

AIDS Research at the NIH: A Critical Review *by Gregg Gonsalves and Mark Harrington*

Part I: Summary. Part II: The NIH, A User's Guide. VIII International Conference on AIDS, Amsterdam, the Netherlands, July 20, 1992

AIDS Research at the NIH: A Critical Review

by Gregg Gonsalves + Mark Harrington

Part I: Summary

Foreword by Larry Kramer

VIII International Conference on AIDS

Amsterdam, the Netherlands

20 July 1992

Acknowledgments

First thanks go to Derek Link, who originally proposed this project and worked on it in its early stages. We also thank Derek, Chris DeBlasio, and Garance Franke-Ruta for helping us with the final agonizing edit. David Gold and Rich Lynn offered helpful suggestions and comments on work in progress. We are grateful to Derek Hodel and the PWA Health Group for the use of their computers. At the NIH, warmest thanks go to Linda Reck and Stan Katzman of the Office of AIDS Research, and their colleagues, Wendy Wertheimer and Jack Whitescarver, who provided much of the source material for this document. Each of the institutes' AIDS coordinators also deserve special mention for sending us additional information on their programs: Judith Karp, NCI; Jim Hill and Deborah Katz, NIAID; Elaine Sloand, NHLBI; Carl Leventhal, NINDS; Marvin Cassman, NIGMS; Joan Wilentz, NIDR; Judith Fradkin, NIDDK; Richard Mowery, NEI; Kenneth Bridord, FIC; Janet Guthrie, NIEHS; Martha Ann Carey, NCMR; Stanley Pillemer, NIAMS; Samuel Korper, NIA; Henry Kissman, NLM; James Snow and Pat Sparks, NIDCD.

TAG's Mission Statement

The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both private and public, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies, and government officials, and resort when necessary to acts of civil disobedience. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

This report is dedicated to Scott Slutsky 1954 - 1992 \*  
President Bush and HHS [the Department of Health] have failed to meet fully their responsibilities in leading the national response to the monumental human suffering and economic loss from the HIV/AIDS epidemic."

-- US National Commission on AIDS 25 June 1992

A lot of research is like shining a flashlight on a dark street corner. We feel good because we're looking where the light is. But who knows how big the darkness is?"

-- Dan Hoth, MD Director, Division of AIDS (DAIDS), NIAID, NIH

"I don't think that we have a mechanism within the executive branch that looks at science priorities."

-- Bernadine Healy, MD Director, NIH  
ABSTRACT

Our goal was to obtain a comprehensive picture of the AIDS programs administered by the US National Institutes of Health (NIH) in order to recommend changes to expedite a cure. We reviewed the \$800M NIH AIDS program from fiscal year (FY) 1991, including 2,625 extramural grants and contracts and hundreds of intramural projects. We read abstracts of these projects generated by the NIH Office of AIDS Research (OAR) AIDS Research Information System (ARIS) database. We reviewed the NIH Annual Report to Congress on AIDS achievements for FY 1991, the quarterly Institute AIDS Science Reports, and the list of new programs requested by NIH for AIDS in FY 1993, which cannot be funded due to President Bush's budget cuts. Finally, we compared a draft of "The NIH Strategic Plan for HIV-Related Research," the Institute of Medicine's 1991 report on the AIDS program, and the recommendations of the National Commission on AIDS to the government.

NIH spent \$800M on AIDS in FY 1991, 9.7% of its total budget. Each of the NIH's 18 Institutes, Centers, and Divisions administers AIDS programs, all of which remain un-coordinated and underfunded. 73% of the programs are administered by two institutes, NIAID (53%) and NCI (20%). Under the President's FY93 Budget Request, AIDS programs will increase only 3.8%, or less than scientific inflation. This is a cut of \$456M from the institute directors' original requests. Over a hundred new initiatives and expansions of existing programs cannot be funded. When new initiatives are mandated by Congress or the Executive Branch, existing programs are cannibalized. For instance, the NIAID pool of basic AIDS research grants shrank by half in 1992 to pay for the ACTG Recompensation and Congressionally-mandated pediatrics research.

We conclude that the entire NIH budget should be doubled, to \$16 billion a year. The AIDS budget should rise to \$1.6 billion. The rate at which AIDS basic research grants are funded should be restored to 40%. The NIH Associate Director for AIDS Research should be given authority to allocate resources and programs across institute boundaries. Pathogenesis research should be emphasized. Developmental clinical immunology programs should be expanded. The six institutes conducting clinical trials (NIAID, NCI, NICHD, NEI, NINDS, NHLBI) should mandate collaboration among their research networks. Orphan research areas such as wasting, neurology, and immune-based therapies should receive special support. NIH should develop a large scale screening program to search for cytokine inhibitors and synthetic immune modulators. Clinical trials should be analyzed and published faster. Community activists should participate in the oversight of basic research programs.

\*

#### TABLE OF CONTENTS

#### I.

Foreword (by Larry Kramer) Page Introduction 1 Materials + Methods 3 Findings + Recommendations 7

#### II. NIH AIDS Programs by Institute

1. NIAID: National Institute of Allergy and Infectious Diseases14 2. NCI: National Cancer Institute 26 3. NCRR: National Center for Research Resources 33 4. NHLBI: National Heart, Lung, and Blood Institute 35 5. NICHD: National Institute of Child Health and Human Development37 6. NINDS: National Institute of Neurological Disorders and Stroke39 7. NIGMS: National Institute of General Medical Sciences41 8. OD/OAR: Office of the Director/Office of AIDS Research43 9. NIDR: National Institute of Dental Research 44 10. NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases46 11. NEI: National Eye Institute 48 12. FIC: Fogarty International Center 49 13. NIEHS: National Institute of Environmental Health Sciences51 14. NCNR: National Center for Nursing Research 52 15. NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases53 16. NIA: National Institute on Aging 55 17. NLM: National Library of Medicine 56 18. NIDCD: National Institute on Deafness and Other Communication Disorders57

### III. Tables

A. Cumulative Summary of NIH AIDS Funding: 1982-1993 B. Summary of Expenditures: FY 1991-National Institutes of Health, AIDS by Functional Category

\*

Dear Fellow Warrior in the Fight Against this Plague of AIDS,

This is one of the most important documents about the AIDS plague and our present moment in this crisis that you will ever be asked to read. I not only urge you to read it as quickly as possible, I implore you to read it as thoroughly as you can. While it may appear, on the surface, to be dry and fact-filled, every figure, every statistic, clothes a scandal or a tragedy or both. Never before has there been such a look at all the AIDS programs at all the institutes that comprise the National Institutes of Health. Even the report issued by the Institute of Medicine only dealt with broad structural issues, deferring the idea of looking at the programs themselves in detail to some future unspecified moment in far-off time.

Why is this report so important for you to read?

Because, for the first time, eighteen institutes, each with its own programs, each with its own goals, each with many strengths and many weaknesses, each completely unable to criticize itself, comes under a long-needed scrutiny.

What does this report conclude?

The AIDS plague is utterly and completely devoid of leadership. At the NIH, no one is at the center, nothing is coordinated, no one is asking the life-saving (and money-saving) questions: what is missing from our efforts, what is being duplicated, why are we being forced into competition with our own fellow institutes, right here on our own campus, when budgets are shrinking and shrinking?

In the middle of this tragically sad situation, as the figures of the newly infected and the newly dead mount and mount to heights once thought inconceivable, sits the President's Point Man for AIDS, Dr. Anthony Fauci, who some of us would like to see removed and many of us prefer to see as helpless, rendered powerless in a quagmire -- forced as he is to bow to the brainless whims of a heartless President, a Congress which claims compassion and a desire

to increase the budget but an inability actually to do so, and an inept Secretary of Health and Human Services whose every utterance in defence of his boss is so lie-filled as to make it hard to accept that the man is a Christian much less a doctor.

Is it, at this late stage of this plague, intemperate or rude to ask what kind of country (or world) is this where a plague can be allowed to rage out of control, where its supposedly premiere scientific research establishment can be allowed to present such a second-rate face to the realities and sufferings it was founded and funded to alleviate?

Is it, at this late stage of this plague, intemperate or rude to suggest that this present state of AIDS affairs leads us even more to the fact that the only out that has not been tried, that still must be tried, is a Manhattan- or Apollo-type project, wherein the leading experts in all areas are granted emergency powers and sent off into the seclusion necessary to produce the cure that must be there if our civilization is to survive?

I value this incredible amount of work and energy and insight and perseverance and heartfelt need that gave birth to this report and sustained its creators to its completion. May bureaucrats learn from this report and gain courage to speak out at last. May activists learn from this report and renew their commitment, now so understandably wounded from discouragement. With this information, may we all enter a new stage of holding our system -- now so dreadfully and woefully off-course -- accountable.

Whoever you are, whatever you do in fighting this plague, you must know this information and respond to it. Do not, as so many have before us, go quiet into the night.

Larry Kramer  
INTRODUCTION

Since 1987, the activist critique of AIDS research has worked its way back: from drug approval at the regulatory level of the US Food + Drug Administration (FDA), to expanded access for drugs still under study (Parallel Track), to the design and conduct of the controlled clinical trials themselves by the National Institutes of Health (NIH), pharmaceutical companies and, community-based clinical trial centers. While this work has generated some useful reforms in an inefficient system (and expanded access and expedited approval for several useful therapies), it often seems that all these accomplishments go for naught. HIV keeps spreading, AIDS keeps striking people down, and researchers appear to have little confidence in the rapid development of a therapeutic cure or an effective vaccine.

Against a background of deepening political reaction, declining research subsidies, and pervasive pessimism about the prospects for a scientific breakthrough, and some activists have grown unsure of the continued value of engaging the scientific infrastructure. What is the point of streamlining access and approval when the result is merely to replace AZT with other mediocre, toxic, expensive nucleoside analogues? What is the point of developing prophylaxis and better treatment for opportunistic infections when these measures simply allow someone to survive long enough to develop lymphoma, visceral Kaposi's sarcoma, wasting syndrome or neuropathology?

If the reforms won by activists are not to become mere stratagems for craven pharmaceutical companies swiftly to develop and market a whole series of

additional nucleoside analogues (d4T, FLT, 3TC, etc.), activists must become more involved in the basic research process itself, forcing academic and industrial researchers to turn their attention to novel treatment approaches of HIV-induced immune suppression, including immune based therapy, cytokine inhibition, and active immunotherapy, with the ultimate goals of elucidating the pathogenesis of AIDS, stopping its progression, and reversing its damage.

The task requires that activists become as familiar with the \$800 million AIDS program of the NIH as they have with its major clinical component, the AIDS Clinical Trials Group (ACTG).

This report is a preliminary effort to map the NIH AIDS Program, evaluate it, suggest useful reforms, and highlight the gruesome cost of the Bush administration's refusal to adjust AIDS research funding to even the rate of inflation, to say nothing of the adjustment appropriate to the opportunities now within reach. These opportunities are graphically documented in the institute directors' "Wish List" for fiscal year 1993, which contains hundreds urgent new programs, few or none of which may be funded.

As a consequence of Administration policy, new initiatives are being smothered in the cradle to pay for large ongoing programs. Prevention competes with care for limited funds. Basic research competes with clinical trials. Immunology competes with virology. Treatment research competes with vaccine research. Adult clinical trials compete with pediatric ones. Entire areas such as oncology, gynecology, wasting, and neurology go begging for funds.

\* Just as the precondition for access to therapies for all who need it is single-payor national health care, so the prerequisite for a rational national biomedical research policy is the immediate doubling of the NIH budget to \$16 billion a year, with high-priority, high-mortality areas like AIDS, cancer and Alzheimer's disease given the lion's share of the newly released funds.

\* In order to justify such new public investment, the NIH must take steps to incorporate community views in its work across the board - not just in the ACTG or in AIDS - but for all the other diseases against which its efforts are directed.

If AIDS activists ever leave any legacy other than their own bodies, it will be, among other things, a movement for national health care and the democratization of research.

The pattern of Federal AIDS research funding from 1981 through 93 is:

NIH AIDS Budget by Year (with rate of increase from previous year)

1982	\$ 3,355,000	--	1983	21,668,000	5115%	1984	44,121,000	103%	1985	63,737,000
										44%
1986	134,667,000	111%	1987	260,907,000	94%	1988	473,285,000	81%	1989	601,316,000
										27%
1990	743,532,000	24%	1991	799,821,000	7.6%	1992	841,417,000	5.2%	1993	873,377,000
										3.8%

After several years (in the mid 1980s) of program growth, the NIH AIDS budget is now falling relative to inflation (a 3.8% increase for AIDS research next year, while inflation is predicted to reach 5.1%, according to the Biomedical Research and Development Price Index computed by the Commerce Department). From 1982 to 1989, Congress always appropriated much more for AIDS than the Administration requested. That pattern has now been reversed. In 1991, Congress authorized \$3 million less than the President requested for AIDS research. For several years,

Congress has imposed new demands on the NIH AIDS program without authorizing new funds with which to carry them out. For example, in 1990 the Congress earmarked \$40M for research on children with AIDS, especially for clinical trials. Since there was no new money appropriated for this purpose, the funds came directly from the adult AIDS Clinical Trials Group (ACTG). The result is that now, in 1992, the US Government is spending \$105.00 for research on every child with AIDS in America, compared with just \$1.00 for each adult. The Pediatric ACTG is now as large as the adult ACTG, which has been cut to make ends meet.

When it comes to research policy, Congress is often like a bull in a china shop, dropping in to make a mess and then storming out again. For example, also in 1991, Congress imposed new restrictions on the right of NIH personnel to travel for work. This was ostensibly because some Congressmen feared that junketeering NIH employees would litter the streets of Florence swilling cappuccino rather than negotiating with drug companies and attending seminars. The result of this mini-scandal was a \$10-million reduction in the overall NIH AIDS budget and severe, ongoing restrictions on NIH travel. This makes it even more humiliating to work for the government. For the last two years, activist groups have sent more members to the international AIDS conferences than has the NIAID Division of AIDS, the lead agency charged with conducting Federal AIDS research. NIH can still spend other funds sending extramural experts to Bethesda for meetings, but its own employees are virtual prisoners on the campus.

While Congress is careless and capricious, the Administration, from the White House down to the Secretary of Health + Human Services [HHS], has adopted an AIDS strategy of "malign neglect," apparently hoping the problem will solve itself. Recently, the US National Commission on AIDS, a third of whose members were named by the President, condemned the Administration for its inadequate, inconsistent, and heavily politicized AIDS policy. Barring a change in administration, it would be foolish to expect leadership from the White House or HHS on AIDS anytime soon. This creates a conundrum; officials relatively low within the Executive Branch are delegated leadership on AIDS policy more or less by default.

At the NIH level, de facto AIDS policy decisions are made by Associate NIH Director for AIDS Research Anthony S. Fauci, who is Director of the Office of AIDS Research (OAR), Director of the National Institute of Allergy + Infectious Diseases (NIAID), and Chief of the Laboratory of Immunoregulation. Extraordinary responsibilities rest by default on a man who turned down the chance to become NIH Director in order to stay more in contact with AIDS research, yet who wears so many hats which demand very different skills and decisions.

In addition, there is a dizzying array of advisory committees which advise every level of NIH, from the overall AIDS effort to specific Institute and Division councils. Every major new program initiative must be approved by an external advisory council, yet these decisions are often simply an elaborately choreographed rubber stamp.

The NIH is actually a collection of fiercely autonomous fiefdoms (designated Institutes, Centers, or Divisions, known as ICDs) loosely administered under an NIH Director. Each ICD Director develops and administers his or her own budget, and there is little the NIH Director can do to allocate resources across institutes (although she now has her own \$20M "emergency fund"). Some ICDs, such as the National Cancer Institute (NCI), have worked out special privileges within the Executive Branch - the NCI "Bypass Budget" skips the desks of Assistant Secretary for Health Mason, Health and Human Services Secretary Sullivan, and Office of Management and Budget Director Darman, and goes straight

to the President's desk. (This didn't stop the President from slashing the 1993 NCI request just as much as he slashed those of every other ICD.) OAR Director Fauci, who is supposed to coordinate AIDS research across ICDs, has little real say in the half he does not directly control as NIAID Director. Thus, there is no truly centralized planning and execution of AIDS research, and no adequate oversight from either Congress or the Administration. Neither is there enough systematic, comprehensive information about existing NIH AIDS programs. Since 1990, activists, the Congress, and the Institute of Medicine (IOM) have all encouraged the NIH to develop a comprehensive plan for its AIDS efforts, and NIH has been working for the last year on a "Strategic Plan for HIV-Related Research."

#### MATERIALS + METHODS

This report is based on the following sources:

\* NIH budget information from 1982-1993; \* "The NIH Strategic Plan for HIV-Related Research," DRAFT of 11.8.91; \* "The NIH Five-Year Plan for HIV-Related Research," a similar DRAFT of 4.29.92; \* "The AIDS Research Program of the NIH" by the Institute of Medicine, NAS, 1991; \* The NIH's "Annual Report to Congress" for 1991; \* The Office of AIDS Research's "Institute AIDS Science Reports", which periodically chronicle AIDS work done by the various ICDs every three (now 6) months; \* Abstracts of 2,625 extramural NIH AIDS awards in Fiscal Year (FY) 1991 obtained from the OAR AIDS Research Information System (ARIS) database, which obtained them from the DRG (Division of Research Grants) CRISP database; \* Abstracts of the intramural Z01 projects from CRISP; \* A list by institute of all 2,624 extramural AIDS awards in FY 1991 obtained from ARIS [this list was not identical to the abstracts from CRISP]; \* Letters, budget information and plans from staff at each Institute, Center or Division; \* A list of the original AIDS budget requests for FY 1993 from each ICD Director, and the subsequent budget history

The uses and weaknesses of these sources are discussed below.

Office of AIDS Research (OAR). Since OAR is supposed to coordinate NIH AIDS research, we began this project at OAR. OAR coordinates the AIDS budget request for the 18 Institutes, Centers and Divisions. OAR also coordinates the NIH presence at the twice-monthly meetings of the PHS AIDS Leadership Committee (a "small, free-wheeling, leak-free forum") composed of Agency Directors (or their deputies) and AIDS Coordinators. This is where the PHS agencies duked out the CDC's proposed health-care worker guidelines. Sometimes CDC Director Roper appears on closed circuit TV from Atlanta. There is also a PHS Executive Task Force on AIDS (EFTA) coordinated by National AIDS Program Office (under the Assistant Secretary for Health), which chairs it. The ETFA meets monthly. It's a forum for information dissemination among agencies.

OAR and the NIH AIDS Budget Cycle. Every winter, NIH Building One (the Office of the Director) sends out guidelines for budget preparation. Program priorities are issued for "New Areas" and "Significant Expansions" within existing areas. Institutes, Centers and Divisions (ICDs) are asked to be "realistic." The ICD Directors' requests specify the amount of new funds requested, the project to be funded, its mechanism (grant, contract, intra- or extramural, etc.), and how many (if any) new full-time equivalents (e.g., staff) are needed to administer (if extramural) or conduct (if intramural) the research. Planning starts 18 months in advance. When we were at OAR in February, 1992, the Fiscal Year 1994 (October 1, 1993 to September 30, 1994) budget requests were coming in from the



Institute Directors, and the President's Budget for Fiscal Year 1993 was being dismantled on Capitol Hill.

A Sample Year: The Gutting of FY 1993's AIDS Budget. For FY 1993, the institute directors requested \$1,329,359,000 for AIDS research. In spring 1991 OAR Director Fauci made the first cut (to \$1.195 billion) and sent it on to NIH Director Healy, who changed nothing. Apparently Healy wants AIDS to grow at the same rate as non-AIDS, though the President apparently disagrees. The last level where specific programs are considered is the office of the Assistant Secretary for Health Mason, who coordinates the entire PHS budget and sends it on to superiors at the Department of Health & Human Services. For FY 1993, Mason cut the request by about \$200M, to \$1,009,561,000. By the time Sullivan's flunkies finished with it, the FY 1993 request was down another \$120 million to \$893,116,000. Sometimes Mason appeals the Secretary's cuts; he did so successfully with vaccine funds for FY 93. The Office of Management & Budget gratuitously cut another \$20M and sent it to the President, who must have been in a good mood - he restored \$2.1M, bringing his NIH AIDS research budget request to \$873,377,000 - a whopping 3.8% increase over FY 1992. The result is a net loss for AIDS: No new programs without slashing old ones. By the time the President's Budget Request is submitted to Congress, various committees receive copies of the ICD Directors' "Wishlist" to determine how much was cut from the budget by OAR/OD, OASH (PHS), HHS, OMB and the President.

An Elaborate Charade? OAR has no power to force the ICDs to do what they say they will; if they refuse to fund an AIDS program, OAR is helpless. Similarly, the putative coordinating bodies such as the PHS AIDS Leadership Committee (ALC), the PHS Executive Task Force on AIDS (ETFA), or the AIDS Program Advisory Committee (APAC) lack information and power to coordinate the NIH's balkanized research projects. Fauci can doodle around by taking non-AIDS programs and calling them "AIDS"; the AIDS budget thus incorporates certain basic immunology, virology and structural chemistry programs into "basic research," and can categorize research on non-HIV vaccines and certain malignancies as "AIDS" also. NCI has its own streamlined "Budget Bypass" process. The NLM and the NCNR refused to follow OAR suggestions for AIDS allocations. The OAR AIDS figures are "guided targets." OAR guesses that when the "AIDS actuals" for FY 1993 come in two years hence, they'll be smaller than what the ICDs promised. ICDs didn't have that leeway when AIDS was a separate earmark by Congress, but for the last two years AIDS hasn't had its own budget line anymore. Every institute has its own budget line.

\* NIH AIDS research should have its own line item in the Federal budget.

\* OAR/OD should have the power to reallocate AIDS resources across institute lines.

\* Congress should fund the full \$1.3 billion requested for AIDS research projects by the ICD directors for FY 1993.

Institute AIDS Science Report (IASR). Every half year the ICDs tell OAR what they've done, but the quality and quantity of reporting varies between institutes. NIAID lists the ACTG trials (in development, pending, open, closed, completed, deferred, withdrawn) for scores of pages ad nauseam without signifying which ones matter, how much they cost, or how they contribute to the standard of care. Other ICDs report small initiatives as though they were major contributions to the field. OAR lacks a clear picture of NIH's intramural AIDS research.

Mason Categories. In 1988, Assistant Secretary for Health James Mason demanded that PHS set up an accounting system to track its AIDS dollars, to ensure they were only counted once, and to assess which program areas were being funded. This resulted in the "Mason Categories," activity codes which define an award (or intramural activity) as basic, clinical, epidemiological, training, virology, immunology, etc. Awards are placed arbitrarily in one category when others might do. For example, if a foreign post-doctoral student were being trained to assess the cytokine response of macrophages to SIV in the vertically-infected pigtailed macaque model, this could be categorized as IA2 "Immunology," IA4 "Animal Models," IA5 "Training", or IIB2e "Transmission: perinatal." The Mason Categories and their code abbreviations are listed in Section III. They should be thought of as a range or approximation rather than as exact figures.

AIDS Research Information System (ARIS). In order to track the dollars, OAR set up a database whose inputs include the Division of Research Grants CRISP system, which tracks most NIH extramural awards. This ARIS database, unlike CRISP, must be complete on extramural AIDS awards by the end of the fiscal year, so OAR can report back to PHS and Congress about NIH AIDS activities. Thus, while CRISP includes perhaps 75% of the AIDS awards, ARIS must have them all: PI, site, title, amount, abstract. The ARIS system is new, and still has some bugs to be worked out, but it is fantastically useful, and its staff have been extraordinarily helpful to us during this project.

Types of Awards. There are many types of NIH research awards. Each has a code. Basically, grants (R01s and other R-codes) are investigator-initiated and have few strings attached. Come back in five years if you find something. Your basic scientist working in glorious obscurity at his lab bench is sustained by R01 grants. Contracts (N01s) give the funding institute more power to direct the work, and sometimes to revoke the contract if the recipient is remiss. Data analysis for large clinical cohorts (SDAC, EMMES, CAMACS) is usually funded by contracts, as is the CPCRA. Cooperative agreements (U01s) are intermediate between grants and contracts. They give lip service to "investigator initiation" and provide some control for NIH. The ACTU sites are funded by U01s. P01s and P30s are program project grants, which are large, long-term, multidisciplinary projects. The NIAID-funded CFARs (Centers for AIDS Research) are P30s. F-awards are fellowships; T-awards are training grants. S-awards are "special" small instrumentation grants (SIG), small business grants, minority training grants, etc. Y01s are interagency agreements between NIH and another PHS agency. Some awards are institute-specific. Only NCRR awards M01s, which are General Clinical Research Center (GCRC) grants. Five mechanisms account for most (>90%) of the NIH extramural AIDS awards: M01s, N01s, P01s/P30s, R01s and U01s. Another special category is intramural research projects. These are sometimes available through CRISP as "Z01" projects, which do not have a budget dollar figure. Some institutes (e.g., NIAID), publish annual directories of their intramural research and tabulate the work of the various laboratories in "man [sic] years" rather than dollars. It's innovative, but they should call them "person years." The final category of NIH spending is on in-house staff who administer extramural awards. This is known as "research management and support."

The Grant Cycle. Grant proposals are solicited with RFPs (Requests for Proposal); contract bids with RFAs (Requests for Application). RFPs and RFAs use the same form. Researchers file applications with the NIH Division of Research Grants (DRG), which refers grants to the appropriate Institute and to a suitable Study Section (peer review committee). The Study Section is chaired by a Scientific Review Administrator (SRA). Institutes submit names of qualified potential reviewers. The SRA assigns a primary and secondary reviewer for each application from the Study Section. Reviewers have 6 weeks to review the

applications. AIDS-related grants are considered in a separate, expedited 6-month review process. This was mandated by Congress, and NIH is pretty good at meeting the 6-month limit. Study Sections allow for 1-3 days to review up to 100 applications. There are 12-18 members per study section. ICD staff attend the review, looking at the primary reviewer's comments so that they may informally discuss the result with the applicant. In addition, formal responses are contained in the Pink Sheet, or summary statement, of the Study Section's decision. Study Section members award each application a rating of outstanding, average, etc. Numbers are then assigned to each score, with 100 being the best and 500 the worst. Grants are funded down to the line at which funds run out. Applicants whose final score is close to payline are encouraged to rewrite and resubmit their application for the next grant cycle. The Study Section does not consider overall research needs, but rather reviews each proposal solely in terms of its scientific merit. Funded grantees file annual progress reports. While basic research on AIDS primarily utilizes grants, treatment research uses mainly contracts and cooperative agreements. Under the "select pay" mechanism, a grant close to but under the funding line may be selected for special review and award if it concerns a priority area. The select pay process is invoked in case there are outstanding projects worthy of funding which didn't make the cut. Select pay allows discretionary funding of grants for program-related reasons.

As can be seen, OAR has a heavy workload. Tracking the money is hard enough, tracking the science (in its entirety) virtually impossible. This, therefore, became our task.

Why Fiscal Year 1991? For our unit of analysis, we selected FY 1991. This was the most recent year for which complete budgetary information and reasonably complete award information was available. Looking at programs halfway through an ongoing year might provide a distorted picture. Therefore, we had ARIS send us a 750-page list of the 2,625 extramural awards by institute, and two boxes of abstracts from CRISP. The two systems did not entirely match, and ticking them off manually was tedious. We reviewed these materials and solicited additional information from AIDS coordinators at the various institutes. Most responded with alacrity, though some failed to provide all the information requested.

The OAR DRAFT "NIH Strategic Plan for HIV-Related Research." The Congress and the Institute of Medicine (IOM) have pressured NIH to adopt a more coherent long-range strategy for its AIDS programs. Strategic plans are becoming all the rage in scientific circles. Healy is working on one for NIH (it's controversial). Even the ACTG Executive Committee wants one. In response to the IOM's request, OAR began developing a "Strategic Plan" in late 1991. A draft was sent to the AIDS Research Advisory Committee (ARAC) in November. Changes were incorporated, a new version printed (its main innovation being a new title: in place of "Strategic Plan," it's now called the "Five Year Plan." That has a nice ring, doesn't it?). Now it's out at the various institutes, under review by directors, AIDS coordinators and senior scientists. Yet another draft will be reviewed over the summer, and perhaps the final version will come out in the fall. Originally we intended to structure our report along the lines of the "Strategic Plan." Close reading, however, revealed the much-vaunted Plan to be simply a statement of ongoing programs. Some tiny programs - such as the NIDDK effort on wasting - were covered at length, while larger ones - such as the multi-institute opportunistic infections effort - were disposed of in a sentence or two. There was no sense of limited resources, of how to prioritize among all the programs promised. The 40 objectives of the Strategic Plan are listed in Section III. Our analysis focused on the institute programs and on their wish list for FY 1993, which was a much more pointed and specific set of goals. Wish list priorities are listed by institute in Section II.

Limitations of our Approach. Our material is incomplete (yet overwhelming), our review preliminary, our conclusions subject to change. Like the NIH itself, we have no completely "objective" means by which to evaluate its programs. Many look good on paper (if they hadn't, they wouldn't have been funded), but as anyone who's ever been to an ACTG meeting (or tracked its accrual, or read its protocols, or sat on its conference calls, or marched in its halls to reform it) knows, the rhetoric and the reality are poles apart. Just as it took several years for activists to infiltrate, activate and transform the ACTG. Therefore, this report about the entire NIH effort can only be regarded as a first step. Programs must be experienced to be known and improved. Scientific culture must sometimes be disrupted to allow research constituents to play a role. NIH itself must centralize and monitor its AIDS program with more rigor than it now does. In particular, the ultimate outcomes of funded research - whether published clinical trials, changes in standard of care, peer-reviewed basic research articles, enrollment quotas met, experiments carried out successfully, or, ultimately, progress made in keeping people alive through understanding and then interfering with their disease - should somehow be scored.

Activist strategies which worked for clinical research will have to be adapted if we are to affect basic research. Activists' claim to expertise in clinical trials came out of lived experience. Most of us cannot claim the same for basic biomedical research. We can, however, only hope to serve as catalysts for better and more coordinated work within the research realm, and as agitators with Congress and the Administration for enhanced resources in the public realm. We hope that by documenting what is being done we can depict the threat posed by the Administration's budget cuts, and that by showing what more needs to be done we can mobilize the NIH to redouble its efforts and the Congress to fund them.

#### FINDINGS + RECOMMENDATIONS

Of the approximately \$800M spent on AIDS research in 1991, \$660M (82%) went for basic biomedical research, including laboratory research (25.8%), neurology (3%), behavioral research (0.3%), drug development and trials (42.3%) and vaccine development (9.4%). \$133.5M (16.6%) was spent on epidemiology, transmission and natural history studies, and \$10.5M (1.3%) on nurse training and facilities construction. Laboratory virology, immunology and animal model studies are relatively underfunded at 25.8% (\$207M) of the total. Drug and vaccine development (preclinical and clinical) make up \$416M, or 51.7% of the total budget. While substantial and important work is ongoing, it remains uncoordinated, unevaluated, and jeopardized by the Administration and the Congress and their careless posturing with the budget.

#### STRATEGIC PLANNING

Attempts at strategic planning have thus far been ineffective. Several steps can resolve this:

##### A. President + Congress

\* Double the NIH Budget. It is time to put an end to pitting people with life-threatening diseases against each other. The US spends but a pittance on biomedical research of all kinds. Sending the space shuttle to rescue the \$150M Intelsat satellite cost the US government more in 1991 than its entire NIH AIDS research program. The only stable long-term footing for biomedical research equity is a commitment to enlarging the entire biomedical research pie.

\* Restore the Institute Directors' \$450 million, making the AIDS research budget \$1.3 billion for FY 1993. When the item above occurs, AIDS research can resume at 10% of the NIH total, or about \$1.6 billion. AIDS research is being cut to the bone in FY 1993. While we found many inadequate programs, their inadequacy was directly due to the funding shortage.

\* AIDS research should have its own line item in the Federal budget for the NIH. Currently, the NIH AIDS budget is an elaborate, meaningless charade. A line item is the only way to hold institutes to their promises.

\* Congress and the Executive Branch Must Stop Legislating Research Programs without Appropriating Specific Additional Funds to Support Them. Broad research priorities are legislated or advocated by Congress and the Executive branch (e.g. pediatrics, opportunistic infections, vaccines) or by crises that can no longer be ignored (e.g. tuberculosis). New initiatives without additional funding drain funds from existing programs. The funding rate for R01 applications should be restored to 40%.

#### B. NIH Director + Office of AIDS Research (OAR)

\* OAR/OD should have the power to reallocate AIDS resources across institute lines. See above. Currently, OAR has no ability to force the rival fiefdoms of NIH - the Institutes themselves, whose budget autonomy is virtually complete - to collaborate, eliminate redundancy and cover all areas of complex fields like AIDS. OAR needs the power to fulfill its responsibilities. Although budget drafts pass through OAR, the institutes retain control over appropriations when the money actually is disbursed.

\* If the items above are implemented, the OAR Director should no longer be an Institute Director. The current system actually benefits from having the director of NIAID as OAR Director, because at least he controls half the overall AIDS budget (the NIAID half). If the OAR Director were to obtain cross-institute AIDS budget authority, however, this would become a problem, since it would be unfair for one institute director to be able to take resources from another. Therefore, when OAR achieves budget autonomy, its directorship should be severed from the NIAID position.

\* NIH's DRAFT "5 Year Plan for HIV-Related Research" needs Priorities, Timelines, Evaluation Criteria, and a Strategy for Implementation. The current draft simply catalogues NIH's current efforts with no analysis of how the program can be improved, where resources need to be increased, where new initiatives are necessary, etc..

\* Advisory committees need to stop being rubber stamps. They could take a more hands-on role in setting research priorities. Although OAR coordinates several advisory committees, none conduct detailed, ongoing evaluations of existing programs. In addition, they need more diverse representation from the many communities affected by AIDS.

\* NIH should develop performance scores for AIDS grantees, contractors, and intramural researchers, using objective criteria including peer-reviewed publications, study accrual rates, program efficiency, and relevance to clinical care.

\* OAR should put out an annual "Guide to NIH AIDS Programs" which includes all awards arranged coherently under the institute, division, branch which

administers them, and with subtopics or keywords accessible by an index or a computer disk. BASIC RESEARCH + IMMUNOPATHOGENESIS

Basic research on AIDS at the NIH stresses the molecular biology of HIV, its structure, and its life cycle. This work has expanded our knowledge about the virus and provides a strong foundation for the development of new antiretroviral therapies and vaccines. However, there is not a commensurate allocation of resources for the study of the basic immunology of the disease.

The central questions of AIDS pathogenesis remain far from resolution after over a decade of research. The lack of attention to the immunopathogenesis of the disease, and the response of the host, reflect a larger problem in basic AIDS research: a general disregard for the physiological in basic research on the disease and a need to bridge the gap between basic and clinical research. While this may be heresy to some, pathogenesis research should look to the body for its future course; it needs a physiological and not simply an in vitro virology-driven foundation. We propose the following:

- \* Establish an Immunopathogenesis Task Force. NIH needs a central office to evaluate and guide efforts to elucidate the pathogenesis of AIDS. Such an ITF would evaluate the state of NIH research in the area; assess new work by US and foreign scientists; determine how NIH should follow up, confirm or extend compelling work; foster cooperation and collaboration between research teams intramurally, extramurally, and internationally; maintain an annual list of unanswered questions on the pathogenesis of the disease; and promote research on these topics through intramural research or the issuing of RFAs. The task force would include prominent immunologists, both those working in AIDS and immunologists from outside the field, to provide a "basic" perspective.

- \* Increase Support for Basic Research on Wasting Syndrome. NIH needs to increase its financial support and stop giving lip service to basic research on wasting and other metabolic and GI conditions.

- \* Increase Support for Basic Research on Neurology. Increase support for studies on the mechanisms of HIV-associated and drug-induced neuropathology. Interactions between the nervous, endocrine and immune systems are a virtually ignored area of research.

#### DRUG DISCOVERY

- \* Coordinate Drug Discovery Efforts. Closer cooperation and more formal ties between various drug development programs at NIH (NIAID's DTB and NCI's DTP, for example) is necessary. The drug development work at the smaller institutes, which focuses on specific conditions such as wasting or dementia, needs to be connected with the bigger programs run by NIAID and NCI.

- \* Institute a Large-Scale Off-the-Shelf Screen for Cytokine Inhibitors. NCI and NIAID should establish a program to screen for immune-based therapies for HIV infection and other immunologically-mediated disorders. This program would include screens for cytokine inhibitors (for TNF, IL-6, acid-labile IFN-alpha, IL-10, etc.), compounds and modalities that selectively boost the immune system (e.g. TH1 upregulators, CTL enhancing agents), compounds and modalities to depress deleterious immune responses (e.g. treatments for autoimmune phenomena or hyperimmune activity, such as hypergammaglobulinemia), compounds or modalities that block the indirect destructive effects of HIV proteins on cells of the immune and nervous systems.

\* Expand Neuro Drug Development. NIH needs a development program specifically for novel treatments for the neurological complications of HIV, including dementia, neuropathy, myopathy, and OI's affecting the nervous system, such as PML. This should include a screen for inhibitors of cytokines and neurotoxins (e.g. quinolinic acid and other kynurenine pathway metabolites) and agents to protect CNS cells from damage (e.g. NMDA receptor antagonists).

#### CLINICAL TRIALS

\* Maintain AIDS Infrastructure Adequately. The US clinical research infrastructure, especially that for AIDS, is shrinking and aging (see NCRR), and needs renewal.

\* Coordinate Clinical Research Networks. NIH supports several massive clinical research networks, all of which should be envisioned as a single entity. Clinical research overlaps sometimes, but more often leaves major gaps. The networks operate independently with either token contact or none at all. In times of shrinking funding, they must develop a mechanism to divide and conquer the entire field of clinical complications of AIDS. OAR should set up a clinical trials network committee, forcing the program officers for each network to interact and develop a plan. The ACTG Oncology Committee and the NCI AIDS Lymphoma Network together should devise a plan for clinical research on the malignant complications of HIV infection. The NEI SOCA system should sit down with the ACTG's CMV Pathogen Study Group. The Neurology Committee of the ACTG should (and actually is going to) open a dialogue with NINDS. The Immunology Committee of the ACTG needs to formally work with the Biological Response Modifiers Program at NCI. Somebody at the ACTG should sit down with NIDDK about wasting. NICHD and the ACTG have to talk about pediatric work. DATRI could do small proof of concept pathogenesis studies for all networks.

\* Study Orphan Diseases. Several complications of HIV disease are traditionally ignored: research on wasting, dementia, neuropathy, enteric pathogens, PML, endocarditis, cardiomyopathy, pelvic inflammatory disease, and malignancies. NIAID should either study these through the ACTG or negotiate with other ICDs to ensure coverage.

\* Develop New Clinical Trial Methodologies. New, more efficient methodologies could generate more powerful answers faster than current designs. The successful use of large simple trials in cardiovascular disease may make this type of trial a candidate for use in HIV research.

\* Simplify Data Collection. Most data gathered in ACTG protocols is never used. Forms could be simplified and research nurses' time liberated by excising unnecessary data.

\* Track Survival. After ten years of AIDS and five years of AZT, we still don't know for sure whether it, or its cousins ddI or ddC, actually extend survival. No mechanism is in place (as it is in cancer) to assess long-term survival rates. To capture rare toxicity and long-term survival data, and to register interested persons in cohorts for future clinical studies, NIAID and NCI should develop a simple, lean long-term follow-up mechanism for participants in the most important AIDS trials.

\* Let Industry Pay. NIH still pays through the nose for the privilege of letting drug companies develop their drugs at public expense. We concur with the IOM that industry should pay for and conduct post-marketing studies and assist the

NIH with site support for NIH-sponsored trials, especially now that it can generate revenue earlier due to accelerated approval.

\* Establish a Clinical Immunology Initiative. Immunology is poor stepsister of NIH's clinical trials effort. Primary infection and OIs have received enormous support within the networks (the latter after vociferous hounding by activists) while immunology languishes, running around conducting flow cytometry for its haughty siblings. The NIH must make a commitment to greater funding for immunological studies within its clinical trials programs for several reasons: first, to generate new and more powerful surrogate markers, which will allow for smaller, faster studies to evaluate antiretroviral agents; second, to increase our knowledge of the immunopathogenesis and progression of the disease; and third, to develop biological response modifiers which will complement antiviral therapies in the treatment of HIV infection.

\* Design Appropriate Trials for HIV+ Children and Their Families. HIV-infected children must be seen in a real-world context -- as members of HIV-infected families. NICHD and the pediatric clinical trials networks at NIH should support research studies of the mothers of HIV+ children and other seropositive members of the family.

#### VACCINE DEVELOPMENT

\* Appropriate New Funds for Vaccine Development. The government must allocate new funds for vaccine development rather than taking them from treatment research. Work on vaccines is going to cannibalize the NIH budget as money is drawn away from existing programs to fund the mandate from Congress and the Executive Branch. For instance, the FIC and NIAID are being asked to prepare the infrastructure for the vaccine trials in the developing world, but are getting no new money for this. The risk prevention programs which they have been developing in conjunction with countries in Africa, Asia, Latin America and the Caribbean will probably have to surrender some financial support for the new initiatives. NIH must go to Capitol Hill to fight for new money.

\* Address Ethical Issues in Vaccine Development. The seronegative vaccine trials raise unprecedented ethical issues which need to be dealt with early on by the NIH with active and demographically diverse community representation. The NIH must devise ways to: - Separate the educational/prevention aspects from scientific research. The two are obviously in conflict; the greater the success of the educational and prevention programs in the study, the smaller the rate of seroconversion and statistical power of the trial. - Involve communities of color, which will be a target study population in the US because of their increasing rate of HIV infection, in the decision-making process for the trials and the NIH program as a whole. - Deal with the "false" seroconversions which will occur when the immunogen is administered. Seropositivity can involve all kinds of discrimination in insurance, employment etc.. - Assure the participation of diverse communities in these trials.

#### EPIDEMIOLOGY + NATURAL HISTORY

\* Coordinate Epidemiological Studies. NIH should streamline and integrate its epidemiological cohorts, as it should its clinical trials networks. NIAID runs the largest collection of studies, including the MACS, SFMHS, WITS, HATS etc.. NCI sponsors several US and international cohorts through its Environmental Epidemiology Branch (EEB). NINDS supports a neurology cohort; NHLBI studies pulmonary and cardiac complications of AIDS; NICHD follows children; NCI tracks lymphomas and Kaposi's sarcoma. The balkanized NIH fragments AIDS research.



\* Diversify Epidemiology Initiatives. NIH epidemiology cohorts should continue to expand to include the diverse communities affected by AIDS. NIH's epidemiology was first concentrated in urban, gay, white men. Recent efforts have only begun to reach out to the diverse groups now affected by AIDS, including women, people of color and IVDUs.

\* Undertake Long-Term Survivor Studies. Intensive case-controlled studies of long-term HIV survivors should be piloted within the MACS/SFMHS and then expanded elsewhere in order to elucidate the reasons for delayed (or thwarted) progression.

#### INFORMATION DISSEMINATION

\* Accelerate Analysis + Dissemination of Results. NIH should establish a mechanism to optimize the standard of care by disseminating the results of clinical trials to physicians and other health care professionals. In addition to prompt publication of trial results, an educational and outreach program to doctors, hospitals and clinics should be set up.

\* Develop a PCP Prophylaxis Campaign. NHLBI's Office of Prevention, Education and Control should develop a nationwide education and outreach campaign on PCP prophylaxis to high-risk groups who may not be aware that PCP is preventable.

\* Evaluate the Productivity of Research. The NLM should track the productivity of NIH AIDS grantees. This could be accomplished, for instance, by cross-referencing researchers with their recent publications in the peer-reviewed literature and the Scientific Citation Index.

\* Expand Access to and Improve the AIDS Research Information System. ARIS is new and can be improved. Mason categories incompletely categorize NIH programs for research policy review. Additional criteria, such as keywords or programmatic subtitles, could help to classify work by specific topic. OAR should devise a more rigorous, specific classification system with NLM. ARIS should also be available on-line to computer systems nationwide.

#### COMMUNITY ACCESS + INVOLVEMENT

In 1990, ACT UP/New York gained access to the thrice-yearly meetings of the AIDS Clinical Trials Group (ACTG). This access was won not just for ACT UP, but for all interested persons - people with HIV, activists, journalists and others. Shortly thereafter, the ACTG established a Community Constituency Group (CCG). The CCG members are a diverse coalition representing gay men, women, African-, Hispanic-, and Asian-Americans, people with hemophilia, and parents of infected children. CCG members have educated themselves about clinical trial methodology and the clinical and basic science behind the treatment of HIV infection and its opportunistic sequelae, and now sit on every committee of the ACTG, where they are valuable participants in the design and conduct of clinical research.

Yet the ACTG is but one eighth of the NIH AIDS program. A cure will never be tested by the ACTG unless it's discovered somewhere else first. In this report we have turned our critical focus on the whole of NIH's AIDS research effort. This is our first venture into a labyrinthine world. We largely followed a paper trail of abstracts of extramural and intramural grants, budgetary documents and program descriptions in order to get a picture of what's going on and offer some preliminary recommendations. The next step for us and other AIDS treatment

activists is to fan out and get a closer look at the undiscovered country of basic AIDS research at NIH and at NIH-funded institutions around the country.

This is a new paradigm for AIDS activists. We have to familiarize ourselves with a wide range of disciplines. For the institutes at NIH (other than NIAID, NCI and NINDS, who have a working relationship with members of TAG and other AIDS treatment advocacy organizations) the first activist to come knocking at their door is likely to come as a shock. Some pointers for both parties to ease the pain: For activists, be willing to take the time to learn about the institute and its research, and the scientific fields with which they are concerned. For the institutes, the establishment of community constituency groups for clinical trials networks is a necessary prerequisite to community involvement in your programs. The manner in which activists and advocates for people with AIDS can be involved in basic research policy is going to have to develop on its own. We have already made significant contributions to clinical research. Be willing to work with us and take our concerns into consideration. As NIAID has learned, if you can't beat them, bring them in. Both sides will learn and profit from the experience.

\*

Part II of this report, The NIH: A User's Guide, includes full descriptions of each institute's AIDS program, with additional commentary and recommendations. If you would like to receive a copy, please send your request and five dollars to The Treatment Action Group, 147 Second Avenue, Suite 601, NY, NY 10003 or call 212-260-0300.

\*

II/1.National Institute of Allergy + Infectious Diseases (NIAID)

In 1902 the Rocky Mountain Laboratory was founded in Hamilton, Montana, to study Rocky Mountain Fever. In 1948 it merged with the NIH Divisions of Infectious Diseases and of Tropical Medicine into the National Microbiological Institute (NMI). NMI was renamed NIAID in 1955 (P.L. 81-692). NIAID grew from a \$5 million institute in 1954 to \$104M in 1970 and \$215M in 1980. Largely because of new AIDS program funds, NIAID grew from the sixth largest institute in 1981 to the third largest in 1991 (behind only NCI and NHLBI). NIAID was given specific AIDS responsibilities under the Health Omnibus Programs Extension ["HOPE"] Act of 1988 (P.L. 100-607). NIAID consists of the Division of Intramural Research (see below) and four extramural divisions, the Division of Extramural Activities (DEA), the Division of Microbiology and Infectious Diseases (DMID), the Division of Allergy, Immunology and Transplantation (DAIT), and the Division of AIDS (DAIDS). DMID studies respiratory infections, hepatitis, sexually transmitted diseases, nosocomial (hospital-associated) infections, mycobacterial diseases, parasitic diseases, enteric diseases, and bacterial vaccines. DMID administers the Cooperative Antiviral Study Group (CASG), a pre-AIDS clinical research network, and the Mycoses Study Group (MSG); both are administered by the University of Alabama at Birmingham. DMID also runs a network of Vaccine Evaluation Units (VEUs), which worked on the hepatitis and influenza vaccines, and are now working on AIDS vaccines. DMID also administers a system of large Program Project (P01) grants focused on sexually transmitted diseases at UCSF, Seattle, North Carolina, and elsewhere. NIAID also runs several international collaborative projects in tropical and parasitic diseases. DAIT focuses on basic immunology, immunogenetics and transplantation, asthma, allergic diseases and clinical immunology. It runs a network of 12 Asthma and Allergic Disease Centers and six Centers for Interdisciplinary Research on Immunologic Diseases (CIRID). DAIDS, which appears to be restructured every six months, now consists of three

programs, the Basic Research & Development Program (BRDP), the Clinical Research Program (CRP) and the Treatment Research Operations Program (TROP). Each program has several subordinate branches. The NIAID director at the start of the AIDS epidemic was Richard Krause, who retired in July 1984. His successor is Anthony S. Fauci, who received his MD from Cornell in 1964, came to the NIH as a clinical associate in the Laboratory of Clinical Investigation (LCI) in 1968, became deputy clinical director of NIAID and was named chief of the new Laboratory of Immunoregulation in 1980. He became NIH Associate Director for AIDS Research in 1988, as well as Director of the Office of AIDS Research (OAR), which reports directly to the NIH Director. The AIDS programs of NIAID are different in scale from those of any other NIH institute. NIAID alone spends 53 cents of every NIH AIDS dollar, or \$431M of \$799M in FY 1991. NIAID's AIDS budget grew by leaps and bounds in the mid-1980s - to \$145M in 1987, \$394M in 1990 and \$433M in 1991. Huge extramural programs were solicited, awarded and administered by a tiny corps of in-house staff. This created nightmarish logistical problems throughout the years of budgetary growth. Now the AIDS budget is flat.

DIVISION OF INTRAMURAL RESEARCH (DIR) Of 15 DIR laboratories, 9 conduct AIDS research. Much NIAID basic immunology, while not coded as AIDS-related, is obviously crucial in providing a foundation for elucidating pathogenesis, immune regulation, and potential methods of immune reconstitution. The Laboratory of Clinical Investigation (LCI), whose chief is Stephen Straus, conducts basic and clinical studies of systemic mycoses, pathogenic fungi, herpesviruses, and HIV. They are trying to develop a peptide subunit vaccine for genital herpes (HSV-2) and are studying Epstein-Barr virus (EBV) and chronic fatigue syndrome, interactions between HIV and HSV, and how EBV immortalizes B cells, sometimes leading to lymphoma. The Laboratory of Immunogenetics (LIG), whose chief is Thomas Kindt, studies MHC antigen presentation and is developing a rabbit model of HIV infection. The Laboratory of Immunopathology (LIP), whose chief is Herbert Morse III, works on DNA viruses, murine leukemia (retro)viruses, MAIDS, oncogenes and hematopoiesis. Morse and co-workers have developed a surprising approach to treating mouse AIDS (MAIDS), which involves using the immunosuppressive drug Cyclosporin A (CsA) with or without AZT; the mice thus treated progressed more slowly or did not develop MAIDS at all. The Laboratory of Immunoregulation (LIR), whose chief is Anthony Fauci, works on T cell and B cell regulation, homeobox developmental genetics, lymphocyte transcription factors, cytokine networks, HIV infection and AIDS, Chlamydia trachomatis and the vasculitides (autoimmune vascular inflammatory conditions). Their AIDS work includes basic, clinical and international components. They are studying the NF-kappa-B (NK-kB) family of transcription factors active in lymphocyte activation and HIV replication, as well as neuroimmunologic mechanisms of HIV. Work published in 1991 documented that HIV is never totally latent in the body, and that even in earlier stages of infection active expression can be detected by HIV mRNA PCR. Other work showed that the viral burden is 5-10 times higher in the lymphoid organs than in the blood. This raised the likelihood that measuring viral load in the peripheral blood provides an inaccurate picture of the overall viral load. LIR workers have also published important work on HIV-infected monocytes, shown in vitro the possibility of infecting CD8+ T cells, and shed light on how cytokines (e.g., TNF-alpha, TGF-beta, IL-6) affect HIV expression and the immune response. The Laboratory of Infectious Diseases (LID), chief Robert Chanock, studies dengue virus, rotaviruses, salmonella, respiratory, influenza viruses, woodchuck virus, HAV, HBV, HCV, SIV and FeLV. The Laboratory of Molecular Microbiology (LMM), chief Malcolm Martin, studies the molecular genetics and protein products of mycoplasmas, oncoviruses, endogenous mammalian retroviruses (e.g., MuLV), HIV and SIV. They are busy looking at the HIV vpu gene and protein product, HIV-encoded inhibitory sequences, env mutants, vif

structure and function, molecular determinants of target cell tropism, rev-RRE interactions, ultraviolet (UV) light activation of HIV transcription, nef and oncogenic Ras protein comparisons, tat and TAR. The Laboratory of Parasitic Diseases (LPD), chief F.A. Neva, studies *Entamoeba histolytica*, *Trypanosoma cruzi*, *Giardia lamblia*, *Schistosoma mansoni* and *Toxoplasma gondii*. LPD work showed how schistosome parasites utilize host TNF-alpha to reproduce faster, turning host defense cytokines to their own use - a strategy which resembles one used by HIV. The Laboratory of Viral Diseases (LVD), chief Bernard Moss, studies pox, vaccinia, adeno-, parvo-, influenza, herpes and HIV. They are studying the two newest members of the human herpesvirus family, HHV-6 and HHV-7. They are also working on vaccinia virus vectors with HIV peptides as potential HIV vaccines. The Laboratory of Persistent Viral Diseases (LPVD), chief Bruce Chesebro, works on rabies, Friend retrovirus, Aleutian disease virus, scrapie, experimental allergic encephalomyelitis (EAE), equine infectious anemia virus (EIAV) and HIV cell tropism.

DIVISION OF AIDS (DAIDS) DAIDS runs most extramural AIDS programs for NIAID. It has three programs. Dan Hoth, MD is the Director, DAIDS. The Deputy Director is Jack Killen, MD. Marilyn Kunzweiler runs the DAIDS Administrative Office. Susan Ellenberg, PhD, heads the Biostatistics Research Branch (BRB). Peggy Johnston, PhD, is Associate Director of the Basic Research + Development Program (BRDP). Lewellys Barker, MD, MPH is Associate Director of the Clinical Research Program (CRP), and Bill Duncan, PhD, heads the Treatment Research Operations Program (TROP).

DAIDS Office of the Director (OD) Each level of the NIH recapitulates the one immediately above it ("Bureaucracy recapitulates hierarchy"). Thus, DAIDS, like NIAID or the NIH itself, has an "OD". The Director of DAIDS, Dan Hoth, came over from the NCI Developmental Therapeutics Branch (DTB) in October 1987. At NCI, Hoth had run several clinical research projects and had also worked on the Group C Cancer Drug system which in certain respects paved the way for later developments such as Treatment IND and Parallel Track. Hoth's Special Assistant, Deborah Katz, RN, MPH, is an invaluable source of information pertaining to DAIDS activities. DAIDS administers 37% of the entire NIH AIDS budget. Its responsibilities are enormous. Yet the DAIDS OD lacks strategic long-range planning staff.

Biostatistics Research Branch (BRB) The BRB provides statistical support for DAIDS clinical trials, including the ACTG, the CPCRA, DATRI, and the AVEG. BRB staff were among the first to forge constructive links with activists in 1989. BRB should work to streamline data collection and analysis in NIAID clinical trials. This is the only way that more could be done with current, limited funds. Cutting back on irrelevant data points can improve the efficiency of the ACTG and other systems. BRB can also help FDA and industry to continue developing more useful trial designs. Whether nucleosides confer a survival benefit is also unknown still unknown, and assessments of survival should be developed.

BASIC RESEARCH + DEVELOPMENT PROGRAM (BRDP) consists of the Pathogenesis, Developmental Therapeutics, Vaccine Research + Development, and Resources + Centers Branches (PB, DTB, VRDB, RCB respectively). Peggy Johnston, PhD, is Associate Director of the BRDP.

Pathogenesis Branch The chief of the Pathogenesis Branch (PB) is Gregory Milman. The PB pilots, standardizes, stockpiles and supplies AIDS-related research supplies and reagents to the international research effort, developing reference HIV isolates and proteins, susceptible cell lines, neutralizing monoclonal antibodies, and other materials for basic research. Rather than focussing on the

unresolved issues of AIDS pathogenesis, the PB principally supports technologically-driven work, especially molecular virology. For example, it helps to support the NIAID HIV Sequence Database + Analysis Unit in Los Alamos; it contracts out to investigators who are cloning and sequencing HIV, SIV, FIV and other retroviruses, and others making monoclonal and polyclonal antibodies. Its activities appear to be rather technology-driven, rather than idea-driven. What does the PB conduct to bring together diverse researchers, to catalyze collaboration, and maximize new research opportunities?

Developmental Therapeutics Branch (DTB) The acting chief of the Developmental Therapeutics Branch (DTB) is Chuck Litterst, PhD. In fall 1991, he confessed his delight that activists were finally beginning to pay attention to pre-clinical research. "We felt neglected before," he said. In FY 1991 DTB administered \$54,766,000 in extramural awards. Half of the awards funded solicited contracts and cooperative agreements, including the National Cooperative Drug Discovery Groups for HIV and for AIDS-Related Opportunistic Infections (NCDDG-HIV and NCDDG-OI, respectively). The other half funded investigator-initiated basic therapeutic research. DTB support accounts for one quarter of the NIH's overall spending on drug discovery and pre-clinical development, which totalled \$144M in FY 1991.

National Cooperative Drug Discovery Groups for the Treatment of HIV Infection (NCDDG-HIV) The first NCDDG awards were funded in fall 1986 and expired in August 1991. Several new rounds are still active. As many as 22 NCDDG-HIV contracts (U01) have been funded, with 10 projected to be funded through 1993-95. The NCDDG-HIV spent \$14.3M in FY 1991 and is budgeted at \$11.5M for FY 1992. Four NCDDG-HIV awards were made in 1991. NCDDG-HIV researchers elucidated the three-dimensional crystal structure of the CD4 molecule. Drugs whose anti-HIV activity was found by NCDDG contractors include the Roche tat inhibitor, the Abbott protease inhibitor, the nucleosides d4T, AZdU, FLT and 3TC, and the tumor necrosis factor (TNF) inhibitor pentoxifylline (Trental). NCDDG grantees include drug companies and academics. The NCDDG underwrote the discovery of the anti-HIV activity of the Roche tat gene inhibitors Ro 5-3335 (the lead compound) and Ro 24-7429 (the compound for clinical development). In FY 1991 alone, Roche received \$773,439 to develop inhibitors of tat and rev. Abbott's protease inhibitor A-77003 was also developed with NCDDG-HIV funds. The Abbott NCDDG received \$666,881 to study integrase and protease in FY 1991. Apparently, Abbott has since decided to develop its protease drug outside the NIH system, and has declined to accept further NCDDG funds.

NCDDG-OI Against a background of criticism from activists and from Congress that NIAID was ignoring the opportunistic infections, in 1990 DTB solicited a series of NCDDG awards specifically for OIs. NCDDG-OI awards totalled \$5.7M in FY 1991 and will rise to \$9.1M in FY 1992. Of the 11 NCDDG-OI awards funded in 1991, four were for antifungals, three for *Toxoplasma gondii*, and one each for *Mycobacterium avium*, *Cryptosporidia*, *Pneumocystis*, and CMV. Some of NIAID's anti-OI work is funded by DMID rather than by DAIDS. DMID funds the Cooperative Antiviral Study Group (CASG), the Mycoses Study Group (MSG), and preclinical herpesviruses (HSV, VZV, EBV, CMV), while DAIDS/DTB funds non-viral OIs. Better in vitro and animal models are critical to further progress against OIs.

DTB Contracts DTB administers contracts supporting research on animal models for anti-HIV, anti-OI, CNS-targeted and immune based therapies. DTB oversees confirmatory tests on the anti-HIV activity of compounds processed through the NCI screening program, using alternative strains, cell lines and syncytia-forming assays. DTB also sponsors contracts for drug synthesis (scaling up from lab quantities to kilograms for animal testing), formulation, quality assurance

methods development, small and large animal toxicology, and pharmacology with radiolabelled drugs. In addition it sponsors industrial production of virus stocks, antisera and recombinant HIV proteins for research use. Six contracts funded development of anti-HIV drugs in animal models [one in MuLV mice, one in HIV-SCID-hu mice, one in FeLV/FIV cats, and three in HIV-infected macaques.] Twelve contracts funded OI research, toxicology and pharmacology, including 4 PCP awards, 2 for candida and 2 for MAI. Six contracts funded development of immune-based therapies, using MuLV mouse models and FeLV/FIV feline models. These BRM contracts are due to expire in August 1992. Will they be refunded?

Vaccine Research + Development Branch (VRDB) The VRDB oversees pre-clinical, animal model, and early phase vaccine trials in both uninfected and infected primates (including macaques, chimpanzees and humans). In FY 1991 the VRDB awarded \$35.6M in grants and contracts. \$27M was in solicited awards, including the NCVDG and the AVEG (see below).

Correlates or Markers of Immunity in AIDS This series of six contracts underwrote vital studies of cell-mediated and humoral immunity in people with HIV and uninfected but exposed cohorts. Investigators included Janis Giorgi (UCLA), Susan Zolla-Pazner (NYU), Fred Valentine (NYU), George Bekesi (Mt. Sinai), Bijan Safai (Sloan-Kettering) and Edgar Engleman (Stanford). Topics included discordant couples (one positive, one negative), HIV-negative men with KS, and dendritic cells. This research is crucial to determining the pathogenesis of HIV-induced immune suppression, yet the contracts were terminated in June 1992 without renewal.

National Cooperative Vaccine Development Group (NCVDG) Thirteen industrial/academic consortia academia are working on pre-clinical AIDS vaccine development. This program cost \$10.7M in FY 1991 and will be cut \$1M to \$9.8M in FY 1992. NCVDG-funded work demonstrated protection of rhesus macaques against SIV challenges in three different systems. This work is vital not only for vaccine development, but for a better understanding of the pathogenesis of AIDS.

SIV Vaccine Evaluation Units (SVEUs) VRDB spent \$2M on primate studies in FY 1991 and is doubling this figure to \$4M in FY 1992. Because protective immunity has been demonstrated on cell-free and cell-associated intravenous (but not mucosal) challenge with homologous SIV isolates, the SIV/macaque model continues to be vital for elucidating the mechanisms of protective immunity in primate immunodeficiency virus syndromes. Therefore, the VRDB issued two contracts at the end of 1990 to conduct further studies of SIV vaccines in the macaque model.

AIDS Cooperative Adjuvant Group (ACVG) Eight sites are participating in a search for better adjuvants (immunogenic preparations which enhance the immune response to a given vaccine).

AIDS Vaccine Evaluation Units (AVEUs) NIAID set up the AVEU system in 1988. Five institutions have studied five immunogens in HIV-negative populations. The AVEUs are not ideally situated for large-scale vaccine efficacy trials. They will continue to be used for preliminary studies. Larger studies will be done by the new VTEB in high-incidence areas. AVEU funding is \$7.5M this year.

Planning International Vaccine Studies The VRDB is working with DMID, the NIH OAR, the Office of International Health, the CDC, the Defense Department, WHO and others to plan the HIV vaccine field trials in Africa, Asia and South America (as well as, possibly, the USA). US travel restrictions continue to impede international vaccine collaboration.

Resources + Centers Branch (RCB) This hitherto obscure branch is mainly administrative in scope, handling grant applications, providing technical assistance to nervous applicants, and negotiating the paperwork to transfer applications from other institutes to NIAID if necessary. AIDS grants receive expedited review compared to normal grants, so they have their own timeline separate from the overwhelming flow of everyday grants. RCB oversees grantees' abilities to dispose of biohazards, to conduct animal and human research, and may conduct site visits from time to time. It also runs the Centers for AIDS Research (CFARs), P30 grants which provide various coordinating and centralizing services for researchers. There are 13 CFARs, involved in everything from X-ray crystallography of host and viral proteins to drug toxicology, animal facilities support, clinical research and data management. The RCB conducts site visits to selected CFARs and other BRDP-administered programs. Given the limitations on NIH staff travel, sites can expect a long time before the next inspection.

Centers for AIDS Research (CFARs) Seven CFARs were funded in 1988, four in 1989, and two more in 1991, making a total now of 13. CFARs cost \$10M in FY 1991 and will be awarded \$7M in FY 1992 (more basic research casualties of the ACTG Recompetition and the Pediatric earmark). They are multidisciplinary research centers often with laboratory, animal, clinical and data components.

CLINICAL RESEARCH PROGRAM (CRP) CRP and TROP were created in 1991 by splitting the former Treatment Research Program into scientific (CRP) and logistical support (TROP) components. The Treatment Research Program (CRP + TROP) is the largest single component (40%) of DAIDS, costing \$124M in FY 1991. The ACTG cost \$92M (\$40.5M for adult units, \$27M for pediatric ones, \$3M for minority sites, \$1M for the National Hemophilia Foundation, \$20M for contracts). CRP consists of the Vaccine Trials + Epidemiology Branch (VTEB, chief Sten Vermund), the Medical Branch (chief Steve Schnittman), the Pediatric Medical Branch (PMB, chief Jim Balsley) and the Community Clinical Research Branch (CCRB, chief Lawrence Deyton).

Epidemiology Branch CRP incorporated the Epidemiology Branch (EB), formerly part of BRDP, into its new Vaccine Trials + Epidemiology Branch (VTEB), whose chief is still Sten Vermund. While the VRDB remains the chief supporter of pre-clinical, animal and early phase vaccine research, the VTEB will develop the domestic and international infrastructure to conduct the vaccine efficacy trials. The EB spent \$33M in FY 1991. The EB's budget of \$33,105,000 amounted to about 1/4 of NIH's \$120.5M budget for "Population-Based Research" (Mason Category IIB). Much early NIH AIDS work consisted of epidemiology. In 1983 NIAID solicited what became the San Francisco Men's Health Study (SFMHS) and the Multicenter AIDS Cohort Study (MACS), which together cost \$5.59M in 1991. After many years, the limitations of focussing exclusively on gay men became clearer. In 1988 NIAID funded the Women and Infants Transmission Study (WITS, \$7M), the Heterosexual HIV Transmission Study (HATS, \$2.9M) and the Newark Perinatal Study. More recently, it started a study of the natural history of HIV infection in women (WIHS). International collaborations with the Pan American Health Organization (PAHO), the International Centers for AIDS Research (ICAR) and others cost \$6.9M in 1991. The EB also paid out \$10M in unsolicited epidemiology research grants, including \$7M in transmission studies and \$2.6M for natural history and cofactors.

MACS Before the discovery of HIV, the NIAID started a multicenter study of epidemiological, behavioral and immunological phenomena in high risk gay and bisexual men -- the Multicenter AIDS Cohort Study (MACS). Four MACS sites - Baltimore, Chicago, LA and Pittsburgh - recruited 4,954 gay and bisexual men into a multiyear study. 40% of the men in the MACS were seropositive at entry in

1984 (seroprevalent) and 350 more (8%) seroconverted during the course of the study (seroincident). The men are seen every 6 months, giving blood (and sometimes sperm) and filling out questionnaires. The MACS yielded over 150 papers in the published literature since 1984 on behavior, clinical medicine, epidemiology, immunology, neurology and virology. More data are now collected on opportunistic infection (OI) and cancer incidence and prevalence, and health care utilization.

Long-Term Survivors Since early 1991, we have been working with the Epidemiology Branch to stimulate studies of long-term HIV survivors. Up to 20% of San Francisco men who were HIV-infected as long ago as 1978 still have not developed AIDS. The MACS and New York Blood Center (NYBC) databases revealed a subset of men long-infected whose CD4 counts have actually increased, or remained steady, over 7 years or more. Further studies of these survivors are crucial if we are ever to learn what constitutes protective immunity against HIV. Sten Vermund has promised a meeting on this topic sometime after Amsterdam.

The San Francisco Men's Health Study (SFMHS) is a similar, though smaller, long-term cohort of around 1,000 gay men chosen randomly from high-AIDS-incidence areas in San Francisco. The MACS and SFMHS awards were renewed for four more years in 1991. Funding for the MACS/SFMHS will rise from \$5.6M in FY 1991 to \$12.3M in FY 1992, but most of the new funds are for "vaccine feasibility study infrastructure development." The MACS and SFMHS sites are going to be used to develop potential high-risk cohorts (including young gay men) to track the incidence of seroconversion in the 1990s. The currently-planned feasibility studies won't use HIV immunogens or vaccines, but may use Hepatitis B vaccine.

Heterosexual AIDS Transmission Study (HATS) was funded in 1988. There are three sites (Newark, Brooklyn, San Juan). The Newark site follows 60 discordant couples (one HIV+, one negative) to assess immunologic and other correlates of infection or protection. The Brooklyn site follows 200 women with a history of multiple sex partners, crack users who may exchange sex for drugs, and sexual partners of injection drug users (IDUs).

Women + Infants Transmission Study (WITS) cosponsored by NIAID and NICHD, was funded in 1989. The four sites are Boston, Chicago, New York and San Juan. Over 170 pregnant HIV+ women have enrolled, over 120 infants have been born, and at least 120 nonpregnant women are also enrolled. The study examines "the effects of HIV infection on pregnant and nonpregnant women, factors that predict transmission from mother to fetus or infant and the timing of transmission, methods for early diagnosis of HIV in the infant, and the natural history of HIV in infants."

Women's Interagency Health Study (WIHS) Women developed AIDS in the early 1980s, but still have not become a focus of research in their own right. After NIAID sponsored a conference in December 1990 on Women and HIV Infection, it began planning a prospective cohort of women with HIV to better elucidate the natural history of HIV in women. The WIHS will take place at 4 NIAID-funded sites and at 4 sites sponsored by other PHS agencies. \$1M will be spent on start-up in FY 1992. The total cost will be \$7M over 4 years starting in FY 1993. Collaborating with NIAID on the WIHS are NIMH, NIDA, NCI, NICHD and the CDC (which should have started this study long ago).

Observational Data Base (ODB) The ODB is a project of the Community Programs for Clinical Research on AIDS (CPCRA). It follows about 5,000 HIV+ patients seen at CPCRA sites, collecting OI incidence and tracks patterns of treatment usage. By 19 June 1992, the CPCRA ODB had enrolled 4,497 (almost 95% of the CPCRA's total)



participants, of whom 57% were minorities, 41% IVDUs and 20% women (see below for more on the CPCRA). [It is probably by counting participants in epidemiological and observational cohorts that HHS Secretary Louis Sullivan has the audacity to claim that over half the participants in NIH AIDS clinical efforts are minorities.]

ICAR ICAR, or International Collaboration in AIDS Research, funds collaborations between US sites and Third World health ministries, including those in Uganda, Mexico, Malawi, Brazil, Kenya, Rwanda, Zambia and Senegal. ICAR projects are examining HIV/MTB interactions, HIV variation, and wasting.

CIRAS ICAR projects are being cut back or defunded in order to make way for a new program, CIRAS or Cooperation in International Research on AIDS and STDs. This new project will involve cooperative agreement research proposals focussing on epidemiology useful in future trials of vaccines for AIDS.

Project SIDA was a multidisciplinary study based in Kinshasa, Zaire, sponsored by NIAID, the CDC, the Belgian Institute of Tropical Medicine and the Zairian Ministry of Health. Conducted since 1984, Project SIDA was terminated in 1991 during a popular uprising directed against Zairian dictator Mobutu Sese Seko. "Project SIDA staff are now all in the US following the recent uprising in Zaire. It is unclear when, if ever, the project will resume its activities."

PAHO The Pan American Health Organization (PAHO) works with NIAID on AIDS studies in Latin America and the Caribbean. Epidemiological studies are currently underway in the Dominican Republic, Mexico and Brazil. PAHO and NIAID are planning a study of tuberculosis prophylaxis in Mexico City. PAHO's Caribbean Epidemiology Centre (CAREC) has established a special research facility to support studies on the natural history of AIDS in 19 Caribbean and Latin American countries.

Medical Branch (MB) The MB, whose chief, Steven Schnittman, worked for many years in the NIAID Laboratory of Immunoregulation, consists of 4 sections: Antiretroviral Treatment Research Section (head: Carla Pettinelli); Opportunistic Infections Treatment Research Section (head: Richard Hafner); Immune-Based Therapies Research Section (head: John Kagan); Clinical Sciences Section. Each Section coordinates DAIDS trials which fall into its purview. The Medical Branch employs a number of other MDs and PhDs who serve as Medical Officers on DAIDS protocols, negotiate with drug companies, attempt to coordinate ACTG research committees, and provide other useful functions.

Pediatric Medical Branch (PMB) was formed in 1991 partly to centralize administration for the burgeoning Pediatric ACTG. Its chief is Jim Balsley, MD.

Community Clinical Research Branch (CCRB) (chief: Bopper Deyton, MD) administers the Community Programs for Clinical Research on AIDS (CPCRA), a contract-based mechanism (N01) which is currently running three therapeutic clinical trials and the Observational Database.

TREATMENT RESEARCH OPERATIONS PROGRAM (TROP) The Associate Director for TROP is Bill Duncan, PhD, who earlier was associate director of the NIAID DAIT and later worked at the Canadian NCI before coming back to Bethesda to manage the logistical and support aspects of the DAIDS Treatment Program. Duncan's special assistant is Rona Schmutter.

The Clinical Research Management Branch (CRMB) Chief: George Counts, MD, is divided into two sections, the Adult and Pediatric Clinical Trial Sections.

Counts and his staff are responsible for tracking the performance of ACTG sites, including their efforts at outreach and enrollment of underrepresented populations. He has the unenviable task of tracking ACTG accrual by site, protocol, sex and race, and of awarding the "incentive funding" which is so often promised to be imminent and eminently available to solve all the ACTG's problems. [Each ACTU, after the recompetition, receives 70-85% of its grant upfront in a "core" award; only certain lucky or competent sites will receive additional "incentive" funds tied to high performance partway through the grant cycle.]

The Operations + Data Management Branch (ODMB) Chief Dennis Dixon, PhD, oversees the many clinical research-related contracts involved in servicing the ACTG, CPCRA and DATRI programs. These include Harvard's Statistics + Data Analysis Center (SDAC); Frontier Science (FRSTRF) in Buffalo, NY - the nightmare computer contractor supposed to provide "on-line real-time data input and analysis" for ACTG trials; Technical Resources Inc. (TRI), which provides support for the ACTG conferences and other ad hoc DAIDS meetings; and SSS (Social + Scientific Systems), the ACTG Operations Office, a 60-person firm which is the ACTG secretariat. Dixon headed the ACTG Protocol Development Review Committee, which developed a plan to cut ACTG protocol development in half. ODMB is also working on a plan to place datasets from published ACTG studies on file with the US National Technical Information Service (NTIS) so that other researchers can work with the data.

The Pharmaceutical + Regulatory Affairs Branch (PRAB), chief Joe Meschino, PhD, has two sections, Regulatory Affairs and IND Management. PRAB handles investigational new drug (IND) issues with the FDA - especially on so-called "routine" protocols in which NIAID holds the IND - and negotiates with drug companies on pharmaceutical supplies, including blinded placebos and blister packs for clinical trials.

AIDS Clinical Trials Group (ACTG). The ACTG is the largest single AIDS program administered by NIH, taking \$92M in grants and contracts in FY 1991 and \$103M in FY 1992. The ACTG accounts for one-eighth of all NIH AIDS spending. It is the program with which activists are most familiar, and the one which they have changed most. In 1985 NIAID released a Request for Proposal (RFP) for AIDS Treatment Evaluation Units in an effort to fund a multicenter clinical trials network. 14 ATEU contracts were awarded in June 1986. In January 1987, 5 additional ATEUs were formed and NIAID funded several Clinical Studies Groups (CSGs) through cooperative agreements. After Dan Hoth was named Director of NIAID's AIDS Program in October 1987, the ATEUs and the CSGs merged into the cooperative-agreement (U01) funded AIDS Clinical Trials Group (ACTG). The ACTG cost \$92M in 1991 (counting both grants and contracts); it is projected to spend \$103M in FY 1992 [a total of \$465 million between 1986-92].

The ACTG has conducted almost 200 clinical trials of scores of drugs enrolling 19,330 patients. ACTG studies led to approval of AZT for people with CD4<500 (016, 019) and for children (003, 043); they also led to halving the licensed dose of AZT from 1200 mg/day to 600 mg (002, 010, 019). The ACTG brought ddI from phase I study (064) through to licensure on the basis of surrogate markers in 1991 and follow-up proof of clinical benefit in 1992 (116B/117). The ACTG also conducted phase I, phase I/II and phase II/III studies of ddC, some of which (012, 047, 050, 106, 114, 119) were included in the Roche NDA submission which was approved in summer 1992. The ACTG also demonstrated antiretroviral activity of d4T in a phase I trial (089), but decided thereafter to let industry pursue efficacy studies of additional nucleoside analogues.

The ACTG demonstrated the following agents to have little or no antiretroviral activity at the doses used: ribavirin (034, 035, NS403), AL-721 (022), dextran sulfate (060, 078, 105), recombinant soluble CD4 (066, 101, 121), N-butyl-DNJ (100), amplitgen (038, 054, 056), and recombinant tumor necrosis factor with or without recombinant interferon gamma (025). ACTG studies of recombinant Interleukin-2 (rIL-2; 024, 042, 067) and of autologous CD8 cells expanded ex vivo with a cocktail of recombinant cytokines (080) suggested but did not prove that they are active and should be subjected to further study.

In the realm of opportunistic infections, ACTG studies (026, 059) contributed to licensing of fluconazole for cryptococcal meningitis. ACTG 159 is attempting to identify the optimal induction and maintenance regimens for this disease. The ACTG has also demonstrated the efficacy of itraconazole (084, 120) for histoplasmosis, but these studies have not been published, nor has the FDA licensed the drug. ACTG 021 concluded in 1991 that trimethoprim-sulfamethoxazole was more effective than aerosolized pentamidine in preventing a second episode of PCP; a comparison of those agents with dapsone as primary prophylaxis is ongoing (081). ACTG 015 was included in the NDA of foscarnet for CMV retinitis. The SOCA study ACTG 129 suggested that foscarnet may provide a survival benefit as compared to ganciclovir in people on CMV retinitis maintenance therapy. The ACTG has also worked on studies of novel anti-herpesvirus agents and indications, such as foscarnet for acyclovir-resistant herpes (095), oral FIAC/FIAU (122) and oral ganciclovir (127). ACTG 981 may suggest the best antifungal prophylaxis (fluconazole or clotrimazole), if any. ACTG 113 showed that spiramycin was ineffective as treatment for cryptosporidiosis. ACTG 135 may help to define a multi-drug standard of care for MAI, and 157 demonstrated anti-MAI activity of clarithromycin. ACTG 154 is studying pyrimethamine with leucovorin rescue for toxoplasmosis prophylaxis, and 156 is studying the combination of azithromycin and pyrimethamine for acute therapy.

The ACTG has also refined chemotherapy regimens, sometimes including bone-marrow protecting colony stimulating factors (CSFs), for AIDS-related malignancies (006, 013, 014, 057, 075, 090, 094, 096, 109, 110 for KS; 008, 074 for lymphomas).

New trials. Recent additions to the ACTG roster include several non-nucleoside reverse transcriptase inhibitors (nevirapine, ACTG 164, 168, 208; L,669 - ACTG 184; U-87201E - ACTG 199); several novel potential antiretrovirals (synthetic hypericin - ACTG 150; CD4-PE40 - ACTG 201); potential immune based therapies (pentoxifylline, ACTG 160); HIV immunogens (rgp160 and others, ACTG 205, 209, 214). 5-fluorouracil (5-FU) will be studied for secondary prevention of cervical dysplasia in HIV-infected women (ACTG 200). The angiogenesis inhibitor AGM-1470 will enter phase I for Kaposi's sarcoma (ACTG 215). Dexamethasone will be tried as supportive therapy for cryptococcal meningitis (ACTG 202). Large prophylaxis studies for MAI (196) and CMV (204) are planned, and a TB prophylaxis study (177) is underway. Albendazole will be tried out in microsporidiosis (207), and letrazuril and humatin are being studied for cryptosporidiosis (198 + 192). Finally, although it depends on the uncertain wisdom of Roche, plans are being made to conduct phase I/II studies of the Roche protease inhibitor (Ro 31-8959, ACTG 212) and tat inhibitor (ACTG 213, Ro 24-7429).

Over the last two years, the ACTG has weathered significant changes, including plateauing and then declining budget growth, the metastasis of the pediatric ACTG system at the expense of the adult one, shifting of resources away to the CPCRA and the DATRI, the recompetition of the adult ACTUs, harsh public criticism from Congress, activists and the pharmaceutical industry, radical shifts in the regulatory climate, incorporation of community representatives into its committee structure, and major leadership transitions in its executive

committee and elsewhere. Several of these developments occurred in response to the original activist critique. Many of the changes have been slow in coming, and many profound changes remain to be made. Following the recompetition of the 35 adult ACTUs, six units were initially defunded, while seven new adult and nine new pediatric units were added to the system, bringing the total to 29 adult ACTUs and 25 pediatric ACTUs. Following an outcry from activists, Congressmen and researchers, NIAID restored interim funding to six defunded adult units through the end of 1992; their ultimate fate will be decided in the presumably calmer post-election climate.

Units competing for the current cycle of five-year cooperative agreements had to guarantee that they would be able to fill 60-150 clinical trial slots annually, depending on the level at which they were funded and the "intensity score" of the protocols they undertook. Funds were to be awarded under a complicated scheme by which 75-90% of the funds are in "core" awards, with the remainder doled out sometime later as "incentive" funds to well-performing sites. The point of the core/incentive system was to tie funding to performance - a long-term activist goal. The problem was that, in order to fund as many sites as possible, but given current budget rises of 2.7% (1991) and 11% (1992), NIAID had to slash many sites' budget requests by up to half. The result is that sites will be hard pressed to meet their "quotas." Many will opt to do large outpatient trials rather than resource intensive oncology, neurology, OI treatment or advanced AIDS trials. Recompeting sites had to guarantee that they would participate in trials of antiretroviral drugs and of OI treatment and prophylaxis. Participation in oncology, neurology and immunology was entirely optional, however. Supplemental funds were available for "developmental virology," and were awarded to 15 sites to continue developing virological assays. Twelve pharmacologists are funded by the ACTG, along with a new central pharmacology lab. Immunology failed to do as well, with only five "advanced immunology awards" being made, of under \$100,000 each (barely enough for a technician, supplies, and 50% indirect costs). No funds were set aside for neurology. In order to deal with the budget cuts, many sites had to lay off productive staff of considerable experience and dedication. Some sites are now dependent for their true "core" funds upon their NCRR-funded M01 General Clinical Research Center (GCRC) awards, rather than upon their ACTG awards. Adult ACTUs have too many patients clamoring for too few trials, while pediatric ones have the opposite situation - too few patients for so many trials.

ACT UP members first attended the 7th ACTG in November 1989. What they found there led directly to a campaign to open up the ACTG and restructure it; this campaign culminated in ACT UP's "Storm the NIH" demonstration on May 21, 1990. Following the demonstration, the ACTG meetings were opened to all interested observers, activists and journalists. In November 1990, at the 10th ACTG, members of the Community Constituency Group (CCG), a 24-member committee including activists, people with HIV, women, African Americans, Latinos, HIV-infected mothers and mothers of HIV-infected children, people living with hemophilia and ex-injection drug users, became voting members of all ACTG research and resource committees, including the Executive Committee. The CCG and other persistent activists have begun to effect some slow but profound changes in the ACTG. Some researchers, especially in OIs, immunology and neurology, have proved eager to work with activists and open to new ideas.

While ACTG leaders have professed a commitment to increasing the study of immune-based therapies, including cytokine inhibitors and HIV immunogens, DAIDS has provided no resources to scale up the necessary immunologic assays (delayed type hypersensitivity, cytotoxic T lymphocytes, proliferative responses, neutralizing antibodies, cytokine or HIV mRNA levels, etc.).

The ACTG's Primary Infection Committee remains refractory, insular, uncommunicative and deliberately uncognizant of resource limitations and logistical obstacles. Community activists have never been happy with the recent series of large, last-gasp nucleoside trials (076 in pregnant women, 175 in asymptomatics, 193 in people with under 50 CD4 cells). Pervasive problems with these large, expensive studies are seldom addressed until after the fact, when much damage has been done. For example, women from 076 who have given birth are not followed up formally. There is no follow-up study for them to enroll in. The baby remains on trial drug, while the mother is dropped. The CCG and the ACTG Data + Safety Monitoring Board have asked for provision to be made for these women for over one year without result. Meanwhile, in ACTG 175, people are choking, vomiting and dropping off study because of the enormous and unpalatable ddI pills used therein. ACTG 193 will subject its participants - people with CD4<50 - to 20-40 pills a day (including up to 2/3 placebos) in a double-blind comparison of alternating vs. combination AZT/ddI and AZT/ddC. This population will also be asked to join two placebo-controlled double-blind studies for MAI and CMV prophylaxis, ACTG 196 and 204. 193 may well crash, since its drugs can be obtained commercially, unlike the study drugs of the more important and more novel OI prophylaxis studies.

There is still no system to streamline ACTG data validation, analysis and publication. Many of the ACTG's most important completed studies - especially OI studies - remain unpublished. Vital contributions to the standard of care thus remain unremarked in the medical literature, and unavailable to most people with HIV and their primary care physicians. Because of problems like these with timely data analysis and other problems of turf, control and paranoia, many pharmaceutical companies have become unwilling to work with the ACTG. Some, such as Roche, do their phase I studies abroad. Others, like Abbott, have withdrawn from collaboration with NIAID even though NIH funds paid for discovery of Abbott's protease inhibitor. In the absence of unanimous pharmaceutical acclaim and the continuing dearth of agents ready for large-scale evaluation, the ACTG could switch its attention to small pathogenesis-directed trials, but has not yet done so. Even if the tat or protease inhibitors were to demonstrate potential activity, the ACTG at its present size and shape cannot afford to take more than one drug through "critical path" studies to licensure at a time. The experience with ddI and ddC (where the phase II studies of the latter were conducted mainly outside the ACTG) shows that the system cannot accommodate more than one NDA program at a time.

Community Programs for Clinical Research on AIDS (CPCRA). The CPCRA was set up with \$9M in FY 1990 (funding started in fall 1989) and grew by 92% to \$17.2M in FY 1991. It is projected to cost about \$19M in FY 1993. The CPCRA's 18 sites include many hospitals and clinics which serve populations previously underrepresented in clinical research. The CPCRA cannot decide whether it wants to be a mini-ACTG or whether it wants to conduct a different kind of research (for example, low-tech trials which optimize the standard of care). So far, most participants have enrolled in the ODB, with 433 enrolled in a toxoplasmosis prophylaxis study (now closed), 467 in a ddI vs. ddC comparison, and an unknown number in a MTB prophylaxis study. A study of fluconazole for vaginal candidiasis is in development. Of the CPCRA's 5,022 participants, 20% (978) are women, 15.6% (703) Latino/Hispanic, 40.8% (1,987) African-American, 42.3% (2,139) white, 0.4% (21) Asian/Pacific Islander, 0.2% (13) Aleutian Eskimo/Native American, and 0.7% (41) Other/Unknown. Underrepresented populations represent more than half of the CPCRA participants, but, needless to say, since 95% of them are on the Observational Database, and only <5% on a treatment trial, most of them are not being treated in Federally-sponsored

protocols. This explains HHS Secretary Louis W. Sullivan's argument that "minorities now represent more than 50% of those participating in all PHS-sponsored HIV-related clinical trials."

Division of AIDS Treatment Research Initiative (DATRI). DATRI is a new, extramural, contract-funded mechanism by which NIAID can conduct fast, early phase studies and trials of compounds which are not high priorities within the ACTG or the CPCRA, but which should be studied for public health or other reasons. The DATRI was formed by NIAID after years of activist criticism that the ACTG was incapable (and sometimes unwilling) to conduct efficient phase one trials of novel agents or approaches. NIAID floated an RFA in 1991 for DATRI, and developed a new network of 40-50 sites willing to conduct studies under contract. DATRI cost \$4.3M in FY 1991 and will cost \$5.9M in FY 1992. DATRI's first four studies are: pharmacokinetic interactions of rifabutin with clarithromycin or azithromycin; 12 weeks of AZT or placebo in people with acute primary HIV (before seroconversion); a study of lymph node viral burden pre- and post-treatment with nucleosides; and megace, dronabinol or both for the wasting syndrome.

Funding + Future Plans. NIAID's AIDS budget was \$431M in 1991, \$450M in 1992 and will be \$471M under the President's 1993 budget. In 1991 AIDS accounted for amounted to 47.7% of NIAID's total budget and 53.4% of the NIH AIDS budget. NIAID requested \$594M in FY 1993 - an increase of \$144M - but received only \$21M in new funds (4.7%), barely enough to keep up with inflation. The President cut \$124M from NIAID's request. NIAID had to cut the award rate (percentage of approved applications which are funded) in half this year, from 40% in FY 1991 to 19% in 1992. The number of AIDS grants awarded this year will also suffer, dropping from 156 last year to just 123 this time. There are 281 full-time equivalent (FTE) AIDS employees at NIAID in FY 1991, of whom 119 were at DAIDS. AIDS FTEs will rise to 355 at NIAID and 133 at DAIDS in FY 1992-93. While in 1991, 40% of the approved AIDS grants were funded, that rate will drop to 19.9% in 1992. According to a NIAID staffer, "the drop in the estimated FY 1992 award rate is because of the substantial amount of resources required for the adult ACTU recompetition and the dollars needed to fund the Pediatric AIDS clinical trial earmark. These in combination will result in fewer competing grants being funded." This year, at least, basic research is being starved to pay for the renewed ACTG. The items which NIAID wished to fund in FY 1993 were:

#### Basic research

\* \$12.6 million for new extramural virology projects (R01s); \* \$12.6M for new extramural immunology projects (R01s); \* \$9M for intramural work on pathogenesis and drug development; \* \$2.3M to study mucosal immunity; \* \$165,000 for animal models of OIs; \* \$2.6M to expand the CFARs; \* \$118,000 to study CD4-induced changes in gp160/gp120; \* \$2M to develop rapid methods to detect antigenic variation among HIV isolates worldwide; \* \$90,000 for intramural development of NF-kB dominant negative mutants; \* \$500,000 to renew the 1988 AIDS Research & Reference Reagents Program; \* \$1.2M to study gut-associated lymphoid tissues (GALT) anti-HIV responses; \* \$5M for mucosal immunity and transmission studies; \* \$630,000 to develop new models for fungal skin infections; \* \$800,000 for "basic research to foster strategies for reversal of immune suppression"; \* \$700,000 to develop models for natural history, diagnosis and disease of microsporidia; \* \$177,000 for add-ons to ongoing neuroscience activities; \* \$3.8M to double NIAID-funded AIDS training fellowships;

#### Drug development

\* \$3M for minority infrastructure clinical trials development; \* \$360,000 to screen new anti-HIV agents in the SCID-hu mouse model; \* \$90,000 for additional studies of CD4-PE40; \* \$500,000 to screen new OI drugs; \* \$1.3M to develop anti-HIV gene therapies; \* \$1.5M in new funds for targeted OI drug delivery; \* \$160,000 to develop intracellular anti-HIV antibodies; \* \$500,000 to study viral resistance to anti-HIV drugs; \* \$930,000 for ACTG drug supply management; \* \$7M in new funds for the CPCRA (for total of \$26M); \* \$300,000 to support ACTG pharmacology labs; \* \$800,000 to support ACTG immunology labs \* \$1M to support reference centers for OI pathogens;

#### Vaccine development

\* \$12.5M for SDAC to manage the data from vaccine trials; \* \$3M to evaluate AIDS vaccines in chimpanzees; \* \$1.6M to develop HIV particle vaccines; \* \$1M to develop vectors to induce mucosal immunity;

#### Epidemiology

\* \$10M for a new cohort study of women with HIV; \* \$13.5M in additional funds to enlarge the WITS study (for total of \$20M); \* \$5.7M to establish and enlarge the WITS data center (to total \$8.7M);

Given the flat funding base, to fund any of these new programs, NIAID will have to cannibalize existing ones and/or cut the amount of new R01s it awards this year.

#### Recommendations:

\* NIAID, as the lead AIDS institute, is responsible for coordinating the NIH AIDS effort, ensuring that efforts are not duplicated and orphan areas are not left unstudied, and for carrying out the substantial recommendations we have listed above and throughout this report.

\* Major increases in basic, applied and clinical immunology are required if the promise of immune-based therapy is to be achieved;

\* A new focus on small, well designed, precisely focused pathogenesis-directed clinical studies may be the best focus for DATRI and for much of the early phase ACTG studies in the future; \* NIAID should streamline and coordinate its 4-5 clinical research networks. The ACTG needs CPCRA subjects for its large antiretroviral efficacy and OI prophylaxis trials. Yet the CPCRA cannot conduct such data-intensive research; the ACTG needs to simplify its larger trials to make them less high tech and more accessible. Statisticians and research nurses must play a more vocal role in streamlining the NIAID research behemoth. Analysis and publication of results must be accelerated;

\* The ACTG must develop new, effective links with research groups funded by other NIH institutes such as the AIDS Lymphoma Network (NCI), SOCA (NEI), Pediatric ACTG (NICHD), and the NIH Clinical Center (NIHCC); \* Previously underrepresented populations must be allowed to enroll in therapeutic and not just observational studies if the hollow promises of Dr. Sullivan are ever to be replaced with a true commitment to diversity in clinical research.

\*

II/2. National Cancer Institute (NCI)

NCI, the largest and oldest of the NIH, was founded in 1937. President Nixon's 1971 "War on Cancer" brought NCI (and NIH) funding to new heights. The ensuing decades brought great improvements in molecular biology - subsidized by the war on cancer - but actual therapeutic progress against the 200 or so human neoplasms, or even a coherent pathogenetic picture of their etiology, lagged far behind. This set the template for NIH AIDS research a decade later. AIDS supplanted cancer as the ultimate scourge in the popular imagination. Initially, the NCI was the leading AIDS agency at NIH. The NCI has five divisions: Cancer Biology and Diagnosis; Cancer Etiology; Cancer Prevention and Control; Cancer Treatment, and; Extramural Activities. The NCI's budget, the largest at NIH, was \$1,711,646,000 in FY 1991. It rose to \$1.95 billion this year. The NCI Director is Samuel Broder, MD, who was born in Poland in 1945, graduated from the University of Michigan School of Medicine in 1970, completed his training at Stanford, and joined NCI in 1972. In 1981 he became associate director of the Division of Cancer Treatment's Clinical Oncology Program (DCT's COP). There he, along with Hiroaki Mitsuya, Robert Yarchoan and others, developed the in vitro screen for HIV reverse transcriptase inhibitors which led in 1985 to the identification of the dideoxynucleosides (AZT, ddC, ddA/ddI, etc.) as potential antiretroviral agents. President Reagan named Broder NCI Director in 1988, after Vincent DeVita, Director through most of the 1980s, left in disgust with the state of Federally-supported biomedical research. Broder was the first chairman of the NIH AIDS Drug Selection Committee, created in 1986. While his current responsibilities are considerable, Dr. Broder remains involved in AIDS research at NCI.

NCI's appropriations for AIDS are second only NIAID's. Its AIDS allocation in FY 1991 was 20% of NIH's total, and 10% of the NCI total budget. This amounted to \$160,869,000 in 1991. NCI's budget skips PHS, HHS and OMB and goes straight to the President under a special "budget bypass" provision. In spite of this privilege, President Bush slashed \$44M from NCI's 1993 AIDS budget request, from \$217.5M to \$175.8M, or less than the rate of biomedical inflation. NCI spends more on AIDS intramurally than any other ICD (including NIAID: NCI \$75M, NIAID \$47M). NCI's AIDS budget is half extramural (\$79.5M), half intramural (\$75.2M). Over half the extramural R+D contracts (N01s) support NCI's intramural work as well (e.g., two contracts totalling \$24.8M support the NCI Frederick Cancer Research Facility). While NIAID has a Division of AIDS, which conducts most (72%) of its AIDS research, NCI's AIDS work is distributed throughout the institute. This makes it harder to get an overview of the entire program and to figure out where responsibility for various programs lies.

Drug Discovery + Preclinical Development. NCI spent \$42.5 million on drug discovery and preclinical development in 1991, one fourth of its AIDS effort. \$24.8M was spent extramurally, and \$16M intramurally. Michael Grever MD, the acting director of the Developmental Therapeutics Branch of the Division of Cancer Treatment (DCT) supervises this effort, the bulk of which is directed at identifying and developing treatments for HIV itself and the AIDS related malignancies, Kaposi's sarcoma in particular. NCI's Developmental Therapeutics Program (DTP) procures, solicits and screens compounds for activity against acutely HIV infected T cell lines. The original assay was developed by Hiroaki Mitsuya in Broder's group, which brought the world the dideoxynucleosides. This screen was standardized and scaled up by 1987 for an intramural, high-volume AIDS drug screen in the Antiviral Evaluations Branch. AEB's chief, John Bader, PhD, heads this project, which has now screened 47,600 agents (23,500 synthetic compounds and 24,100 natural product extracts) since its inception. 416 (or 0.8%) of these showed selective anti-HIV activity, but fewer than 1% of these will go on to clinical development. Supplementing its in-house screen, NCI farms some work out to extramural contractors and grantees. Some compounds are tracked



down through computer databases, and if they are not commercially available, NCI can have them synthesized or purified from natural sources. NCI supports synthetic chemistry to develop new nucleoside and folate analogues, and congeners and prodrugs of lead compounds identified by screening.

NCI's Natural Products Program (NPP) contracts out plant collection in Central and South America, Africa and Southeast Asia; and supports harvesting of marine microorganisms from the world's oceans. Extracts of novel plant or microbial species are then tested for activity against HIV in NCI's intramural screen or by extramural grantees. Intramural researchers are also testing Chinese medicinal herbs for anti-HIV activity, and synthesizing less toxic single-chain ribosome inactivating proteins (SCRIPs) derived from trichosanthin and other plants. The NPP has prioritized four compounds for development: Bryostatins, an anti-cancer agent which might be useful in treating AIDS lymphomas; Prostratin, a phorbol ester which might protect cells from the damaging effects of HIV; Sulfolipid, a compound with anti-HIV activity; and Camptothecin, a potent anti-tumor compound, which also inhibits HIV topoisomerase I. The NPP identified six new classes of tropical plant-derived compounds which are active against HIV.

NCI also supports so-called "rational drug design" approaches to anti-HIV therapy, using structure-activity relationships to devise inhibitors of viral proteins and enzymes or host receptors, proteins and transcription factors. NCI is also focusing on the cell cycle and its division in order to develop new cancer drugs. Much of this work occurs at the AIDS Basic Research Program at the Frederick Cancer Research Facility. Compounds which pass the NCI anti-HIV screen with flying colors (and which don't do so by killing the cell line used) are sent on to preclinical development programs administered by the Laboratory of Drug Discovery, Research and Development (LDDR), which studies the agent's toxicology, animal pharmacology, formulation and mechanism of action. NCI has contracts to scale up production of the compound if necessary. Several labs in the Division of Cancer Treatment (DCT) also perform preclinical evaluations of candidate agents. NCI highlighted four drugs for high-priority preclinical development in FY 1993: Fluorodeoxycytidine (F-ddC), a ddC derivative which may cause less neuropathy than its parent compound [flush away your troubles with fluorine!]; Oxathilin carboxanilide, which inhibits HIV binding to the CD4+ cell surface; SP-PG and TIMP-2, two angiogenesis inhibitors

Immune-based Therapies are also part of NCI's AIDS program. Intramural investigators are working cytokines and other biological response modifiers (BRMs). The Laboratory of Experimental Immunology, in the Biological Response Modifiers Program (BRMP), in the Division of Cancer Treatment (DCT), has been investigating the effects of cytokines on blood progenitor cells, the effects of flavone acetic acid on cytokine expression, and the cytotoxic mechanisms of natural killer (NK) cells and cytotoxic T-lymphocytes and methods to enhance the activity of these cell populations. Immunotoxins - conjugates of Pseudomonas exotoxin + TGF-alpha, IL-2, IL-4, IL-6, IGF-1, acidic FGF, CD4, anti-Tac(Fv), or antitransferrin(Fv), are in development for the treatment of cancers and HIV infection. NCI researchers are developing assays to quantitate the production of cytokines in HIV infection. Of particular interest, is the institute's development of an assay for IL-6 production, which they are using to screen agents that will inhibit that cytokine. IL-6 has been implicated in the perpetuation of several different cancers, including the KS and NHL.

Clinical Trials. NCI spent \$39M on clinical trials for AIDS in 1991 (40% of the ACTG's allocation). \$31M of this went for NCI's intramural clinical program, which conducts early clinical evaluations of potential treatments for HIV in adults and children. NCI conducted the first phase I trials for AZT and ddI.

Robert Yarchoan, MD, of the DCT's Clinical Oncology Program (COP) runs the adult trials, and Philip Pizzo, MD, of the DCT's Pediatric Branch administers the trials for children. Adult trials in 1991 included studies of rCD4-IgG, alternating AZT+acyclovir/ddI, ddC, rHGH + rIGF, 3TC, and pentosan polysulfate (the last for KS). Pediatric trials included various nucleoside combinations, G-CSF/EPO with AZT, Clarithromycin and 3TC. A study for pregnant women and neonates used rCD4, then rCD4/ddI in neonates and rCD4 alone in the mother during labor and delivery.

The AIDS Lymphoma Network takes up half of the extramural clinical trials funds (\$3,150,718). It is administered by Ellen Feigal of the DCT Cancer Therapy Evaluation Program (CTEP). Twelve ALN sites are funded, of which 9 are also ACTUs. Since the ACTG has been unwilling to focus on AIDS-related cancers, it's lucky NCI stepped in to fill the gap. The ACTG Oncology Committee has done a good job against enormous odds. Oncology was "optional" (e.g., dispensable) in the recent ACTG recompetition. The AIDS Lymphoma Network supports clinical trials and studies of the pathogenesis of AIDS-associated lymphomas, including the involvement of cytokines (e.g. IL-6) and co-infections (e.g., EBV), proto-oncogene expression (e.g., C-myc, p53) in the etiology of these increasingly common neoplasms.

Basic Biomedical Research. Of NCI's \$45.5M for basic research on AIDS in 1991, \$23.8M went for extramural projects and \$19.8M for intramural work. However, \$9.2M in extramural contracts simply supported NCI's intramural programs, which reduces the amount for autonomous extramural work down to about \$14.6M. \$4.3M goes for core grants to NCI's Comprehensive Cancer Centers.

Virology. About \$4.23M supports investigator-initiated R01s and other awards to extramural researchers working on virological and molecular biological studies of HIV infection. Intramurally, \$13,151,000 has been set aside for work in this area. Kenneth Cremer, PhD, of the Division of Cancer Etiology (DCE) Biological Carcinogenesis Branch (BCB) administers an extramural program called AIDS Virus Studies, which supports a several grants investigating the molecular biology of the gene expression of HIV, SIV, EIAV, MuLV, HTLV-I, HTLV-II, and some RNA tumor viruses. Grantees are also studying interactions between HIV and CMV or adenovirus at the molecular level; the role of HIV and its proteins such as tat in the development of KS; the role of EBV in AIDS lymphomagenesis and leukoplakia; retroviral mutation rates; HIV-induced CD4+ cell membrane injury; cytokines and HIV activation; and retrovirus infection of the reproductive tract.

Immunology. In 1991, NCI spent \$8.7 million on the immunology of HIV infection. Of this, \$2.7M went for extramural projects, and \$5.7M for intramural work. (\$450,000 in extramural contracts supported the Frederick facility.) \$2.2M remaining in extramural funds supported investigator-initiated work (R01s) in T cell development; biochemistry of CTL-target interactions; herpes infection effects on leukocytes; hematopoietic cell tumors; genetic analysis of normal and malignant lymphocytes; molecular biology of HIV and CD4; T cell colony formation in AIDS; identification of suppressor T cell phenotypes; immunosuppression by avian leukemia viruses; cell-mediated immune response to human retroviruses; idio/anti-idio modulation of immunity in MuLV infection; liposomal IL-1 and immune function; lymphocyte homing in SIV infection; immunology of FIV infection; ontogeny and function of T helper cell subsets; TGF-beta in the pathogenesis of AIDS.

Animal Models. NCI allocated \$6.3M in 1991 to study animal models of HIV infection. \$5.18M went for extramural awards, and \$1M to support the Frederick Cancer Research Facility. \$300,000 helped maintain a colony of monkeys for NCI

intramural research. \$877,000 went for intramural work on animal models. Extramural researchers studied transgenic KS mouse models; primate type D retroviruses; EBV and oncogenesis; the SIV pol gene; SIV and murine type C viruses; immune responses to SIV and murine retroviruses; role of T cells in FIV; pathogenesis of FIV; EIAV gene expression; protective immunity and vaccines for CAEV; SIV genetic diversity; mice coinfecting with HIV and CMV; CMI in MAIDS; cytokines in MAIDS; BIV pathogenesis; EIAV genes and virulence; copathogens in FAIDS; and HIV-1 transgenic mice.

Vaccines. NCI spent \$15M on vaccine development in 1991, of which \$11.6M was extramural (of which \$6.5M went to Frederick - they just can't get enough!) - and \$2.5 intramural. \$2.1M went to the US Army research facility in Fort Detrick, Maryland, for their vaccine development efforts. Another \$100,000 provides for administrative support for Dr. Broder's office. \$2.4M went to contracts for technical support to intramural labs providing for production of mAbs and polyclonal antibodies, small quantities of purified human retroviruses and large quantities of viral proteins; Ab testing of sera for HTLV-1 and HIV; maintenance of colonies of subhuman primates, mice, rats, goats, and rabbits; and supplies of tissue and cell lines. One \$263,000 R01 vaccine development grant supported the design of synthetic multicomponent immunogens for protective HIV vaccines combining epitopes eliciting NABs, ADCC, ACC, and T-helper and CTLs.

Epidemiology, Transmission, Cofactors. NCI spent \$18,549,000 in 1991 on risk assessment and prevention research including surveillance studies, sexual, hemophilic, perinatal and other transmission studies, and natural history and cofactor studies. Studies focus on HIV-associated lymphomas, HPV and cervical or anal intraepithelial neoplasia (CIN + AIN), KS, and HIV/HTLV-I coinfections. NCI cosponsors the MACS with NIAID. An additional \$500,000 went to fund a study by Margaret Fischl of Miami to assess the likelihood of household transmission of HIV in a cohort of discordant heterosexual couples.

NCI Intramural AIDS Research. In 1991, NCI spent \$75M on intramural AIDS research. This figure rises to \$81M by 1993. This is about 46% of NCI's AIDS budget, the largest intramural amount of any of the NIH. In February 1992 we met with Dr. Broder and several intramural researchers including Gene Shearer of the Experimental Immunology Branch (EIB), Jay Berzofsky of the Metabolism Branch (MB), Robert Yarchoan of the Clinical Oncology Program (COP), and Steven Creekmore of the Biological Resources Branch (BRB) to learn about NCI's in-house AIDS efforts. Berzofsky and Shearer described their research and Steven Creekmore detailed the work of the Biological Response Modifiers Program.

DIVISION OF CANCER BIOLOGY + DIAGNOSIS (DCBD). Laboratory of Pathology, Comparative diagnosis of pulmonary complications of AIDS. Experimental Immunology Branch: Gene Shearer PhD: TH1-TH2 cross-regulation in HIV infection; Mario Clerici MD: Exposure to HIV-specific T helper cell responses before detection of infection by PCR and serum antibodies; Allan Weissman MD: Immune-inhibitory role(s) of HIV-1 gp120. Laboratory of Molecular Biology: Immunotoxin, oncotxin therapy; conjugates of Pseudomonas exotoxin + TGF-alpha, IL-2, IL-4, IL-6, IGF1, acidic FGF, CD4, anti-Tac (Fv), or antitransferrin (Fv) to treat cancers or HIV. Laboratory of Biochemistry: Samuel Wilson MD: HIV RT, DNA synthesis in mammalian cells. Metabolism Branch: Jay Berzofsky MD, PhD: Vaccines for malaria and AIDS. Laboratory of Cell Biology (LCB): E. Appella: T-cell antigen recognition and tumor antigens; Laboratory of Mathematical Biology (LMB): JN Weinstein: Dipyrimadole and AZT.

DIVISION OF CANCER TREATMENT (DCT). Clinical Oncology Program: Basic and clinical studies, including novel antiretroviral therapies and treatments for

lymphomas. Nucleoside resistance studies. Development of novel HIV-1 protease inhibitors. Nucleoside prodrugs. Laboratory of Biological Chemistry: Myristoylation and retroviral replication. Pharmaceutical Resources Branch: Tooling with prodrugs. Pediatrics Branch: Philip Pizzo MD: drugs for kids with AIDS and cancer. Medicine Branch: Carmen Allegra MD: Tyrosine protein kinase regulators as T cell activation blockers. Laboratory of Molecular Immunoregulation (LMI, Frederick), Francis "Frank" Ruscetti, PhD. Cellular regulation of retroviral expression. William Farrar, PhD: Growth factors, cytokine receptors and HIV. A transcriptional regulatory element within the promoter regions of the IL-1R-alpha gene and the homologous element in the HIV-1 LTR has been purified and found to be under the control of a cytoplasmic inhibitor. The activation of this protein is inhibited by cyclosporin A. Laboratory of Molecular Pharmacology: Effects of UV light and other stressors on HIV replication. Laboratory of Biochemical Physiology: Hsiang-fu Kung, PhD: Cytokines and HIV+ macrophages. Laboratory of Experimental Immunology: NK cells, CTL and cytokines. Surgery Branch: Steven Rosenberg, MD, PhD: Adoptive immunotherapy for AIDS. Laboratory of Medicinal Chemistry: Fluoro-ddNs. Laboratory of Biochemical Pharmacology: Chain terminators III. Developmental Therapeutics Program: Antiretroviral compounds from the Euphorbiaceae; a marine sponge and a tunicate, *Buchenavia capitata*; a xanthophyll with anti-HIV activity; anti-HIV dimeric alkaloids from *Ancistrocladus* spp.; antiviral plant diterpenes.

DIVISION OF CANCER ETIOLOGY (DCE). Environmental Epidemiology Branch (EEB). William Blattner, MD: Epidemiology of human lymphotropic viruses - Adult T-Cell Leukemia, AIDS and cancer. Laboratory of Comparative Carcinogenesis: Jerrold Ward, DVM, PhD: Biology of natural and experimentally-induced tumors. Laboratory of Experimental Carcinogenesis: Aminoacyl-tRNAs in HIV+ cells. Biostatistics Branch: Mitchell Gail, MD, PhD: Projecting incidence of AIDS-related NHL through 1992; assisting members of the Viral Epidemiology Section on the design, conduct, and analysis of the studies of the natural history of HIV and of biological markers. Laboratory of Molecular Oncology: DNA topoisomerase I activity in retroviruses. See if topoisomerases play a role in retroviral life cycles and if these enzymes might be a target for therapy. In vitro, a specific topoisomerase I inhibitor, camptothecin, blocked HIV infection of uninfected cells and inhibited EIAV production in chronically infected cells. Laboratory of Cellular and Molecular Biology: Dharam Ablashi, DVM: HHV-6, EBV and HIV. Activation of latent HHV-6 infection in PWAs, people with CFS, SLE and BMT. HHV-6 induction of IL-1-beta and TNF-alpha in human PBMC. HHV-6 antigen also present in Hodgkin's disease and Sjogren's syndrome, African and American Burkitt's lymphomas. Steven Tronick, PhD: Studies in the gene expression of EIAV and CAEV. Laboratory of Molecular Virology: Jeffrey Green, MD: Gene therapy for HIV and HTLV-I using HIV LTR-HSV thymidine kinase construct in defective retroviral vector. Stem cells transformed with the construct and subsequently infected with HIV should be able to be selectively killed with acyclovir, while allowing uninfected cells to replenish the T-cell population. Laboratory of Viral Carcinogenesis: Human genetic loci which influence susceptibility to HIV. Vaccines, epitopes, pig-tailed macaques, genetic drift in SIV+ monkeys. Challenge stocks. Dean Mann, MD: association of HLA antigens with disease progression and outcome in individuals with HIV infection. Biological Carcinogenesis Program: Edward Tabor, MD: Inhibition by desferrioxamine of in vitro replication of HIV-1: Desferrioxamine, an iron-chelating agent used as an antidote in iron poisoning, was shown to inhibit HIV-1 replication in vitro, possibly by interfering with RNA-dependent DNA synthesis.

Laboratory of Tumor Cell Biology: Robert Gallo, MD: Studies on T cell malignancies, lymphomas and AIDS. KS studies showed growth of KS cells in

enhanced by corticosteroids; AIDS-KS cells secrete factors, which induce angiogenesis, increase vascular permeability; AIDS-KS cells produce IL-6, and IL-8; AIDS-KS cells have high affinity receptors for IL-1, IL-2, IL-6, PDGF, BFGF, TNF, hydrocortisone, the HIV-1 Tat protein and Oncostatin M; ability of SPPG to inhibit KS growth and development in vitro and in a mouse model. Mechanisms of HIV-1 pathogenesis: Studies of the role of cytokine production by monocyte/macrophages in disease pathogenesis which have discovered: macrophages infected with HIV produce factors which accelerate the proliferation of cells derived from the synovial lining of uninfected individuals. Quantitation of cytokines from supernatants from infected macrophages showed that although several cytokines were expressed, none were present in amounts adequate to explain the proliferation of test cells and therefore, monocytes/macrophages may produce substimulatory concentrations of cytokines which may act additively or synergistically; the interaction between HHV-6 and HTLV-1 and HIV-1 results in an expanded host cell range due to phenotypic mixing of the viruses as well as the modulation of CD antigens on infected cells. HHV-6 infection increases the surface density of the CD4 antigen as well as de novo expression on otherwise CD4- cells.

FREDERICK CANCER RESEARCH FACILITY. ABL Basic Research Program: HIV proteases, X-ray crystallography, rev mutants, fusion proteins... Biological Products Laboratory: Stephen Nigida: Monoclonal antibody production for HIV-1 gag proteins. David Waters: Multi-assay screening HIV and HTLV antibodies for DCE epidemiology. AIDS Vaccine Program: Preparation of HIV challenge stocks for vaccine trials in chimpanzees. Laboratory of Cell and Molecular Structure: Development of a transgenic-BIV mouse model. Development of noninfectious pseudovirions as candidate vaccines for HIV and AIDS. Laboratories Unknown: Genetic drift in vivo as a means to follow viral transmission and movement of ancient human populations; Linear polymers of CD4 as polyvalent molecular decoys.

Future plans. NCI asked for \$217.5M for AIDS in FY 1993 and got \$175.8M. NCI's budget request would have funded the following:

1. \$2 million for prevention and treatment studies in women with cervical dysplasia and cancer in the context of AIDS through the Community Clinical Oncology Program;
2. \$500,000 for one new FTE for intramural research on the genetic regulation of HIV;
3. \$250,000 for one new FTE to develop "negative HIV replication regulation" immunotherapies;
4. \$1.5M for 6 new FTEs to develop new diagnostic approaches to AIDS-related cancers;
5. \$500,000 for 2 contracts screening new agents for lymphoma;
6. \$1,500,000 for 5 new grants on the biology and immunology of AIDS-related cancers;
7. \$284,000 to add two FTEs for intramural phase II studies of protease inhibitors;
8. \$2M for eight new FTEs to study T-cell biology and develop immune enhancing therapies;
9. \$204,000 to add three FTEs for intramural research on B1 antibody for B-cell lymphomas;
10. \$4.5M for studies on AIDS lymphomas, anogenital tumors through the cancer centers (\$1.5M) the clinical cooperative group program (\$3M);
11. \$2M for 4 four FTEs to new anti-HIV drugs;
12. \$315,000 for four FTEs to study G-proteins as regulators of secretion in HIV-infected cells;
13. \$3.9M for one FTE (\$500,000) to fund 7 new grants (\$2.1M) for vaccine development;
14. \$103,000 for one FTE to develop treatment for high-grade lymphomas and AIDS.
15. \$300,000 to add one FTE (\$80,000) and add one contract to establish a registry of all HIV-infected hemophiliacs in the U.S. to monitor them for the occurrence of all types of cancers;
16. \$1.5M for 4 new grants to develop directed therapies using cell specific targets expressed on the surface of AIDS-related lymphomas;
17. \$1.5M to set up an epidemiological network assessing risk factors for lymphoma, anal and cervical carcinoma and unusual sarcomas in HIV-infected children, women and minorities;
18. \$800,000 for 11 new for treatment of AIDS-related malignancies

with new treatment modalities (e.g. topoisomerase inhibitors, MAb-toxin conjugates, angiogenesis inhibitors, cytokine-toxin conjugates) which will enter clinical trials over the next few years; 19. \$150,000 for 1 neuropsychological testing study in AIDS patients under treatment; 20. \$236,000 to add two FTEs for intramural research in the development of adoptive immunotherapy with programmed T-cells in HIV-infected children; 21. \$500,000 for 5 contracts for large-scale production of natural products for drug development; 22. \$600,000 to fund one new contract to establish a biophysical chemistry laboratory at the Frederick Cancer Research Facility; 23. \$500,000 for three FTEs to develop new bioassays to isolate and chemically characterize new anti-HIV lead compounds in the Natural Products Program; 24. \$350,000 to expand the FCRF Laboratory of Human Retrovirus Pathogenesis; 25. \$250,000 to expand the Southern Research Institute primary screening program; 26. \$800,000 for 3 new grants investigating the neurodiagnosis of HIV complications; 27a. \$1.125M for 4 new FTEs to investigate the basic immunology of autoimmunity and AIDS and develop therapies using animal models; 27b. \$1.25M to construct an addition to the existing animal facility for animal breeding (transgenic and congenic strains) for the new intramural project on autoimmunity and AIDS (27a); 28. \$300,000 to fund four new FTEs for intramural research on the target ligands for NK and LAK effectors on tumor and virus-infected cells; 29. \$500,000 for 1 contract to screen IL-6 inhibitors for the treatment of AIDS lymphoma; 30. \$500,000 for 1 contract for clinical and preclinical data management; 31. \$500,000 for 2 contracts to optimize biological activity of natural product lead compounds; 32. \$300,000 for a commercial chemistry database contract; 33. \$500,000 for 1 contract for collection of deep-water marine organisms from the Indo-Pacific for screening for potential activity against HIV; 34. \$400,000 for 2 contracts to optimize synthesis of complex agents with up to 1520 reaction steps; 35. \$300,000 to fund one new contract to produce soft gelatin capsules for the administration of anti-AIDS agents;

NCI has 306 AIDS FTEs in FY 1992. For 1993, it wanted to add 42, for a total of 348 AIDS FTEs.

Recommendations and comments. The NCI has been vital to NIH's AIDS effort ever since 1981. The Developmental Therapeutics Program has brought us all three of the currently approved antiretroviral therapies, AZT, ddI and ddC. Dr. Gallo, despite his recent troubles, has been instrumental in helping to elucidate the mechanisms leading to Kaposi's sarcoma and the development of potential angiogenesis inhibitors for its treatment. Other intramural labs have been at the forefront of basic immunological research (e.g. Laboratory of Molecular Immunoregulation) and the immunology of HIV infection (e.g. Experimental Immunology Branch). The NCI's AIDS Lymphoma Network filled a national void on the study of the etiology and pathogenesis of these malignancies in HIV infection, when NIAID refused to take the lead in this area. Recommendations for the future for NCI's AIDS program include:

\* Closer and formal collaboration between the NCI's AIDS Lymphoma Network and the Oncology Committee of the AIDS Clinical Trials Group, NIAID.

\* The establishment of a joint NCI-NIAID task force on malignancies in HIV infection to coordinate clinical and basic oncological research.

\* The establishment of a joint NCI-NIAID biological repository for serum, tissue, and other biological materials from people with HIV to allow the study of epidemiological and biological correlates of AIDS-related oncogenesis.

\* NCI's \$3.5 million requested for cervical cancer studies in women with HIV and cut by President Bush should be restored.

\* Closer collaboration between NCI's Eastern Cooperative and Southwest Cooperative Oncology Groups and the Oncology Committee, ACTG, NIAID.

\* The establishment of a formal collaborative arrangement between the Immunology Committee, ACTG, NIAID, and NCI's Biological Response Modifiers Program, especially the Laboratories of Molecular Immunoregulation and Experimental Immunology.

\* Full funding for NCI's proposed basic and preclinical program on AIDS and autoimmunity.

\* Full funding for NCI's FY 1993 Wish List.

\* Since NCI has the expertise and experience in the therapeutic use of biological response modifiers and strong basic and clinical immunology and drug discovery programs, it should establish a new program (of which its proposed AIDS/autoimmunity project, its new screen for IL-6 inhibitors, and its new project on T-cell biology and immune enhancement in HIV infection, can be the starting point) to develop therapies based on the diverse mechanisms of immune activation and immune dysregulation with the objective of:

a. Correcting the cytokine dysregulation which has been observed in HIV infection, including the development of inhibitors of TNF-alpha, IL-6, IFN-alpha, IL-10 and other cytokines;

b. Inhibiting acute phase reactants and arachidonic acid metabolites;

c. Depressing the generalized immune activation which may contribute to the hypergammaglobulinemia, and even the depletion of the CD4+ cell population in HIV;

d. Inhibiting the indirect effects of HIV proteins (e.g. gp120 and tat) on CD4+ and other cells of the lymphoid lineage.

\*

### II/3. National Center for Research Resources (NCRR)

The NCRR was established in February 1990 by merging the Division of Research Resources (DRR), which originally provided extramural support to NIH-supported institutions, and the Division of Research Services (DRS), which provided support for NIH intramural programs. Major NCRR programs include the General Clinical Research Centers (GCRCs) in medical schools around the USA, the seven regional Primate Research Centers, primate colonies and other animal models. NCRR also supports biomedical engineering, instrumentation research, and research and training in minority institutions. The NCRR director is Robert Whitney, Jr., DVM. NCRR spent \$47M on AIDS in FY 1991. In 1991, NCRR spent \$22.8 million on AIDS research at the GCRCs, \$19.7 million to primate research centers in the Comparative Medical Program, and \$2 million to the Research Centers in Minority Institutions (RCMIs). NCRR funds in 1991 were allocated thus: \$8.6 million for HIV related virology and immunology; \$3.2 million for blood products, diagnostic methods and animal models; \$1.2 million for neuroscience; \$1.4 million for behavioral research and prevention research; \$20.7 million for drug development and clinical trials; \$7 million for vaccine development; \$2.5

million for work on transmission; and \$2 million for natural history and cofactors.

Regional Primate Research Centers. "The Regional Primate Research Centers (RPRC) Program, a component of NCRR's Comparative Medicine Program (CMP), supports the development of nonhuman primate animal models and resources, specialized facilities, scientific and technical personnel, and the appropriate research environment for AIDS-related research... The seven centers maintain over 15,500 nonhuman primates representing 32 species... Increasingly, research on the Simian Immunodeficiency Virus (SIV) animal model for human AIDS has dominated the research and resource development programs of the seven RPRCs." The seven RPRCs are at UC Davis, Tulane, New England, Oregon, Washington, Wisconsin and Yerkes (Atlanta). The chimpanzee program is expensive. Encumbered by regulations foisted upon the PHS by animal rights activists, the government must establish a \$30,000 endowment per research chimp to provide for a "socially stimulating" retirement after the research protocols are over. Vaccine research may have been unduly delayed because the original chimpanzee HIV challenge stocks were made with the laboratory isolate HIVHTLV-IIIB, rather than more clinically widespread strains such as HIVMN or HIVSF2. In spite of such setbacks, RPRC workers had a productive year in 1991. For example, University of Washington RPRC investigators developed a new animal model for HIV infection, the pig-tailed macaque *Macaca nemestrina*. RPRC researchers are crucial players in the search to elucidate the pathogenesis of mammalian retrovirus-induced diseases, including HIV, and in vaccine development. Their recent work is a highlight of the annual NIAID-sponsored vaccine conferences. CMP also runs the AIDS Animal Model Program (AAMP), which has several programs involving chimpanzees, specific pathogen-free (SPF) rhesus monkeys, and other nonhuman primates and nonprimate mammalian animal models.

The Chimpanzee Breeding and Research Program is "the first and only national program to join the expertise of chimpanzee breeders and researchers to provide a stable supply of healthy chimpanzees for biomedical research... Chimpanzees are currently the only nonhuman primate model available for the study of HIV-1 infection... Currently, 453 disease-free adult breeding chimpanzees and 166 offspring are in the program, and the population is increasing at the rate of 5% a year."

The Specific Pathogen Free (SPF) Rhesus Breeding and Research Program "was developed to create self-sustaining breeding colonies that are free of simian retroviruses and herpes B virus, which are made available for PHS-supported AIDS studies... More than 1,200 animals are now included in the colonies."

Laboratory Animal Sciences Program (LASP) is developing transgenic animals for the study of human infectious, immunological and neoplastic diseases. Animals studied include rhesus monkeys, squirrel monkeys, rabbits and mice. CMP spending on AIDS in FY 1991 totalled \$17,153,000 including all the animal programs mentioned above; this was a decrease of 64.7% from FY 1990.

The Biomedical Research Support Shared Instrumentation Grant (SIG) program is "the only grant program in the PHS that equips biomedical research scientists with sophisticated, up-to-date instrumentation in the \$100,000 to \$400,000 cost range. Funds are provided for instruments including electron microscopes, confocal microscopes, mass spectrometer, NMR spectrometers, cell sorters and image analysis centers. In FY 1991 the SIG Program provided \$765,000 for AIDS-related research in partial support of 29 instruments." General Clinical Research Centers (GCRCs). The GCRC program spent \$117 million in 1991 to support 74 General Clinical Research Centers (GCRCs) and an array of smaller programs



including physician support and computerized database management systems. About one sixth (\$22.8M) went for AIDS research at the GCRCs, which are funded through a unique mechanism, the M01 GCRC award. The 1991 figures were down 80% from 1990. Of the \$22.8M, \$17.5M went for clinical trials. The GCRC program is almost 3 decades old, and is intended to "provide the clinical research infrastructure for investigators who receive their primary research support from other components of the NIH... and the private sector. GCRCs are present in 59 of the nation's 127 medical schools." Many GCRCs are also ACTU sites and receive multiple funding streams for clinical research from NIH. Tracking GCRC funds is even harder than tracking those awarded by other institutes. Accounting for GCRC funds appears somewhat arbitrary. GCRC support for the ACTG is significant but hard to track. For example Duke spent \$127,486 in GCRC funds on ACTG trials. NYU got \$2.1 million from NCCR. Did NIAID take GCRC funds into account when judging the performance needs of the ACTUs in the recent Recompetition?

Research Centers in Minority Institutions (RCMIs). Congress mandated the RCMI program in 1985 to enhance support for biomedical research at institutions with over 50% students from racial or ethnic minorities. By 1991 there were 17 RCMI programs at 7 medical schools, 3 pharmacy schools, 6 graduate schools and 1 veterinary school at a cost of about \$25 million (including \$2.7 million from NIAID). RCMI awards have a special grant category, G12. AIDS-related RCMI awards included almost \$1.3 million in six projects in Puerto Rico, Tennessee, Hawaii, Alabama and Georgia. The RCMI program also sponsored the first two RCMI AIDS Symposia at Morehouse School of Medicine in 1990 and 1991. The three NIAID-funded minority infrastructure grants supported efforts to develop AIDS Clinical Trials Units (ACTUs) at Howard University; University of Puerto Rico Medical Sciences Campus, San Juan; and the University of Hawaii at Manoa. One tenth of the RCMI's annual \$20 million budget goes to support AIDS related research. NCCR also supports development of "a comprehensive, culturally sensitive questionnaire (CCSQ) concerning AIDS for African-American women (AAW)."

Funding and Future Plans. NCCR AIDS spending reached a peak in 1989 at \$67.6 million, which fell to \$46M in 1990 and \$47M in 1991. Current services (that is, the cost of existing programs from last year plus inflation) for FY 1992 cost \$52 million. Yet the President included just \$51.5M in his budget for NCCR AIDS research. The present administration is starving the basic and clinical research infrastructure - including the AIDS infrastructure. NCCR sought the additional \$100 million for the following programs:

- \* \$20 million for primate models for vaccine studies;
- \* \$45.7 million to build extramural AIDS research facilities.
- \* \$8.3 million to buy sophisticated high technology machines for shared use'
- \* \$5.2 million for new pilot studies (BRS program).
- \* 17 million to expand the General Clinical Research Centers (GCRCs);
- \* \$6.4 million for new initiatives at the RCMI sites;

Recommendations:

- \* After several years of unusual growth, the AIDS research infrastructure is shrinking drastically. New initiatives must compete with ongoing programs funded since 1987. New ideas go begging, while old ones are drastically slashed. Congress and the Administration should grant NCCR its requested \$100 million to accelerate vaccine animal model research, appropriate technology, renovate and build new research facilities, and expand the RPRC, GCRC and RCMI systems.
- \* Congress should provide NCCR with (1) the \$20 million it requested to extend the RPRC AIDS program; (2) the \$17M it requested to enhance AIDS research at the GCRCs [this would help allay the NIAID ACTU funding cuts; and (3) the \$6.4M it requested to enhance AIDS research at minority institutions through RCMI awards.

\*

#### II/4. National Heart, Lung, + Blood Institute (NHLBI)

NHLBI started out as the National Heart Institute (NHI) in 1948 when President Truman signed the National Heart Act. In 1969 the NHI became the National Heart and Lung Institute (NHLI), and in 1976, the institute received its current title. NHLBI is the second largest institute at NIH (only NCI is larger) and for FY 1991 had a total budget of \$1,126,942,000. NHLBI supports and conducts basic and clinical research on cardiovascular, pulmonary and hematological diseases, and administers demonstration and education projects on their causes, prevention, diagnosis and treatment. NHLBI also sponsors research on the use of blood and bone marrow for transfusions and transplantation, including a blood resources program concerned with the management of the US blood supply. NHLBI's current director is Claude Lenfant, MD. NHLBI's 5 divisions are: Heart and Vascular Diseases; Epidemiology and Clinical Applications; Lung Diseases; Blood Diseases and Resources; and Intramural Research. In addition, the Office of Prevention, Education and Control functions as "the institute's technology transfer arm, relaying the results of heart, lung, and blood research" to an eagerly waiting world. NHLBI spent \$46.4 million on AIDS research in 1991. For next year, it requested \$66M, but the President offered just \$48.2M, barely above the level of current services. NHLBI supports research on the pulmonary, hematological and cardiovascular complications of HIV infection, and sponsors research designed to assure the safety of the nation's blood supply.

In FY 1991, NHLBI disbursed \$39,544,729 in extramural AIDS awards.

Heart. NHLBI funds a natural history study of AIDS-associated heart disease in an adult population. Three of the six originally funded institutions were funded in 1991 at a cost of \$1M. The project charts the incidence and clinical course of cardiomyopathy in HIV infection and will investigate their etiology and pathogenesis. NHLBI funds a grant on cardiac abnormalities seen in AIDS, a study looking for the presence of HIV proteins and RNA and associated morphological damage in the heart tissue of HIV+ individuals.

Lung. NHLBI's efforts on the pulmonary complications of HIV infection have largely been confined to multicenter natural history studies in adult and pediatric populations, several studies on the pathobiology of Pneumocystis carinii infection and the pulmonary immunology of HIV infection and its opportunistic sequelae. NHLBI sponsors two programs which are concerned with natural history of the pulmonary complications of HIV infection. Both are administered as NOIs (R+D contracts) granted individually to participating institutions. In 1987 the NHLBI initiated the "Pulmonary Complications of HIV-1 Infection" study in collaboration with NIAID. This study now involves five sites and a data collection center and costs about \$3.5M annually. Since 1989, NHLBI has run the "Study of Pediatric Lung and Heart Complications of HIV Infection," at six sites and an annual cost of \$6.5M. Six basic research grants support laboratory studies of Pneumocystis carinii and the activity of pentamidine. Ten grants are looking at the pulmonary immune system in HIV-infected persons. Other studies are examining impaired phagocytosis of alveolar macrophages against cryptococcus, MTB and MAI.

Blood. 25 NHLBI grants fund studies of hematological abnormalities associated with HIV infection and its treatment, which include bone marrow suppression, thrombocytopenic purpura and other platelet disorders, AZT myelotoxicity, and the specific dynamics of HIV infection in hemophiliacs. In FY 1987 NHLBI issued

an RFA to study bone marrow suppression in HIV infection. Fourteen resulting grants were funded in 1991. Four NHLBI grantees study platelet disorders. Curiously, none seems to be concerned with specifically HIV-associated ones. Three are looking at AZT's bone-marrow toxicity. Three more examine HIV infection in hemophiliacs. NHLBI devotes a fat portion of its extramural resources to programs to assure the safety of our nation's blood supply. Current work falls into six general areas: blood screening tests; epidemiological and natural history studies of blood donors and recipients; educational and outreach programs; behavioral studies of donors; novel methodologies for transfusion practice, and; inactivation of HIV and other viruses. Seven investigators are developing assays for HIV and other human retroviruses. The Epidemiological Studies of Human Retroviruses in Volunteer Blood Donors program began in FY 1989. Six institutions participate in the program, which cost over \$8M in 1991. The Transfusion Safety Study runs a cell and serum repository to study HIV-infected transfusion recipients in LA, NYC, SF and Miami. Strategies are being pursued to improve the safety of the US blood supply.

Other topics. Two contracts maintain a colony of chimpanzees for research on post-transfusion viral hepatitis or AIDS and a blood specimen repository for NHLBI-sponsored studies; a coordinating center for a study of HIV hyperimmunoglobulin in HIV-infected infants, which it plans to conduct in conjunction with NIAID and Abbott Laboratories; and a study of NK cells in HIV infection.

Intramural research. In FY 1991, NHLBI appropriated \$5,571,000 for intramural research on AIDS. Projects range from myosin expression in cells infected with HTLV and HIV-1; rat basophilic leukemia exocytosis signaling pathways; antisense anti-HIV RNA sequences; fusion proteins; gene therapy for HIV infection: retroviral vectors encoding sCD4, IFN-alpha, transdominant rev mutants or HIV-inducible diphtheria toxin; a clinical trial of aerosolized IFN-alpha and glutathione in patients with HIV-infection and their effects on the pulmonary macrophage; anemia caused by bone marrow failure in HIV infection; IVIG in the treatment of parvovirus induced anemia.

Future Plans. NHLBI asked for \$20 million in new funds for FY 1993 to support:

1. \$1.2M to vascular cell proliferation in KS;
2. \$3M for HIVIG clinical trials to prevent vertical transmission during the third trimester;
3. \$310,000 for work on anti-HIV gene therapy;
4. \$1M to study the etiology and mechanisms of non-infectious HIV pulmonary complications;
5. \$1M to develop methods of inactivating viruses in blood and blood products;
6. \$73,000 to buy an electrospray attachment for a mass spectrometer for intramural research on the structure of HIV peptides which may be candidate targets for vaccines;
7. \$1.5M to investigate whether transfusions from CMV-negative donors reduce active CMV in PWAs.
8. \$1.2M to study myocarditis and dilated cardiomyopathy in children with AIDS;
9. \$1.2M to study lung immunocytes in children with AIDS and pulmonary disease;
10. \$4M to extend the Pulmonary Complications of AIDS natural history study.
11. \$1M to assess the efficacy of thin section computerized tomography in the early diagnosis and management of the lung complications in pediatric HIV infection.
12. \$1.5M to investigate, post-mortem, the conduction system of the heart in children with AIDS.

NHLBI also asked for funding to add 5 new AIDS FTEs, which would bring their total to 44. With the President's parsimonious budget for FY 1993, NHLBI will barely be able to support its current commitments. Few of these new initiatives are likely to see the light of day.

## Recommendations:

\* Congress should fully fund NHLBI's budget request and its wish list for FY 1993; \* NHLBI should not be forced by budgetary constraints to decrease its natural history studies in the pulmonary complications of AIDS to support similar pediatric studies. If Congress wants pediatric studies, they should appropriate extra money for the institute; \* NHLBI should fund studies of MTB in HIV infection, and Congress should give them the money; \* NHLBI should investigate lymphoid interstitial pneumonia in children with HIV; \* NHLBI's program on thrombocytopenia purpura in HIV infection should be expanded to focus more explicitly on platelet abnormalities seen in people with HIV; \* NHLBI should investigate cardiac complications of HIV infection seen in injecting drug users. \* NHLBI should broaden its work on the other pulmonary OIs seen in AIDS.

\*

## II/5. National Institute of Child Health

### + Human Development (NICHD)

Created in 1962 by act of Congress (P.L. 87-838), NICHD has five large components - the Center for Research for Mothers and Children; the Center for Population Research (both extramural programs); the intramural research program; the Prevention Research Program; and the Scientific Review Program. NICHD spent \$32.6 million on AIDS in FY 1991.

Basic research. NICHD spent \$1.3 million on intramural AIDS research programs, investigating genetic transcription factors, mammalian retrovirus genetics, protein structure (including trichosanthin and its less toxic derivative, TAP 29), HIV-1 aspartic protease inhibition, prevention of AIDS-associated neuronal deficits, studies of T cell activation, interleukin-2 and T cell receptor structure/function studies. Extramural basic research is eclectic, ranging from in vitro models of transplacental transmission and animal models of vertical transmission to fetal toxicity of AZT. NICHD also supports a broad range of epidemiological and behavioral studies in high-risk populations, STD clinic patients, drug users, students and others. NICHD grantees are developing new and better condoms, spermicides and other barrier methods of contraception.

Clinical research. Most NIH intramural pediatric trials in children with HIV are conducted by the NCI pediatrics branch, so NICHD focuses on extramural support. NICHD was the original sponsor of the placebo controlled study of intravenous immunoglobulin (IVIG) in children with AIDS. This effort used up \$8 million in FY 1991, awarded to the contractor, Westat Inc. Later NIAID joined this study through the pediatric AIDS Clinical Trials Units (ACTUs). The study was controversial because of the use of an intravenous placebo. Eventually it showed a statistically significant decrease in the rate of serious bacterial infections in the treatment group. NICHD and NIAID jointly support the Pediatric ACTUs. Since 1991, this program has significantly expanded. "10 new sites [were added] in 8 states following approximately 620 pediatric patients. The NICHD network now totals 30 sites following approximately 1,760 pediatric patients in 12 states and Puerto Rico... NICHD centers currently participate in 6 large-scale pediatric or perinatal Phase III clinical trials... NICHD-funded centers have accounted for nearly 30% (221/828) of patients enrolled in the three largest ACTG pediatric protocols to date." NICHD is also nesting a neurodevelopmental study within ACTG 152. In conjunction with NIAID and NHLBI, NICHD may conduct a study of HIVIG/AZT vs. IVIG/AZT in pregnant women and their offspring to assess

the effects of this combination on reducing vertical transmission of HIV. This study is projected to enroll 800 women and infants.

Children with HIV. NICHD is supporting research into the effects of being born to HIV-infected women on pediatric growth. The "relationship between the incidence and outcome of diarrhea and wasting and enteric infection, immunologic dysfunction, diminished caloric intake, and nutrient malabsorption" will be studied in a cohort of HIV+ and HIV-children born to HIV+ mothers.

Sexual transmission/barrier methods. NICHD is trying to develop animal models for genital transmission, and to develop better spermicides, stronger condoms, and other barrier methods. Like humans, macaque monkeys can be infected via genital mucosa. In the macaque model, SIV infection appears to impair humoral and mucosal immunity, with reduced levels of secretory IgA found in macaque vaginal washes. NICHD is also preparing 3 studies in humans of barrier contraception and of condom use in high risk populations, including STD clinic patients, family planning clinic patients, gay men and lesbians, a singles network, substance users, HIV+ persons and members of college sororities and fraternities. "Development and Testing of New Spermicides" proposals were due in March 1992.

Vertical transmission. Artificial models are being developed for transplacental HIV transmission. Other grantees are determining the transplacental pharmacokinetics of AZT, ddC, ddI and d4T (the latter three alone and in combination with AZT) in a "chronically catheterized maternal fetal macaque model," and in the "in vitro perfused human placental model." [A problem here is that no simian model exactly parallels vertical transmission in humans.]

Funding and Future Plans. NICHD is still flush with new funds from Congress' pediatric earmark of 1991; its budget will rise by 6.1% in FY 1993 to \$38.2 million. NICHD had requested \$64.7M for:

- \* \$10 million in new funds to double the pediatric clinical trials network and 10 new FTEs;
- \* \$3M to double current studies of risk behavior;
- \* \$6M to study of adolescent risk behavior and HIV infection, the American Teenage Study;
- \* \$1M for monkey models for mucosal immunity and \$1.3 million to test new virucidal spermicides;
- \* \$1M for behavioral prevention studies in high-risk teenagers;
- \* \$1M for NIAID's RFA on "Mothers + Infants: Early Diagnosis + Correlates of Immunity";
- \* \$2.4M to train adolescent health providers to address sexual development "in inner cities";
- \* \$1.3M for behavioral intervention studies;
- \* \$500,000 for epidemiological studies of HIV-infected adolescents;
- \* \$1M to develop transgenic mice to screen for antiretroviral drugs;
- \* \$1.4M to develop and test "new stronger condoms";
- \* \$775,000 for a case-control study of reversible contraception and HIV seroconversion in women;
- \* \$250,000 to study the effects of spermicides and sex hormones on STDs and HIV in vitro;
- \* \$650,000 for a comparative study of growth in HIV+ and HIV- children with hemophilia;
- \* \$400,000 for a NAS panel on international issues and behavioral research;
- \* \$775,000 for vaginal insertion product abrasion studies;
- \* \$575,000 for a study of barrier contraception to prevent STDs in high risk populations;
- \* \$775,000 for a prospective study of causes of mechanical condom failure among volunteers recruited to use condoms and keep diaries for 6 months;
- \* \$750,000 for immunodevelopmental studies of HIV+ infants;
- \* \$750,000 for neurodevelopmental studies of HIV+ infants;
- \* \$750,000 for studies of HIV transmission via human milk;
- \* \$315,000 for studies of HIV+ women to assess how oral contraceptives affect progression;

The breadth and ambition of NICHD's requests stands out among the ICD's wishlist for FY 1993. Perhaps this is because funding patterns for pediatric AIDS research have not yet suffered the plateau which has afflicted adult AIDS research funds. It is notable how many of the questions NICHD seeks to address relate to adult and adolescent sexual behavior, barrier methods, and women with HIV. These areas are crucial, and have not been adequately addressed by NIH efforts hitherto. OAR cut \$14 million from NICHD's original request of \$78 million; Mason cut \$22 million more (to \$42,466,000); Sullivan cut \$4 million to the final President's request for \$38 million. NICHD now has 28 AIDS FTEs and wanted to add 25 for a total of 53.

Recommendations:

- \* More behavioral and sexual studies should be supported.
- \* Mothers and families of HIV+ children should have access to research, including clinical trials, conducted at NICHD funded sites.
- \*

II/6.National Institute of Neurological Disorders + Stroke (NINDS)

NINDS originated in 1950 as the National Institute of Neurological Disorders and Blindness (NINDB), and evolved its present name in 1980. NINDS is the sixth largest funder of AIDS research at NIH, spending \$16.65 million on AIDS in 1991. President Bush slashed NINDS' 1993 budget request from \$34M to \$18.6M. While substantially below the amount the institute originally requested and like most other institute's budgets, barely over the amount needed to maintain current services, NINDS's 7.9 % increase over 1992's budget is higher than other institutes. NINDS's extramural research is all funded under Mason category IB: Neuroscience and Neuropsychiatric Research. NINDS supports basic and clinical research on the neurological complications of HIV infection, including, but not limited to, AIDS dementia complex and the opportunistic infections affecting the nervous system, and investigations of potential therapies for these conditions. According the 1991 NIH "Annual Report to Congress," the goals of the NINDS's AIDS program are:

- \* To study the natural history of HIV-1, with emphasis on its predilection for the nervous system;
- \* To discover how the virus enters and damages the brain and nervous system;
- \* To prevent or ameliorate the effects of the virus and of the opportunistic infections of the nervous system that often accompany AIDS;
- \* To develop predictive criteria for the onset and severity of neurological symptoms in HIV+ persons;
- \* To develop methods to deliver antiviral agents through the blood-brain barrier;
- \* To investigate the differing course and manifestations of the disease in children and adults;
- \* To study the role of the immune system and substances it elicits (such as cytokines and TNF) during viral infection and their effects on the brain;
- \* To conduct studies of other retroviruses, such as HTLV-1, applying findings to HIV;
- \* To include minority populations in clinical studies of the neurological complications of AIDS.

Extramural Research. In 1991, 72% - or \$11.9M - of NINDS's AIDS support for extramural research - went to fund 25 R01s, 4 R29s and 7 P01s. Two grants supported diagnosis of the neurological OIs of AIDS. One correlated the presence of JC virus DNA in the CSF with PML. The other was an investigation of the use of NMR to distinguish CNS toxoplasmosis from CNS lymphoma in AIDS.

Primary HIV Infection of the Nervous System. 26 of NINDS' 29 basic AIDS research grants go to the study of the neuropathogenesis of HIV infection, including the pathogenesis and natural history of AIDS-related encephalopathy; peripheral neuropathy and myopathy; the development of animal models for the neurological effects of HIV; and potential therapeutic approaches.

14 grants studied the pathogenesis of CNS involvement in AIDS, including identification and characterization of neurotropic variants of HIV; identification of receptors for HIV in the brain; the extent and distribution of cortical atrophy; the role of macrophage or astrocyte produced cytokines in mediating CNS damage; correlation of regional CNS damage with the local presence of HIV, the CD4 surface receptor, HLA-DR MHC marker; the role of microglia-derived IL-1 in inducing astrogliosis and neuronal dysfunction and degeneration, as well as immunosuppressive neuroendocrine responses; the effects of HIV and its proteins (e.g. gp120) on the function and structure of specific cells of the nervous system.

In addition, NINDS funds four R01s to assess the natural history of the neurological manifestations of HIV infection in children (3 grants) and gay men (1 grant).

NINDS-supported researchers are also investigating the pathogenesis of other lentiviral infections in other species (visna virus, CAEV, FeLV and borna disease) as animal models for HIV infection.

Finally, two grants are investigating therapies for the neurological effects of HIV infection. One grantee is investigating the use of probenecid and salicylic acid to alter the distribution of AZT between the CNS and the plasma, in the hope of achieving higher levels in the brain. The other is investigating myopathy in HIV infection, both HIV-associated and AZT-associated, comparing corticosteroid therapy with AZT withdrawal in the treatment of this condition.

AIDS Dementia Centers. Seven NINDS-supported research projects are studying AIDS Dementia Complex and other neurological complications of HIV infection. Of these, six support AIDS Dementia Centers at UNC (Chapel Hill), Johns Hopkins, U. Miami, U. Minnesota, U. Pennsylvania and U. Maryland. These awards total \$6 million and utilize a diverse array of molecular, cellular, diagnostic and epidemiological tools to improve understanding about the diverse neurological sequelae of HIV and AIDS.

Intramural Research. NINDS's intramural AIDS budget for 1991 was \$4,711,973 The following is a list of intramural laboratories and their AIDS-related projects: Laboratory of Viral and Molecular Pathogenesis: Recombinant Chimeric Glycoproteins and Recombinant Pseudotype Viruses for the Study of HIV Replication and HIV Receptors; Studies of HIV-1 Neuropathogenesis; JC Virus Induced Demyelination, Progressive Multifocal Leukoencephalopathy, in the Immunodeficient AIDS Patient; HIV-1 Infection of the CNS in the Pediatric AIDS Patient; Neurotropism of HIV-1; Viral Gene Therapy for HIV Infections Using Defective Interfering HIV Particles. Laboratory of Molecular and Cellular Neurobiology: Investigation of the Molecular Pathogenesis of Demyelination and Myelin Abnormalities in the Central and Peripheral Nervous System of AIDS Patients. Medical Neurology Branch: Neuroimmunological studies of HIV+ asymptomatics; neuromuscular diseases associated with HIV; dorsal root ganglia and neuropathy; immune responses in HIV-Related inflammatory myopathy; muscle cell susceptibility to HIV; inflammatory myopathy; myotoxicity of AZT; polymyositis, dermatomyositis, and inclusion body myositis; HTLV-1 myopathy and T-cell leukemia. Laboratory of Central Nervous System Studies; Epidemiology of

Tropical Spastic Paraparesis (TSP) and other HTLV-1-Caused Diseases in the western Pacific; retrovirus antibodies in Jamaican schizophrenics; HIV+ chimpanzees vaccine studies; SIV and HTLV-I in macaques. Developmental and Metabolic Neurology Branch: Synthesis of Inhibitors of Protein Myristylation. Neuroimmunology Branch; TSP; retroviral involvement in multiple sclerosis; HTLV-1 envelope gene products; HTLV-2.

Future plans. NINDS had quite a hefty little tome for its FY 1993 wish list, including:

- \* Extramural expansion of \$4.9M for 12 grnts to study of neuro-AIDS in adults and children; neurovirulent strains of human retroviruses; cofactors affecting the growth of neurovirulent strains; opportunistic infections; CNS control of the immune response; viral alterations of nerve cells; HIV's role in neuronal damage, including the effects of cellular toxins, lymphokines and HIV proteins on the nervous system; and other retroviruses which affect the central and peripheral nervous systems.

- \* \$2.8M for 5 new FTEs to study neurotoxins produced by HIV+ cells in the CNS; mechanisms of action and treatments for neurological HIV manifestations; neurovirulence of certain HIV strains and the mechanism of their molecular control; cooperative clinical research on the effects of HIV infection on neurological, behavioral, cognitive and affective function, in order to develop diagnostic procedures for use in longitudinal studies of HIV infection;

- \* New extramural efforts totaling \$7.6M to study; HIV's effects in the developing and pediatric CNS; collaboration with ACTG to identify and evaluate treatments for neuro-AIDS and assess the neurological side effects of new drugs; prevention and control of neurological disease in pediatric AIDS; new animal neuro-AIDS models; HTLV-1 and the CNS; support of centers studying large populations of PWAs, emphasizing children and people of color; longitudinal studies to assess early neurological effects; and the effects of maternal immune response on transmission to neonates.

- \* \$1M for 6 new FTEs to study neuroimmunological response to retroviral infection; HIV-1 products in neural (and lymphoid) cells; and to develop new assays and reagents to detect low levels of HIV infection in CNS cells.

With its 7.9% budget rise for FY 1993, NINDS be unable to fund most of these initiatives.

Recommendations:

- \* Congress should fully fund NINDS's original budget request for FY 1993;

- \* NINDS should allocate additional resources for the development and evaluation of novel therapeutics for the neurological manifestations of HIV infection. A search for inhibitors of cytokines and neurotoxins (e.g. quinolinic acid and other kynurenine pathway metabolites) implicated in the pathogenesis of ADC, as well as for agents that might protect cells of the CNS from damage (e.g. competitors for the NMDA receptor) should be pursued;

- \* NINDS should increase its extramural support for investigations of the mechanisms of HIV-and drug-induced neuropathies and myopathies, and for the development of therapies for these conditions;



\* NINDS should increase its extramural support for work on the neurological opportunistic infections of AIDS, especially orphan OIs such as PML;

\* NINDS should be commended for its periodic Science Reports which succinctly and comprehensively catalogue the institute's work on AIDS.

\*

## II/7. National Institute of General Medical Sciences (NIGMS)

Established in 1963, NIGMS supports 6 extramural basic biomedical research and training programs [it has no intramural research of any kind]: Cellular and Molecular Basis of Disease Program; Genetics Program; Pharmacological Sciences Program; Biophysics and Physiological Sciences Program; Minority Access to Research Careers (MARC) Program; Minority Biomedical Research Support (MBRS) Program. NIGMS funds over half of the predoctoral trainees and 1/3 of all trainees who receive assistance from NIH. The current NIGMS Director is Ruth Kirschstein, MD, who also recently served as acting associate director of the NIH Office of Research on Women's Health. NIGMS first awarded \$180,000 for AIDS in 1987, and now provides over \$15 million in extramural research and training awards.

The NIGMS extramural FY 1991 AIDS portfolio of 81 awards totalling \$15,548,253 was divided into \$9.7M for "HIV and HIV genome" (1A1) and \$5.8M for "research training" (1F1), but the former might also be co-classified as 1D1 "therapeutic agents - development." The NIGMS abstracts make for fairly dry reading unless you are a synthetic chemist. 30 abstracts for awards totalling \$9 million are on-line in CRISP for R01 and P01 awards. Six P01 awards (Research Program Projects) totalling \$5,191,352 and involving at least 21 subprojects in which heavy duty high-tech molecular biology is brought to bear on the problem of elucidating the shape of HIV proteins in their native forms and when bound to substrates, and developing pharmacological agents to inhibit viral enzymatic activity. 17 R01 awards (traditional research projects) and one FIRST R29 award totalling \$2,736,280 are examining the structural biology of idiotypic and anti-idiotypic antibodies, 3-D DNA mapping of HIV provirions, the 3-D structure of GM-CSF by X-ray crystallography, synthesis of pradimicin A analogues for anti-HIV and anti-fungal activity, synthesis of beta-keto phosphonates, rational design of biological receptor ligands to inhibit gp120/CD4 binding, synthesis of boradeoxyribonucleosides (in which boron replaces carbon in deoxyribonucleosides), synthetic transmembrane anti-HIV agent carriers, comparison of antigenicity of differentially glycosylated peptides by T- and B-cells, glycosidation inhibitors, synthesis of avarol derivatives, and the role of the "zinc finger" amino acid sequences of retroviral gag proteins. Training Awards. 51 abstracts are missing for \$6 million in training awards and interagency agreements. Because these abstracts are missing, and their listed titles uninformative, it is unclear how, if at all, these awards - especially the training awards - relate to AIDS. The training awards are intended to help fill the gap in qualified basic researchers. 3 S06 Minority Biomedical Research Support (MBRS) Grants are supported by NIGMS for AIDS. These grants are intended "to strengthen the biomedical research and research training capability of ethnic minority institutions," and are in this case supporting work at Fisk University, and at Rio Piedras in Puerto Rico.

Recent Progress. NIGMS held its Sixth Meeting of Groups Studying the Structures of AIDS-Related Systems and Their Application to Targeted Drug Design on June 8-10 at the Hyatt Regency Bethesda. Papers were presented on reverse transcriptase, virus-cell fusion, gp120/CD4 binding, CD4-pseudomonas exotoxin as an

antiretroviral agent, gag proteins, integrase, tat, rev and protease. Eddy Arnold presented the three-dimensional structure of HIV-1 RT recently published in Nature.

Funding + Future Plans. NIGMS AIDS programs are the 7th largest at NIH, amounting to 2.1% of NIGMS' total budget and 1.9% of the NIH AIDS budget. \$9.9 million will be spent on rational antiretroviral drug design and related structural biology in FY 1992, and \$10.8 million in FY 1993. \$5.825 million will be spent on these training grants in FY 1992 and FY 1993. NIGMS requested \$14.5M in new funds for FY 1993, but the President awarded just \$912,000. Among other things, these new funds would have supported:

- \* \$5.4 million in additional support for research enhancement and training (for a total of \$11.7 million).

- \* \$50,000 for additional structural biology and drug design awards.

Recommendations:

- \* NIGMS should document the specific contributions to AIDS, if any, being made in the structural biology training award program. What guarantee is there that the trainees will actually work on AIDS when they are finished?

- \* NIGMS should fund additional Minority Access to Research Careers (MARC) and Minority Biomedical Research Support (MBRS) awards specifically for AIDS research.

- \*

II/8. Office of the NIH Director (OD)

The NIH Director "gives overall leadership to NIH activities and maintains close liaison with the DHHS Assistant Secretary for Health in matters relating to medical research, research training, health professions education and training, manpower resources, and biomedical communications... He [sic] also maintains close communications with other constituents of DHHS in order to provide more effective program relationships". The current NIH Director is Bernadine Healy MD, who took office in April 1991. Before coming to NIH, Dr. Healy chaired the Research Institute of the Cleveland Clinic Foundation. In FY 1991, the OD received \$11,737,000 for AIDS. The OD requested \$14,677,000 for AIDS in FY 1993 but will only \$14,372,000 in the President's budget. The OD AIDS budget supports 42 FTEs, half in OAR. Others work in the Intramural AIDS Targeted Antiviral Program (IATAP), and the Protein Expression Laboratory (PEL).

The Office of AIDS Research. OAR was established by the Health Omnibus Programs Extension (HOPE) Act of 1988. Anthony Fauci, MD, is its first director. OAR's Deputy Director of the OAR is Jack Whitescarver, PhD. OAR's functions and responsibilities are: to coordinate NIH intramural and extramural AIDS research; centralize various AIDS-related policy and operating functions; to represent the Director, NIH, on AIDS-related matters; to develop and coordinate of the NIH AIDS budget request; to develop information strategies with interagency collaboration to inform the public of NIH and PHS AIDS research activities; to recommend solutions to ethical/legal issues; to foster national and international information exchange with government, industry, and academia concerning AIDS research; to manage the NIH Loan Repayment Program for AIDS researchers. The OAR coordinates the meetings of the AIDS Program Advisory Committee (APAC) which advises the HHS Secretary, the Assistant Secretary for

Health, the NIH Director and the Associate Director for AIDS Research. Although OAR coordinates several advisory committees, none seems to be concerned with detailed evaluations of existing programs. Broad research priorities are legislated or pressured by Congress and the Executive branch (e.g. pediatrics, opportunistic infections, vaccines) or by crises that can't be ignored any longer (e.g. tuberculosis).

The OAR is working on a draft "NIH Strategic Plan for HIV-Related Research," also known as "The Five-Year Plan," in response to repeated requests for such a plan from activists, Congress and the Institute of Medicine. A November 1991 DRAFT "Strategic Plan" was presented to the APAC, then revised and sent to the Directors, AIDS Coordinators and intramural scientists at the 18 ICDS for comment and review. Further revisions will take place this summer. While the forthcoming "Strategic Plan" may be a step in the right direction, the drafts we have seen are a catalogue of NIH's current efforts without any analysis of how the program can be improved, where resources need to be increased, where new initiatives are necessary, what evaluation measures should be used, or what timelines should be imposed.

OAR has developed the AIDS Research Information System (ARIS), a database containing information on all NIH AIDS research projects funded since FY 1989. This report could not have been written without the information centralized and made accessible through ARIS and its able creators, Stan Katzman and Linda Reck. The ARIS system is new and can still be improved upon. Mason categories, while useful in budgetary administration, do not accurately categorize NIH programs for research policy review. There is a great need to track projects with keywords, to generate more flexible and user-friendly formats, and, perhaps, to generate an annual "NIH AIDS Resource Book" summarizing its AIDS Programs in a more accessible format. OAR could work with NLM to develop a system to track the productivity of NIH AIDS grantees by cross-referencing researchers with their recent publications in the peer-reviewed literature.

Finally, the OAR administers the AIDS Research Loan Repayment Program (LRP), which pays up to \$20,000 in educational debt per year (and a 39% tax reimbursement on the amount of loans repaid) to researchers recruited to conduct intramural AIDS research. Thirty-four researchers have participated in the program, including physician/scientists from NIAID, NCI, NINDS, NICHD, NIDR, NEI, NHLBI and the Clinical Center. OAR estimates that 20 new participants will enroll in the LRP in FY 1992 and 20 more in 1993.

The OAR, although vested with the responsibility to coordinate AIDS research at NIH, has not been given the power or developed a mechanism for doing so. The only real power lies in the hands of those who set budgets (the Institute Directors.) Healy has an additional \$20 million emergency fund (now renamed "high priority" fund), but OAR itself has no direct power to reallocate programs or resources across institutes.

While it is an old and maybe tiresome complaint, Dr. Fauci's many responsibilities are unlikely to leave him much time to concentrate on the responsibilities of the OAR. Dr. Fauci's stature in the research community and his position as director of NIAID, however give the OAR a legitimacy which it might not enjoy with a lesser figure at its helm. As director of NIAID, an institute that consumes over half of NIH's total expenditures on AIDS and which devotes almost half of its own resources to AIDS research, Dr. Fauci also has at least a theoretical conflict of interest in setting budgetary and research policy as part of his other roles as OAR Director and NIH Associate Director for AIDS Research.

Intramural AIDS Targeted Antiviral Program (IATAP). The IATAP supports basic research on the structure and function of HIV. Currently, 49 teams from 12 institutes are supported by IATAP. Using structural biology and molecular biochemistry techniques, IATAP researchers are attempting to elucidate the structure of HIV proteins, the molecular mechanisms of action of viral enzymes, the mechanisms of viral DNA integration, proviral activation and gene expression and the cellular processing and modification of viral peptides necessary to assemble complete functional virions. Recent accomplishments of intramural IATAP researchers include: 1) Determination of the complete three dimensional structure of the two zinc finger domains of the p7 nucleocapsid protein of HIV, which packages the RNA in the virion; 2) Development of a simple assay for the activity of the HIV integrase, which can be used to screen inhibitors; 3) Discovery of new mechanisms for the high rate of error in HIV reverse transcription; 4) Development of a CD4 fusion protein-bacterial toxin conjugate which can selectively kill cells expressing HIV. This supplementary funding for intramural research is commendable. The success of the program in bringing highly-talented NIH researchers into AIDS research for the first time is notable. This model should be duplicated for other AIDS research areas, especially those which lack the already high level of support and scientific interest that molecular and structural biology have, particularly, pathogenesis, wasting syndrome, and neurology.

The Protein Expression Laboratory (PEL) was established under the aegis of the OD to provide IATAP with highly purified HIV proteins, including RNase H, reverse transcriptase, rev, tat, protease and integrase, for structural, physiochemical and pharmacological studies.

Future Plans. The small increase in the OD's budget for FY 1993 will be used to maintain current programs.

Recommendations. Aside from the comments above, recommendations for the OD will largely reflect the recommendations made for the NIH as a whole.

\*

## II/9. National Institute of Dental Research (NIDR)

The Public Health Service created a Dental Hygiene Unit in 1931. The PHS DHU pioneered the study of fluoride on tooth decay, leading to widespread and controversial fluoridation of drinking water in the US. In 1948 the National Dental Research Act (P.L. 80-755) created the NIDR. The current NIDR Director is Harald Loe, DDS, DO. NIDR researchers spent \$2.6 million on intramural research and program support in 1991. NIDR investigators are investigating parallels and differences between Sjogren's syndrome and HIV-associated salivary gland disease. NIDR researchers are cloning HIV into transgenic mice to determine the role of various viral proteins on murine cells and tissues; studying how TGF-beta induces macrophage chemotaxis, possibly recruiting HIV-infected macrophages into the CNS; studying the role of HIV in the oral cavity and how saliva protects against infection; examining the infection of monocytes by HIV; developing diphtheria toxin conjugates fused to the binding domain of the interleukin-2 receptor which kill HIV infected monocytes expressing high affinity IL-2 receptors; polymerizing HIV peptides as vaccine candidates; trying to develop human monoclonal antibodies to HIV antigens, and trying to identify salivary antifungal, antibacterial and possibly antiviral histidine-rich proteins. Five extramural grantees have found that different fractions of saliva exhibit

varying degrees of anti-HIV activity. Other bodily fluids are also being examined:

Tears and saliva alike exhibited modest [HIV-] inhibitory effects, while breast milk exhibited a monumental effect. Future studies will attempt to identify and characterize the inhibitory component and determine mechanism(s) of action.

NIDR spent \$3.7 million on 18 extramural awards in 1991. These included six epidemiological studies of the oral manifestations of AIDS (totalling \$1.7M: two in monkeys, one in the Army and one in hemophiliac children), six studies of antiviral (anti-HIV, HSV, CMV, EBV) factors in human saliva (\$1.2M), 4 thrush studies (\$506,008) of candidiasis, and one study monocytes (\$183,955) and of oral drug delivery (\$21,183). Oral epidemiologists are finding treponemes, mycoplasmas, and previously unknown species of lactobacilli.

Funding + Future Plans. NIDR spent \$6 million on AIDS in FY 1991 - 4.4% of its total budget (and 0.8% of the NIH AIDS budget). NIDR requested an increase of \$2.41M to \$8.948M in FY 1993, and President Bush granted it \$473,000. NIDR now has 19 AIDS FTEs and wanted to add 9 for a total of 28. Included in the NIDR Director's request for FY 1993 were the following new programs:

- \* New extramural programs toalling \$2.9M for 15 grants and contracts to improve the early detection of HIV related clinical manifestations; to improve management of HIV-related oral lesions; and to further determine the role of salivary constituents in inhibiting HIV infectivity.
- \* New intramural programs totalling \$1.43M for virus-host interactions involving infected T cells; role of HIV genes in Kaposi's sarcoma; neuropathology; nephropathy; and new antiretroviral therapies using cell surface antigens to target infected cells without damaging uninfected tissue.

Recommendations:

- \* Congress should replace the \$2M taken from NIDR's AIDS budget by President Bush.
- \* NIDR should expand its studies of monocytes to include tissue macrophages and other mucosal antigen-presenting cells (e.g., langerhans/dendritic cells), elucidating the mechanisms of cytokine induction, defective antigen presentation, and immune dysfunction seen in HIV infection and AIDS - possibly in collaboration with NIAMS, NIDDK, etc.
- \* Support extramural studies of other oropharyngeal manifestations of HIV, including possibly autoimmune phenomena such as Sjogren's-like syndrome and the unusual salivary or lacrimal gland lymphomas associated with the diffuse infiltrative lymphocytosis syndrome (DILS).
- \* Develop animal models for oral/genital retroviral transmission.
- \* NIDR should initiate new studies of mucosal immunity to HIV, HSV, CMV, and EBV (comparing oral immunity to genital, pulmonary, gastrointestinal)...
- \* Studies of the etiology, diagnosis and treatment of (AIDS and ddC-induced) oral and esophageal aphthous ulcers (stomatitis) in PWHIV, including studies of thalidomide.

\*

II/10.National Institute of Diabetes + Digestive + Kidney Disorders (NIDDK)

NIDDK began in 1950 as the National Institute of Arthritis and Metabolic Diseases (NIAMD) and was originally chartered to investigate rheumatic diseases, diabetes and other metabolic, endocrine and gastrointestinal illnesses. In 1972, it became the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD); in 1981, the National Institute of Arthritis, Diabetes, and Digestive

and Kidney Diseases (NIADDK); and finally, in 1986, NIDDK, when its Division of Arthritis, Musculoskeletal and Skin Diseases spun off to form NIAMS. NIDDK's Division of Intramural Research supports investigations of a wide variety of diseases, including diabetes, other inborn errors of metabolism, endocrine disorders, mineral metabolism, digestive diseases, nutrition, urology and renal disease, and hematology.

NIDDK spent \$6.3 million for AIDS research in 1991. It asked for \$10M more next year, and the President offered \$500,000. NIDDK's AIDS work focuses on immunology (\$5.2M in FY 1991) and preclinical drug development (\$1 million), funding a range of studies of endocrine, metabolic, gastrointestinal, renal, urologic and hematological complications of HIV and AIDS. The wasting syndrome receives more attention from the NIDDK than from any other ICD (which isn't saying much). NIDDK also conducts and supports studies on basic mechanisms of HIV infection, the structure of HIV and the development of antiviral therapies.

In FY 1991, NIDDK funded 33 research project grants, all R01s, at a cost of \$5M. All grants were classified as immunology. Since 1987, NIDDK issued 6 AIDS RFAs for 1) Pathogenesis of Intestinal Dysfunction in AIDS; 2) Effects of HIV Infection on the Kidney and in Dialysis and Renal Transplant Patients; 3) Genitourinary Tract Manifestations of HIV; 4) Pathobiology of Bone Marrow Suppression in AIDS and ARC; 5) Endocrine Aspects of AIDS; 6) Endocrine Basis of Wasting in AIDS

Nutrition + Wasting. Some grantees are investigating diagnosis, etiology and treatment of HIV-related nutritional and metabolic disorders, measuring body composition, caloric intake, energy expenditure, and metabolism in adults and children with HIV. These studies include nutritional and metabolic disorders found in HIV infection, including abnormalities in intestinal enzymes, perturbations of normal intestinal flora, endocrine and cytokine dysregulation as contributing factors to wasting and other metabolic disturbances, and development of nutritional interventions for AIDS and evaluating parenteral nutritional therapy. In September 1990, the PHS called for increased research on wasting and other nutritional deficiencies associated with AIDS. The NIH's AIDS Program Advisory Committee (APAC) echoed the recommendations of the PHS on this matter. In FY 1991, seven NIDDK grants were funded for research on wasting and other metabolic and nutritional disorders at a cost of \$1.2 million. For FY 1993, NIDDK put research on wasting at the top of its wish list, asking to fund 13 new grants on wasting. PHS and DHHS cut NIDDK's budget request, making these new wasting grants unlikely. This is lip service at its worst. First the PHS recognizes research on wasting as a priority and then refuses to fund it. In 1991, NIDDK grantees also conducted studies on how TNF and IL-1 contribute to metabolic dysfunction in AIDS; the biochemical basis of muscle wasting in AIDS; hepatic metabolism in patients with the wasting syndrome; the therapeutic use of indomethacin, hydrazine sulfate, and fish oil in the wasting syndrome.

Digestive Disease. NIDDK also supported investigations of the complications of HIV and its opportunistic sequelae in the digestive system. This work has focused on studies of GI cell infection by HIV, the physiological basis of AIDS enteropathy, the pathogenesis of cryptosporidiosis, and liver damage. Despite voluminous documentation by NIDDK, actual work supported in 1991 on the effects of HIV and OIs on the GI system amounted to just two grants costing \$331,992. NIDDK wanted to award 10 new grants for this work in FY 1993, but expansion was rebuffed by the Executive Branch.

Endocrinology. In 1991, NIDDK funded 11 grants on the neuroendocrine-immune interactions in HIV infection. Endocrine, immune and nervous system interactions

in HIV infection have received little attention. The PHS "Strategic Plan for AIDS," in 1990, called for increased emphasis on research on these endocrine abnormalities. NIDDK wanted to fund an additional eleven grants in this area for FY 1993.

Kidney + Urologic Disease. NIDDK supports research on AIDS and HIV in the genitourinary tract; renal complications of AIDS; and the effect of cytokines on glomerular epithelial cell pathology, the effect of vasectomy on transmission of HIV, and the result of kidney transplants among patients with HIV. In 1991, NIDDK funded five awards for genitourinary and kidney AIDS research at a cost of \$1.4M.

Hematopoiesis. Work in 1991 largely focused on the hematopoietic defects in AIDS: whether they were caused by impaired production of colony stimulating factors, such as IL-3 and GM-CSF, by hematopoietic accessory cells (e.g. T cells and/or monocytes) or by direct infection by HIV of progenitor cells? Other work focused on the effects of AZT, acetaminophen, and other drugs on the production and differentiation of myeloid and erythroid progenitor cells. NIDDK supported eight grants in this area in FY 1991 at a total cost of \$1M. For 1991, NIDDK requested \$741,000 for three additional grants on bone marrow function in AIDS. While NIDDK's efforts should be applauded, perhaps since the institute has a small AIDS budget, it might be wiser to leave support of studies in this area to the larger institutes sponsoring investigations in this area such as NHLBI, and direct the funds towards the work on wasting, neuroendocrine and immune system interactions, and gastrointestinal complications of HIV infection, which have little support outside of NIDDK.

Intramural Research. NIDDK spent \$1M on intramural AIDS research in 1991 at the following labs: Laboratory of Chemical Biology: AIDS-Transcriptional regulation by tat-protein and LTR of HIV in vitro; Laboratory of Chemical Physics: Structural studies of AIDS proteins by NMR; Investigations of macromolecular structures and dynamics by NMR; Laboratory of Bioorganic Chemistry: Mechanistic enzymology of HIV proteins; Halogenated biogenic amines in biochemistry and pharmacology; Laboratory of Molecular Biology: Studies on the mechanism of retroviral DNA integration; AIDS related proteins - structure and function; Study of the potential use of catalytic antibodies against AIDS; Genetics + Biochemistry Branch: CD4 receptor structure/function project; Target ribozymes to HIV sequences; Laboratory of Molecular and Cellular Biology: Function of DNA virus genomes in animal cells; Regulation of HIV by AAV. These laboratories have 1) identified of two glycosylation sites on the CD4 molecule required for proper protein folding and transport to the cell surface; 2) identified the protein necessary for integration of HIV into the host genome and the development of an assay to screen for inhibitors of this enzyme; 3) generated preliminary evidence suggesting that the human parvovirus AAV rep gene blocks growth of infectious HIV by inhibiting the function of the HIV tat gene; 4) shown inhibition of HIV gp120-induced impairment of signal transduction in human CD8+ cells by sCD4. The heavy emphasis on molecular biology and related disciplines in NIDDK's intramural AIDS program is disappointing. Work of this kind is heavily subsidized elsewhere and NIDDK's efforts don't particularly stand out from the crowd, except for the research on the HIV-1 integrase and the negative regulatory properties of the AAV rep gene. Perhaps NIDDK's intramural branches could supplement NIDDK's extramural work on wasting and related topics.

For FY 1993, NIDDK wanted to double its AIDS FTEs from 10 to 20 for intramural research projects. If money were available, NIDDK should not simply double its efforts in the area of molecular virology and drug design, but should also attempt to involve intramural researchers in projects on wasting and related

metabolic disturbances, gastrointestinal infections and abnormalities, neuroendocrine and immune system interactions, thymic pathology, hematopoietic dysfunction, and renal complications.

Recommendations:

\* NIDDK's request for an additional \$10M for FY 1993 should be honored and funded by Congress.

\* NIDDK should consider initiating collaborative efforts with the NIAID-funded ACTG, specifically in the areas of nutrition and wasting, and gastrointestinal infections (crypto- and microsporidiosis, etc.). \* NIDDK should fund work on opportunistic enteric pathogens; the gastrointestinal mucosal immune response in HIV infection; the mechanisms of AIDS enteropathy and malabsorption; microsporidiosis; enteropathic/enteroadherent E. coli infection; herpesvirus infection of the GI tract; cryptosporidiosis: animal models and in vitro screening assays for drug development; interactions between HIV and hepatitis viruses; hepatobiliary pathology in AIDS; aphthous and large idiopathic ulcers in the GI tract.

\* Further research the role of the thymus, the effects of neuroendocrine hormones and peptides on lymphocyte development and function, and on the regulation of the immune response.

\* Further study the renal toxicities of drugs currently in use in HIV infection.

\* Study effects of transplant-associated immunosuppressive chemotherapy in HIV-infected persons at various stages of disease.

\* II/11. National Eye Institute (NEI)

NEI was established in 1968 (P.L. 90-489) to support "basic and applied research, including clinical trials, related to the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system." Carl Kupfer, MD, is its first and hitherto only director. NEI's commitment to AIDS was \$5.68 million in FY 1991. Most NEI AIDS funds go to the SOCA program (see below) and to an intramural clinical trials program, with much smaller extramural awards in diagnostic methods, animal models, neuroscience and diseases related to HIV (principally CMV, toxoplasma and microsporidia-related retinitis).

Basic research. Of the 11 non-SOCA extramural awards, two involve developing mouse models for CMV retinitis; one small training grant targets ocular manifestations of SIV in primates; two are attempting to develop new methods to diagnose HIV, HHV-6 and CMV in people with AIDS; three are looking at other mechanisms of HIV- and/or CMV-induced optic neuropathy; and one each is looking at ocular toxoplasmosis and ocular microsporidiosis in AIDS.

Intramural clinical trials. NEI conducted the pivotal study which led to FDA approval of foscarnet for CMV retinitis. In FY 1991 NEI spent \$1 million on its intramural clinical trials, developing a surgical implant to deliver ganciclovir directly to the eye over a period of months; this trial will begin in mid-1992. NEI's Laboratory of Immunology is jointly carrying out epidemiology on the ocular manifestations of AIDS in children with the NCI Pediatrics Branch, following 150 children. They have recently identified VZV retinitis as a new opportunistic infection in these children. These conditions are a diagnostic challenge, since children - especially infants - are less likely to report



visual problems. NEI also studied the ocular toxicity of ddI in children. NEI participated in a preliminary study of oral 566c80 for ocular toxoplasmosis.

Studies of the Ocular Complications of AIDS (SOCA) is a series of three cooperative agreements (U01s) funded by NEI to conduct clinical trials of interventions for eye pathogens in people with AIDS and HIV infection. The structure and operations of SOCA are a dramatic contrast with those of the ACTG system, also funded with cooperative agreements. SOCA was initiated in 1988 and funded in 1989, and is supported by over \$3 million a year. Two U01s go to fund the Chairman's Center (PI Douglas Jabs, MD) and the Coordinating Center (PI Curtis Meinert, PhD), both at Johns Hopkins in Baltimore. The third U01 supports the Fundus Photograph Reading Center in Madison, Wisconsin, where retinal photographs are analyzed. The entire SOCA system is subcontracted and administered from Hopkins. [Imagine the ACTG funded as a series of subgrants from Harvard and Stanford and you'll get the picture.] Thus, the \$2.8 million which supports the 11 clinical centers around the country is all filtered through Curtis Meinert's Coordinating Center at Hopkins. Each SOCA unit, with the exception of Baylor College in Houston, also receives ACTU funds. The SOCA took a radically different approach from the ACTG. Rather than trying to do everything, the SOCA tried to do one thing well. In this case, SOCA took on the most pressing single question about CMV retinitis -- which treatment is better, foscarnet or ganciclovir? -- and answered it in just 18 months.

Funding + Future Plans. NEI's AIDS program spent \$5,680,000 in FY 1991, 2.2% of its total budget and 0.7% of the NIH AIDS total. NEI requested an increase to \$14,368,000 in FY 1993, but the President granted a mere \$319,000. Included in the NEI's request were the following four programs:

- \* \$2 million more in the SOCA program for a total of \$5.5 million;
- \* \$2.9 million in new funds to compare oral with intravenous ganciclovir;
- \* \$3 million in new funds to study CMV prophylaxis;
- \* \$1.4 million to triple current funds to study animal models of the ocular complications of AIDS.

#### Recommendations

- \* NEI should work on elucidating the ocular immune defects (possible vascular breakdown, cytokine involvement, etc.) which lead to eye disease in AIDS.
- \* NEI should dispense with the delayed treatment arm of its new study of intraocular implants for CMV retinitis. The SOCA study should have made clear that PWAs are generally unwilling to be randomized to delayed treatment regimens.
- \* NEI should develop a study of CMV prophylaxis in pediatric populations.
- \* In view of the increasing use of ddI in children with HIV infection, NEI should work with NCI, NICHD and NIAID to develop and publicize a diagnostic and therapeutic algorithm for optic neuritis in children receiving ddI therapy.
- \* SOCA should work with ACTG, CPCRA, AmFAR, FDA and Burroughs-Wellcome to persuade Syntex to contribute oral ganciclovir for a 3-arm, 2-drug study of CMV prophylaxis in 1993, using any or all of the above networks.
- \* SOCA should consider piloting multicenter trials of albendazole for ocular microsporidiosis and of 566c80 vs. pyrimethamine for ocular toxoplasmosis.
- \* SOCA should improve relations with the ACTG Viral PSG and should include community activists on its protocol steering committee(s).
- \* OAR should list the NEI and SOCA projects in the section of the Strategic Plan concerning treatments for opportunistic infections.

\*

II/12. Fogarty International Center (FIC)

for Advanced Studies in the Health Sciences

FIC was established in 1967 as a memorial to Rep. John E. Fogarty (Rhode Island). FIC sponsors two large international AIDS training projects, and is also an NIH liaison to WHO, PAHO and the European Medical Research Councils. FIC spent \$5.35 million on AIDS in 1991. For next year, it asked for \$8.5M; the President cut this down to \$5.8M, which is barely enough to maintain current services. A third of FIC's total budget is devoted to AIDS. The International Training in Epidemiology Related to AIDS program is funded through D43 grants, a unique activity code specially created for the program. The International Postdoctoral Research and Training in AIDS program is funded through T22 grants, which are institutional research fellowships "to support an institution with an approved preceptor for a number of postdoctoral research training fellowships in a limited number of specified shortage biomedical science areas." Over the next two years, FIC's efforts are being redirected towards vaccine development. \$2M will be taken from prevention, education and epidemiology to fund training for vaccine field trials. This transfer of resources away from prevention and natural history to vaccine infrastructure development is a major development in the NIH's AIDS program which has, hitherto, received little attention or broad discussion. What is the impact in developing countries of cutting back on prevention and epidemiology? Are the vaccine products to be tested promising enough to justify the expense? Are local communities involved? Will the vaccines, if proven effective, be distributed in the countries where they were proved?

The AIDS International Training and Research Program (AITRP) was initiated in 1988 in response to Congressional pressure to address the international scope of the epidemic. Its goals are 1) to train foreign epidemiologists; and 2) to foster US-international collaboration on AIDS research. AITRP is an integral part of the NIH's strategy for developing an infrastructure for future HIV vaccine trials. Other emphases include the prevention and treatment of opportunistic infections and the unique problems of women and children with HIV infection. FIC's efforts are coordinated with other international AIDS research efforts administered by the NIH and other federal agencies, as well as those supported by the World Health Organization's Global Programme on AIDS (WHO/GPA).

The International Postdoctoral Research and Training in AIDS Program supports collaborative research and training for US and foreign scientists who want to expand their capabilities in the epidemiology, diagnosis, prevention and treatment of AIDS. While AIDS researchers from any country and career level may apply through this program, priority is given to those from developing countries. Four US institutions conduct the program: San Diego; UCLA; Seattle; and Miami. Each program is at a NIAID-funded AIDS Clinical Trials Unit (ACTU) site.

The International Training in Epidemiology Related to AIDS Program. program is designed to increase foreign scientists' expertise in epidemiological research related to AIDS and its use in clinical trials and prevention research. Ten participating US institutions train scholars from a wide array of countries, including Zaire, Cote d'Ivoire, Caribbean lands, Brazil, China, Philippines, Singapore, Thailand, Taiwan, Mexico, ex-USSR, Columbia, Haiti, Argentina, Uganda, Mozambique, Senegal, Dominican Republic and Zimbabwe.

Future plans. The FIC wanted to expand both the International Training in Epidemiology Related to AIDS and, the International Postdoctoral Research and Training in AIDS programs for FY 1993 by adding new sites and increasing funding for current sites with \$2.5M in new funds. Of course, the FIC received little more for FY 1993 in the President's budget than it was allotted for FY 1992.

Recommendations:

\* The AIDS International Training and Research Program should be expanded to provide more extensive training of foreign clinicians and health professionals in diagnosis and treatment of AIDS-related conditions so they can bring better clinical care to the affected populations in their home countries.

\* One of the most apt criticisms of an otherwise praiseworthy program is embedded in one of the grant applications which are part of the FIC's "Third Year Progress Report":

"The majority of the research projects initiated by our trainees in their host countries include serosurveillance, evaluation and behavioral interventions. Training in anti-retroviral drugs and vaccine trials, e.g. immuno-modulatory vaccines [post-infection therapeutic vaccines], have been taught for largely philosophical purposes as most of the countries of Central America and Caribbean have few resources for such products and must find other ways to manage the HIV-1 disease in infected individuals. Our trainees from Mexico, Argentina, and Costa Rica are now developing a protocol to emphasize those interventions likely to be available to HIV-1 infected individuals in Central and Latin America, e.g., affordable prophylaxis for opportunistic infections (bactrim, dapsone, INH), nutrition intervention, exercise, psychosocial support, etc." [emphasis added]

\* Sophisticated and technologically-driven basic scientific training of scientists and health professionals from poorer countries may not be the most practical use of the program's resources. While it is fine for the AITRP to help build scientific infrastructure in the developing world, FIC should also stress training in disciplines most likely to be of use in combatting the AIDS epidemic in countries with limited resources.

\* The program should re-emphasize its commitment to developing nations.

\* The new FIC emphasis on building an infrastructure for trials of preventive HIV vaccines, and the lack of additional funding to support this work, means that the FIC will be forced to defund other vital areas of the AITRP. The AITRP should remain a training program in epidemiology and basic and clinical biomedical research. It should not become a vaccine development program unless extra money is specifically allocated for that purpose. This is one of the more obscene choices forced upon NIH by the Executive branch and Congress. While breathing down the neck of the NIH to hurry along the vaccine effort, they provide no extra money for the endeavor.

\* The FIC stands out among the ICDs for its thorough and detailed accounting and description of its AIDS programs. The progress report issued by the FIC should be a model for other ICDs at NIH.

\*

II/13.National Institute of Environmental Health Sciences (NIEHS)

The Division of Environmental Health Sciences was established in 1966 at Research Triangle Park, North Carolina, where it became the NIEHS in 1969. Its mission is to investigate "the effects of chemical, physical and biological environmental agents on human health... [supporting] training in environmental toxicology, pathology, mutagenesis, epidemiology and biostatistics." NIEHS is part of the National Toxicology Program (NTP). Its AIDS toxicology program is supervised by the Systems Toxicity Branch of the Division of Toxicology Research

and Testing. By the end of 1991, this program had evaluated the effects of acute and chronic administration of AZT, ddC, ddI, d4T, alpha interferon, and pentamidine isethionate on mice and rats, measuring "effects on body weight, survival, food and water consumption, hematology, clinical chemistry, organ weights and histopathology". NIEHS is carrying out 2-year mouse studies of single drug and combination (AZT/IFN) carcinogenicity in rodents. It is also studying the immunomodulating effects of drugs like pentamidine and dapsone. A new 5-year award cycle started in September 1991 measures reproductive and developmental toxicity and carcinogenicity in rodents given single, 28-day, 90-day and 6-month doses of single drug and combination therapies. They are also looking at toxic interactions between mouse retroviruses and anti-retroviral agents, and at nucleoside neurotoxicity (myopathy and neuropathy) in rodents. The NIEHS intramural program is examining molecular structure of HIV proteins such as reverse transcriptase and protease. One intramural collaboration is with Brendan Larder of Wellcome UK to determine the fidelity of retroviral reverse transcriptases.

Funding + Future Plans. NIEHS spent \$4.5 million on AIDS in 1991, 1.9% of its total budget and 0.5% of the NIH AIDS total. Its comparable budget in FY 1992 went down to \$4.32M. For next year, NIEHS requested \$7.11M, and the President responded with \$148,000 for an increase of 3.4% (less than inflation). NIEHS has 8 AIDS FTEs and wanted to add 12 for a total of 20. NIEHS would like to initiate studies of how "'substance abuse' drugs affect the action of AIDS therapeutics," but how it will do so in the absence of new funding is unclear. Other program requests for FY 1993 included:

- \* \$143,000 for an FTE to study the cellular molecular biology of Kaposi's sarcoma;
- \* \$1 million for a NMR spectrometer to study the enzyme binding of ddNs to reverse transcriptase;
- \* \$1.2 million for 5 new toxicology grants;
- \* \$270,000 to study protease and the CD4 receptor;
- \* \$426,000 to study neuroimmunology (5 new FTEs);
- \* \$70,000 to study lactoferrin as an immune modulator in rodents and humans;
- \* \$427,000 to study the mechanism of pentamidine's activity in the lung (5 FTEs);
- \* \$492,000 to study haloperidol derivatives as possible antiretrovirals in mice;
- \* \$737,000 to study neuroconductive and behavior changes induced by drugs.

Recommendations:

- \* Industry, which profits from ddNs, should support NIEHS in its toxicology research [\$7M is nothing to a major drug company whose nucleoside has just been approved!]

- \* NIEHS should coordinate its projected studies of substance use drugs and AIDS drugs with NIDA.

- \* NIEHS should expand studies of the effects of various OI drugs on cells and cytokine expression.

\*

II/14. National Center for Nursing Research (NCNR)

NCNR was established in 1986. Its current director is Ada Sue Hinshaw, PhD, whose trained in both nursing and sociology. NCNR supports research and training in three major areas: (1) health promotion and disease prevention, (2) understanding and ameliorating the effects of acute and chronic illness, and (3) improving patient care and the environment in which it is delivered. NCNR also

supports pre- and post-doctoral research training and career development for nurse-scientists and other experienced investigators. NCNR's small intramural research program is devoted almost entirely to HIV infection and AIDS. With the National Advisory Council on Nursing Research and others in the field, NCNR has developed a National Nursing Research Agenda, whose priorities include: Low birth weight: mothers and infants; HIV infection: prevention and care; Long-term care for older adults; Symptom management; Health promotion for children and adolescents. In FY 1991, NCNR's AIDS budget was \$2,545,000. NCNR requested \$6.8M for AIDS next year, but the President offered just \$3.3M, which is below the level of current services. NCNR's AIDS programs in 1991 included about \$1M in basic science research (immunology, behavior, prevention), \$300,000 in transmission/natural history, and \$1.1M in training. NCNR's AIDS program focuses on four major areas: (1) physiological aspects of nursing care, (2) psychosocial aspects of nursing care, (3) delivery of nursing care and (4) prevention of transmission.

For FY 1991, NCNR funded twenty awards in the areas of physiological aspects and delivery of nursing care to people with HIV; psychosocial aspects of the same; and prevention of transmission of HIV, hepatitis B and other pathogens. These programs are difficult to evaluate because the abstracts for many of the awards are not available in the DRG, OAR, CRISP databases [training grants are not abstracted in these databases]. The NCNR was among the more refractory of the institutes in terms of information sharing during this project. NCNR's prevention and education programs are geared towards women, adolescents and young adults. In conjunction, with NIA, NICHD and USAID, NCNR is participating in an international behavioral research program. As part of this effort, NCNR has funded a grant to develop an AIDS prevention program in Chile utilizing the country's network of health care clinics.

NCNR runs a small intramural program in collaboration with NIAID and the NIH Clinical Center to assess the physiological and psychological effects of HIV infection. Studies completed or currently underway included investigations of myopathy; nutritional problems, such as weight loss, decreased appetite and malnutrition; compliance with IND regimens; and quality of life issues for people with HIV infection. These studies are carried out at the NIH Clinical Center.

Future plans. NCNR requested a substantial increase for its FY 1993 budget in order to expand existing programs and fund new ones. NCNR's top priorities for FY 1993 were:

1. Expansion of NCNR intramural research on symptom management (an additional \$750,000);
2. Expansion of intramural research on quality of life (an additional \$250,000) for people with HIV.
3. Two new grants on symptom management and quality of life for \$1.1 million;
4. \$201,000 for nursing research training initiatives;
5. \$264,000 to evaluate the efficacy of universal precautions;
6. \$1.1M to fund four research project grants studying high-risk behavior and educational interventions in women and people of color; and
7. Four new AIDS FTEs (for a total of 11).

Under the President's budget for FY 1993, none of these initiatives can be funded.

Recommendations:

\* NCNR's program does a great deal with little resources. The establishment of an intramural program, largely devoted to research on HIV infection, is to be commended.

\* If new resources were forthcoming, NCNR might consider establishing a collaboration with the ACTG, CPCRA or other clinical trials programs to provide their expertise to the patient care and quality of life programs in those networks.

\* In a summary of its programs, NCNR remarks on the difficulty of getting nurse scientists to work in AIDS. Perhaps some educational and/or recruiting program could be established in conjunction with national nursing schools to ensure that as the epidemic expands, the supply of highly-trained nurse scientists across the nation will be sufficient to meet the demand for them.

\*

## II/15. National Institute of Arthritis and

### Musculoskeletal + Skin Diseases (NIAMS)

The NIAMS goes back to 1950 with the foundation of the National Institute of Arthritis and Metabolic Diseases (NIAMD), which by 1980 had evolved into the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). In 1985, NIADDK was bisected into the NIAMS and the NIDDK (P.L. 99-158), with NIAMS to focus on arthritis, musculoskeletal diseases, muscle biology + skin disease. NIAMS' Intramural Research Program consists of a Laboratory of Physical Biology and the Arthritis and Rheumatism Branch. Its four extramural branches are: 1) Rheumatic Diseases; 2) Musculoskeletal Diseases; 3) Skin Diseases; and 4) Muscle Biology and Training. There is also an Epidemiology/Data Systems Program and the three Centers programs: a) Multipurpose Arthritis and Musculoskeletal Diseases Centers (1974); b) Specialized Centers of Research (1987); and c) Skin Diseases Research Centers (1988). NIAMS spent \$1,633,000 on AIDS in FY 1991. \$1.2M went for 5 extramural immunology grants. "NIAMS supports research on the natural history and pathogenesis of rheumatic and cutaneous manifestations of HIV infection. The Institute also conducts studies of the relationship between HIV and its infectivity." Alasdair Steven at the NIAMS Laboratory of Structural Biology Research is using electron microscopy to carry out structural analyses of gp160, gp120, gp41 and rev.

Epidemiology of AIDS related skin disorders. NIAMS is giving the US Army Medical Research + Development Command and the US Navy \$450,000 to study: "the full spectrum and the natural history of these [skin] manifestations ... in US Army and Navy personnel. Approximately 600 individuals [now over 680 have been evaluated..." NIAMS would like to extend these studies to community-based populations.

Dendritic cells and autoimmune skin phenomena. NIAMS issued two program announcements for AIDS-related research in FY 1991: 1) Association of arthritis, inflammatory muscle diseases, and other rheumatic manifestations with HIV positivity and AIDS; and 2) Cutaneous manifestations of HIV infection and AIDS. In response, NIAMS awarded three AIDS-related basic research grants in 1991, and one so far in 1992. These projects focus on skin and joint disorders in AIDS; the role of dendritic cells and skin cytokines; the possible role of autoimmune phenomena in HIV-related psoriasis, arthritis and Reiter's syndrome [PARS]; diffuse infiltrative lymphocytosis syndrome [DILS]; and parallels between AIDS and lupus. The four grantees are studying questions which go to the heart of

several unresolved issues of AIDS pathogenesis. The Columbia investigators have hypothesized that persons developing DILS may progress much more slowly. Elucidation of the mechanisms of PARS and DILS, and development of treatments if necessary, is a vital area long ignored by mainstream research. The NIAMS program, while tiny and new, needs rapid expansion to address these and other questions. Cutaneous and rheumatic manifestations of HIV affect quality of life and may affect disease progression. The skin is perhaps the largest immunological organ of the body, and one of the least well understood (along with the mucosal epithelia within). Studies of homing patterns among lymphocytes, macrophages and dendritic cells, and of primary and secondary immune responses occurring in situ as well as in peripheral lymphoid organs, should help to further elucidate the pathogenesis of AIDS.

Funding. NIAMS spent \$1.63M on AIDS in FY 1991, comparable to \$1.73M in FY 1992. This amounts to 0.8% of its total budget, and just 0.2% of NIH's AIDS budget. NIAMS wanted to double its program in FY 1993 (to \$3.431M), but the President provided a mere \$86,000 increase (5%) to \$1.81M. NIAMS has 4 AIDS FTEs and would have added 2 more next year.

Future plans. The ICD Directors' Wishlist for FY 1993 included the items on the list below. These new initiatives are infeasible without more support:

- \* \$848,000 to double the current R01 program investigating skin and joint disorders in AIDS;
- \* \$576,000 to triple current studies of Langerhans/dendritic cells as potential reservoirs or accessory cells in HIV infection;
- \* \$360,000 to expand epidemiological studies of the rheumatic and skin manifestations of HIV in military populations, minorities and children with HIV.

Recommendations:

- \* NIAMS, in its intramural program, should address the parallels between AIDS and autoimmune phenomena such as lupus and rheumatoid arthritis, and alloimmune phenomena such as GVHD.

- \* Congress should increase the NIAMS AIDS budget to the \$3.7M requested for FY 1993.

- \* Studies of cutaneous and autoimmune (PALS, DILS) manifestations of HIV should be expanded.

II/16. National Institute on Aging (NIA)

NIA was founded in 1974 following the 1971 recommendation of the White House Conference on Aging, and was given responsibility for "biomedical, social and behavioral research and training related to the aging process and diseases and other special problems and needs of the aged." NIA runs a Gerontology Research Center in Baltimore, MD, where most of its intramural research is conducted. The NIA Laboratory of Neurosciences conducts basic and clinical research at the NIH Clinical Center. NIA runs eight intramural laboratories in Clinical Physiology, Behavioral Sciences, Personality and Cognition, Cellular and Molecular Biology, Biological Chemistry, Molecular Genetics, Cardiovascular Sciences, and Neurosciences. NIA's Extramural Division has eight subdivisions: Biomedical Research and Clinical Medicine, Molecular and Cell Biology, Geriatrics, the Neuroscience and Neuropsychology of Aging, Behavioral and Social Research, Adult Psychological Development, Social Science Research on Aging, and demography and Population Epidemiology.

NIA spent \$985,000 on AIDS-related projects in 1991. For next year, it requested \$3M. The President cut this down to \$1.05M, less than that needed to maintain current services (\$1.13M). NIA AIDS research focuses on the biomedical, clinical and behavioral aspects of HIV infection in middle-aged and older individuals. NIA is concerned with how aging and its associated immune changes affect the course of HIV disease and response to treatment in these populations. NIA places a special emphasis on behavioral research focused on AIDS-related behaviors and behavioral change in the middle and later years, the impact of a diagnosis of AIDS on families and social networks, and the impact of AIDS on health care of older individuals. In addition, NIA, in collaboration with NICHD, NCNR and USAID, supports an international behavioral research program involving AIDS education program for women in Botswana.

In FY 1991, NIA supported three extramural projects at a cost of \$385,000, including an interagency agreement with CDC to support part of a study social and behavioral aspects of AIDS (the PI is Gary Noble); a study of the effect of age on HIV disease and immunosuppression in mice; and the education program described above. In FY 1991, NIA spent \$600,000 on intramural AIDS research. "The Clinical Immunology Section conducts research on the immune deficiency of aging as well as the host response to HIV. The goals of the age related research are to understand and reverse the appearance of non-function[al] lymphocytes in the older individual. The work deals with activation events, pathways leading to activation, and the effect of growth factors and cytokines on activation and suppression. The HIV related research deals with the increased morbidity and mortality seen in the older AIDS patient and the response of the immune system to the HIV which is responsible for the appearance of HIV-related illnesses." The CIS also collaborated on a trial of HIV gp160-vaccinia recombinant vaccine with investigators at Johns Hopkins. Two additional clinical trials, one of human growth hormone and the other of arginine (which stimulates endogenous production of HGH), were conducted to investigate the immunomodulatory effects of these agents in non-HIV-infected subjects. No effect on immunological parameters was observed.

Future Plans. In its wish list for FY 1993, NIA asked for:

- \* An extra \$499,000 for intramural immunology work on the host response to HIV;
- \* \$1.5M to expand AIDS information and risk behavior studies to persons 55 years and older;
- \* Five new AIDS FTEs for a total of ten.

NIA's request for an increased allocation was denied. For FY 1994, NIA will again request an additional \$1.5M for AIDS-related behavioral and social research.

Recommendations. NIA's basic research on the host response to HIV and the particular course of HIV infection in older individuals is a valuable program. The other basic immunology conducted by the Clinical Immunology Section, LCP, on lymphocyte activation, growth factors and cytokines, and its interest in boosting the immune response of the older individual are useful and applicable to AIDS. The budget increases requested by NIA, a modest amount - only \$1.5M - should be honored in full.

\*

II/17. National Library of Medicine (NLM)

The NLM Act of 1956 mandated an NLM to collect, preserve and disseminate the world's published medical information. Since 1964, NLM initiated several on-line



computerized medical information databases, including MEDLARS and MEDLINE. In the Health Omnibus Program Extension (HOPE) act of 1988 [P.L. 100-607] Congress directed the NLM to develop several AIDS-related research databases. The AIDSLINE database was created within the NLM's MEDLARS information retrieval system. AIDSLINE is updated with over 800 citations monthly, which are also available in its printed periodical AIDS Bibliography. Additional databases are being added to AIDSLINE, including AVLINE, BIOETHICSLINE, CANCERLIT, CATLINE, HEALTH and POPLINE. "Access is charged at MEDLINE rates... [and] is available ... on both the IBM and Macintosh versions of GRATEFUL MED." NLM also worked with NIAID, FDA and CDC to develop the AIDSTRIALS and AIDSDRUGS databases, which provide on-line access to clinical trials information also available through ACTIS (AIDS Clinical Trials Information System, 1-800-TRIALS-A). These databases contain more information on publicly funded clinical trials than on those sponsored by industry. [In this respect, AmFAR's and many local or regional directories may be both more complete and more timely than the ACTIS/NLM system.] The DRAFT "NIH Strategic Plan" assigns NLM roles in "Information Dissemination," where NLM is supposed to help "expedite the dissemination of the latest information on state-of-the-art therapies, health care and prevention techniques" through its on-line databases, by supporting the supporting the "'clinical alerts' mechanism for the rapid dissemination of critical clinical trials results to health professionals," by pursuing "collaborations with the WHO, the PAHO, and international AIDS agencies to obtain and disseminate in AIDSTRIALS information about international clinical trials," and by publishing "full text of abstracts from meetings, where available, online..." Since NIAID has no system to expedite analysis and publication of its AIDS clinical trials, many ACTG studies (especially opportunistic infection trials, drug-company sponsored studies, and early phase studies) remain inaccessible years after their completion.

Funding + Future Plans. NLM spent \$519,000 on AIDS related activities in FY 1991, 0.6% of its total budget. This amounts to 0.1% of the NIH AIDS budget. NLM requested \$3.8M next year, but the President cut this to \$1.1M (barely enough for one more librarian!). NLM has 8 AIDS FTEs and wants to add 10 new ones for a total of 18 next year.

#### Recommendations:

\* NLM should conduct a survey of the users of its databases to assess their utility, timeliness, and solicit improvements if necessary. NLM and ACTIS should network with AmFAR and other community-based clinical trials directories (e.g., that of Massachusetts, or of San Francisco's Community Consortium) to fill the gaps in its listing of ongoing clinical trials.

\* OAR, DRG and NLM should collaborate in developing a database to track the publications of principal investigators funded by NIH AIDS-related awards, and to track the usefulness of those publications (e.g., by using the Science Citation Index or a similar tool).

\*

#### II/18. National Institute on Deafness + Other

##### Communication Disorders (NIDCD)

NIDCD was formed in 1988 (P.L. 100-553) after developing as a Division within what is now NINDS. James D. Snow Jr., MD, is the first and so far only NIDCD Director. NIDCD "conducts and supports research and research training with

respect to disorders of hearing and other communication processes, including diseases affecting hearing, balance, smell, taste, voice, speech and language." NIDCD first funded AIDS-related research in FY 1991. NIDCD is doubling its AIDS program in FY 1992 to \$985,000. The President's FY 1993 budget offers NIDCD a tiny increase [4.5%] for FY 1993, raising its AIDS allocation to \$1,029,000. NIDCD has just one AIDS FTE. NIDCD claims its AIDS research focuses on aspects of HIV infection that may involve impairment of hearing, balance, smell, taste, voice, speech, and language. These awards include a clinical research center for communicative disorders to better detect, treat and prevent childhood communicative disorders; a study of auditory processing in hearing-impaired children; and a study of congenital CMV infection and auditory pathology in mice at UCSD. None of these appears on its face to have any direct AIDS-related application. NIDCD also provides otolaryngic and audiological consultation and care to people with AIDS participating in research protocols run by other ICDS (two NIAID adult and two NCI pediatric protocols).

Future plans. For FY 1993, NIDCD asked for new funds to research CMV-related conditions such as Meniere's disease, perilymphatic fistulae, sudden onset hearing loss, and hearing and balance disorders emerging in people with AIDS. NIDCD wants \$1.865M to support 6 new research grants in this area.

#### Recommendations

- \* NIDCD should direct its program towards more specifically AIDS-related projects.

- \* Recent studies have found auditory or cochleo-vestibular impairment in people with HIV infection in the absence of opportunistic infection of the CNS or ear. Olfactory impairment has been reported in HIV infection as well. NIDCD should fund studies to follow up on these findings.

- \* Finally, in conjunction with the epidemiological and natural history studies funded by NIAID, NIDCD could investigate the incidence of sensory impairment in HIV infection.

- \* NIDCD could study ways of improving communication and research participation in populations whose primary language is not English. This is a major impediment to research diversity, and sometimes (e.g., with Roche) an explicit exclusion criterion!

- \*