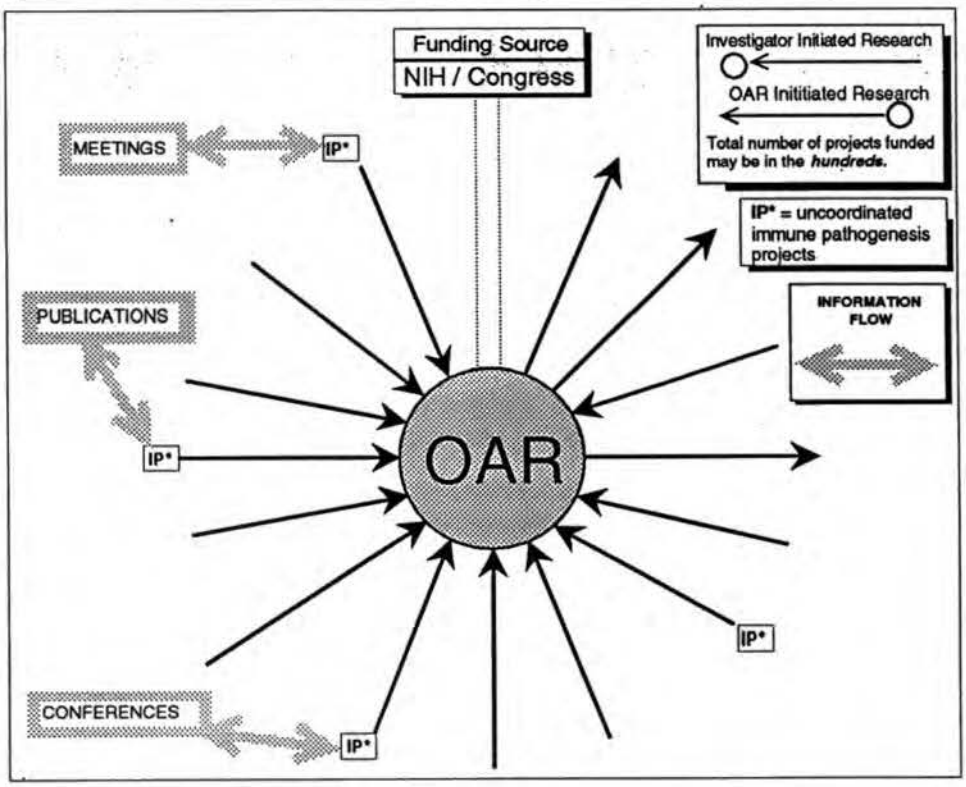
b. Funding sabbaticals, fellowships and other training programs in AIDS and non-AIDS-related fields to encourage participation in and contribution to AIDS research.

c. Expanding the use of small interdisciplinary meetings to foster dialog on innovations in AIDS and other fields as they may be applied to AIDS pathogenesis or treatment.

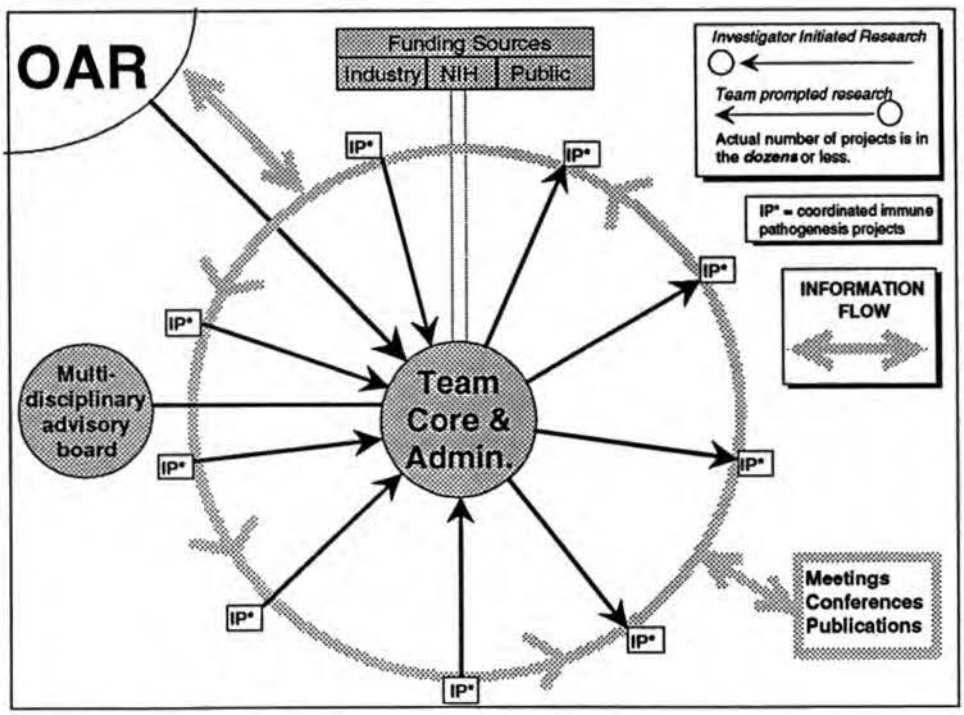
d. Encouraging (by small-money, fast-response grants) clinical scientists to conduct research on AIDS and novel therapeutics and similarly encourage basic scien-

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Existing Model, Research Management and Funding
Example: Immune Pathogenesis



Proposed Model (Working Draft)
Example: Immune Pathogenesis



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Existing Model, Research Management and Funding

Description:

- OAR creates and maintains strategic plan, overseeing all areas of research for prioritization and minimizing duplication of effort.
- OAR lightly oversees drug development, basic science, vaccine development, population studies, clinical programs, and discretionary funds.
- OAR oversees budget and distribution of funds across NIH institutes, academic grantees and contractors and private laboratories and institutes.
- Because so many areas and responsibilities are involved in managing OAR, opportunity for intensified oversight in specific areas is slim.
- Cooperation and coordination among research sites is coincidental, rather than by design.
- Some number of the hundreds of grants may be loosely directed toward immune pathogenesis, but most of those who receive such grants are in no deliberate way coordinated with each other or working with each other toward achievement of anything but their own particular interests.

Accelerated Research Initiative Proposed Model (Working Draft)

Characteristics:

- A central, critical issue is assigned to a team for concentrated discovery or accelerated development.
- Team members commit a minimum of 50% of their time to the project; management 100% of their time.
- Goals are chosen in collaboration with OAR; objectives and methods chosen by the team; team core may or may not include some lab facilities, depending on goals and resources.
- Project would have its own granting, contracting and hiring authority, with simplified requirements concentrating on achievement of goals rather than process compliance.
- Some research would be "investigator initiated," though always in concert with team goals, while other work would be assigned through specific grants; the balance would be decided by the team.
- All personnel would serve as part of a unified team, with regular "think-tank" style meetings; coordination and collaboration is by design; information would flow by design within the team and to the outside.
- Team would work in collaboration with an independent, multidisciplinary advisory board, including membership by the affected community and senior scientific advisors from outside the field.

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tists to apply laboratory discovery to the clinical setting.

6. Set Up a Project to Test Methods for Accelerating AIDS Research Using Modern Management Methods

The present management structure of much of AIDS research does not fully exploit modern management methods of team work, goal orientation and process control. These methods are employed in some areas of AIDS research, the best example perhaps being the Biotech Industry. Many believe that the real advances in AIDS therapeutics will come from Biotech companies, whose hands are free from the cumbersome bureaucracy found in large industry and government, and whose economic survival is dependent on a successful product. Because AIDS discovery is not always defined by a 'sellable product', many factors must be incorporated into the thinking of a coordinated research effort. Modern management technique can be employed to foster individual creativity and facilitate the process of discovery, however. How these principals will fare when applied to a large bureaucracy is less certain. Therefore, the FDAR group called for moving forward by defining a pilot project for an accelerated research initiative, in coordination with the Office of AIDS Research, focusing on a single but highly important aspect of AIDS research. The area of focus should be an area which might best benefit from increased attention and which could ultimately benefit AIDS research overall. An example of how such an approach might be used to accelrate discovery in immune pathogenesis, is described in the diagrams on page 2.

1. For more information on the OAR Reforms, see the February 1993 *PI Perspective*.

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Executive Summary: The Accelerated AIDS Research Initiative

Overview: Improved management methods in various fields of science and industry have lead to a virtual revolution in the way goals are set and achieved. Many American industries, including their basic research departments, have literally reinvented themselves in the last decade to more efficiently meet their objectives. Such methods are the very foundation of the emerging bio-technology industry and have been similarly employed at the world's most successful pharmaceutical companies. Federally funded biomedical research, however, continues to employ older approaches. The following proposal describes a pilot project to test whether such reorganization, or "reinvention" of the government model for biomedical research, might benefit AIDS research. The proposed project is an effort to take what was best from such celebrated programs as the Manhattan Project and the Apollo Project, while capitalizing on the hard lessons learned in the War on Cancer.

The Accelerated AIDS research initiative is designed to:

- improve collaboration and teamwork among researchers, while avoiding duplication of effort
- eliminate excessive time demands on individual scientists caused by multiple grant-writing requirements
- concentrate resources in a high potential subject area, permitting researchers to concentrate their efforts
- minimize the overhead on researcher time caused by inflexible government requirements
- reward researchers for results, rather than conformity, paperwork compliance, and academic achievement

Benefits to AIDS Research: *The Accelerated AIDS Research Initiative would:*

- concentrate new resources and focused energy on a critical obstacle or opportunity for advancement
- benefit from the proven synergy of well-managed teamwork
- provide an opportunity to test high-potential new methods without endangering existing programs
- increase the likelihood of achieving certain important goals in shorter time period
- benefit from the experiences and management advances demonstrated in other fields

Benefits to the Clinton Administration: *The Accelerated AIDS Research Initiative would:*

- demonstrate genuine new commitment and new direction in AIDS research
- provide a laboratory for improving research efficiency in critical health problems, at low financial risk
- define a meaningful initiative in AIDS closely identified with the Administration
- demonstrate a new model of public/private partnership in targeted research concerns
- be consistent with the Administration's goal of "reinventing government"
- demonstrate commitment, even in research, to goal orientation and modern management methods

Project Proposal

Advanced management methods have been employed in other scientific fields and industry which can help achieve these interests. The key management aspects of an improved program would include:

-Team structure and responsibilities
-Goal orientation and evaluation
-Use of project management methods
-Creativity orientation
-Quality orientation
-Minimized bureaucratic overhead
-Streamlined granting mechanisms
-Long-term funding

An interdisciplinary group should be given responsibility for achieving research goals in a specific subset of AIDS research. Objectives of the pilot program would include:

1. Addressing, in a focused manner, certain parts of the AIDS research agenda which may need special attention, or certain technologies which might benefit from accelerated development; examples of potential subject areas include immune pathogenesis, preventive vaccines, and molecular therapies.

2. Pilot testing advanced management structures which have proven effective elsewhere.

3. Uniting government, academia, private industry, and the public in the form of a public/private consortium to fund and support this initiative.

Pilot-testing in a limited area would serve as an investment, giving government the ability to assess the utility and applicability of this approach before contemplating its wider application. If it succeeds, the pilot may

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lay the groundwork for establishing a new, more effective process for managing goal-oriented research in other aspects of AIDS as well as other biomedical research, such as breast cancer and Alzheimer's.

Structure

As envisioned, this pilot project would:

- Create a multidisciplinary team of scientists working together to achieve clearly defined, limited goals.
- Funds dedicated to the project would be used to support central facilities for coordination and administration, while other funds would be distributed to individual researchers, university centers or institutes, all working as part of a unified team, subject to streamlined peer-review processes.
- To the greatest extent possible, overhead due to traditional government/NIH requirements regarding paperwork compliance would be minimized, in hopes of minimizing unproductive use of research time. Team members would be primarily responsible for the achievement of goals. The team should have its own unencumbered ability to hire.
- All members of the team would be expected to devote at least 50% of their time to the project, and project leaders would devote 100% of their time. Since they would be paid from a single grant center, this should diminish the time currently required for grant writing (estimated as 30-40% of researchers' time).
- The goals of the project would be chosen in careful coordination with the Office of AIDS Research and the Director of the National Institutes of Health. Once selected, the management and team of the pilot project would be responsible for the methods and approaches for achieving goals.
- The Project would be guided by a steering committee or advisory group, composed of senior and diverse scientists, AIDS clinicians, and people with AIDS and their representatives. The team and advisors would meet semi-annually or quarterly in a "think tank" in which action plans would be jointly determined.

Continued...

How would this differ from existing and planned OAR approach?

- Because of the broad scope of the job, OAR's ability to focus on a specific issue and orchestrate resources toward one area is limited. Experience in the Project Inform Immune Restoration Think Tank and the Pediatric AIDS Foundation Ariel Project shows that the single task of coordinating communication and facilitating interaction in a given small area by itself is a full time job.
- OAR oversees a far broader range of subjects and issues, but cannot maintain great depth in any.
- Virtually all management models recognize the concept or functional, departmental, or subject area management, yet none exists in the present management model for AIDS research. Current OAR model is the equivalent of a system which employs only two levels of management - a senior executive with overall responsibility for everything, and unrelated line level people working more or less independently except for central budget planning. Similar management models exist only in very small enterprises or in the arts.
- The Team Core and Administration model of the Proposed Project is quite similar to the model sometimes employed by managers of large laboratories. The goal here is to apply that model to a critically needed subject area.
- Within the existing structure, there is no collaboration by design - only by coincidence or mutual interest. This diminishes cooperation and minimizes any chance for synergy among independent groups. In the proposed model, the attractiveness of the team operation would warrant working together in a new way.
- Existing independent groups divide their time between a fairly large number of projects, principally to create multiple revenue streams to support workgroup activities without the risk of placing too much emphasis in a single area, where a funding failure could spell disaster. This not only dilutes their focus, but greatly increases the amount of time which must be devoted to grant writing and follow-up. In the proposed model, resources and personnel would be focused to a minimum of the 50% level. The proposed accelerated project has three advantages: (1) team synergy, (2) the proven efficiency of doing like tasks together, and (3) minimizes the number of grant sources which must be courted and managed.

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Funding and Input: A Public/Private Consortium

This project is envisioned as a presidential investment in the fiscal year 1995 budget. The principal and start-up funder of this *Presidential Initiative* would be the federal government. To fully capture public, private, and Congressional support, the Initiative will call for creation of a Public/Private consortium to unite three independent funding and resource streams: government, industry, and the public. This approach, somewhat similar to events in the history of the polio epidemic, will best concentrate the interests of all involved, as well as share the risks and potential benefits. Startup funds from government should serve as the basis for seeking some percentage of matching funds from industry, and a smaller percentage from the public. The public/private consortium will also serve to create a united front around AIDS research, in which all parties share both the risks and the opportunities.

The government portion of funding for this project must be secured independent of and in addition to existing funds for AIDS research. Any program which is funded at the expense of existing efforts would meet with undue resistance from those whose funding might be jeopardized. In effect, the Initiative will be best received by the scientific community if seen as a source of potential new money, money which will not otherwise be accessible to NIH programs. Any funding which detracts from existing program will cloud the debate over the scientific worthiness of the pilot project with concerns about funds transfer or loss.

The Second Front? A History

While many voices have been calling for a more aggressive approach to AIDS research since the middle 1980's, the later half of 1992 and the first half of 1993 saw a tremendous increase in the fervor for such a change. For some people, the concept was manifest in a so-called "Manhattan Project," some kind of a highly focused research program that mimicked at least the sense of urgency demonstrated by the famous project that created the first atomic bombs. This approach was most concretely demonstrated by several editorials published by Larry Kramer, and by the creation of the Barbara McClintock Proposal by ACT UP/New York. Other voices saw problems with the analogy but agreed with the spirit that indeed, more could be done. Some of the interest in change took the form of the Office of AIDS Research reform bill which was eventually passed by the US Congress. Although supportive of this internal NIH reform package, still other voices urged even more sweeping actions. Many of those voices were quoted in the special AIDS issue of Science Magazine which preceded the VIII International AIDS Conference in Berlin in June of 1993. At the very least, it is fair to say that the interest in aggressive, palpable change was demonstrated by patients, researchers, activists, and governmental people alike.

Continued...

Future Directions in AIDS Research
Mission Statement

Many individuals and groups, both scientific and community - based, have called for a special project on AIDS with the hope that the new administration will be favorable toward innovative and potentially life-saving new programs in HIV/AIDS biomedical research. President Clinton both reiterated and resounded that call in his campaign statements. Turning this call into government policy and scientific action will be a formidable task.

The purpose of this meeting is to bring together a small group of senior scientists, clinicians and public activists to explore the critical questions that must be asked to initiate such a project. The group is composed of people who have both supported and opposed the concept of a directed or targeted research effort, and to the best of our knowledge, includes all groups that have advanced proposals on this topic.

Primarily, this forum is intended to address the question of whether a targeted research effort for AIDS is warranted, given the current state of scientific knowledge regarding the disease and, if so, what recommendations will be made to the administration on how best to proceed. Questions about the purpose, function, and funding of any special project will be addressed along with how any such program would relate to existing AIDS research programs. The conclusion of this meeting will be a report or recommendations from the group to the Clinton administration.

Bringing together representatives from government, academia, industry, and the community with their significant skills, motivation, and dedication to is essential fully address the questions involved in the development of a strategic targeted HIV/AIDS research effort

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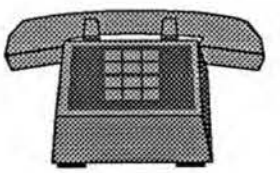
From the fall of 1992 through the first half of 1993, discussions about how to turn this talk into action began independently in various quarters. Discussions between individual scientists, within and outside of government, quickly led to the discovery that at least two groups were preparing to propose the creation of a process or meeting in which these issues could be raised. In particular, the Harvard AIDS Institute had developed a proposal to hold a conference, with a special interest in discussing the National AIDS Research Agenda and new approaches to communication between researchers. Simultaneously, Project Inform was discussing the possibility of calling a conference which built upon the successful model of its Immune Restoration Think Tanks, a unique privately-sponsored setting which seemed to stimulate valuable input and planning from top scientists. Because the planning for these two events included overlapping personnel and goals, the ideas were joined into a single plan.

Because both the Harvard AIDS Institute and Project Inform were already widely engaged in the public and scientific fight against AIDS, it was felt that the hosting of any first conference would best be left in the hands of a third party and at a site not associated with the status quo. For this reason, the Harvard/Project Inform team contacted Noble Laureate Howard Temin at the University of Wisconsin at Madison, and asked if he would serve as the conference host. Later, due to health concerns, Dr. Temin passed the responsibility on to Dr. David Pauza of the University of Wisconsin Primate Research Center, who in turn began coordinating all efforts with the staffs of Project Inform and the Harvard AIDS Institute. Throughout the planning period, the three organizations were supported and advised by a core team of researchers both in and out of government.

The purpose of the initial conference was to bring together those voices in the AIDS research, policy, and activist communities who were calling for an aggressive new re-evaluation of AIDS research, in hopes of creating a unified voice about how to proceed. Dr. June Osborn, former head of the National Commission on AIDS, joined this effort as an advisor and facilitator for the meeting.

Because all present at the first meeting in Madison felt that effective treatments will someday be developed for HIV disease, the goal of the process became much clearer: How can we achieve those treatments more quickly together, rather than separately through only traditional channels? The first meeting, therefore, concluded with the development of a list of consensus statements, describing unmet needs and opportunities for progress. Subsequently, four working groups were formed to run the consensus statements into policy and action proposals. Those proposals were presented and debated at the second meeting in Boston, with the hopes of making specific recommendations from the group not only for the Clinton Administration, but also for all of us involved in the efforts to end this epidemic.

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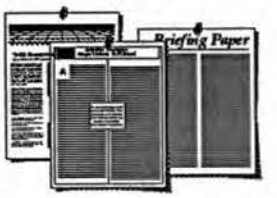
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Consensus Statements

- ✔ Effective treatments will be discovered. We are committed to the belief that it is possible to develop new therapies, within a reasonable time, capable of providing long-term survival without clinical disease.
- ✔ Insufficient resources inhibits the pace of both general biomedical research and AIDS-specific research. More resources will accelerate the pace of progress.
- ✔ Identify gaps or discontinuities in programs of research and in the implementation of clinically relevant findings.
- ✔ Targeted special programs should be considered for emerging, gap-filling, or risky innovative research areas. Mechanisms for prioritization are possible and should be utilized.
- ✔ Improve communication pathways and coordination among investigators, for example develop high quality repositories for defined clinical samples.
- ✔ The urgent challenge of AIDS highlights the problem of constituting complex drug trials using multiple compounds from distinct public and private sources. A rational and comprehensive strategy should be implemented to overcome barriers at all levels that mitigate against these novel therapeutic trials.
- ✔ There is a need for the further stimulation and support of creative thinking in the AIDS research community. This should include an assessment of different management styles/structures and an emphasis on the training and development of new investigators.
- ✔ Expand the program of by infusion of money and talent from outside the current NIH structure.
- ✔ The president, his administration and Congress must take a leadership role in educating the American public and world community on why these initiatives are important and urgent.
- ✔ The government should create a mechanism to evaluate and institute incentives to attract the pharmaceutical industry to participate in these efforts.
- ✔ No amount of structural review or proposals for change will happen, without first defining mechanism for implementation, and then finding the will and courage to carry them out.

Where Do We Go From Here?

A number of primary recommendations have been developed, which require fleshing out with input from both the broader scientific community and the community of people living with HIV/AIDS. This process is taking place in consultation with the FDAR Working Group and cosponsors of the meeting, who developed the initial outlines of the proposals. Other initiatives from the meeting are being carried forward with the cosponsors of the event, the Harvard AIDS Institute and the University of Wisconsin at Madison, utilizing FDAR participants as advisors in detailing developing recommendations.

Initial discussions have taken place with members of Congress and other national policy-makers to look at realistic options for new funding for an accelerated AIDS research initiative. Finding funding in a time of budget constraints will prove challenging but not only can it happen, it must happen. It is important that we never lose sight of our ability to rise to the occasion and find the courage and will to bend the system to focus time, energy and attention on this problem.

Pilot-testing an accelerated initiative will not fix all of the problems of AIDS research. Ongoing attention must be paid to legislated reforms to the Office of AIDS Research (OAR), which are currently in jeopardy of being thwarted by a lack of commitment on behalf of both the Administration and the NIH. It is critical that the community monitor closely the activities of the NIH and the Administration to insure the OAR reforms are implemented in the spirit that they were legislated.

The next step in moving forward with the 'Second Front' proposal is to identify funding mechanisms and secure interest in funding, as well as gather broad community input into a more detailed initiative. The initial framework for the 'Second Front' must be examined critically to insure that each proposed component will solve problems inherent in the current system, and that each proposed solution is deemed the optimal solution. Parallel to these activities is the need to act quickly and take advantage of opportunities. It is possible to impact the direction and pace of AIDS research, move the dinosaurs of science at the NIH to respond to this national crisis, and focus the Administration's attention on the urgency of AIDS as a research priority. Whether the proposals generally outlined in the preceding pages are the exact proposals which will be implemented or not, one thing is certain, it's time for a change and we will no longer support the continuation of the current research structures without substantive and meaningful reform.

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THE CRISIS IN CLINICAL AIDS RESEARCH

by Mark Harrington

1 December 1993

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Telling people with AIDS the truth isn't taking away their hope -- it's giving them the information they need to make informed treatment decisions.

-- Saundra Johnson
CCG/Women's Health Committee
CCG Retreat, Chicago, July 1993

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Treatment Action Group (TAG)

New York, NY, USA

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In Memoriam. This report is dedicated to the memory of those who served on the ACTG Community Constituency Group (CCG) and who are no longer alive: Ortez Alderson, Jesse Dobson, Dick James, Chuck Mayer, Bob Pearson, Jose Perez, Maritza Ramos, and Andy Zysman.

THE CRISIS IN CLINICAL AIDS RESEARCH

Introduction. In November 1989, AIDS activists attended our first AIDS Clinical Trials Group (ACTG) meeting. We were not given a warm welcome. After many months of struggle, activists and people with HIV were integrated into the ACTG system and given voting representation on each committee, and many ACTG sessions were opened up to community observers.

Four years after those events, however, many of the initial criticisms of ACTG research remain relevant[1]. Moreover, new problems have emerged which demand changes in the design, conduct and analysis of clinical trials for AIDS and HIV-related conditions. In addition, hard-won victories by activists (e.g., parallel track, active-controlled studies, accelerated approval) have produced a new set of issues of their own which must be addressed. Finally, results of recent, relatively large-scale clinical trials have been disappointing; despite substantial aggregate improvements in quality and length of life since the mid-1980s, the hoped-for long-term benefits of early or combination intervention with antiretroviral therapies have not materialized.

Those designing the latest batch of clinical trials have tended to ignore these setbacks, proceeding as though nothing was wrong with the assumptions, some of which are now undermined by the data, underlying these studies. This report is an effort to critically assess the current impasse.

A Few Words of Praise. Many of the interactions between activists and researchers within the ACTG and elsewhere have been positive, productive, and indeed historic. I myself was lucky enough to serve on the ACTG Opportunistic Infections (OI) Core Committee in 1990-91, when for the first time (and following concerted pressure from activists and from Congress) appropriate resources were being allocated to the OI prophylaxis and treatment effort. In my experience, the OI Committee did not suffer internally from the ego and turf problems which characterize some other ACTG committees. Both Core discussions and those in Pathogen Study Groups (PSGs) focused on the problems at hand, and debate was full and frank.

The recent ACTG Scientific Review panel commended the OI committee's "young, energetic, high-quality investigators"[2], noting that "the OI Committee has the broadest scope and charge of the ACTG committees... has focused on the most prominent clinical problems in AIDS... conducted well-conceived, comparative studies that had power and led to clear conclusions [and]... contributed significantly to

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1 Mark Harrington. A Critique of the AIDS Clinical Trials Group. Edited by Ken Fornataro. Introduction by Jim Eigo. Treatment + Data Committee, ACT UP/New York, May 1, 1990.

2 Report, ACTG Ad Hoc Scientific Review, 16-18 August 1993, p. 7.

standards of care and a better quality of life for AIDS patients... The program is moving in the right direction -- of co-enrollment, collaborations with CPCRA [and others], and rollover studies... prophylaxis of multiple pathogens and... polypharmacy."[3] The OI Committee, once given appropriate support from NIAID, has contributed greatly to the standard of care for AIDS and HIV disease. As they shift focus from an emphasis on treatment to one on prophylaxis, they too will face many of the problems related to large sample size, long duration, losses to follow-up, subset analysis, etc., now afflicting the primary infection effort.

Other ACTG committees too have made progress since 1989. The Oncology Committee, with new support from the NCI AIDS Lymphoma Network, and brilliantly advocated for by the late Andy Zysman, has created a comprehensive research agenda. More support from NIAID (including an oncologist medical officer) is needed.

The Neurology Committee still receives inadequate support from NIAID and from many site principal investigators (one Neurology chair resigned because his site PI failed to support his work), but has a new arrangement with the National Institute of Neurological Disorders and Stroke (NINDS) to collaborate in a Neurology AIDS Research Consortium (NARC). Hopefully, this may lead to the sort of synergistic collaboration which the NCI/Oncology Committee link now provides.

The Immunology Committee has spread its wings from its initial role as a laboratory-based, resource committee to once conducting increasingly important but still preliminary studies of immune-based therapies for HIV infection. Again, the pointed activism of CCG Immunology representative Jesse Dobson was critical in mobilizing this talented group. Like Oncology and Neurology, the Immunology Committee still receives inadequate support from the Division of AIDS (though the tireless work of medical officer Jonathan Kagan deserves high praise).

Rearranging the Deck Chairs. The new ACTG restructuring ratifies the complete separation of adult and pediatric components. In its new HIV/AIDS Research Agenda, NIAID separates out pediatrics research, apart from pathogenesis, epidemiology, treatment and vaccine research, as though children were a separate species[4].

Among those who will suffer from the separation, which NIAID has done nothing to discourage, are 1) mothers whose HIV-infected children will be treated at pediatric ACTUs where there are no research facilities for the adults in the family; 2) adolescents with HIV who will fall between the logistical and eligibility cracks in protocols and programs which focus either on adults (many drug companies don't like to have patients under 18 in their studies) or children (some pediatric studies cut off

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[3] Ibid.

[4] NIAID. HIV/AIDS Research Agenda. October 1993, Section V, "Pediatric HIV Disease".

enrollment at age 12); 3) HIV infected children themselves. This is for several reasons: The Pediatrics Committee's agenda privileges interruption of vertical transmission, and antiretroviral therapy, over OI prophylaxis and treatment[5]. There are too few children to fully enroll many efficacy studies at statistically necessary levels. The Pediatrics Committee is studying many means of potentially interrupting vertical transmission (e.g., AZT in ACTG 076, envelope-based vaccines in ACTG 233-235), but too few dealing with the complications of HIV in children post-infection. They appear to feel that pilot studies of envelope-based immunogens offer more clinical promise than OI prophylaxis or treatment studies[6]. As the Pediatrics Committee splits off to form its own wasteful, duplicative, redundant structure, the remainder of the ACTG is now dubbed "Adult". Yet only these supposedly "adult" research committees will be able to obtain sufficient sample size to obtain definitive efficacy information for treating HIV-infected persons <u>of all ages</u>.

Meanwhile, the "adult" system lacks rigor and vision. Protocols are not costed out properly. The committees have their own research agendas, but the group as a whole does not. No one at DAIDS knows where all the dollars go. Efforts to reduce collection of unnecessary data have been token at best. In the meantime, the ACTG cannot follow most of its study participants to the end of the trials. This cripples large-scale, long-term studies, like that of AZT in persons entering with CD4 $<$ 500/mm^3, ACTG 019, of whom over three-quarters had left before the study closed out this fall. The Executive Committee has, according to one member, already approved trials for 1994 which will take up the entire year's resources. Thus, no new ideas can be tested in 1994, unless some currently planned trials are dropped.

The new Executive Committee will give more power to the site principal investigators, from whom the majority of its members will be drawn. The EC will remain ineffective, however, unless new systems for budgeting trials up front and tracking costs throughout the system are implemented. No EC composed of site PIs can administer the far-flung ACTG apparatus without responsible, committed staffing by DAIDS. Hopefully the new Division Director will recognize this.

<u>The Crisis in Clinical Trials</u>. Still, the current dilemma of treatment research in AIDS extends far beyond the ACTG system. These are the components of the dilemma: 1) inadequate drugs; 2) inadequate markers; 3) inadequate clinical trials. After the Berlin conference, SDAC honcho Steve Lagakos commented to one community

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[5] Pediatrics Core Committee Research Agenda, July 1992.

[6] ACTG 218 + 230 enrolled 23/72, and 11/124 children, respectively, in phase I studies of rgp160 and rgp120. Just <u>one</u> recently approved pediatric OI study is even open. 10/24 patients enrolled in a phase I study of atovaquone in HIV+ infants and children (ACTG 227). ACTG 253 will evaluate 16 HIV+ children with herpes or zoster in a phase I study of BW256 (Valacyclovir); ACTG 254 will evaluate 614 symptomatic HIV+ children, comparing TMP/SMX to Atovaquone/Azithromycin for PCP prophylaxis. The second regimen is wholly untested as a prophylactic regimen. Each study uses a new drug from Burroughs-Wellcome; couldn't they fund such developmental pediatric studies themselves?

member that "those activists wouldn't be so mad [about the much-hyped "subset trend analysis" from ACTG 155] if the drugs were better." Well that's right, Steve! -- if the drugs were better, then the trials wouldn't need to be bigger, or better designed, or analyzed more honestly -- in fact, if the drugs were good enough, we might not need answers from randomized studies at all, as in the case of ganciclovir[7]. But the drugs aren't better -- and that's why we turn to statisticians in the hope that they will help design studies competently, and analyze them honestly, keeping in mind that the primary goal is the development of information useful to patients and doctors.

The fact is, that of the three inadequacies listed above, clinical trials designers have the most control over the third. They cannot invent good drugs -- that is the job of basic researchers; they cannot invent better markers -- though they can help to develop them; they can, however, design trials adequate to answer clinically relevant questions, and they can do so without resorting to exaggeration, hype, or well-meaning distortion in the face of disappointing overall results. People with HIV obviously want, and need, better drugs. But until those come along, it is imperative to use the drugs we have now better, to provide clearer information to people with HIV and their providers, so that we can make the best use of what is out there.

Three Case Studies. It might be useful to approach the issue by reviewing three episodes which exemplify troubling aspects of the design, conduct, analysis and interpretation of clinical trials for HIV disease. The impact of these examples has been profound. First, hopes were raised by a catchy hypothesis. Then, trials were conducted, ostensibly designed to answer the question. Later, when results proved less than hoped for, innovative methods were used to suggest greater benefit than actually occurred. In fact, the researchers, in each case, failed to completely acknowledge what their studies really showed.

There was a double fallout from this: on the one hand, many people (particularly researchers and clinicians) went about in a state of denial about the truth, by citing the "innovative" methods (e.g., responders vs. non-responders, or post hoc subgroup analysis); on the other hand, hopes once raised too high crashed, and the entire community (or most of it, particularly people living with HIV) went into a prolonged, not-yet-over state of clinical depression about clinical trials and the lack of truly effective therapies.

The Army Phase One gp160 Study. The first case study is taken from outside the ACTG, as the problems in trial design and analysis are hardly restricted to the ACTG.

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[7] See "Design Considerations for AIDS Trials" by DP Byar, DA Schoenfeld, SB Green, DA Amato, R Davis, V deGruttola, DM Finkelstein, C Gatsonis, RD Gelber, S Lagakos, M Lefkopoulou, AA Tsiatis, M Zelen, J Peto, LS Freedman, M Gail, R Simon, SS Ellenberg, JR Anderson, R Collins, R Peto, T Peto, in The New England Journal of Medicine 323:19, 8 November 1990, pp. 1343-1348.

If there is still someone who feels that a classical "Manhattan Project" approach might be an appropriate way to structure AIDS research, perhaps a look at the Army AIDS research program will disabuse them of that notion. In both cases, centralized, top-down research was the basic paradigm. The Manhattan Project itself had such talent on-site that a permanent kind of in vivo peer review system was in operation, but the Army AIDS program has suffered from too little outside, objective review. What was originally a small program grew to $50 million a year (exclusive of the $20 million FY 1993 gp160 earmark; $50M is about as large as an NIH institute with a large, but not gargantuan, AIDS program, e.g., NCRR, NHLBI or NICHD).

In line with its resistance to admitting the ubiquity of homosexuality (in and out of uniform), a 1992 Army document states that "the focus [of Army HIV studies] is on heterosexual transmission... The prevention of infection is a priority over the prevention of the progression of disease, which is a priority over the prevention of death."[8] Vaccine research is thus a priority, and collaborative studies with the Thai army are in the works.

The Hypothesis. Therapeutic vaccination for HIV disease was first proposed by Jonas Salk in 1987[9]. The hypothesis was that immunization with non-infectious whole virus (or, later by other sponsors, with viral proteins) would elicit new protective immunity (cell-mediated, humoral, or both) against HIV and prolong the asymptomatic state. The hypothesis had the added convenience of justifying safety and activity studies in HIV-infected patients, which seemed "safer" to many vaccine sponsors than exposing uninfected persons to possibly immunosuppressive antigens.

In 1987, prevailing dogma held that the viral load was very low during the asymptomatic phase of infection, that the virus was not particularly immunogenic (that is, that it was hard for the immune system to "see" HIV), and that antibodies to HIV were protective. Thus, exogenous killed-virus (or antigen fragments) might stimulate new and enhanced immunity, helping the immune system to "see" the virus, and eliciting new antibodies.

In 1993, it is clear that viral load is much higher than previously believed[10], even during the asymptomatic phase; that the virus is highly immunogenic and clearly recognized by both cytotoxic T lymphocytes and by antibodies, some of them

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8 "AIDS/HIV Research Activities in the U.S. Military, June 26, 1992," by Don Burke, Division of Retrovirology, Walter Reed Army Institute of Research.

9 J Salk. "Prospects for the control of AIDS by immunizing seropositive individuals." Nature 1987; 327:473-6.

10 M Piatak et al., Science 259, 1749 (1993); BK Patterson et al., Science 260, 976 (1993); G Pantaleo et al., Nature 362, 355 (1993); JJ Embretson et al., Nature 362, 359 (1993).

neutralizing -- and it is unclear how protective antibodies are[11].

Thus, the entire basis for the 1987 therapeutic vaccination hypothesis has been reversed by later discoveries. Yet, because drug and vaccine development remains many years behind new insights about pathogenesis, we are still locked into a 1987 hypothesis about therapeutic vaccination, assessing it using first-generation vaccine products based on laboratory isolates of HIV which lack many features of the clinical isolates which infect people or those which later make them sick.

The Product: MicroGeneSys VaxSyn™ recombinant gp160. Even among the first-generation vaccine products, most of which are based on envelope sequences of laboratory isolates such as IIIB, the MicroGeneSys rgp160 stands out as one uniquely unlikely to elicit relevant cell-mediated or humoral responses to the virus strains that circulate in infected people.

gp160 is the protein complex, composed of gp120 and gp41, which studs the surface membrane of HIV, and which mediates binding to the CD4 receptor on target host cells. The gp160 protein itself breaks down in vivo into its two components, and is not as immunogenic together as gp120 is alone.

MGS rgp160 (like many of its sister products) is based on the canonical laboratory strain $HIV^{HTLV\text{-}IIIB}$, the pesky lab strain which first invaded a French culture, then turned up in Bethesda, overtaking several other isolates along the way. IIIB is particularly well-adapted to growth in permanent T-cell lines, and differs in many important respects from HIV strains that are found in vivo[12].

MGS rgp160, unlike many of its sisters, is grown in an insect virus vector (baculovirus), and so it is not synthesized as are viral proteins are made in mammalian cells. Many other vaccine products are made in mammalian cell lines.

While other vaccine products are synthesized as three-dimensional proteins in mammalian cells, with sugars attached at glycosylation sites, MGS rgp160 is synthesized as a denatured, nonglycosylated, linear peptide. Thus, the antibodies which could be stimulated by injection with MGS rgp160 are presumably antibodies to linear peptides. By contrast, the vast majority of neutralizing antibodies to HIV in

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[11] J Salk, PA Bretscher, PL Salk M Clerici, GM Shearer. "A Strategy for Protective Vaccination Against HIV." Science 260, 28 May 1993, 1270-1272.

[12] JP Moore, JA McKeating, Y Huang, A Ashkenazi, DD Ho. "Virions of Primary HIV Type 1 Isolates Resistant to Soluble CD4 (sCD4) Neutralization Differ in sCD4 Binding and Glycoprotein gp120 Retention from sCD4-Sensitive Isolates." J. Virol. 66:1, Jan 1993, 235-243. JP Moore, LC Burkly, RI Connor, Y Cao, R Tizard, DD Ho, RA Fisher. "Adaptation of Two Primary HIV Type 1 Isolates to Growth in Transformed T Cell Lines Correlates with Alterations in the Responses of Their Envelope Glycoproteins to Soluble CD4." AIDS Res. Hum. Retrovir. 9:6, 1993, 529-539.

vivo are to conformational (three-dimensional, non-sequential) epitopes[13]. [While even rgp160 could elicit cytotoxic T cells (CTLs) to rgp160 peptide fragments, but the new CTLs too may fail to recognize autologous envelope sequences.

Finally, the envelope gene env itself has been programmed through millennia of escape from a vigorous host immune response to be the most variable gene of HIV (along with reverse transcriptase [RT] itself). Thus, within a single host, HIV mutates its gp160 and gp120 coat constantly to evade detection. Therefore, basing vaccines (whether prophylactic or therapeutic) on this viral element, rather than on highly conserved elements necessary for viral replication, could prove to be a disaster. Recent laboratory findings, showing that all current vaccine candidates failed to neutralize field HIV isolates, confirm this[14].

For all these reasons, then, one can certainly understand why John Moore, George Lewis and James Robinson opined that "In short, based on existing in vitro data, our opinion is that there could not be a worse choice from the current envelope glycoprotein vaccine candidates than MGS gp160 to stimulate at least one important arm of the immune system, the production de novo of cross-neutralizing antibodies to the V3 loop and discontinuous epitopes around the CD4-binding site."[15] These considerations did not deter the Army AIDS research program, however.

The Experiment. One disturbing but inevitable result of the urgency engendered by the AIDS crisis is that both researchers and community members tend to invest preliminary trials with more significance than they can possibly bear. This was the case with the pilot combination therapy study ACTG 106 [see below], and it was the case with the Army's phase I gp160 study in 30 HIV-infected persons as well. In the first case, that of ACTG 106, The New England Journal of Medicine refused to publish the preliminary data[16]; but in the second, for reasons unknown, they chose to publish results of a non-randomized, exploratory phase one study, in the American journal of record for the standard of medical care. This decision played no insignificant role in helping to fuel the subsequent hype.

In the Redfield study, 30 HIV-infected Army personnel with initial CD4 counts over 400/mm^3 were given one of two injection schedules of MGS rgp160 -- on days 0, 30

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13 JP Moore, DD Ho. "Antibodies to Discontinuous or Conformationally Sensitive Epitopes on the gp120 Glycoprotein of HIV Type 1 Are Highly Prevalent in the Sera of Infected Individuals." J. Virol. 67:2, Feb 1993, 863-875.

14 J Cohen. "Jitters Jeopardize AIDS Vaccine Trials." Science 262, 12 November 1993, 980-1.

15 J Moore, GK Lewis, J Robinson. "Which gp160 vaccine?" Nature 261, 11 February 1993, 503.

16 ACTG 106 appeared in The Annals of Internal Medicine instead, after a fight between DAIDS and the authors about the analysis and interpretation of the data. See T Meng et al., "Combination Therapy with Zidovudine and Dideoxycytidine [why not 'Zalcitabine'?] in Patients with Advanced Human Immunodeficiency Virus Infection: A Phase I/II Study." Ann. Intern. Med. 116:1):13-20, 1992.

and 120; or on days 0, 30, 60, 120, 150 and 180. The major endpoints of interest included new or enhanced antibody responses to gp160 sequences, as well as T cell proliferative responses to gp160.

The Analysis. The investigators divided the group into "responders" (those with new or enhanced antibody or T cell responses) and "nonresponders" (those without). Such post hoc analyses are a popular way of reading more into nonrandomized studies than is really there. In later stages of follow-up, "nonresponders" were converted to "responders" by a more frequent schedule of injections. The initial "responders" had higher CD4 cells at baseline, and allegedly sustained a slower slope of CD4 decline than the initial "nonresponders". The investigators suggested that this might be the effect of the rgp160 injections.[17]

Several things are notable about these results, and their interpretation. First, the "new and enhanced responses" noted in the "responders were all to linear epitopes of IIIB rgp160 (in the case of the antibodies), or T cell proliferative responses to IIIB/rgp160. No results were presented demonstrating that the newly-elicited antibodies or T-cell proliferative responses applied to autologous, clinical HIV isolates from the study participants.[18] Thus, it remains unknown whether the newly elicited immune responses did anything at all to the viruses circulating in the patients in the study. If they do not, the result is as relevant as immunizing people to classical laboratory antigens -- i.e., not relevant at all.

Secondly, the difference in the CD4 slopes among the initial "responders" and "nonresponders", if real, could have been due to differences in baseline immune competence (hence a higher baseline CD4 predicted the likelihood of being labelled "responder"), and consequent differences in the rate of decline[19], rather than differences due to the administration of the antigen itself[20]. In addition, some

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17 RR Redfield, DL Birx, N Ketter, E Tramont, V Polonis, C Davis, JF Brundage, G Smith, S Johnson, A Fowler, T Wierzba, A Shafferman, F Volvovitz, C Oster, DS Burke, and the Military Medical Consortium for Applied Retroviral Research (MMCARR). "A Phase I Evaluation of the Safety and Immunogenicity of Vaccination with Recombinant gp160 in Patients with Early Human Immunodeficiency Virus Infection." The New Englend Journal of Medicine 324:24, June 13, 1991, pp. 1677-1683.

18 At the NIH/FDA gp160 panel hearing in November 1992, I asked Dr. Redfield if they had conducted studies to assess the in vitro response to participants' autologous viruses. He said they had not.

19 The rate of CD4 decline may not be linear over time in individuals; it may be biphasic. Detels 1988; Miedema 1992. Lower baseline CD4 may be associated with a steeper slope (more transitions to "fast decliners").

20 Larry Corey pointed this out at the NIH/FDA panel: "One potential interpretation of the CD4 data is ... that the vaccination is an in vivo marker of better innate host resistance... Drs. Burke and Redfield have recognized this issue and have used rabies as a way to evaluate this issue in their ongoing phase II trial." Lawrence Corey, letter to Anthony Fauci + Charles Carpenter, 16 Nov 1992.

participants were taking AZT[21], which obviously can affect short-term CD4 levels.

Thirdly, as it emerged later, there were problems with the analysis of the data published in The New England Journal. The authors compared different "moving averages" of the CD4 slopes over time, rather than using the actual levels. This undermined the validity of Figure 4 in the New England Journal paper[22].

Fourthly, subsequent presentations based on longer-term follow-up from the phase one study were used to inveigle Congress into appropriating an extra $20 million to the Army AIDS research program for a large-scale, phase three study of MGS rgp160. At the Amsterdam AIDS conference in July 1992, the Army's Dr. Redfield reported "dramatic reductions on both the levels of HIV proviral DNA... as well as full length HIV RNA when compared to natural history controls" in "the first 15 AIDS patients treated with the MicroGeneSys vaccine"[23]. Subsequently, the Army's Dr. Birx reported on viral burden reductions in a single patient at the annual vaccine conference that year[24].

There were several problems with this analysis. The patients were not the first fifteen patients, they were fifteen selected patients (and, as noted above, some may have been on concomitant AZT). There were no statistically significant reductions in the group of 30 patients overall. The natural history controls were not comparable to the study participants. The list goes on[25].

The Aftermath. The gp160 affair has been an enormous drain on everyone's energy and time. The Congress was tricked into diverting $20 million on a useless, unnecessary trial. The AIDS community was once again subjected to the old game of bait and switch, with temporarily raised hopes doomed to be dashed once again.

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21 Statement of William F. McCarthy, PhD, Director, Department of Biostatistics, Henry M. Jackson Research Foundation for the Advancement of Military Medicine, 7 December 1992, p. 2.

22 Ibid., p. 4-5: "My department determined that there was no statistical significant difference between the responders and the non-responders CD4 count longitudinal profiles using the actual CD4 count data that was used to generate the various versions of NEJM figure 4."

23 MicroGeneSys press release, Amsterdam, July 21, 1992. "VaxSyn Reported to Stabilize T4 Count and Reduce HIV Levels -- Results from Five Independent Treatment Studies Reported". The press release was later included by Senator Bennett Johnston (D-LA) in the Congressional Record as supportive documentation to H.R.5504, the defense appropriations bill containing the $20 million earmark.

24 NL Michael, MT Vahey, G Chang, JD Cooley, PK Ehrenberg, J Ruderman, DL Birx, RR Redfield. "gp160 Vaccine Therapy in an HIV-1 Infected Patient is Associated with a Fall in Viral Burden, Antigenic Shift, and Viral Regulatory Sequence Mutations." Poster 71, 5th Annual National Cooperative Vaccine Discovery Group (NCVDG) Meeting, August 30-September 3, 1992, Chantilly, Virginia.

25 See WF McCarthy, op. cit., and his "Memorandum to Maryanne Vahey, Department of Retroviral Research," 20 August 1992: "Based on the data provided by Maryanne Vahey and the analyses done in this report, there is no significance reduction in viral load in the intervention cohort from the rgp160 Phase I Trial."

The NIH wasted thousands of hours of staff time convening blue ribbon panels and meetings, developing plans for a "large, simple trial" that will never be mounted. The Army has already spent $1 million in "planning costs"! The Jackson Foundation's chief statistician, William McCarthy, resigned rather than condone the misuses to which the Army's data was being put. Army researchers were subjected to an internal investigation. Recently, Representative John Dingell suggested he might undertake a full-scale Congressional inquiry[26]. ACT UP/New York members demonstrated at the corporate gates of MicroGeneSys in Meridien, Connecticut[27]. In November 1993, Congress passed conference language giving the Executive Branch another six months to change its mind -- to divert the money to more scientifically justifiable AIDS research[28]. And HIV vaccine manufacturers are arming themselves with high-powered Washington lobbyists to push their agendas in the future. A horrible precedent has been set for biomedical research in general, and for AIDS research in particular.

Often forgotten during the debate is the fact that there are almost 2,500 patients around the world already enrolled in phase II studies of rgp160 and other therapeutic vaccine candidates[29]. If any of these trials shows anything useful, it is likely that a phase III trial will eventually be mounted. [Indeed, if such data were now available, MicroGeneSys would have no trouble raising capital for such a study from its partners, Wyeth-Ayerst and American Home Products.] But it would simply be a waste of money to conduct a phase III trial now -- it would amount to throwing up our hands in the air and saying who needs markers, who needs preliminary signs of activity, we might as well throw everything into large simple trials.

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26 P Brown. "Anger over 'selective' data on HIV therapy." The New Scientist, 17 July 1993, p. 4; C Macilwain. "Key statistician ousted as Waxman enters gp160 fray." Nature 354, 29 July 1993; J Cohen. "Army Clears Redfield... But Fails to Resolve Controversy." Science 261, 13 August 1993, pp. 824-5.

27 The town police chief, in an unprecedented gesture, bought Big Macs for the demonstrators' lunch.

28 Although some suspect the Army may just award MicroGeneSys a $20 million contract to make Chiang-Mai HIV strain gp160 for its Thai Army vaccine trial.

29 Current Phase 2 Therapeutic Vaccine Trials

PI	N	Agent	Sponsor/Dose + Adjuvant	
Redfield	600	rgp160/LAI	MGS	160 ug + Alum
Tsoukas	250	rgp160/LAI	MGS	320 ug + Alum
Wahren	1,000	rgp160/LAI	MGS	120 ug + Alum
Turner	60	Salk	IPL	50, 100, 200, 400 ug + IFA
Multicenter	103	Salk	IPL	100 ug + IFA
Schwartz	55	rgp160/MN	Immuno	50 ug + MCC
Goebel	170	rgp160/LAI	Immuno	100 ug + MCC
Genentech	500	rgp120/MN	G-tech	600 ug + Alum

Participants on MGS rgp160 = 1,820; on Salk whole-inactivated envelope-depleted virus = 163; on Immuno AG gp160 = 100; on Genentech rgp120 = 500; grand total = 2,583.

Data are wilfully misinterpreted. Time is wasted. Money is wasted. Lobbyists and legislators set research priorities. Hopes are dashed.

We are trapped in the outdated clinical research paradigms of the mid-1980s -- not only in vaccine research, but also in antiretroviral research, with its plethora of me-too nucleoside analogues and their non-nucleoside reverse-transcriptase inhibiting cousins -- while pathogenesis research moves on into uncharted territory, its promised clinical payoff cruelly far off to anyone now living with HIV.

A Second Case Study: Combination Nucleoside Therapy

The Hypothesis. In general terms, as we've heard ad nauseam for years, certain therapeutic combinations are more effective than single agents for chronic diseases such as tuberculosis or cancer. In addition, certain combination antibiotics [with different molecular targets] are useful clinically, e.g., trimethoprim-sulfamethoxazole. Two nucleoside analogues can be more powerful than one in vitro; two antiretrovirals generally (even clinically ineffective ones, such as dextran sulfate or CD4) can be "synergistic" in vitro. Finally, preliminary data from pilot combination studies (e.g., ACTG 047, 050, 106, 143; as well as Yarchoan's NCI study, Collier's AZT/ddI study, and Schooley's viral resistance study for Burroughs-Wellcome) suggested (but did not prove) that combination nucleoside therapy might be clinically superior to monotherapy, at least temporarily.

The Agents. "Until there's a cure, there's Retrovir"[30]. When ACTG 155 was designed, everyone with CD4 $<$ 500/mm^3 was recommended to go on AZT for an indefinite period. Therefore, a clinical study of combination therapy could have addressed two populations: 1) a first-line population, randomized to AZT alone vs. AZT and another nucleoside; 2) a second-line population, randomized to continue AZT, add another ddN, or switch to the new ddN. The first-line population had a greater chance of demonstrating efficacy (because they would not yet be resistant to AZT), while the second-line population was more relevant clinically (because everyone was supposed to be on AZT already). The designers of ACTG 155 chose the second population, and for some reasons unknown chose HIVID™ brand ddC (zalcitabine) as the relevant second nucleoside. One wonders why they didn't use both available nucleosides, ddC and ddI, as the British Medical Research Council (MRC) did in designing its Delta trial (AZT vs. AZT/ddI vs. AZT/ddC as first-line therapy, N = 1717), since it was already evident in 1990 that ddC as a monotherapy was definitely no better, and quite possibly worse, than ddI alone. In this case, it appears that the ACTG leadership succumbed to the resistance of the corporate sponsors to a head-to-head comparison of the "new" nucleosides.

ACTG 155 was riddled with investigator bias and sponsor-disseminated hype from the

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[30] Jon Engbretson, 1989.

very beginning. The investigators were "sure" combination therapy was better. It was used as a recruiting tool[31] and then, when the guaranteed crossover to combo was proffered, as a bribe to patients for staying in the trial on blinded therapy until they reached a primary endpoint[32].

Indeed, as early as August 1990, at a meeting with ACT UP, Roche's Dr. Whaijen Soo told us: "I'd like to confide a remark of Margaret's... The difference she sees among people on the ddC/AZT combination [in ACTG 106] is a big difference -- like the difference between people on AZT versus placebo in the original trial. She can almost tell them apart by looking at their behavior."[33] Say that around the country for three years and you can create a huge demand for an unproved drug.

Thus it is no wonder that ACTG 155 was one of the fastest-enrolling ACTG trials ever, and that demand for the regimen far outstripped the capacity of the trial. Roche continued to delay implementing a true expanded access program, and underground use of ddC, procured from chemical supply houses in the USA and abroad, burgeoned. In early 1992, FDA analyses showed that some batches of this underground ddC contained unacceptable dose variations, and the supply was cut off. Only weeks before the FDA hearing on the ddC NDA, Roche finally opened a true expanded access program for ddC used in combination with AZT. Nonetheless, this use obtained only the slenderest of approvals at the FDA, being licensed under the new conditional "accelerated approval" regulations based on a 150-patient resistance study sponsored by Burroughs-Wellcome (not by either the ACTG or by Roche!). Understandably, then, all concerned were eager for the hoped-for clinical confirmation from ACTG 155 of combination therapy's long-touted benefit.

The Experiment. Principal investigator Margaret Fischl, of the University of Miami School of Medicine, who will become chair of the ACTG Primary Infection Committee next year, presented the ACTG 155, the first study of combination therapy to use clinical endpoints, to the FDA advisory committee on September 20, 1993:

> We did a study to ask whether [1,001] patients on long term (over six months) of AZT therapy, and symptomatic with CD4<300 or asymptomatic with CD4<200, would be better off adding ddC, switching to ddC monotherapy, or staying on AZT. We stratified at baseline for duration of AZT therapy, PCP

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31 By such means as the 2:2:3 AZT:ddC:AZT/ddC randomization ratio, which has no other point other than to demonstrate to patients which arm the investigators think would prove superior.

32 The 155 study team offered this "benefit" to participation in March 1992, only days before the Roche expanded access program for combination therapy was due to open.

33 ACT UP Meeting with Hoffman-LaRoche, August 16, 1990. My notes.

prophylaxis, etc. Partway through the study[34] we added a crossover option to open-label combination therapy for patients who reached a primary endpoint [new AIDS-defining condition; presumably those who died were not offered combination therapy]... At the time we designed the study we still thought we might see a difference between combination therapy and monotherapy... In retrospect this was probably the worst population to study... We're presenting a non-traditional analysis for your information.[35]

The Analysis. In Berlin, at the first public presentation of the data from ACTG 155, Dr. Fischl hailed it as "the first study to demonstrate the clinical benefit of combination therapy."[36] While NIAID hurriedly redrafted a press release to eliminate such remarks, she continued to maintain this line throughout the Berlin conference, and at the ACTG Retreat during July. By September, the 155 team had gotten its act together for the FDA hearing, and solemnly admitted the null overall results before presenting their now famous "post hoc subgroup trend analysis" based on three baseline CD4 strata (>150, 50-150, <50). Later in the day, Roche scientists produced their preferred two subgroup analysis (>/<100), claiming that the benefit "appeared to change direction" around a baseline CD4 of 100/mm^3. Either way, the results suggested a benefit to combination therapy at higher CD4 levels, and one to monotherapy (especially AZT monotherapy) at lower ones. Overall, combination therapy was 50% more toxic than either monotherapy, but no more effective.

The development of ddC was accompanied from the start by inappropriate exaggerations of its benefit. Last year, Roche decided to ignore the bad news of ACTG 114 and the inconclusive results of ACTG 119, to tout the improbable ACTG 106 results as showing more than they did, and to apply for approval in the absence of any evidence of benefit. This year, they continued that pattern, distorting the disappointing results of CPCRA 002 and ACTG 155 into a shaky package, apparently fully confident that the FDA, its advisory committee, and the AIDS community will continue to embrace ddC in spite of the failure of all the previous hopes.

In ACTG 155, ddC monotherapy patients had the highest proportion of clinical events, and ddC combination patients had the highest proportion of deaths. But overall the study failed to show statistically significant differences among the three arms.

The much-touted "subgroup trend analysis" shows very little. The trial wasn't stratified by CD4 counts at the outset. The high baseline CD4 group (150-300) -- the one with the claimed "benefit" of combination therapy -- was exactly the arm with the

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[34] In March 1992, days before Roche opened its expanded access program for ddC combination therapy.

[35] Mark Harrington. "ddC IN WONDERLAND", notes from the FDA Antiviral Advisory Committee, 20 Sep 1993.

[36] Fischl at the Harvard AIDS Symposium, 8 June 1993, quoted in "ACTG 155: Points to Consider," by Derek Link, Department of Medical Information, Gay Men's Health Crisis.

fewest clinical events, and thus the least power[37]. The high CD4 subgroup had just 15.5% of the clinical endpoints, and only 8% of the deaths. Thus, this subgroup lacked the number of events to provide enough power to clearly tell us anything -- especially when those groups with the most endpoints tell us quite a different story.

The people who entered in the lower two CD4 subgroups (<150) had 85% of the progressions and 92% of the deaths. This is where the study's power is. Moreover, in the lowest CD4 subgroup, ddC alone was the worst for progression, and combination therapy was worst for death. The sponsor handles this apparent contradiction with the statement that "the treatment differences reversed directions at a baseline CD4 count of approximately 100 cells/mm^3"[38].

How can one accept the putative "benefit" of combination therapy in people with CD4>150 of one ignores the potential "harm" of ddC monotherapy or combination therapy in people with CD4<50?

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[37] From the ddC NDA Package, ACTG 155 section, Table 2, page 11:

Table 2: Rates of clinical progression and mortality by treatment and CD4 cell count subgroup

	Therapy regimen		
	ZDV	ddC	ZDV/ddC
Rates of clinical progression (AIDS-defining events or deaths per 100 person-years of follow-up)			
Overall	36.4% (118/283)	39.5% (123/285)	32.9% (164/423)
> 150	16.6 (26/118)	11.5 (17/111)	8.8 (20/157)
50-150	39.6 (43/ 94)	42.8 (42/ 89)	36.5 (65/153)
< 50	83.0 (49/ 71)	92.3 (64/ 85)	85.1 (79/113)

	Therapy regimen		
	ZDV	ddC	ZDV/ddC
Mortality rates (deaths per 100 person-years of follow-up)			
Overall	11.0% (43/283)	13.0% (51/285)	13.3% (78/423)
> 150	4.1 (7/118)	1.9 (3/111)	1.7 (4/157)
50-150	9.0 (12/ 94)	12.3 (16/ 89)	11.2 (24/153)
< 50	27.4 (24/ 71)	30.3 (32/ 85)	36.5 (50/113)

(The figures in parentheses are the number of failures/number of patients.)

The total number of endpoints per subgroup is:

	Progression	Death
CD4 > 150	63 (15.5%)	14 (8.0%)
CD4 50-150	150 (37.0%)	52 (30%)
CD4 > 50	192 (47.4%)	106 (62%)
Overall	405 (100%)	173 (100%)

[38] Roche NDA package, ACTG 155 section, p. 40.

ACTG 155 is a wash. It's time to rethink how NIH and industry design and analyze efficacy studies, and how FDA regulates them. An NIH statistician recently told me that all the ACTG phase II/III studies are underpowered[39]. But NIAID has too few statisticians to review the protocols before they start. It's as if NASA didn't have enough engineers to make sure their rockets could fly. [Indeed, lately it looks like they don't.] But when a rocket blows up, at least everyone knows about it. When a drug trial crashes, the sponsor goes ahead and demands an NDA. In any case, the benefits of these drugs are so marginal that they may only eventually be revealed by much larger studies.

In the end, ACTG 106 showed very little, and ACTG 155 showed us no difference at a much higher resolution. Yet the team wrote to the patients, "In summary, the study showed that patients with advanced HIV disease who have received long-term ZDV therapy and who have CD4 cell counts $\geq$ 150 cells/mm^3 have a better outcome if they receive combination therapy with ZDV and ddC than if they continue on ZDV therapy..."[40] The participants who survived the trial deserved to hear the full truth, but the investigators denied them this courtesy. But then again, if researchers can tell who's on what regimen, and which regimen is a winner, by obvious behavioral clues, why do trials at all?[41]

The Implications. Once again, as with the Army's phase one gp160 study, data are wilfully misinterpreted. Time is wasted. Money is wasted. Hopes are dashed. We are trapped by assumptions refuted by the Concorde study and by ACTG 155.

And all of the ACTG's follow-up trials -- ACTG 175, 193, and the phase two trials of the NNRTIs[42] -- are based on the outdated, or at least far from secure, notion that preliminary CD4 changes predict clinical benefit. None of these studies (with the exception of 193, which is a useless travesty) is powered to show which regimen is more beneficial clinically.

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39 With one exception, ACTG 241; see below.

40 M Fischl; AC Collier for the ACTG 155 Protocol Team, letter to ACTG 155 Participants, 28 May 1993.

41 This text is excerpted from my testimony to the FDA Antiviral Drugs Advisory Committee, 20 September 1993. Both FDA and the AVDAC accepted the data from CPCRA 002 which, while not spellbinding, is not as egregious as ACTG 155. Combination therapy will have to be further validated by Roche if it wants a combination indication; ACTG 175 alone will not be enough [because a) the population started out with such high CD4 levels that benefits may be obscured, b) 175 isn't powered to detect a clinically significant difference]; nor will ACTG 193 [CD4 levels are too low, the trial too complicated, the population too sick; it will show nothing]. The British Delta study (AZT vs. AZT/ddI vs. AZT/ddC, N=1717) may also help answer the combination nucleoside question. If these studies are inconclusive, however, we'll be back at square one..

42 NNRTIs = Non-nucleoside reverse transcriptase inhibitors, e.g., Nevirapine, Pyridinone (L-697,661), Atevirdine (U-87), Delavirdine (U-90), etc.

Increasingly -- in ACTG 229, 241, 244 and 261[43] -- control arms in antiretroviral studies use combination AZT/ddC, or AZT/ddI, as though these had been clinically validated as the standard of care, when, after ACTG 155 and until something better comes in, THE OPPOSITE IS THE CASE: Combination therapy with AZT/ddC in the 155 population is 50% more toxic and no more effective than monotherapy with AZT alone. Using combination regimens as pseudo-control arms in current studies will only further confound their results, leaving us farther than ever from providing people with HIV and their providers with clear, relevant, useful treatment information.

A Third Case Study: Convergent Combination Chemotherapy

The Hypothesis. See notes on the generic rationale for combination antimicrobial therapy in the previous section. In this case, the usual, and rather pedestrian insight of combining three antiretroviral agents in vitro to produce "synergy" was originally presented, without undue attention, at the Amsterdam AIDS meeting in 1992[44]. Later these results were dressed up with a catchy theory about the "use of evolutionary limitations of HIV-1 multidrug resistance to optimize therapy" and published this February in Nature[45]. In the meantime, the ACTG Executive Committee approved ACTG 241, a phase II study of the "convergent" regimen of AZT/ddI/Nevirapine compared to AZT/ddI alone, using the standard Combination Therapies Working Group master protocol format of 100 patients per arm with CD4 counts as the primary outcome measure. So far, all seemed ordinary.

But February 1993 was not an ordinary time. A new administration was in power, one that seemed more interested than the previous ones in AIDS research. A bill was being debated on the Senate floor which would radically reform the structure of the NIH AIDS research program[46]. Some NIH officials were waging a furious campaign

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[43] ACTG 229 = Ro 31-8959/AZT vs. AZT/ddC vs. AZT/ddC/Ro 31-8959 N=301
ACTG 241 = AZT/ddI vs. AZT/ddI/Nevirapine N=400
ACTG 244 = AZT vs. AZT/ddI vs. AZT/ddI/Nevirapine N=300
ACTG 261 = AZT/ddI vs. AZT/ddI/U90 vs. ddI/U90 vs. AZT/U90 N=456

Of course the "hypotheses" of 241/244 (if they remain valid) demand a two-drug control arm; in the cases of 229 and 261 there is no justification for such "control" arms. I fought a losing battle against these wasteful designs in the PI Core Committee.

[44] Y-K Chow, MS Hirsch, DP Merrill, LJ Bechtel, JJ Eron, JC Kaplan, RT D'Aquila. "Replication Incompatible and Replication Compromising Combinations of HIV-1 RT Drug Resistance Mutations." Poster PoA 2450, page A78, Poster Abstracts, VIII International Conference on AIDS, Amsterdam, the Netherlands, 19-24 July 1992. Inhibition of HIV replication for three days in culture was here taken as a demonstration of the "significant advantages to convergent combination therapy... targeting multiple drugs simultaneously against the same HIV gene product".

[45] Y-K Chow, MS Hirsch, DP Merrill, LJ Bechtel, JJ Eron, JC Kaplan, RT D'Aquila. "Use of evolutionary limitations of HIV-1 multidrug resistance to optimize therapy". Nature 361, 18 Feb 1993, 650-653.

[46] S.1, the NIH Revitalization Act of 1993, (including Title XVIII, Research with respect to Acquired Immune Deficiency Syndrome), passed the Senate by 93-4 on February 18 -- coincidentally, the same day as the Nature paper was published.

to defeat this initiative, using professional societies (such as ASM and AAMC) and a minority of academic researchers as proxies. Meanwhile, Harvard was circulating a plan to take over AIDS research[47].

So the Nature paper, for a number of unrelated reasons, was subjected to an unusually bright glare of publicity. Massachusetts General Hospital issued a press release describing the discovery as a potential "Achilles heel" of HIV. The mass media went wild. The story was front-page news across the country. Yung-Kang Chow, the medical student who was the primary author, was showcased as ABC News' "Man of the Week"; his concept of drug-inducible evolutionary limits to HIV's ability to mutate was presented as a scientific breakthrough on the lines of Archimedes' "Eureka!" Beleaguered OAR and NIAID Director Anthony S. Fauci appeared on television news playing the drug (presumably AZT/ddI/Nevirapine, the new trinity), saying, "You're the virus. I'm the drug. I'm giving you two choices: either I kill you, or I make you mutate yourself out of existence." NIAID put out a press advisory listing the ten sites where ACTG 241 would take place. One week later, NIAID issued a second advisory noting that six sites were being added[48]. Quickly the Primary Infection Core Committee recommended that the study size be doubled, to 400 patients. No scientific rationale for expanding the study was presented, and no one from the protocol team objected. An AZT/ddI/Nevirapine arm was added to the ACTG 193 study, in an effort to make this pointless and unnecessarily complicated study more "attractive" (if yet more complicated) to potential participants, who must have $CD4 < 50/mm^3$. The research team began to claim it had begun to discourage media interest, but not until several mass-market magazines had already published photos of Dr. Chow holding up vials labelled "AZT", "ddI", "Nevirapine"[49], like some new magic elixir. After stoking the flames with its press release, Mass General spokesman Martin Bander charged that the media "revisited the subject too many times and gave it too much prominence."[50] Within weeks, Harvard Medical School received a multi-million dollar gift.

Privately, many were skeptical. One researcher involved with the work privately told an ACTG colleague the night before the story broke not to get too excited. A DAIDS executive quietly asked a reporter from a major scientific journal not to hype the

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47 "Just before the press erupted, the Harvard AIDS Institute quietly submitted a plan to the White House to create a new office outside of NIH to coordinate AIDS research. Under the plan, Harvard would coordinate the new office." Robert Massa, "Three-Drug Monte, the Hope and Hype of a New Approach to Treating AIDS." The Village Voice, March 9, 1993, p. 15.

48 Marion E. Glick, Chief, Information Projects Section, NIAID. "To: Editors, Producers and Reporters", February 22, 1993; and March 3, 1993.

49 G Cowley. "The Future of AIDS," Newsweek, March 22, 1993, pp. 47-52 [and cover story]; J Rennie. "Triple Whammy - Will an AIDS therapy live up to its advance billing?" Scientific American, May 1993, pp. 18-22.

50 MC, "Hype Springs Eternal." Discover, August 1993, p. 68.

story. But it was too late.

Phyllis Sharpe, a 41-year-old woman from the Bronx living with HIV with an infected daughter, told The New York Times that "To me, this is really the first big hope. I'm scared to even talk about it. I'm just praying within that this is really true."[51] Sites enrolling patients into ACTG 241 were besieged with people clamoring to get onto the waiting list. One volunteer later said, "I was surprised at how jealous many of my fellow members of the support group were when I got into the trial [ACTG 241] - 1 of only 25 people accepted out of more than 400 applicants"[52]. Boehringer Ingelheim, manufacturer of Nevirapine, was besieged with inquiries from the community, and a team toured the country meeting with treatment activists during March and April[53].

The Agent. What was all the fuss about? Nevirapine was just one of a number of second-generation reverse-transcriptase inhibitors (the so-called non-nucleoside RTIs, or NNRTIs), along with Merck's L-697,661 ('Pyridinone'), Upjohn's U-87 ('Atevirdine') and U-90 ('Delavirdine'), which several drug companies discovered in the late 1980s during expansion of routine HIV RT inhibition assays to non-nucleoside compounds. These compounds had decent in vitro antiretroviral activity and entered phase I studies within and without the ACTG, alone and in combination with AZT[54].

The usual roller-coaster ride of expectations within the community started to take off. First euphoria (as though another generation of RT inhibitors were just what everyone needed -- schematic pictures of Nevirapine in action were even published in Artforum!), then despair (when the first reports of rapid viral resistance to Nevirapine and L-697,661 were made in December 1991[55]).

The ACTG kept plugging away, slowly completing the 168 trial, which suggested that higher doses of Nevirapine might delay the onset of resistance, reigniting interest in

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51 M Navarro. "The Sharp Edge of Hope and Fear: New AIDS Report Brings a Wrenching Mix of Emotions." The New York Times, February 21, 1993, page B1.

52 J Schmalz. "Whatever Happened to AIDS?" The New York Times Magazine, Nov 28, 1993, p. 86. Jeffrey Schmalz, one of the few journalists to acknowledge he was living with AIDS, died on November 6.

53 To their credit, no one from Boehringer Ingelheim ever appeared to put much credence in the notion of "convergent combination therapy".

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ACTG 164, Nevirapine alone	N=62	ACTG 184, L-697,661 ± AZT	N=22
ACTG 168, Nevirapine + AZT	N=81	ACTG 187, Atevirdine alone	N=33
ACTG 180, Nevirapine ± AZT in Children	N=19	ACTG 199, Atevirdine/AZT/ddI	N=20

55 See Boehringer Ingelheim Pharmaceuticals, Inc. "Summary Statement on Recommendations for Nevirapine Clinical Trials," 16 December 1991. Also see John Doorley, Executive Director, Corporate Communications, Merck & Co., letter to B Bahlman, M Becker, M Ravitch, T Smart, J Thomas, February 18, 1993. High-level resistance to L-697,661 on monotherapy developed within four to six weeks, and to combination therapy over a longer period of time, with "no activity in any arm as measured by CD4 or clinical parameters."

the 164 monotherapy study, for which enthusiasm was now understandably somewhat diminished in the community. In addition, ACTG 208 was deployed to address whether giving the drug to people with CD4 > 500/mm^3 might delay the onset of resistance, and 20 patients enrolled[56]. Nothing untoward occurred until 1993.

The Experiments. The February 1993 Nature paper discussed a number of in vitro experiments combining various nucleosides and non-nucleosides, including AZT with ddI and Nevirapine, Pyridinone (Merck's L-697,661), or Foscarnet [thankfully, most coverage did not focus on the third agent, which is licensed, highly toxic, and outrageously expensive]. The work was carried out by Harvard medical student Yung-Kang Chow and colleagues under the supervision of virologist Richard D'Aquila and Martin Hirsch, current chair of the ACTG Primary Infection Committee.

1. Proviral DNA Mutants. The team tried to construct "mutant provirus DNAs" by introducing known resistance-associated point mutations into DNA plasmids and then transfecting these "into COS-7 cells..."[57]. Then they assessed whether the transfected mutant proviral DNA could infect T cells -- which it couldn't. They took this as proof that the drug-associated mutations they'd introduced were responsible for the failure to infect, assuming that therefore they had constructed lethal mutations in reverse transcriptase.

2. Convergent Therapy in A Laboratory T-Cell Line. Secondly, the administration of the AZT/ddI/Pyridinone combination [Nevirapine wasn't mentioned here] to established HIV-infected T cell cultures was said to eliminate viral DNA from culture at 21 days, to eliminate p24 antigen by 35 days, and to continually suppress virus for 101 days, including 45 days after removal of the drugs[58]. The HIV strain used was not stated.

3. Convergent Therapy in A Clinical HIV Isolate. Thirdly, "after ten PBMC passages of a clinical HIV-1 isolate with AZT- and ddI-selected mutations in AZT + ddI + Nevirapine we were unable to select for viruses triply resistant to AZT + ddI + Nevirapine..."[59]. On reading this passage one immediately wondered what would happen after 20 or 30 passages -- which we were to learn by June.

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[56] Diane Havlir of UCSF distribute an "ACTG 208 Progress Report" at the 16th ACTG Meeting in February 1993. 10 patients with CD4 > 500/mm^3 enrolled. By 24 weeks, the median CD4 count had risen from 500 to 700, and the median percent change over baseline was 14%. Nevertheless, viral isolates rapidly became resistant in 7/10 patients whose results were in, with the drug becoming one-hundred-fold less active within 2-14 weeks of starting therapy. Subsequently 10 more patients were enrolled.

[57] Y-K Chow et al., op. cit. 1993.

[58] Ibid., Figure 4.

[59] Ibid.

The Aftermath. While the mass media exulted, and people with HIV clamored to enter the trials, many virologists were concerned. Even the "News and Views" piece, written by virologist Douglas Richman, which accompanied the February Nature article, commented that "HIV is a highly mutable and wily opponent, however, and that it may be able to avoid checkmate with a large array of alternative moves (mutations) is a real possibility. Both in vitro[60] and clinical data (unpublished observations) suggest that this may be the case."[61]

Others were even more critical the April issue of The Journal of NIH Research: "The experiments are technically flawed... The combination of mutations is not representative of the drug-resistant genotypes we see in the clinic... They did not prove in any rigorous way that the mutations they built into the reverse transcriptase lead to a defective enzyme," said Wellcome's Brendan Larder, co-discoverer of HIV's ability to mutate into an AZT-resistant phenotype[62]. "The data are shaky. It is surprising Nature published the paper... [the Harvard team] are dealing with a negative result, and negative results are notoriously difficult to interpret," said the Pasteur Institute's Simon Wain-Hobson[63]. Larder went on to inform the reporter from The Journal of NIH Research that "We have made a virus that contains mutations [associated with] resistance to all three drugs. These viruses are viable. They grow, replicate, and infect cells."[64]

The team reacted defensively to the skepticism of its peers, retorting that "The finding of such [a triply-resistant] virus in vitro does not diminish our interest in evaluating the combination of AZT, ddI, and an NNRTI in clinical trials."[65] Fine. But do then do not commence the trials in a blaze of publicity based on a hypothesis which you are already moving away from. The team went on to address "contentions that technical artifacts might have occurred in constructing or transfecting our mutants and that the mutations we studied are not 'representative'"[66], stating that "We did not use these experiments to support the hypothesis that combinations of mutations that are incompatible with virus replication can limit multiple drug resistance"[67]. What were

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60 BA Larder. Antimicrob. Ag. Chemother. 36, 2664-2669, 1992.

61 DD Richman. "Playing chess with reverse transcriptase." News and Views, Nature 361, 18 February 1993, 588-589.

62 R Nowak. "Debate Erupts Over Report of HIV-1 Achilles' Heel". J. NIH Research, April 1993, 30-31.

63 Ibid.

64 Ibid.

65 RT D'Aquila, Y-K Chow, MS Hirsch, letter, The Journal of NIH Research, July 1993, pp. 16-17.

66 Ibid.

67 Ibid.

they suggesting, then? That was exactly the point of Chow's "Eureka!" experience so widely touted in the press. They then defended the rigor of their proof that their induced RT mutations "led to a defective enzyme," noting that another manuscript was in preparation documenting this, and said that "undetected cloning anomalies are a far-fetched explanation for our results..."[68]

The team may later have come to regret its tone of infallibility. As early as the International AIDS conference in Berlin during June -- just as its letter was appearing in The Journal of NIH Research, Yung-Kang Chow announced at a plenary session that triply-resistant viruses did, in fact, emerge after between 20-30 in vitro passages[69]. Larder's team from Wellcome and Emini's from Merck also reported their success in culturing multiply-resistant HIV that month at the Second International HIV Drug-Resistance Workshop in Noordwijk, the Netherlands.

Apparently the Wellcome and Merck team's results motivated the Harvard team to offer to exchange mutants and see what the discrepancy was. Before sending off the Harvard mutants, Hirsch thought it would be prudent to check their sequences, and in doing so found that the proviral sequences had extra, previously unnoticed nucleotides. The drug-resistance point mutations were not the ones which made the mutants nonviable. The unnoted nucleotide substitutions coded for nonsense protein, and the provirus could not replicate at all. A retraction letter was sent to Nature.

Shortly thereafter, The New York Times broke the story in public[70]. In this case, the newspaper addressed the troubling underlying issues with more frankness than would the scientific press. Chow was forbidden to speak to reporters. The Times reporter noted the usual rationale for combination therapy, but said "scientists have not yet come up with documented evidence that any combination of drugs is beneficial for HIV or any other viral infection."[71] Despite the retraction, "Dr. Hirsch and Dr.

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68 Ibid.

69 Y-K Chow, D Merrill, J Kaplan, R D'Aquila, M Hirsch. WS-A19-6, "In Vitro Selection of Multi-Drug Resistant HIV-1." This was given on Wednesday, June 9, 1993. The original abstract (WS-A19-6, p. 35, vol. I, Abstracts, IX International AIDS Conference, Berlin, June 6-11, 1993) states that "these passage experiments have been ongoing for over 20 passages in 15 months." This is probably a fair description of the Harvard team's state of mind in the months before the Nature paper came out; the deadline for Berlin abstracts was in January. Chow and colleagues had many abstracts accepted for Berlin, including WS-B25-5 (vol. I, p. 68), "Convergent Combination Therapy May Prevent HIV Multi-Drug Resistance," PO-A03-0065 (vol. I, p. 145), "Evolutionary Limitations of HIV-1 Multi-Drug Resistance," PO-A26-0635 (vol. I, p. 240), "A Novel Genetic APproach to Study HIV-1 Drug Resistance in Monocyte/Macrophages," PO-B26-2029 (vol. I, p. 473), "Convergent Combination Therapy Effectively Inhibits HIV-1 Infection of Monocyte/Macrophages In Vitro": "All four regimens [AZT + ddI + Nevirapine ± Foscarnet, as well as AZT + ddI + Pyridinone ± Foscarnet] completely inhibited HIV-1 replication in monocyte cultures at IC95 & IC99". Let's hope these trials don't start prematurely!

70 LK Altman. "Flaw Is Discovered In Crucial Research on AIDS Treatment," The New York Times, July 22, 1993, p. A1; and LK Altman, "Faith in Multiple-Drug AIDS Trial Shaken by Report of Error in Lab," The New York Times, July 27, 1993, p. C3.

71 LK Altman, "Flaw Is Discovered..." NYT, 7.22.93.

Anthony S. Fauci... said in separate interviews yesterday that the flawed laboratory study was not a reason to stop the combination drug trials. The concept of combination therapy remains valid, they said, based on a widespread belief [emphasis added] among experts..."[72]. Sometimes the belief in combination therapy seems to overtake the need for a careful exploration of how best to study it. Having failed to show that two drugs are better than one, we are now comparing three drugs to two, as though the issue were settled. Moreover, the choice of which agent(s) to add seems arbitrary. Why not establish optimal two-drug regimens (if there are any), then base three-drug regimens on the outcome of careful, replicated laboratory and pilot clinical work? To his credit, Dr. Hirsch made a rapid public retraction. But it was full steam ahead on ACTG 241; "the confused volunteers are being asked to plunge ahead and subscribe to the belief that three drugs may be better than one or two"[73]. Many will surely do so, since they have been so effectively programmed by years of pro-combination propaganda from the leading researchers in the field. "The error also revealed a surprising degree of sloppiness in the quality of bench research conducted by researchers at one of the most prestigious hospitals and medical schools in the world... Mr. Chow published without repeating crucial steps to verify ambiguous data... The team misread laboratory data and failed to detect a fifth mutation in the virus... This incident adds to a list of the times when the much-heralded peer review system failed to detect the flawed research it was designed to weed out... Reflecting its initial enthusiasm, the Harvard team generated publicity by issuing a news release saying its research might have found the 'Achilles heel' of HIV. But a few days later, the Harvard team stopped talking to reporters because the publicity got out of hand, a reaction that the team naively says it never anticipated."[74]

On August 5, the editors of Nature announced that "Chow et al. have sent a retraction of part of their work... The authors admit that the discrepancies between their data and those of their critics (some of whom had earlier submitted them to Nature) can be explained by four [emphasis added] previously unnoticed mutations in the reverse transcriptase of one of their HIV-1 clones. They go on to say that this development does not affect the accuracy of their other data, but it does invalidate their claim to have proved that multidrug therapy will be effective by avoiding drug resistance."[75] The editors go on to congratulate themselves for publishing the correction quickly, sadly noting that "the publicity does not help". They did not address whether their own decision to publish had helped to fuel the publicity (Nature rarely publishes drug development papers, just as The New England Journal rarely publishes phase I studies like the Army gp160 trial).

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[72] Ibid.

[73] LK Altman, "Faith in Multiple-Drug AIDS Trial Shaken..." NYT, 7.27.93.

[74] Ibid.

[75] "Saying sorry quickly," editorial, Nature 364, 5 August 1993, p. 468.

In its retraction letter to Nature, the study team confessed that the explanation which it had previously found "far-fetched," that is, "undetected cloning anomalies,"[76] is actually correct: "The clones... of mutant 4 had unintended mutations in addition to the intended mutations in reverse transcriptase codons 74, 103, 215 and 219... We believe that all the other data in our report are correct."[77] They go on to note that they, too, "have also been able to select for triply resistant viruses similar to those described by Larder et al."[78] Accompanying their letter is one from scientists at Merck Research Laboratories describing their successful efforts to culture HIV-1 variants resistant to AZT, ddI, L-697,661 and/or BI-RG-587 [Nevirapine], thus suggesting that quadruply resistant mutants are feasible, and suggesting that "such variants are likely to be selected during multiple therapy"[79] By September 30, Larder and colleagues had reported that "HIV-1 co-resistant to AZT, ddI and the NNRTI Nevirapine can be readily selected in cell culture starting with dual AZT- and ddI-resistant virus. We found no evidence for 'replication incompatible' combinations of resistance mutations."[80] Passage of one construct "concurrently in AZT, ddI and Nevirapine led to the rapid [emphasis added] development of Nevirapine resistance, and, curiously, an actual increase [emphasis added] in AZT resistance."[81] They also constructed the mutant which the Harvard team stated it had made in the February paper, and found that "recombinant reverse transcriptase containing these mutations... was virtually as active as the wild-type enzyme."[82] Having demolished virtually the entire ensemble of claims made in February, the Wellcome team went on to determine that an HIV-1 variant triply resistant to ddI, Nevirapine and the nucleoside analogue FTC had actually regained susceptibility to AZT! This, if it could be replicated in the clinic, would be a perfect strategy for returning people, several years, drugs and thousands of dollars later, to the AZT-susceptible state at which they began therapy -- and a boon for Burroughs-Wellcome[83]. But the deeper lesson

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76 D'Aquila, Chow, Hirsch, letter, J NIH Research, op. cit., July 1993.

77 Y-K Chow, MS Hirsch, JC Kaplan, RT D'Aquila. "HIV-1 error revealed." Scientific correspondence, Nature 364, 19 August 1993, p. 679.

78 Ibid.

79 EA Emini, DJ Graham, L Gotlib, JH Condra, VW Byrnes, WA Schleif. "HIV and multidrug resistance." Scientific correspondence, Nature 364, 19 August 1993, p. 679.

80 BA Larder, P Kellam, SD Kemp. "Convergent combination therapy can select viable multidrug-resistant HIV-1 in vitro." Nature 365, 30 September 1993, pp. 451-453.

81 Ibid.

82 Ibid., Table 2.

83 Wellcome appears to be completely serious about this. "Dr. Larder suggested a pilot study in which people with a zidovudine resistant strain of HIV would be treated with a combination of zidovudine, FTC or 3TC, and an NNRTI. 'We predict sensitivity to zidovudine would be restored,' he said. Effective treatment could be maintained with a combination of zidovudine and an NNRTI, with the possible continuation also of FTC or 3TC." From "Countering Resistance," HIV Focus, 6 June 1993, p. 3. Report from the Wellcome Foundation Satellite Symposium 'Early and

is that HIV quite rapidly can evade any regimen composed exclusively of reverse transcriptase inhibitors. Perhaps RT alone is the wrong target.

The Implications. Larry Altman of The New York Times made a key point in his wrap-up on the whole affair: "Anyone can come up with a theory about the treatment of a disease. But there is not enough time, money and expertise, let alone willing volunteers, to test every new theory."[84] Not all theories are equally meritorious. Nor are all investigators equally good, or all journals equally reputable. But when a highly-regarded, powerful investigator publishes something catchy in a top-ranked journal, it may not be subjected to the same skepticism with which most new and unexpected results are received. Within the ACTG, there is no true peer review in the Primary Infection Committee, and too little oversight by the Executive Committee. Therefore, it was smooth sailing from the first for a catchy hypothesis that more careful work would have doomed from the outset.

But the impetus for studying combination therapies in the clinic is not deterred even for a moment by such retrospective setbacks. The trial is underway, is it not? -- and it's twice as large as it needs to be -- who needs a hypothesis now? The machine is working! Who cares if its output is unreadable, or that people with HIV have poor information on which to base their treatment decisions, or that other approaches will not be studied because the machine is clogged with nucleosides and NNRTIs? The ACTG has already programmed all its trials for 1994. New approaches cannot be studied unless old ones are scaled back. Each new antiretroviral trial seems to show less and less obvious clinical benefit. Rather than assessing why we can't even answer clinically relevant questions for antiretroviral therapy in the ACTG, those running it simply pile on more reverse transcriptase inhibitors (RTIs), cross their fingers and hope for the best. Statistically, if they run twenty combination therapy trials, at least one will break "positive" simply by chance. And that one statistical fluke will then be taken and broadcast around the world as proof of the "efficacy" of combination therapy.

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late phase treatment of HIV infection.' Published by Cambridge Medical Publications with support from the Wellcome Foundation.

[84] LK Altman, "Faith in Multiple-Drug AIDS Trial Shaken...", New York Times, 7.27.93.

Follies of 1993, or How Did We Get Into This Mess (And How Do We Get Out)?

> The Omni-Drug Revolution. In the campaigns against disease, researchers have attained some success by utilizing two or more drugs together. Recently, this approach has led to the development of omni-drug therapy, in which hundreds of different drugs are administered together. Proponents argue that the body's immune system selects only those drugs that are beneficial, and renders the other drugs inert. Opponents argue that the claim is farfetched and extremely dangerous. Omni-drug therapy has received much favorable attention in the general press. Patient support groups for several diseases are applying political pressure to allow experimenters to skip preliminary laboratory trials with animals and proceed directly to human clinical trials.
>
> -- The Journal of Irreproducible Results, September/October 1993[85]

The report of the recent Ad Hoc Scientific Review of the ACTG questioned "whether many of the current large efforts (such as the nevirapine trials) are scientifically sound or whether the trial design will answer the study's research question."[86]

Having failed to prove that two nucleosides are better than one, the potentates of the ACTG primary infection effort are busy designing multiple phase 2 studies, incompletely controlled with ill-defined "control" arms like AZT/ddI or AZT/ddC, comparing three drugs (2 nucleosides plus an NNRTI) with two. It seems that the "Omni-Drug Revolution" is already well underway in the ACTG.

Samuel Broder once commented that with AIDS, as has already occurred in cancer, we are in danger of being locked into mediocre therapeutic regimens[87]. So far, the clinical data on combination therapy with AZT/ddC indicates that, overall, it is 50% more toxic than monotherapy, and no more effective[88]. So participants on the control arms of these new studies (ACTG 229, 241, 244, 261) may be being exposed to useless toxicity and inconvenience without corresponding benefit, and those "lucky" enough to receive triple-drug therapy are exposed to the toxicities (rash, etc.) and the ill-understood, transient anti-HIV activities of the NNRTIs.

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85 From "Scientific Gossip -- Contains 100% gossip from concentrate," compiled by Stephen Drew in The Journal of Irreproducible Results, the Publication of Record for Overly Stimulating Research and Ideas, Volume 38, Number 5, September/October 199 (Blackwell Scientific Publications Inc., Cambridge, MA).

86 Report, ACTG Ad Hoc Scientific Review, August 1993, p. 6.

87 S Broder, personal communication.

88 ACTG 155 by intention-to-treat analysis, FDA hearing, 9.20.93.

Meanwhile, those evaluating the current "state of the art" in terms of antiretroviral standard of care, have apparently moved away from reliance on ACTG studies, and are framing the question of how best to use current anti-HIV drugs in terms of "patient choice" and "the art, not just the science, of medicine." The new NIAID-sanctioned guidelines contain a total of twelve optional regimens based on stage of disease, and can be summed up basically in two words: "Anything Goes." It is as though the research establishment is simply giving up on the need to discover how best to use current therapies. This implies equal pessimism about how to define optimal regimens with new therapies. And the hypotheses now being studied in the ACTG are unlikely to provide clear, rapid answers to these questions.

> The [Primary Infection] Committee appears to lack specific guiding principles by which to set its priorities and guide its future work. For example, should they test the best available drugs, drugs that are hard for industry to test, or orphan drugs; concentrate on trials that set standards of care; be involved in the eraly evaluation of every drug, or in fine tuning earlier established data? Once the overriding principles are clear, the committee could then define and follow its priorities. In addition, the committee appears to have few criteria for evaluating what many on the review panel view as junk drugs (dextran sulfates, nevirapines, or therapeutic vaccines).[89]

ACTG 175 was designed in the heyday of optimism about surrogate markers. Primary Infection chair Douglas Richman once commented that "ACTG 155 will be the last PI study to use clinical markers."[90] 175's designers supposed that they were extending the results of ACTG 019 vis-a-vis early intervention, by comparing AZT to ddI monotherapy, and to AZT/ddI and AZT/ddC in combination, in a similar population. Unlike 019, however, the endpoint of interest was to be CD4 cell changes. The results from 019 had never been analyzed to show whether AZT-induced CD4 changes were in fact predictive of benefit. And most of the endpoints in 019 were PCP ones, because PCP prophylaxis was strongly discouraged during that study. Now, with virtually everyone in ACTG studies on prophylaxis when their CD4 drops below 200, there would be very few PCP endpoints. Thus, CD4 changes were regarded as a more practical and "affordable" option than waiting several years longer for clinically significant differences to show up. After Concorde's results were released, the ACTG 175 team added clinical endpoints to the primary objectives, but there is only enough power to compare "immediate vs. deferred combination therapy" rather than to compare the 4 arms individually to each other.

The controversy during the planning of ACTG 175 divided activists and scientists alike. Some thought the trial a wholesale waste of time ("You don't combine 2 drugs

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[89] Report, ACTG Ad Hoc Scientific Review, August 1993, p. 5, "Primary Infection Committee -- Weaknesses".

[90] PI Core conference call, March 1992.

with the same mode of activity -- like ampicillin and penicillin," one researcher told me), while others thought it was a prudent and sensible step forward ("A Spanking for T+D," Bob Huff, September 1991). The original protocol chair, Deborah Cotton, stepped down rather than lead a trial which she thought ill-designed. There was no forum within the ACTG for the essential scientific differences to be openly debated. The protocol team slimmed down the study to get it through the Executive Committee at an N of 2,100 and an estimated cost of $16 million. Later the trial ballooned in size to over 3,000 and was extended in duration for another year; thus the ultimate cost will approach $25 million or more, including the nested virology substudies. The trial appears to be too large for the ACTG, and too small to answer its question definitively. First of all, the rate of clinical progression in the original 019 population was tiny -- about 3% overall, 4% on placebo and 2% on AZT. Nonetheless the study was used as a basis for recommending that the whole 019 population <500 be placed on AZT, though 97% of them wouldn't even progress within the 19 months median follow-up from 019. Now three other regimens were being compared with AZT (2% progression in 19 months) with concomitant use of PCP prophylaxis. The rate of clinical progression will be minuscule. The other regimens would have to be dramatically better or worse than AZT if 175 was to show a difference, and given what we know of these drugs, that's highly unlikely. In commenting on the amount of time that the gp160 controversy took in 1992-93, an NIH employee said "$20 million? That's nothing! We throw that kind of money away around here!" The ACTG 175 story makes that all too abundantly clear.

ACTG 193 is a mess of a study. Rather than allowing people with late-stage disease in to the studies of the newer antiretrovirals, the ACTG designed a "salvage study" using agents that had already failed in the study population. People with <50 CD4 cells, most of whom have already been on the three available nucleosides, are randomized to AZT with ddI or ddC, to an alternating regimen, or to triple drug therapy, and followed until death. In the subgroup analysis from ACTG 155, combination therapy was more toxic and less effective than AZT monotherapy in the subgroup with CD4<50/mm^3. More recently, people with low CD4 levels have been excluded from the tat inhibitor trial (ACTG 213) and the new Upjohn U-90 studies (NIH intramural study and ACTG 261). After excluding the most endangered population from its studies, the investigators go on to lament the lack of clinical endpoints in their "pivotal" trials using healthier populations. The solution is staring them straight in the face -- stop excluding people with low CD4 counts!

> The [Primary Infection] committee's reliance on a single investigator's consulting role with industry to bring in new drugs is a potential problem source. Lack of full disclosure of relationships to industry erodes credibility.[91]

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[91] Report, ACTG Ad Hoc Scientific Review, August 1993, p. 5.

ACTG 229, the Roche protease inhibitor study, was designed in an egregious and secretive manner. The company refused to provide preliminary anti-HIV activity data from its three European trials to the Primary Infection committee or the Combination Therapies Working Group. We were asked to vote blind on an expensive combination study. Roche also insisted that AZT/ddC be the "control" arm, though this lacked validation either vis-a-vis virology, CD4 changes, or clinical outcomes. If the protease/AZT arm appears "equivalent" to the ddC/AZT arm, does that mean the protease inhibitor is "equivalent" to ddC? Hardly. Roche later showed the investigators a few shreds of activity data but again refused to allow the working group or the full committee to evaluate the results. Here, ACTG resources were being manipulated by a pharmaceutical company for its own purposes, and ACTG investigators were so eager to get their hands on a new class of compounds that they waived their duty to evaluate the concept sheet critically. Still later the trial was extended in duration, again piling on costs, thus limiting the number of new studies for 1994. Apparently Roche, like many pharmaceutical companies, still believes that CD4 changes in small phase 2 studies are adequate for approval of new drugs, even new classes of compounds.

Rather than comparing critically the various non-nucleoside reverse transcriptase inhibitors, and choosing the one(s) which had the best activity, safety, immunological response, and resistance profile before going into expensive phase 2 studies, the primary infection committee simply rushed with a combination based on a laboratory study later proved to be inaccurate, and mounted not one but two expensive, high-tech trials (ACTG 241 and 244) using just one of the available possible combinations -- AZT/ddI/Nevirapine. It would have made more sense to use a comparative format in which other NNRTIs were compared with Nevirapine in vitro and in small pilot clinical studies before rushing forward with unsubstantiated hypotheses about a single regimen. ACTG 244 adds another twist, which is to add a therapy (ddI to the AZT monotherapy arm, Nevirapine to the AZT/ddI arm) when patients develop an AZT-resistance mutation at codon 215 in their HIV RT RNA. Again, recent developments in the field were not incorporated into this design. In Berlin, virologist Victoria Johnson of Birmingham, Alabama, presented analyses of the development of AZT resistance from participants in ACTG 116B/117. Development of AZT resistance was an independent predictor of progression, and those who developed resistance to AZT did not appear to benefit from switching to ddI. These results might undermine the approach being taken in ACTG 244, but the Primary Infection Committee was not permitted to evaluate the hypothesis, but simply the design of the study, as though those two things were so easily separable.

Finally, the ACTG 261 study design replicates the unreflective clutter and lack of coherence found in ACTG 229. Upjohn's U-90 (Delavirdine) will be combined with AZT, with ddI, with both, and compared with AZT/ddI together, in a 456-patient study using CD4 changes as the primary endpoint. Again, AZT/ddI remains an incompletely validated "control" arm. Again, surrogate markers are privileged, while

clinical endpoints are sidelined, with people with <100 CD4 cells excluded.

So far, then, it appears that the leading researchers in the ACTG Primary Infection Committee are incapable of framing a hypothesis in a clear and simple manner. They sometimes base large and expensive studies on anticipated confirmation of methods (e.g., CD4 changes predicting clinical benefit) which are not ultimately confirmed. Thus, every trial builds upon the unproved assumptions which helped to shape previous trials. When previous assumptions are disproved, the subsequent trials are not modified or redesigned in light of the new knowledge. The entire edifice appears to be a house of cards built upon a foundation of quicksand. The cost of the trials, in aggregate, will total hundreds of millions of dollars, and yet we are not much further with the standard of care than the helpful motto "Anything Goes".

> We have not devoted much attention to how we actually do these trials...
>
> -- Daniel F. Hoth, 11.20.89[92]

> Although it is difficult to prove, treatment of HIV has likely resulted in prolonging the life of HIV-infected individuals and improving their quality of life.
>
> -- Margaret I. Johnson + Daniel F. Hoth, 5.28.93[93]

As I said in the introduction, the results of recent clinical trials have been disappointing. They have been so in two quite distinct ways.

First, the trial results are disappointing because there is not a large benefit associated with currently available antiretroviral drugs. That is, the drugs are disappointing and inadequate.

Secondly, they are disappointing because they do not reliably answer the question of what magnitude of benefit might exist with these drugs. That is, the trials are disappointing and inadequate.

Many people still do not understand that, while Concorde and ACTG 155 failed to demonstrate clear clinical benefits, this does not preclude clinically meaningful, but less dramatic, differences from existing; the trials were simply unable to provide a

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[92] D Hoth at the FDA/NIAID Conference on AIDS Clinical Trials, A Symposium on Methodological Issues, 20-21 November 1989, Bethesda.

[93] MI Johnston, DF Hoth. "Present Status and Future Prospects for HIV Therapies." Science 260, 28 May 1993, 1286-1293.

high enough degree of resolution.

If we choose, as ACTG investigators and SDAC statisticians would prefer, to emphasize the first sense in which the trials have been disappointing, e.g., that the drugs don't do very much, then presumably we may correct this by finding fabulous new agents -- perhaps the omni-drug revolution beckons here. The same-sized trials we have now, with similar designs, would be adequate for finding drugs with dramatically superior activity to anything we now have. The problem is that such breakthrough discoveries are infrequent and impossible to predict. The normal work of clinical research will be in testing agents with modest efficacy at best, refining what's already available, and improving the standard of care. The current SDAC/ACTG paradigm is inadequate to this task. In ACTG terms, a "big" trial is one with over 1,000 patients. Yet to detect differences of say 15-30% between treatment arms, an early intervention study might need several thousand patients.

> The Primary Infection Committee should assess whether it is attempting to field too many protocols... Many protocols fail; mid-size trials often do not have sufficient power to answer questions; and studies do not seem to build well on one another. Although the committee has a capacity of 3,000 patients per year, its concepts require 9,000 patients.[94]

Perhaps the ACTG is simply the wrong place to do truly definitive phase 3/4 studies, at least for antiretroviral drugs. As long ago as May 1990, while ACT UP was "storming the NIH," a coalition of AIDS advocates stated that:

> We urge that the ACTG concentrate its efforts on conducting technology-intensive Phase I/II studies with a greater variety of new compounds than in the past. Larger Phase II, III and post-marketing studies should generally be conducted by community-based groups in conjunction with pharmaceutical company sponsors...[95]

While the new NIAID HIV/AIDS Research Agenda notes that "treatment research is supported through four complementary clinical trials mechanisms,"[96] the institute has never made an effort to create a truly coordinated treatment research infrastructure, strengthening the unique advantages of each mechanism (ACTG, CPCRA, DATRI and NIH Clinical Center) and fostering collaboration. The ACTG Opportunistic Infections Committee has undertaken difficult, but encouraging collaborative studies (TB prophylaxis, ACTG 177; and MAI prophylaxis, ACTG 196)

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[94] Report, ACTG Ad Hoc Scientific Review, August 1993, p. 7.

[95] "HIV/AIDS Biomedical Research Priorities: Recommendations to the National INstitutes of Health, May 17, 1990." Endorsed by ACT UP/NY, AIDS Action Council, AmFAR, CRI/NY, GMHC, HRCF, Lambda, etc.

[96] NIAID HIV/AIDS Research Agenda, October 1993, pp. IV-4.

with the CPCRA, but the Primary Infection Committee has done nothing of the sort.

NIAID's Research Agenda also fails to address the unresolved issues about the standard of care for HIV disease, and hence it is no surprise that the "Primary Disease Therapeutics -- Critical Scientific Questions" section does not focus on how best to utilize NIAID's clinical research resources to provide clearer answers on how to use antiretroviral drugs. In addition, the ad hoc panel which reviewed the ACTG panel criticized the lack of accountability once protocols were underway:

> The [Primary Infection] committee's responsibility beyond developing a specific protocol is unclear. There appears to be no systematic accountability for trial logistics. For example, if trials have poor accrual, take too long to complete, have a high drop out rate, or data are not analyzed, specific responsibility appears to be diffuse. Poor co-enrollment, which is scientifically as well as logistically desirable, needs to be addressed because it prevents multi-modality studies from occurring.[97]

One proposal that deserves serious consideration is for all phase 3/4 studies to be largely conducted in CPCRA-type settings, with high priority questions addressed in well-designed, adequately powered studies with minimal data collection, an emphasis on clinical outcomes, comprehensive long-term follow-up, conducted in community primary-care settings. Each of the ACTG's primary infection phase 2/3 studies, with the exception of ACTG 241, is underpowered[98]. Too much data are collected on too few people for too short of a period of time. Unnecessary data points clog the system. ACTG studies continue to focus on laboratory markers, though there has been inadequate validation even for CD4 counts, and there is still no consensus on virological assays. ACTG studies tend to dump participants from studies when they reach their first endpoint, while CPCRA studies follow all clinical events occurring during the study period. Is the time of the first OI really as relevant as the aggregate picture of the intensity of the disease course over a longer period of time? ACTG studies are abominable at carrying out long-term follow-up, especially in early intervention studies. One reason why Concorde's results appeared so compelling was that virtually every participant's fate was recorded. By contrast, in the higher CD4 cohort of ACTG 019, which is now closing out, only 456 of the original 1,620 participants were still being followed earlier this year. The losses to follow-up were so huge (and so biased) that the study may be unreadable.

In order to carry out meaningful phase 3/4 studies, NIAID will have to distribute clinical research resources in a different manner. The CPCRA enrolled one-third as

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[97] Report, ACTG Ad Hoc Scientific Review, August 1993, p. 5.

[98] Mary Foulkes, PhD, Biostatistics Research Branch, DAIDS, NIAID, personal communication, August 1993.

many patients as the ACTG did, in half the time, at one-tenth of the cost[99]. And yet some still feel the CPCRA could conduct simpler, more streamlined studies[100].

Thus, an emerging paradigm for carrying out studies designed to optimize the antiretroviral standard of care would shift resources from the ACTG model to the CPCRA model. The two networks would collaborate on phase 3/4 studies, with CPCRA enrolling most of the participants, and ACTG carrying out necessary, nested virological, immunological and pharmacological studies. Data would have to be sent to one central site (perhaps the CPCRA statistical unit is more appropriate for this than SDAC). ACTG would continue to carry out phase 1 and 2 (preliminary randomized studies of new agents and new combination regimens, hopefully ones justified by high-quality preclinical research) studies, and would maintain, possibly even expand, its crucial national network of laboratory-based committees (virology and pharmacology) along with the clinical-laboratory hybrids Immunology, Oncology and Neurology.

Finally, it is critical to demand from those analyzing and disseminating the results of publically-sponsored clinical trials that they tell people the truth about their results. The realities of AIDS are intractable enough without subjecting people to unnecessary joyrides on the rollercoaster of hype and subsequent disappointment. Spurious statistical tools should not be deployed to suggest more clinical benefit than trials actually demonstrate. Particular care should be taken to avoid the interpretive gaffes of Redfield et al in their "responder/nonresponder" analysis, and those of Stanley, Lagakos[101], and Fischl in their "nontraditional post hoc subgroup trend" analysis from ACTG 155.

The refusal to squarely face the setbacks and surprises which are characteristic of scientific progress in any field, especially AIDS, makes it harder to develop strategies to overcome the setbacks and learn from the surprises.

This week, astronauts on the space shuttle Endeavor are trying to fix the Hubble space telescope, which cannot see the cosmos clearly. It will take more than one week -- and more than just a handful of astronauts -- to fix the mechanism conducting

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99 CPCRA External Review, September 1992.

100 Bopper Deyton, personal communication, October 1993.

101 Lagakos is promulgating these "innovative" techniques at the American Association for the Advancement of Science (AAAS) meeting in San Francisco during February, 1994, in a talk entitled "Interpretation of HIV trials based on heterogeneous populations." Hopefully he will note previous work done in this area, such as the analysis by astrological birth signs (Gemini/Libra vs. all others) in Figure 5 from ISIS-2: Second International Study of Infarct Survival Collaborative Group, "Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2." The Lancet 13 August 1988, 349-360. Geminis and Libras benefitted disproportionately from placebo, as compared with the other signs, for whom aspirin was better. Presumably this analysis did not lead to a placebo new drug application, indicated for MI amongst Geminis and Libras only.

AIDS research. That mechanism, too, cannot see clearly. But it can be fixed, if scientists will start to design studies which can provide clear answers to important questions. It's long past time to turn over antiretroviral clinical trials to a new generation of scientists schooled by AIDS and eager to address the clinical complexities of AIDS competently, openly and honestly.

* * *



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Basic Research on HIV Infection:

A Report from the Front

Prepared by
Gregg Gonsalves

June 1, 1993

Acknowledgments

This report was made possible by generous grants from the **Red, Hot & Blue Foundation** and the **Royal S. Marks Foundation**.

The author would like to thank **Mark Harrington** and **Rich Lynn** who assisted in the final edit, and **Peter Staley** who handled the layout and printing of this report.

About TAG

Founded in January, 1992, the Treatment Action Group, or TAG, is the first and only AIDS organization dedicated solely to advocating for larger and more efficient research efforts, both public and private, towards finding a cure for AIDS.

TAG supports the work of approximately fifty treatment activists as they meet with researchers, pharmaceutical companies, and government officials, ensuring a voice for people living with HIV in the process of finding and accessing promising treatments. TAG's treatment activists, most of whom are living with HIV, strive to develop the scientific and political expertise needed to transform policy.

In 1993, TAG successfully lobbied for a radical restructuring of the management of our government's AIDS research effort. Our recommendations for change, first presented in 1992 at the International AIDS Conference in Amsterdam, were incorporated into the 1993 reauthorizing legislation for the National Institutes of Health. Through the creation of a powerful Office of AIDS Research, this legislation will finally provide for the coordination, strategic planning, and leadership that our government's AIDS research effort has lacked to date.

TAG is a 501(c)(3) tax-exempt organization, and can be reached by writing to 147 Second Ave., #601, New York, NY 10003, or by calling us at (212) 260-0300, or faxing to us at (212) 260-8561.

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Introduction

For over five years now, AIDS activists have focused their energies on clinical research and the drug development process, hoping to speed promising therapies for HIV infection to the people who need them. We have watched as AZT and then its cousins, ddI and ddC, have slowly crawled through clinical studies and on to the market. However, as the preliminary results of the British-French Concorde study have underscored, AZT and the other nucleoside analogues have only a limited usefulness.

Our efforts have not only been concentrated on treatments targeting HIV. In December of 1991, AIDS activists with ACT UP New York's Treatment and Data Committee launched a campaign, Countdown Eighteen Months, to expedite research on the opportunistic infections that affect people with AIDS and the development of treatments and prophylaxes for these conditions. More recently, Project Inform of San Francisco has enlisted prominent AIDS researchers to take part in its Project Immune Restoration, a think tank devoted to developing immune-based interventions for people with AIDS. Despite all our efforts, new treatment strategies are desperately needed for people living with HIV, yet there are few new drugs on the horizon.

In 1992, the Treatment Action Group commissioned a study of the AIDS research programs sponsored by the U.S. National Institutes of Health. While AIDS activists had scrutinized the clinical trials networks run by the federal government in excruciating detail, no one had ever taken a look at the entire portfolio of AIDS research activities being sponsored by the NIH. TAG issued its report on the NIH AIDS research program at last year's International Conference on AIDS in Amsterdam.

The report cited a lack of coordination and direction within the program as a whole, and proposed a sweeping reorganization in the management of the effort. In particular, the TAG report outlined a proposal for the strengthening of the NIH's Office of AIDS Research to serve as the central coordinating and planning body for all research on the disease throughout the NIH. TAG's proposal for the Office of AIDS Research, with the support of the Clinton administration, prominent extramural scientists, and members of Congress, has been included in the reauthorizing legislation for the NIH and will be signed into law in the near future.

However, even our best attempts to grease the wheels of clinical research and to bring a coherent management strategy to the administration of AIDS research as a whole will draw us no closer to a cure unless we make significant advances in our basic knowledge of its pathogenesis. Right now, we stand on the edge of a vast abyss of scientific ignorance which we must traverse if we are to develop rational therapies for HIV infection. The lives of millions of people worldwide hang in the balance. The world of basic research on AIDS is the final frontier for AIDS activists; it is here that we make our last stand.

We must forge a partnership with those scientists who have devoted their lives to studying the basic biology of HIV and the immune system and quicken the pace of discovery. This will demand new collaborative efforts and structures to link pathogenesis with clinical research.

The progress of science is often said to be incremental with as many advances developing out of serendipity as grow out of years of diligent experimentation (though controlled data are never cited to prove this assertion). The idea of accelerating the rate of scientific progress in AIDS research may therefore sound hopelessly naive. Nonetheless, TAG decided to ask thirty-six leading basic scientists working on AIDS in the United States to outline the scientific challenges for the field in the years ahead and the ways in which they thought their work could be better facilitated.

The following report is a synthesis of the comments of these researchers. It is intended to provide a survey of the state of basic research on HIV infection from the scientists at the bench. We also hope that the report will highlight the importance of the work being done. Unlike clinical research in AIDS, basic research has not had a powerful constituency to advocate on its behalf. The relevance of basic science to the lives of PWA's is far less apparent than clinical studies which hold the promise of proving a new drug's efficacy. Yet, new treatment options for people with HIV and a vaccine to protect the uninfected largely depend on the success of basic investigation. Finally, the report offers an assessment of the non-scientific obstacles confronting these scientists in their day-to-day work and practical recommendations to move these hurdles aside.

Materials and Methods

Thirty-six basic scientists working in AIDS were interviewed, in person or by telephone, during April and May of 1993. The majority of those interviewed were academic scientists affiliated with universities, medical schools, and teaching hospitals. The others interviewed were predominantly drawn from the ranks of intramural researchers at the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, NIH, with two others representing, respectively, industry and Department of Defense-supported research. The researchers interviewed work in a variety of disciplines, including virology, immunology, and molecular biology and have a wide range of specific professional interests. An attempt was also made to talk to both senior established investigators, as well as up-and-coming younger scientists.

Each researcher was asked to address two general topics:

1. The key scientific questions facing basic AIDS research, and;
2. The practical, non-scientific problems confronting their work.

While individual contributions to this project are acknowledged below, their specific comments will remain unattributed. The promise of a certain amount of anonymity provided a degree of candor in these discussions which may not have otherwise been achieved.

The report is divided into three sections. The first addresses the scientific issues brought up in the discussions; the second, the practical problems of most concern to researchers; and the third outlines some practical means of remedying the situation. While there was wide agreement on the importance of many scientific and non-scientific issues, no opinion was shared by all. A few topics strongly divided the scientific community sampled in this report. An attempt was made in this report to present both sides of the contentious issues as well as dissenting opinions where most agreed.

*

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Jay Berzofsky
Irvin Chen
Cecilia Cheng-Mayer
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Ronald Desrosiers
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Michael Saag
George Shaw
Gene Shearer
Robert Siliciano
Joseph Sodroski
Ralph Steinman
Mario Stevenson
Bruce Walker
Steven Wolinsky
Flossie Wong-Staal
Jerome Zack
Susan Zolla-Pazner

Part I: Scientific Issues

Three scientific areas were mentioned so often that they deserve to be recognized conceptually as encompassing many other points, and for these reasons we list them here first. Each area points to the need to take basic AIDS research from the pristine *in vitro* laboratory setting to more difficult, but critical, work with wild-type HIV isolates and clinical samples, often using *in vivo* settings with animal models or humans. After twelve years, we may "know more about this virus than any other in history," as researchers constantly chorus, but we yet lack the most crucial knowledge of all -- how it makes people sick.

Correlates of Immunity

The correlates of immunity to HIV infection -- both immunity protecting against infection after exposure, and immunity protecting against immune dysregulation after infection -- hold the key to designing effective vaccine and treatment strategies. These can be broken down into the cellular and soluble components of the cell-mediated and humoral branches of the immune system, and their interaction with HIV infection and other pathogens at all stages of HIV disease. Thus, many researchers interviewed asked a plethora of questions focusing on this labor-intensive, understudied area.

For example: What is the specific nature of the immune response one would hope to elicit in designing an effective prophylactic vaccine against HIV? Would one hope to evoke a strong neutralizing antibody response, a strong cytotoxic T-lymphocyte (CTL) response, a combination of the two or none of the above? Against which part of the virus would one hope this immune response would be directed: the outer sugary envelope of the virus, its capsid proteins, its RNA-bearing core, or yet some other viral component? What will protect against infection? Does infection most often result from cell-free or cell-associated HIV? Most who commented in depth on the topic agreed that a successful vaccine will induce a broadly-reactive neutralizing antibody and CTL response, although there were several individuals that stressed the importance of the latter in protection.

There were numerous specific questions raised regarding the nature of the correlates of immunity to HIV infection. The first group of inquiries focused on the humoral response to the virus, including: What is the extent of cross-reactivity and cross-neutralization by anti-HIV antibodies against various virus isolates? When protection is achieved, what parameters of antibody specificity and reactivity correlate with protection? Can protection be achieved against primary isolates as well as laboratory isolates? What is the difference in the way primary isolates and laboratory isolates are neutralized and why do they appear to have different levels of sensitivity to *in vitro* neutralization? Does antibody confer sterilizing immunity? Does antibody prevent against infection with

cell-associated virus? What is the extent of cross-reactivity and cross-neutralization between the five subtypes of HIV-1 that have been identified on the basis of sequence analysis? Which neutralizing antibodies, if any, will protect *in vivo*? Do anti-CD4 binding domain antibodies (or other antibodies to host proteins carried on the viral envelope) have a role in *in vivo* protection? Are there conserved epitopes for neutralization (if so, these will be critical in developing vaccines for worldwide use)? What, if any, is the *in vivo* role of enhancing antibodies to HIV?

The remaining questions in this area spanned a wide array of scientific and practical issues: Are there particular phenotypic virus variants which are important to target, such as macrophage-tropic, non-syncytium-inducing strains? Do immune responses to cellular proteins associated with the viral envelope offer *in vivo* protection? Is the type of helper T-cell response (TH1 vs. TH2) generated by immunization important in conferring protection? Can we generate protective immune responses using epitopes in *gag*, *nef*, or *pol* as targets for CTL or antibody? Do we need to know correlates of immunity to proceed with vaccine trials now? Can one protect against different strains, infection through mucosal routes and through cell-to-cell contact? What is the role of IgA antibody in mucosal protection?

"In Vivo Veritas"

One frequently mentioned issue that cut across virtually all of the scientific areas discussed was the need to move way from *in vitro* analyses of HIV infection and to start looking at the interaction of the virus with the complete host ("*in vivo veritas*"). By many accounts of the history of AIDS research offered by those interviewed, basic research on the disease began with a greater attention on the nature of the disease *in vivo*, but with the discovery of HIV, molecular analyses gradually superseded the earlier focus on the body. Many of the interviewees criticized the relevance of *in vitro* work ("pristine, beautiful, irrelevant systems"). In moving back towards an assessment of the disease *in vivo*, many recommended the use of primary isolates, cells and tissues in experiments, rather than tumor cell lines and laboratory strains of virus. Where clinical samples aren't available, many suggested taking greater advantage of animal models, particularly the SIV-infected macaque, in looking at questions of disease pathogenesis.

Many investigators wanted *in vivo* corroboration of data previously established *in vitro* or postulated on the basis of *in vitro* evidence, while many asked for *in vivo* answers to new questions. Some of the topics needing further investigation *in vivo* mentioned over the course of the interviews include: antibody and CTL responses to autologous virus; the quantitative CTL response; cell tropism of viral strains; cytopathic effects of the virus; the role of defective virions; rate of turnover of virus population; rate of the development of viral resistance to therapy; rate of viral spread within the host; mechanisms of CD4+ cell depletion; viral gene function in different cell types; virus-mediated dysregulation of macrophages and other antigen-presenting cells;

occurrence of syncytia; and localization of the virus in various tissues and organ systems.

The Pathology of HIV Infection

As a corollary to the increasing emphasis on the need for *in vivo* analyses, many researchers stressed the importance of developing a better descriptive profile of the pathology of HIV infection. Recent new studies have focused the attention of many of the researchers interviewed on the lymph node. These studies have offered a trajectory of lymph node pathology beginning with acute viremia, clearance from the peripheral blood by a strong host immune response; viral seeding of immune cells throughout the body and viral deposition on follicular dendritic cells (FDCs) in lymph node germinal centers; the progressive degeneration of the FDC network with an eventual spillover of virus back into the blood in late-stage disease.

The mechanism behind the destruction of the FDCs is unknown, although several researchers interviewed postulated killing of FDCs was mediated by CD8+ cells or cytokines (for some reason, no one postulated that antibodies might be involved, though the FDC-associated virions are coated with them). Since the FDCs in germinal centers may be T-cell dependent, their degeneration may be due simply to the progressive loss of CD4+ T-cells in the disease (the reverse may also be the case). Several researchers also pointed out that the fate of the lymph nodes in HIV infection was noticed by researchers early on in the epidemic, and that the current interest is a revival of an old concern.

In addition to the lymph nodes, researchers were interested in the pathology of HIV infection in the thymus, an important organ in T lymphopoiesis. The disruption of the thymic microenvironment and the infection of thymocytes and thymic epithelial cells by HIV could make the organ an important site in the pathogenesis of the disease. There is a virtual vacuum of knowledge about thymic function in adults, although bone marrow studies in cancer patients hold out the possibility that there is residual thymic function and an ability to reconstitute a functional immune system. Researchers were also concerned with the pathological effects of HIV in the brain, gastrointestinal tract, and in the bone marrow. In general, the researchers wanted to know where HIV is sequestered in the body: in what cell types, tissues and organ systems, at which stages of disease. Then, they wanted to know the virus's varying local effects.

Events in the Viral Life Cycle

Transmission. Many of the researchers interviewed had strong interests in sexual and vertical transmission of HIV infection. Several thought it was important to discern whether cell-free virus or HIV-infected cells are the primary vector of infection in sexual

transmission. Is there free infectious virus present in vaginal secretions or in the seminal plasma? Are spermatozoa themselves infected with HIV or carrying HIV bound to their surface? Are monocytes or macrophages in cervical-vaginal or seminal fluid infected with HIV? Why, twelve years on, are well-controlled studies of sexual fluids only now being initiated?

Other investigators were concerned with characterizing the nature of the viruses passed on from one person to another. Recent studies have reported that, within an individual, early in infection, sexually transmitted viruses demonstrate a relative homogeneity of envelope sequences, a tropism for macrophages and are non-syncytium-inducing strains. In addition, the strain transmitted usually represents a minor variant within the population of viruses of the person who transmitted the infection. What accounts for this effect? (This phenomenon appears to be at work in vertical infection as well.) Is there selective transmission or amplification of these strains? If there are preferentially transmitted strains, what are the implications for vaccine development?

The Viral Life Cycle. There was considerable interest by researchers in the various phases of the viral life cycle. In addition, many of the investigators interviewed mentioned in passing that it was critical to determine the mechanisms behind viral latency and activation. However, there was more active interest in the virus's needy relationship with the cell over the course of its residence.

Several researchers thought it was important to more finely elucidate the steps in viral uncoating and its dependence on cellular enzymes. One researcher commented that in a murine model of retroviral disease, infection is blocked at the level of uncoating in mice strains missing certain enzymes. Other researchers believed that the mechanism behind the transport of the preintegration complex to the nucleus was still relatively obscure. In particular, the way in which the preintegration complex negotiates its passage across the intact nuclear membrane of the cell remains to be clarified. Transport of the preintegration complex to the nucleus is also dependent on the cooperation of the cell. HIV can bind to and enter a resting(G_0) T-cell, but transport of the preintegration complex to the nucleus and integration of the viral genome is an ATP-dependent process which requires activation of the cell.

Several researchers stressed the importance of defining these early phases of the virus life cycle, especially for the development of therapeutic interventions. Others stressed that current therapeutic modalities (mostly attempting to inhibit viral reverse transcriptase) were of limited durability, and that therapy should be targeted towards chronically infected cells. Obviously it would be more useful to shut off viral replication at its source rather than to temporarily shield uninfected CD4+ T cells from new infection.

HIV also does not replicate in resting T-cells. The contribution of T-cell activation to the activation of HIV out of latency was also a concern of several researchers. Activation of

T-cells by antigens, mitogens, cytokines or with the help of the gene products of other viruses such as Epstein-Barr virus, cytomegalovirus, hepatitis-B virus, or herpes simplex virus can spur high levels of HIV replication, probably mediated by cellular transcription factors, including the NF-kappaB proteins, Sp1 and TFIID. In addition to T cell activation, macrophage activation by HIV or other antigens remains a critical area for future study.

Several researchers were particularly concerned about the adverse clinical implications of immune activation in HIV infection. Whether by secondary infections, HIV itself, or even by vaccination (including therapeutic HIV immunogens), immune activation may speed the progress of the disease. There is considerable interest in using *in vivo* models, such as nonhuman primates, to assess the role of selective immune inhibitors in delaying or preventing retrovirally-mediated immune destruction.

Envelope Structure and Function. The envelope of HIV is obviously of critical importance in the virus' interaction with the immune system. The researchers interviewed were particularly concerned with the envelope's role in dodging immune surveillance, in facilitating viral entry into cells, in viral cytopathicity, and in viral tropism for different cell types.

The role of the virus' envelope in the failure of the humoral response to HIV infection was a strong focus of several researchers' comments. Some said that HIV's envelope glycoproteins do not elicit strong antibody responses (although there are those who maintain the opposite). Some have had trouble measuring consistently high titers of neutralizing antibody even to autologous virus over the course of infection. Antibodies that do develop must contend with the high variability of the viral envelope which allows the virus to escape their recognition.

A number of researchers interviewed are attempting to more clearly define the structure of the envelope and the regions, both variable and conserved, responsible for key steps in infection, such as viral binding with the CD4 receptor and fusion with the cell, including delineating the conformational changes associated with interactions with various cell types. Others are trying to assess the maximum allowable variation in the envelope permissible for infectivity and its underlying conserved structural properties. Most researchers interviewed stressed the importance of work of this kind for the development of a vaccine and possible therapeutic strategies.

The envelope's role in viral cytopathicity and in the development of pathogenic strains was also an object of concern among the investigators. The envelope glycoproteins may be important in mediating direct killing of CD4+ cells either by syncytium-formation or by the accumulation of gp120-CD4 complexes within the cell's organelles. Indirect immunopathology may be mediated by soluble envelope proteins or by defective, replication-incompetent virions still able to transduce inappropriate signals to uninfected CD4+ T cells. In addition, the Dutch work on macrophage-tropic, non-syncytium and T-cell-tropic, syncytium-inducing strains described above has identified a correlation

between these phenotypic variants and changes in the structure and charge of the viral envelope. The development of more highly pathogenic forms of the virus during the course of infection, as well as the tropism of the virus for different cell types may therefore hinge on characteristics of the virus's outer shell.

Mechanisms of Viral Persistence. Earlier assays of HIV replication and burden in the blood originally led researchers to believe that there was minimal viral replication throughout much of the course of HIV infection. Now, with more sensitive detection methods, it has been shown HIV is a chronic viral infection with measurable viral replication at all stages of disease. Unlike other viral infections, it now appears that HIV is never completely latent within an infected host, although at any given time most infected cells are not replicating virus. This implies either that a few chronically infected cells are manufacturing most of the virus measured, or that virus cycles rapidly through CD4+ T cells in short lytic infectious bursts.

How can either mechanism survive the apparently vigorous initial immune response? Very early on in HIV infection the immune system mounts a potent, multipronged attack on the virus; starting, it seems, with a cell-mediated response which is joined soon after by a humoral response, including the development of neutralizing antibodies. How does HIV persist and replicate at such high levels in an apparently immunocompetent host? In a related question, if HIV, a cytopathic virus with a tropism for CD4+ cells, is so successful at replicating at high levels right under the nose of the immune system, why is the course of HIV disease so often protracted, variable, and slow?

These questions raise the issue of which cells and tissues serve as reservoirs for HIV. (Although the recent lymph node work has shown virions attached to FDC processes, no one is implying that the FDCs are producing HIV -- it most be coming from elsewhere.) Several researchers postulated a central role for the macrophage in the mechanism of viral persistence. One individual went as far as to say that HIV infection is a monocyte/macrophage disease. Some researchers report that the macrophages of primates who develop retroviral immune dysregulation (such as humans with HIV and rhesus macaques with SIV) are infected with these viruses, while primates which do not become sick (chimpanzees with HIV or African green monkeys with SIV) do not experience macrophage infection (others dispute this).

This, if true, implies that to cause disease, HIV or SIV must replicate in both CD4+ T cells and in macrophages. Still other mammalian retroviral diseases depend on dysregulating multiple arms of the immune system (e.g., MAIDS is a T cell dependent B cell disorder). Recent studies have suggested that macrophage-tropic, non-syncytium-inducing strains are selectively transmitted in the passage of HIV infection from one person to another. Once transmission occurs, HIV may use the macrophage as a "Trojan Horse" to disseminate itself throughout the body and as a reservoir of heavy viral production. Indeed, some studies report large numbers of viral particles localized almost exclusively with intracellular vacuoles in macrophages, with little or no virus detected at the plasma membrane. With little virus at the surface of the

cell, the infected macrophage may be able to produce large amounts of virus without being "seen" by the immune system. Release of infectious virus and infection of other macrophages and T-cells can occur upon some event that perturbs macrophage function. Other immune cells, such as skin Langerhans cells and blood dendritic cells, may play a role in fostering viral persistence as well, though further research here is required.

Clearly, the immune system is able to control HIV replication to some extent for some period of time, which accounts for the slow progression of the disease in most cases, yet it is not able to eradicate it once infection has taken hold. The researchers interviewed stressed the need for studies of the natural history and pathology of HIV infection to elucidate the mechanisms of viral persistence. We need to know where HIV goes when it enters the body, where and how it hides from the immune system, what cells is it killing, and what cells are producing virus.

Events in the Host Life Cycle

Exposed, but Uninfected. There are two other unique cohorts of individuals that the interviewees thought deserved special scrutiny: those people who show signs of exposure to HIV without detectable infection, and those people who are extremely likely to have been exposed to the virus, yet remain uninfected. The first set of individuals includes gay men and intravenous drug-users who have continued to practice high-risk behaviors as well as health care workers who have received accidental exposures to HIV. They all remain seronegative, yet their helper T-lymphocytes proliferate or produce IL-2 in culture in response to HIV envelope peptides. The second set includes gay men who have continued to engage in unprotected sex and a cohort of Kenyan sex workers who have done the same, with members of both groups remaining seronegative. (Perhaps the most common group of individuals who may have been exposed to HIV, yet do not become infected are the two-thirds or so of initially HIV-antibody positive children born to HIV+ mothers who serorevert some months after birth. However, this cohort has characteristics distinct from the others and is really a separate case.)

The researchers interviewed thought the lymphocyte proliferative responses and IL-2 production seen in response to viral peptides in HIV- individuals needed further confirmation in other experimental systems, in larger numbers and perhaps in an animal model (these findings have apparently been confirmed in a monkey model). If there is indeed exposure to HIV in either cohort of people, there are a number of hypotheses to account for the phenomenon.

There may be a low level infection present undetectable with the methods used in these studies. It is also possible that these individuals may have some sort of genetically determined resistance to infection. The persistently seronegative individuals in the

Kenyan Sex Workers Study actually share common HLA alleles (Aw28, Bw70). One researcher interviewed offered the hypothesis that these individuals might have been immunized by defective virus. Lastly, it is conceivable that these individuals have mounted a successful and sterilizing immune attack on the virus, perhaps through the agency of CTL's. Certainly HIV-specific CTL precursor frequencies in exposed, uninfected persons should be compared with those in low-risk seronegative persons.

Acute HIV Infection. Although the importance of natural history studies was stressed throughout the interviews, there was a particular interest in the initial phase of infection for many researchers. In acute infection, which is sometimes marked by flu-like illness, high levels of virus are detectable in the peripheral blood. However, within several weeks, this acute viremia subsides. The mechanism by which virus replication is brought under relative control in acute infection was the primary focus of the comments on this topic.

Several researchers made reference to recent data suggesting that CTL responses to the virus are responsible for its control in acute infection. A early rise in HIV-specific CTL responses has been observed in several individuals and correlates well with the initial reduction in viral load. Neutralizing antibody responses specific for the infecting strain occur later and after the viremia has ebbed. However, one researcher postulated that antibody may still be involved in controlling initial viremia, but not detectable in serum and bound to cells.

While additional studies of acutely infected persons will be important, such persons will be difficult to identify, and the public health impact of such early monitoring will remain elusive as long as this remains the case. Indeed, it is still unknown what proportion of initially-infected persons display the acute clinical syndrome, since those without symptoms will not present for medical surveillance. The symptoms themselves are far from HIV-specific, and could reflect virtually any acute viral episode, and questions such as whether those without symptoms experience viremia will remain hard to assess. This area is ripe for intensive studies using primate models.

Long-Term Non-Progressors and Long-Term Survivors. Most individuals with HIV infection experience a gradual decline in CD4+ cells over a period of time with a deterioration in clinical status accelerating as CD4+ cell counts drop below 200/mm^3. There is a small group of individuals, however, who have not experience a drop in CD4+ cell numbers even a decade or more after infection with HIV and another group that despite having very low CD4+ counts have remained clinically stable for three years or more. These two cohorts of individuals have been dubbed "long-term non-progressors" and "long-term survivors" of HIV infection. Two years ago, TAG members began a drive to get the Division of AIDS, NIAID, NIH to sponsor studies of these unique populations. This year, the Division of AIDS held a conference on the topic.

Many of the researchers interviewed suggested that both cohorts of individuals merited intensive investigation. Others described actual experiments being planned within the Multicenter AIDS Cohort Study (MACS) in the U.S. on matched "triplets" of those who manifest no, average, and rapid immunological progression. The experiments will look at CTL responses, comparatively, using different targets, different strains; lymph node pathology; antibody responses; natural killer (NK) cell activity; suppression of HIV by a putative novel soluble factor secreted by CD8+ cells; viral load; rate of viral mutation; genotype and phenotype of viruses; HLA alleles associated with protection or progression; and other parameters of interest.

Others spoken to had firmer opinions on the correlates of long-term survival. Several individuals postulated the existence of naturally attenuated strains of HIV based on a cohort of long-term survivors in Australia who were all infected with the same isolate. Other hypotheses advanced included CD8+ cell-mediated suppression of HIV and the possibility of the retention of key certain CD4+ cell subsets in long-term survivors with low CD4+ cell counts but without clinical progression.

Mechanisms of CD4+ Cell Depletion. How CD4+ lymphocytes are destroyed *in vivo* during HIV infection was the topic most frequently cited by the researchers interviewed as one of the key unanswered questions in basic AIDS research. The hypotheses offered ranged from those who believed the direct cytopathic effects of the virus alone ("its the virus, stupid") were responsible for CD4+ cell loss to those who maintained that CD4+ cells are killed by indirect effects of the virus or by the immune system itself ("AIDS is a virus-induced immunological disease"). However, most researchers settled on a middle ground maintaining the possibility or likelihood of a multifactorial etiology for CD4+ cell decline in HIV infection.

Those who maintained that direct cytopathic effects of the virus alone are killing CD4+ cells referred to recent work from the laboratories of Shaw, Fauci and Wolinsky, respectively, that have identified higher levels of viremia in the peripheral blood and lymph nodes and a greater number of infected CD4+ cells than previously believed. (Of note, however, in the first mentioned paper, only 1/60,000 plasma virions appeared to be infectious, implying that most were defective, and thus incapable of direct infection or subsequent cell killing.) The direct cytopathic mechanism which may be responsible for cell death was not often discussed, but those postulated included single cell lysis upon viral budding through the cell membrane, lysis after accumulation of circularized viral DNA intracellularly, and the accumulation of intracellular CD4-gp120 complexes. Syncytia formation between infected cells bearing gp120 on their surface and uninfected cells via CD4 was also mentioned as a possibility.

Several researchers entertained the possibility that the immune system itself may participate in CD4+ T cell depletion through one of several mechanisms. For example, CD8+ T cells may be killing uninfected CD4+ cells -- either because the uninfected cells have bound soluble gp120 onto their CD4 receptors, or because the immune system responds to cellular proteins on HIV's envelope, and then mounts an attack on the cells

whence the virus emerged, e.g., the CD4+ T cells themselves. The role of CD8+ T cells remains controversial. Some hypothesized that CD8+ cells are mainly protective, either using MHC class I restricted HIV-specific CTLs, or by releasing a putative cytokine which inhibits HIV replication. Others maintain that some CD8+ cells are immune suppressive and inhibit cell-mediated immunity. Some postulate that CD8+ cells may be involved in lysis of uninfected CD4+ cells or of thymic and follicular dendritic cells.

Detailed immunopathologic studies with *in vivo* samples from HIV-infected persons at all stages of disease will be required to answer these questions. Technologies for detailed subset analyses of lymphocytes and the other arms of cell-mediated immunity remain at a primitive state in comparison with antibody studies, and substantial investment will be required to bring this critical area up to speed.

The potential of aberrant cell signalling leading to programmed cell death or apoptosis of CD4+ cells was another topic often brought up. The primary hypothesis advanced is that HIV gp120 or gp120-antibody complexes can inappropriately prime T lymphocytes through the CD4 receptor to undergo apoptosis upon restimulation by antigen through the T-cell receptor (TCR). (This hypothesis does not address the fact that most T cells never meet their antigen, and thus does not explain why all CD4+ T cells are eventually depleted.) Variations on this hypothesis proposed that MHC class II proteins associated with the viral envelope and/or portions of the envelope itself acting as a superantigen can inappropriately activate CD4+ cells, leading to programmed cell death. Finally, some hypothesize that HIV-mediated signals result in a state of antigen unresponsiveness (anergy) which allows antigens to escape immune surveillance, leading to CD4+ cell killing.

Immune Dysregulation. HIV infection induces a spectrum of profound immune dysregulation as well as its hallmark depletion of CD4+ cells. One researcher interviewed has often said she thinks AIDS would be more accurately called an acquired syndrome of immune-dysregulation, rather than immune deficiency because some functions of the immune system are clearly debilitated, but others are performing with wild abandon. The researchers interviewed stressed the importance of a wide selection of the immune abnormalities seen in the disease, involving a broad range of cell types and tissues.

Several researchers were interested in the mechanism behind early defects in CD4+ cell function, which include the inability to respond to recall antigens such as tetanus toxoid and influenza A virus, to alloantigens and to mitogens. Each of them postulated a different cause of these defects: the selective killing of memory (CD29+) T-cells by HIV; defects in antigen presentation by antigen-presenting cells; and active immune suppression mediated by cytokines.

Another immunological abnormality characteristic of HIV infection is the polyclonal activation of B-cells and an attendant hypergammaglobulinemia. Several researchers

were interested in the origin of the B-cell disorders in HIV infection and their contribution to the pathogenesis of both the lymphomas seen in AIDS and the primary immune dysregulation of the disease. In this regard, it is striking that the HIV isolated from lymphoid tissue localizes to the B cell rich germinal centers, where the virus may elicit cytokines (e.g., IL-4, IL-6, IL-10) which contribute to a B cell activation cycle, possibly leading in some cases to malignant transformation of B lymphoblasts and later lymphomas. If MAIDS is a T-cell dependent B cell disease, perhaps, one investigator suggested, AIDS is a B-cell dependent T cell disease.

Further immunopathological studies correlating immune activation (including cytokine expression, and cell subset populations) with HIV progression will shed light on the role of inappropriate immune activation on the pathogenesis of AIDS.

The derangement of lymphopoiesis in HIV infection was another topic that recurred several times throughout the interviews. Several researchers wanted to know why the immune system is unable to reconstitute the CD4+ cell population. Where is the defect? Are stem cells or thymocytes infected? How does the immune system monitor the level of lymphocytes in the body? What is the signal which spurs the production of new lymphocytes? Is the rise in CD8+ cell population seen in the disease a byproduct of the immune system's attempt to compensate for the ongoing loss of CD4+ cells by producing more lymphocytes? Isolating the interruption of lymphopoiesis -- at the level of the bone marrow, the thymus, or the peripheral lymphoid tissue -- will be critical in devising strategies to protect and reconstitute the immune system.

In addition to a descriptive profile of the pathology of HIV infection, several researchers suggested we specifically need a profile of the immunopathology of the disease. We do not yet have a clear picture of the activity and function in HIV infection of each of the different types of cells and tissues that make up the immune system. Such work will be difficult, expensive and labor-intensive. Substantial resources and ingenuity will be needed to ensure that this critical area receives the attention it deserves.

The Final Phase of CD4+ Cell Decline. The pattern of CD4+ cell loss in HIV infection rarely proceeds in a straight downward-sloping line. In fact, two sets of investigators, one with the Multicenter AIDS Cohort Study (MACS) in the U.S. and the other with the Amsterdam Cohort Study of HIV Infection and AIDS in Homosexual Men in the Netherlands, have noted a biphasic decline. According to the Dutch group, until eighteen months or so before developing AIDS, the number of CD4+ cells declines slowly and continuously. After that point in time, CD4+ cell loss occurs at a rate three to five times faster than before.

Many researchers interviewed were interested in the cause of the second, precipitous decline in CD4+ cells. The Dutch have hypothesized a correlation between the second phase of CD4+ cell decline with the emergence of high-replicating, T-cell tropic, syncytium-inducing (SI) strains of virus which overgrow low-replicating,

macrophage-tropic, non-syncytium-inducing (NSI) strains. In feline leukemia virus (FeLV), a similar shift from low-replicating, less cytopathic to high-replicating, more cytopathic viral variants precedes the onset of the symptomatic phase of disease. While a shift from NSI to SI viral strains often seems to coincide with the shift from asymptomatic to symptomatic disease in HIV infection, it is not always the case. People die with AIDS without SI viruses. In addition, recent experiments using the SCID-hu mouse model have shown that viral isolates which are macrophage-tropic and non-cytopathic in *in vitro* assays can induce a rapid decline in CD4+ cells *in vivo*, while highly cytopathic *in vitro* strains can induce a restrained decline in CD4+ cell numbers.

While many of the researchers interviewed were interested in the *in vivo* evolution of pathogenic strains and its correlation with clinical progression, others postulated an immunological event as the trigger of the final, rapid decline in CD4+ cells. (For example, thymic or lymphoid involution might mark the end of the immune system's ability to contain HIV, resulting in renewed viremia and final destruction of CD4+ cells in the periphery.)

In particular, several researchers hypothesized that before the onset of symptomatic disease there is a switch in the nature of the T-helper lymphocyte response from a TH1 to a TH2 state. A TH1 response is carried out by clones producing IL-2 and IFN-gamma and preferentially mediates CTL activity. A TH2 response is carried out by clones producing IL-4, IL-5 and IL-10 and preferentially mediates antibody responses. Cytokines produced by TH1 clones can downregulate the cytokines produced by TH2 clones and vice versa. When TH1-mediated CTL activity is downregulated, HIV escapes immune control and virus is allowed to grow relatively unchecked. While provocative, the TH1/TH2 hypothesis needs further confirmation in human, rather than murine, studies. In addition, the contribution of other pathogens (e.g., herpesviruses, parasites) to TH1 or TH2 immune states needs further investigation.

In sum, it is apparent that ambitious new efforts need to be carried out to correlate insights on HIV's behavior in the test tube with its behavior in the bodies of infected people. The mechanisms of CD4+ cell depletion *in vivo* are the critical events which must be explained in order to delay progression to AIDS, and the multivalent nature of the damage to the immune system must be defined if immune reconstitution is to become a possibility. Researchers are enthusiastic about attempting to conduct basic research in a more clinically relevant fashion. Meeting this need will be a major challenge for the administrators of AIDS research over the coming years.

Part II: Events in the Researcher Life Cycle

The Funding Crunch

Far and away the most often cited topic by scientists was the crisis in funding of basic research. There was a level of chronic, serious demoralization on this issue among the extramural researchers interviewed, which bodes extremely ill for the future of basic research on AIDS.

Most researchers are spending between 30-40% of their time writing grants. In one lab, six out of seven M.D./Ph.D.s were busy writing grants at the time of these interviews. Another researcher submits between one to four grant proposals for each of the review cycles for AIDS (January, May, September) in addition to responding to Requests for Applications (RFAs). Still, this individual is downsizing their laboratory. This person's concerns about funding have "tripled over the past two years." Many researchers complained that instead of writing papers or planning experiments with graduate students of post-doctoral fellows, they are forced to spend much of their time trying to solicit funding. One researcher put it plainly and said the constant, grueling search for funding adversely effects the quality of research.

In addition to believing that too much of their time is taken up with searching for financial support for their laboratories, many researchers feel as if they can't count on support from one year to the next. With increasing numbers of people entering the field and funding levels remaining stable or decreasing slightly, the competition for funding has become intense.

One researcher said it is no longer enough to be an excellent scientist. Many of those interviewed, some being current or former members of study sections, believed that the there was no qualitative difference between the top 20-30% of grant applications and the top 10%, except that only the top 10% or so gets funded. The competition for funding is so acute that many believe the peer review process has increasingly resorted to finding minor, often irrelevant excuses to send grants back for revision, or to reject them altogether.

Many laboratories are being forced to scale back research plans, putting off hiring post-doctoral fellows, and letting go of technicians. The funding crisis in basic research is affecting both the younger, up-and-coming scientists and the more senior, well-established researchers. One senior investigator commented that they had a program project grant for $500,000 for four years, but it is split between five researchers to keep the laboratory going.

Needless to say, Congressionally-imposed pressure on universities to account for and cut back on indirect costs is resulting in a climate of fiscal contraction throughout the nation's biomedical research infrastructure. Another Washington-imposed headache results from Congress' reluctance to fund much-needed construction of new laboratory facilities, which means that many AIDS researchers work in inadequate, antiquated facilities.

Clearly, the present climate is inhospitable to basic research, as one scientist described the situation. Too much time is devoted to writing grants, the competition for research dollars makes each funding cycle a game of chance rather than competence, and there is simply not enough money around to adequately support the current scientific infrastructure. Some scientists are leaving academia for industry, where their research can be sufficiently and consistently supported. Younger researchers are being discouraged from pursuing a career in science at all. Of course, these problems are not unique to AIDS research and mirror the state of basic biomedical research as a whole.

However, in the case of AIDS, the lack of adequate support for basic research has grave implications for the development of a cure for the disease and a vaccine for the uninfected. In the current fiscal climate in the U.S., it will be difficult to secure additional funding for biomedical research. Yet our failure to support basic research on AIDS and other diseases will have a devastating impact on the health of our nation and its economic future.

The Future AIDS Researchers of America

The first generation of AIDS researchers were scientists who had already established their careers working in related fields. Several researchers interviewed believed that because of recent trends there may be a shortage of highly talented AIDS researchers in the U.S. in the years ahead.

In particular, one researcher who is involved with his university's M.D./Ph.D. program is concerned with the decreasing number of U.S. students in graduate science programs. Many Ph.D. candidates in biomedical science are foreign students, some of whom intend to return to their countries of origin after completing their education, while others are becoming indispensable to the U.S. research and health care system. Another scientist, who is the director of his medical school's training program, worries about the caliber of U.S. students entering the program in recent years. Both researchers believe that the infrastructure of American science is in a precarious state. (It's the education system, stupid!) Without a steady source of talented young scientists, biomedical research in the U.S., once the finest in the world, is headed for a period of decline.

Researchers see several reasons for the problems facing graduate science education in the U.S. First, the current problems facing the field, particularly around funding, have

made the profession less than attractive to young students. As one researcher put it, "People are suffering in basic research...you give up almost everything but your family for science, and then you're jerked around by bureaucrats... Budgets are flat, when labs should be growing." Science education, especially the M.D./Ph.D. programs, is expensive. M.D./Ph.D. candidates are ideally situated to carry out the synthesis of basic and clinical research which many scientists believe holds the key to progress in the future. One researcher estimates the average cost of training an M.D./Ph.D. student at $200,000-$300,000. Thus, support for these programs is hard to come by. One researcher said the NIH subsidizes only five out of twelve M.D./Ph.D. candidates at his university. Several scientists thought the pharmaceutical industry should be approached to financially support graduate scientific education through donations to universities.

Pilot Grants

Several researchers also suggested a new system of pilot grants in basic AIDS research to be funded by the NIH. The purpose of these awards would be to encourage the work of junior researchers in AIDS; to entice senior investigators in related fields to pursue projects in AIDS research; to encourage the pursuit of novel, "risky" approaches; and to encourage work in neglected areas of research.

The awards might amount to $100,000 per year and would involve a short, simple application followed by an expedited peer review process. Several scientists suggested that the American Foundation for AIDS Research (AmFAR) might consider shifting its basic research portfolio to accomplish some of these goals.

Investigator-Initiated Research

The NIH's R01 award, the investigator-initiated grant, is the primary funding mechanism for much of basic research. Most researchers interviewed thought that the number of R01 grants awarded in AIDS, currently around 12% of the total number of submitted applications, needed to be significantly increased. As was mentioned above, the top 10% and top 20-30% of applications were thought to be indistinguishable in quality.

Researchers interviewed believed the R01 was the most successful and productive mechanism for supporting basic research. In addition, the R01 was thought to be a comparatively good bargain. For example, the recent $20M appropriation for a large simple trial of therapeutic vaccines in HIV infection could support approximately 50 R01 awards. Suggestions were also made to shorten the length of the proposals and to extend the awards from three to five years.

Block Grants

Several researchers thought that a new mechanism was needed to fund basic research on AIDS which would provide a single source of significant and consistent funding to fully support the most productive researchers in the field for up to five years at a time. The primary model raised for this new mechanism was the British system of five-year program grants in AIDS. The awarding of these block grants would be done strictly through a peer-reviewed process, with funded investigators returning to the applicant pool at the expiration of their award. However, their was a dissenting voice on this matter, one researcher thought scientists receiving these grants would become "fat and lazy."

Perhaps AIDS research could adapt a model successfully used in the academic setting. Currently, The Howard Hughes Medical Institute funds researchers at approximately 50 sites around the U.S. in basic biomedical science. Researchers are supported for either three, five or seven years. Investigators and their labs are fully supported for these periods of time. Researchers are characteristically up-and-coming scientists in their thirties, and are chosen by the Institute. Applications for these awards are neither solicited nor accepted. The Institute currently favors non-disease-specific work in genetics, cell and structural biology, immunology and neuroscience. Several researchers interviewed thought it would be useful if the Institute would consider initiating a program in basic AIDS research.

Peer Review: the Good, the Bad and the Ugly

While most researchers interviewed thought that peer review was the best and fairest method for selecting which scientific proposals merited funding, many scientists had harsh words for the current state of the process. In particular, many investigators questioned the competence of some study section members. Often the individuals sitting on study sections were criticized for lacking knowledge of the most pressing issues in AIDS research or for having little experience with the field at all. In addition, some thought that study section members were frequently not senior, well-respected scientists.

The intensely competitive funding environment has also put a strain on the peer review system which is forced to justify the rejection of excellent applications simply because there is not enough money to go around. A vicious cycle has been created where those whose grants were rejected on the basis of minor or irrelevant points do the same to others when they are sitting on a study section.

On a constructive note, several researchers suggested that peer review incorporate appraisals of productivity into the decision-making process. Looking at researchers'

track records would help insure that grants were supporting the most fertile minds in the field.

Big Science vs. Little Science

Much of basic research is supported by the relatively small R01 grant. It was not surprising then that many of the basic researchers interviewed looked to the larger AIDS research programs run by the NIH as a source of wasteful spending. However, their criticisms were often justified and merit serious attention.

There was extremely strong concern among many of the researchers interviewed about the NIH's HIV vaccine evaluation program. In particular, the new PAVE (Preparation for AIDS Vaccine Evaluation) program which is preparing the infrastructure for both domestic and international large-scale efficacy trials of prophylactic HIV vaccines, was thought to be a grossly premature endeavor. Many of the scientists thought we were far from having a viable candidate immunogen for testing, and some doubted that we ever will. It was commonly felt that pushing for large-scale testing of vaccines at this point was motivated primarily by political considerations and had little basis in scientific reality.

The AIDS clinical trials networks run by the NIH were also a source of great consternation among the basic scientists. The AIDS Clinical Trials Group, NIAID, was singled out as an expensive, inefficient, unproductive, colossal mess. There was a general feeling that the system was unreasonably large, with 35 adult ACTUs alone, and that the studies being conducted were often of little scientific value or clinical significance. Several of the researchers interviewed thought that the ACTG should be scaled back and that pharmaceutical companies should either take responsibility for clinical trials of already approved agents or offer some form of financial support for the studies within the ACTG.

The Women and Infant Transmission Study (WITS) was also a target of special scorn by several researchers. Apparently, a majority of the samples stored by the WITS were improperly cryopreserved and are useless. Thus the large investment of resources into this epidemiological cohort study has gone to waste.

Despite the importance of animal models, the Regional Primate Research Centers (RPRCs) were thought to be ill-equipped to conduct AIDS research. In addition, the RPRC principal investigators keep a tight reign over use of their monkeys and the RPRC's charge researchers unaffiliated with their centers $2,400 per monkey with a $4.60 per diem surcharge.

The researchers interviewed were split over the usefulness of the Centers for AIDS Research (CFAR) program. Those interviewed who were not at a Center questioned

the program's productivity as a whole, while those who were part of a Center admitted that some of the CFAR's were not performing up to par.

Although these researchers' appraisals of many of the larger research programs were harsh, the criticisms are largely true. While no one questions the necessity for some of these programs, there is a serious need to rigorously evaluate their productivity and base future funding on their performance. Basic researchers clearly feel that they are held to a higher standard when it comes to funding and only wish that "everyone was judged by the same yardstick." Basic researchers might feel better if there was some effort made by NIH to streamline clinical research and ensure that clinical trials were both efficient and relevant. Clinical trials might even become useful sources of material for basic researchers, if there were a mechanism in place to link up the disciplines.

The Decline of Molecular Biology

Enormous strides have been made in understanding the molecular biology of *in vitro* strains of HIV over the past decade. The HIV genome was sequenced and cloned; its proteins synthesized and studied in many model systems. Now, there is a growing feeling that molecular biological studies of the virus have often become an end in themselves with little concern for their own significance *in vivo*. While many researchers outlined areas of viral gene expression which are still not fully understood, others thought their might be an overemphasis on the study of the regulatory genes of the virus, and that we are seeing diminishing returns from studies in this area. Many thought molecular biologists need to be prodded into working with clinical materials and animal models where possible to expand the relevance of their insights.

The Rise of HIV Immunology

With a growing emphasis on *in vivo* analyses of the pathogenesis of HIV infection, there is a growing coolness among researchers to solely molecular approaches. Along with this shift, there seems to be an attempt to redress previous imbalances in research priorities. Several researchers commented on the relative lack of attention in basic research on AIDS to the immunology of the disease and the host response to the virus.

As an example, one researcher pointed to the small amount of time devoted to immunological topics at the major basic scientific meetings on AIDS in the U.S., such as the Keystone Symposia. Others lamented the absence of the U.S.'s top immunologists from AIDS research, and wondered how they might be enticed into taking on some critical aspects of HIV disease. Perhaps fundamental immunologists are too comfortable with the highly artificial use of inbred mouse models to deal with polymorphic humanity.

Many scientists felt that studying the immunology of the disease and the host's response to the virus was technically exacting and that investigators have shied away from this kind of work. As one research put it: "People study what's easy to study and molecular virology in tissue culture is relatively easy. HIV immunology is hard to do, you can't manipulate a chimp like a piece of DNA." Another researcher, in discussing the difficulty of CTL assays, compared the practice of cellular immunology to the work of an artist. In addition, the complex nature of the immune system and the limits of our current knowledge of its workings make the study of the immunology of AIDS a daunting task. Yet, many researchers interviewed thought that a new emphasis needs to be placed on the host response in the coming years.

Collaborative Efforts: New Ways of Working

Many researchers interviewed made a strong point of their opposition to and the limited usefulness of directed research. Yet, many researchers also made it clear that new ways of working, especially those stressing collaboration, might have a place in basic AIDS research. Several investigators made it clear that the current scientific culture is not well-predisposed to cooperation and teamwork, but thought it was important to start bringing researchers together within single institutions and between different institutions; within single areas of emphasis and between related fields.

Two models of a collaborative effort arose in these interviews: the Manhattan Project and the Ariel Project. The Manhattan Project, of course, was the massive development effort undertaken by the U.S. to build the atomic bomb during World War II. Activists and researchers are still awaiting a coherent explanation of how the World War II nuclear physics model can be applied to the post Cold-War biomedical problems we now face. While one researcher interviewed was an adamant booster of a Manhattan Project for AIDS, another commented "A Manhattan Project for AIDS scares me: the same people in charge with more power is frightening."

The Ariel Project to Prevent Transmission of HIV from Mother to Infant is a more recent endeavor sponsored by the Pediatric AIDS Foundation. The model of The Ariel Project, however, had wide support among several researchers. This collaborative effort to elucidate the virological, immunological and clinical mechanisms of vertical transmission was praised as bringing researchers together to work on well-defined topics while retaining individual initiative. One researcher said The Ariel Project "points in a direction, rather than directs."

There were other suggestions for fostering collaborative relationships between researchers. Several investigators stressed the importance of funding scientists in their own environments, but thought it would be a good idea to bring them together on a regular basis, perhaps in small regional meetings on specific topics, to compare notes, to brainstorm, to hash out what we really know and don't know about the issue at hand.

A few researchers thought the NIH program project grants and centers programs were useful mechanisms for promoting collaboration within institutions. Finally, some suggested that NIH could foster collaboration between institutions by funding individual researchers as part of consortia in certain scientific areas -- as is already widely practiced in applied research programs such as the National Cooperative Drug Discovery Groups, National Cooperative Vaccine Development Groups and the ACTG.

Cross-Pollination

Many investigators interviewed thought that basic AIDS research could profit from greater interactions with work being done in related fields. In particular, several researchers wanted to see a greater effort made to entice basic immunologists into working on AIDS, perhaps by offering individual scientists pilot grants as described above, or by setting up AIDS programs within the nation's best immunology centers. Several researchers thought the vaccine development effort would be enhanced by involving scientists working on human genital tract and mucosal immunology or vaccines against other sexually-transmitted diseases.

Researchers also thought new advances in understanding HIV gene expression and the mechanisms of viral latency and activation are going to need to turn to the work of scientists studying the cell cycle and cellular gene expression. Others thought we could learn some lessons about HIV from looking at other viral diseases. For instance, Mason-Pfizer Monkey Virus induces a lymph node pathology similar to the one seen in HIV, yet MPMV does not target the CD4+ cell. Are there any common pathways in the two infections that might lead to the same effect?

National Network of Tissue and Cell Repositories

Several researchers expressed concern at the difficulty of acquiring clinical samples for basic research. Many basic researchers have little or no contact with the clinical setting. In addition, the collection of clinical material other than from a blood-draw, such as lymph node tissue, is hard to get. Retrieving specimens from special populations, such as long-term survivors or those individuals presenting with acute infection, are especially difficult. Obtaining samples from the epidemiological cohort studies run by the NIH is reported to be an arduous task, and, as is the case with the WITS, the quality of the material is not assured.

As a solution, several researchers suggested the institution of a national tissue and cell repository system with strict quality control procedures. However, supplying basic researchers with clinical samples is only half the solution. Basic researchers will have to learn how to collaborate with clinical researchers and real live infected people if this is to work.

From the Bench to the Clinic

Several interviewees hope for faster translation of new laboratory insights into clinical settings. Current clinical trial mechanisms do not provide for such a fast-track setting. Many agents currently under study both for vaccines and for therapy reflect the outdated insights of five or six years ago.

There was little agreement though on who should provide the support to help translate the insights of basic research into clinical applications. Some thought that pharmaceutical companies need to take a greater interest in developing therapies based on rational drug design strategies because they have the development capacity which academic labs don't have. Others believed that the large pharmaceutical houses also needed to become involved in vaccine development, which has been the province of small biotechnology firms thus far. However, several researchers said that the pharmaceutical industry was unlikely to follow risky, innovative approaches (e.g. live, attenuated HIV vaccines) and that the government needed to expand both its drug and vaccine development efforts, including an enlargement of NIAID's National Cooperative Drug Discovery Groups and National Cooperative Vaccine Development Groups. Others cautioned that the vaccine effort could easily become a sinkhole of bogus science sucking millions from more productive fundamental or therapeutic research.

Part III: Conclusion and Recommendations

Conclusion

A wide range of scientific and structural issues were brought up in the course of the thirty-six interviews which are the source of this report. Only a small offering of the total collection of concerns mentioned are presented here. These are the leitmotifs running through all of the conversations.

The red thread running through all of the scientific discussions was a new concern for the body in basic research. "*In vivo veritas*" seems to be a current call-to-arms. This trend was manifested in the acknowledgement by researchers of the importance of trying to conduct experiments in conditions that more closely approximate those found in people with HIV infection. It was also apparent in the focus on all stages of the natural history of the disease (from acute infection through the final decline in CD4+ cells and the development of symptomatic disease), its pathology in the tissues of the body, and the interaction between the virus and its human host, including both the defensive immune response and the aiding and abetting of HIV by cells and their machinery.

The degree of frustration in the AIDS research community as evidenced by these interviews was remarkable. Although the concerns about the level of funding and the enormous amount of time and paperwork taken up soliciting these scarce resources are shared by investigators throughout biomedical research, an inhospitable climate for basic research on AIDS is no place from which we should expect a cure to grow. The researchers interviewed were not shy about what they think is wrong with the state of their profession and what they think needs to be done to set things right. They had a number of suggestions about how to foster the current work of basic researchers and provide for a new generation of scientists.

What was missing from these conversations with researchers was almost as important as what was mentioned by them. Particularly noticeable by its absence was a discussion of the opportunistic pathogens affecting people with AIDS, their pathogenesis and their contribution to the progress of the underlying HIV infection. In addition, the basic mechanisms behind the neurological manifestations of HIV infection, the development of Kaposi's sarcoma and cancers seen in the disease, and the pathogenesis of the profound wasting syndrome often accompanying AIDS, were mentioned only by a few of those interviewed. These underemphases can largely be accounted for in a selection bias in the choice of scientists interviewed who are almost exclusively virologists or immunologists.

Recommendations

This report marks the beginning of a campaign by the Treatment Action Group to focus attention on the importance of basic research on HIV infection to the development of a cure for the disease and a vaccine for the uninfected. TAG will also be advocating for changes in policy to insure that the work of basic scientists in AIDS are supported with the funds, resources and leadership necessary to speed their progress. We make the following recommendations:

On Scientific Issues

1. The Office of AIDS Research (OAR), NIH with the cooperation of the National Center for Research Resources, should encourage the Regional Primate Research Centers to provide greater access to their animals to extramural researchers not associated with their institutions for *in vivo* studies of the pathogenesis of SIV and HIV.

2. The OAR should encourage both the epidemiology and clinical trials networks funded by the NIH to provide greater access to clinical samples to basic researchers in AIDS.

3. The OAR should convene an ad hoc advisory group of clinical and basic scientists to assess the need for and feasibility of establishing a new national repository for clinical samples, which might include, but not be limited to samples from unique populations such as long-term survivors, individuals presenting with acute infection, etc.

4. The OAR should sponsor a major conference in 1993 on the immunology of HIV infection and encourage the attendance of immunologists not currently working in the field.

5. The OAR should consider encouraging the establishment of novel programs which would foster collaborations among basic, clinical, academic and pharmaceutical company researchers. Basic researchers could have access to clinical materials; clinical researchers could initiate therapeutic protocols based on insights of basic research; pharmaceutical researchers could develop new molecular entities based on the latest, instead of the oldest, ideas on pathogenesis.

On Research Review

6. The OAR should conduct a review of all its study sections on AIDS, their composition, their scope (for instance there are no study sections for work on opportunistic infections or neoplasms) and consider restructuring where necessary.

7. The OAR should institute a system of ongoing program review for all its AIDS efforts, including the larger directed programs. These reviews should rigorously consider the programs's productivity and scientific merit and should be the primary basis for future funding.

8. The OAR should institute a system of ongoing portfolio review for all its AIDS efforts, which will assess the gaps and redundancies in research and make recommendations for reallocation of resources when necessary.

9. The Division of Research Grants, NIH should establish a plan with the advice of extramural scientists to streamline the grant application process for both AIDS and non-AIDS research.

10. The OAR should set up a Pathogenesis Working Group (modelled on the current Vaccine Working Group sponsored by NIAID) to prioritize, strategize and evaluate the overall NIH effort.

On Research Funding

11. Congress should mandate a uniform flat rate of between 25-50% for indirect costs paid to universities for research.

12. The Howard Hughes Medical Institute should initiate a program to support basic researchers in AIDS, similar to its existing programs in genetics, cell and structural biology, immunology and neuroscience.

13. The OAR should consider initiating, on a limited basis, a new competitive mechanism of program grants (based on the model currently in use in the U.K.) to fully support the most productive basic researchers in AIDS for a period of five years.

14. The OAR should institute a new program of pilot grants in basic research on AIDS. The awards should offer approximately $100,000 for each of two years to: junior researchers in the field; investigators pursuing novel, or "risky" hypotheses or understudied areas of research; scientists working in related fields (e.g. T-cell immunology, the cell cycle), but who have not thus far worked in AIDS; teams of investigators wishing to pursue collaborative projects in single research areas. The applications for these awards should be short, and the time from the

submission of the application until receipt of funds should be from three to four months.

15. The OAR should initiate a mechanism to issue expedited awards to researchers in new areas of emerging scientific importance. Currently, there is a two-year lag from the identification of a critical issue until the awarding of a grant in that area.

16. Large pharmaceutical companies should be encouraged to offer targeted donations to universities for graduate science education in AIDS-related disciplines and to support basic scientific research in AIDS.

Tables

Table 1

Review of Current (FY 1993) NIAID Supported

AIDS Pathogenesis Research Grants[1]

The following is presented for descriptive purposes only, to suggest the balance of extramural work funded through the major supporter of basic extramural investigator-initiated AIDS research, the NIAID Division of AIDS (DAIDS). This data reflects awards made by the DAIDS Pathogenesis Branch (PB), with a few from the Developmental Therapeutics Branch (DTB) and others. Work supported by other divisions of NIAID and other NIH institutes, centers and divisions is not summarized here. Thus, it reflects only a part of the diverse spectrum of AIDS related basic research currently underway (perhaps $60-70 million, or 25%, of the $230 million NIH spends on basic AIDS research).

TOPIC	AWARDS
Molecular Virology of HIV Reproduction + Regulation	**118**
HIV entry through CD4 receptor	22
HIV entry through other receptors	5
3-dimensional structure of HIV envelope	5
Mechanisms of HIV integration into host DNA	12
Mechanisms of HIV reverse transcriptase	11
Mechanisms of HIV *tat* + associated cellular proteins	20
Mechanisms of HIV *rev* + associated cellular proteins	11
Mechanisms of HIV regulatory genes, etc.	18
HIV virion synthesis + maturation	14
Cellular + Physiological Immunopathology of HIV Infection	**26**
Natural history of acute (primary) HIV infection	3
Levels of viral expression in different tissue reservoirs	9
Mechanisms of HIV entry into CNS + neuropathology	6
Technologies to improve detection of HIV	8

[1] Source: NIAID Division of AIDS Program Review: HIV Pathogenesis workbook, 20 May 1993, tab VII.

Viral Factors Affecting HIV Progression **38**

Genetic variation within individuals + populations 7
Viral gene variation affecting disease progression 19
Viral variants affecting transmission or progression 3
Genetic determinants of cellular tropism 9

Host factors regulating HIV disease progression **50**

Viral escape from protective humoral immunity 9
Viral escape from cellular immunity 16
Host genes, proteins, cytokines affecting HIV course 19
Mechanisms of host resistance to HIV infection 4
Non-genetic co-factors affecting progression 2

Cofactors affecting disease progression **13**

Effects of co-infection with other viruses 10
Effects of co-infection with other microbes 3

Direct/indirect mechanisms of HIV immunodeficiency **29**

Role of CD8s, NK, B cells, macrophages, DCs, FDCs 6
HIV-induced aberrant signalling + superantigens 21
T cell homeostasis 2

Animal models of HIV-mediated pathogenesis **49**

Viral genes affecting pathogenesis 23
Time course of infection 10
Clinical course of disease with tropism variants 1
Lentivirus effects on T cell development/regulation 1
Autoimmunity, viral escape, antibody enhancement 14

Mechanisms of sexual/mucosal transmission **8**

Subtotals

Viral factors 156
Host factors 99
Cofactors 13
Animal models 49
Sexual transmission 8

TOTAL **331**

Table 2

NIAID Extramural AIDS Funding Trends

FY 1990-1994

*

AIDS awards (N)	1990	1991	1992	1993 Est.	1994 Est.
Total reviewed	776	536	580	620	662
Total recommended	713	475	459	546	583
Total funded	215	191	198	227	258
AIDS awards ($ in millions)					
Total reviewed	$210	$148	$297	$302	$256
Total recommended	147	114	222	257	267
Total funded	45	47	67	71	81
AIDS award/success rate					
Award rate	39%	40%	43%	42%	44%
Success rate	28%	36%	34%	36%	39%
NIAID AIDS payline					
Percentile for unsolicited[2]	22%	18%	16%	14%	10%
Percentile for all awards	22%	25%	23%	19%	15%

Award rate = grants deemed fundable by study section.
Success rate = grants actually awarded given fiscal realities.
Percentile = grants awarded as proportion of applications.

*

Source: Wayne Crum + Steve Berkowitz, Financial Management + Information Systems Branch, NIAID, NIH, 28 May 1993.

[2] This is the payline for unsolicited investigator-initiated R01 research grants.

DHHS-NATIONAL INSTITUTES OF HEALTH
AIDS BY FUNCTIONAL CATEGORY
(Dollars in thousands)

Category	FY 1989 Actual	FY 1990 Actual	FY 1991 Actual	FY 1992 Actual	FY 1993 Approp.	FY 1994 Estimate
I. BASIC SCIENCE RESEARCH:						
A. Biomedical Research:						
1. HIV and HIV genome	$62,120	$83,564	$81,009	$80,222	$81,922	$102,395
2. Immunology	52,623	85,925	101,485	96,900	97,344	117,159
3. Blood/Blood products	11,063	11,643	8,476	8,034	7,838	10,261
4. Diagnostic methods/reagents develop	7,869	14,369	11,935	12,158	11,777	15,103
5. Animal models and related studies	31,382	31,652	30,970	29,961	30,965	37,353
SUBTOTAL, Biomedical Research	165,057	227,153	233,875	227,275	229,846	282,271
B. Neuroscience and Neuropsychiatric Research	29,038	42,185	45,503	50,152	51,842	59,220
C. Behavioral Research:						
1. Mechanisms of behavior and behavior change	16,944	17,038	22,122	23,810	24,462	29,347
2. Prevention of high-risk behaviors	49,916	68,322	103,139	100,980	103,494	117,743
SUBTOTAL, Behavioral Research	66,860	85,360	125,261	124,790	127,956	147,090
D. Therapeutic Agents:						
1. Development	131,421	125,422	143,517	141,458	141,059	170,540
2. Clinical Trials	103,840	178,382	219,579	234,161	247,445	300,160
SUBTOTAL, Therapeutic Agents	235,261	303,804	363,096	375,619	388,504	470,700
E. Vaccines:						
1. Development	49,238	52,629	48,926	62,498	65,507	80,314
2. Clinical Trials	10,581	17,281	11,000	16,823	23,214	42,263
SUBTOTAL, Vaccines	59,819	69,910	59,926	79,321	88,721	122,577
F. Research Enhancement:						
1. Training	8,780	12,732	15,244	17,361	16,525	20,751
2. Construction (Extramural)	28,875	195	111			
SUBTOTAL, Research Enhancement	37,655	12,927	15,355	17,361	16,525	20,751
TOTAL, BASIC SCIENCE RESEARCH	593,690	741,339	843,016	874,518	903,394	1,102,609

Category	FY 1989 Actual	FY 1990 Actual	FY 1991 Actual	FY 1992 Actual	FY 1993 Approp.	FY 1994 Estimate
II. RISK ASSESSMENT AND PREVENTION:						
A. Surveillance:						
1. Diseases associated with HIV	$7,206	$3,380	$2,966	$1,964	$2,054	$2,433
2. HIV surveys (incidence, prevalance)	641	1,171	109	1,500	1,500	1,700
3. Knowledge, attitudes, behaviors	975	1,460	1,375	2,188	2,201	2,540
SUBTOTAL, Surveillance	8,822	6,011	4,450	5,652	5,755	6,673
B. Population-Based Research: Natural History, Transmission, Risk Factors:						
1. Transmission:						
a. Sexual	33,201	27,279	24,063	31,416	31,670	38,329
b. Intravenous drug abusers	12,911	8,764	8,532	6,917	6,953	7,823
c. Hemophilia populations	4,692	6,651	3,290	4,463	4,620	2,034
d. Blood recipient/donor studies	9,420	7,003	10,615	11,158	6,492	8,304
e. Perinatal infection	18,480	27,411	33,008	33,958	30,851	35,755
f. Occupationally related	83	87	119	63	84	21
g. Other/Miscellaneous	13,560	4,617	5,608	5,890	6,509	8,644
SUBTOTAL, Transmission	92,347	81,812	85,235	93,865	87,179	100,910
2. Natural history and cofactors	23,889	50,073	55,439	55,582	63,665	73,685
SUBTOTAL, Population based research	116,236	131,885	140,674	149,447	150,844	174,595
C. Information and Education/Preventive Services:						
1. High risk or infected persons:						
a. Health education/risk education	2,352	2,896	3,016	2,654	2,348	2,602
b. Counseling, testing, partner notification	275	859	457	276	269	300
c. Perinatal AIDS prevention projects	447		2	9	9	11
d. HIV prevention among drug abusers	631		782	800	800	900
e. Special projects:						
(1) Conference of Mayors						
(2) HIV-related tuberculosis demonstration projects						
(3) National Hemophilia AIDS/HIV prevention project						
(4) Community-based demonstration projects						
SUBTOTAL, Special projects						
SUBTOTAL, High-Risk or Infected Persons	3,705	3,755	4,257	3,739	3,426	3,813
2. Special Minority Initiatives						

Category	FY 1989 Actual	FY 1990 Actual	FY 1991 Actual	FY 1992 Actual	FY 1993 Approp.	FY 1994 Estimate
3. School and college aged youth:						
a. National efforts	$533	$468	$208	$17	$16	$18
b. State and local projects						
c. Program development and training						
SUBTOTAL, School and college aged youth	533	468	208	17	16	18
4. General Public and Special Programs:						
a. National:						
(1) Clearinghouse						
(2) Hotline (general public)						
(3) Treatment trials and therapy, information services	10,552	4,771	3,780	4,720	3,969	6,423
SUBTOTAL, National	10,552	4,771	3,780	4,720	3,969	6,423
b. Regional, state, and local	9		1		1,239	748
SUBTOTAL, Gen. Pub. and Spec. Prog	10,561	4,771	3,781	4,720	5,208	7,171
5. Health-Care Workers and Providers:						
a. Education and training centers	999	1,353	956	670	982	1,318
b. Other types of training	1,110	542		386	320	341
SUBTOTAL, Health-Care Workers and Providers	2,109	1,895	956	1,056	1,302	1,659
6. Prevention Capacity Enhancement		2				
SUBTOTAL, Information and education/preventive services	16,908	10,891	9,202	9,532	9,952	12,661
TOTAL, RISK ASSESSMENT AND PREVENTION	141,966	148,787	154,326	164,631	166,551	193,929
IV. Clinical Health Services Research and Delivery:						
A. Services						
B. Health Services Grants						
C. Construction						
D. Research	1,000	1,449	2,517	2,702	3,317	3,462
TOTAL, CLINICAL HLTH SERV. RESCH AND DEL	1,000	1,449	2,517	2,702	3,317	3,462
V. PHS-Wide Activities:						
A. OASH/NAPO						
C. Construction (PHS Faciltites)	5,772	12,880	4,966	7,758		
TOTAL	742,428	904,455	1,004,825	1,049,609	1,073,262	1,300,000

NOTE: Reflects transfer for tuberculosis research in FY 1993.