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

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Part II: The NIH, A User's Guide

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INTRODUCTION

Part II: The NIH, A User's Guide, is the final section of our report on the AIDS programs of the National Institutes of Health. The material contained here is summarized, under separate cover, in Part I. We have provided this unexpurgated sourcebook as a tool for AIDS activists and advocates and others who want to learn about the AIDS programs sponsored by each of the institutes and centers at NIH in greater detail than is offered in our summary. You will find in the following pages: brief histories of each of the institutes and their AIDS funding, including the evisceration of the fiscal year 1993 AIDS budget; descriptions of each of their extramural and intramural programs, often with the principal investigators and their institutions listed; the "wish lists" of new programs and expansions of existing ones each institute would have liked to initiate for fiscal year 1993; and the lists of our recommendations for each fo the institutes, the NIH and Congress and the President.

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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, and the Biologics Control Laboratory was established. In

1948, these labs were consolidated 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).

NIAID AIDS Spending by Division, FY 1991

(dollars in thousands)

DAIDS $310,293 DMID 24,389 DAIT 22,922 DIR 47,116 RMS 27,735

AIDS $430,940 Non-AIDS 489,106

NIAID Total $920,046

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 hepatitis and influenza vaccines, and are now working on AIDS vaccines. While the DAIDS Developmental Therapeutics Branch (DTB) funds most basic science work on opportunistic organisms, DMID specifically funds work relating to herpes viruses (HSV, VZV, CMV, EBV). 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.

AIDS Programs. 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. It was not always so. In the first two years of the epidemic, NCI spent more than NIAID. From a scientific standpoint, NCI was ahead of NIAID. From a bureaucratic standpoint, however, NIAID was entitled to

the lion's share of AIDS funds. Two commentators tell different stories of how NIAID won the primary role in AIDS research:

To transform NIAID from an institutional weakling into an NIH powerhouse, Fauci had to fight for a bigger piece of the AIDS research pie... Fauci took on Dr. Vincent DeVita, head of the NCI... [After weeks of maneuvering] Fauci pulled out his big gun and told DeVita that AIDS was due to a virus and the NIAID was the place for research on such a disese. The NCI had entered the AIDS picture only because one of the earliest opportunistic diseases had been Kaposi's sarcoma... Now that everyone knew that AIDS was a virus [sic], it belonged to NIAID, he said... The bargaining was over.

Or:

Backstage jockeying and political compromises determined how NIAID and NCI ultimately divided their AIDS research responsibilities, although the leadership at both agencies claim the disagreements never became serious. After informal negotiations, NIAID eventually earned the privilege - some would say it carried the burden - for conducting most of the work... NIAID was in charge.

However it happened, by 1984, NIAID was ahead of NCI with $20 million to NCI's $17M, and its AIDS funding grew by leaps and bounds - to $63M in 1986, $145M in 1987, $223M in 1988, $311M in 1989, $394M in 1990 and $433M in 1991. Enormous extramural programs were solicited, competed, 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)

There are 15 laboratories in NIAID's DIR. 11 are located in Maryland, and four at the Rocky Mountain Laboratories in Montana. DIR also has a Biological Resources Branch, an Administrative Branch, and the Animal Care Branch (ACB), which provides "over 60 different strains of mice, hamsters, cotton rats and rabbits for NIAID investigators." Nine of the 15 DIR labs are working on AIDS research. The intramural laboratories spent $114.2 million in FY 1991, of which $47M (41%) was charged to AIDS. DIR employs 865 persons including 93 tenured scientists, 604 nontenured scientists and 172 nonscientists. Of 618 total person years worked in FY 1991, 200 (32%) went for research on basic immunology, 232 (38%) for parasitic, viral and bacterial (non-opportunistic) infections, 132 (21%) for retroviral research including HIV, and 55 (9%) for research on AIDS-associated opportunistic infections.

NIAID Intramural Laboratories working on AIDS

Code Laboratory of Chief Phone % HIV % OI % Other

LIR Immunoregulation AS Fauci 301/496-1124 73% - 27% LMM Molecular Microbiology MA Martin 301/496-4012 92% 5% 3% LIP Immunopathology HC Morse III 301/496-1150 100% - - LPVD Persistent Viral Dis. B Chesebro 406/353-3211 39% - 61% LID Infectious Diseases RA Chanock 301/496-2024 15% 22% 63% LVD Viral Diseases B Moss 301/496-9869 11% 22% 67% LIG Immunogenetics TJ Kindt 301/496-9589 20% - 80% LCI Clinical Investigation SE Straus 301/496-5807 - 45% 55% LPD Parasitic Diseases FA Neva 301/496-2486 - 3% 97%

Much of the NIAID basic immunology research, while not coded as AIDS-related, is obviously crucial in providing a foundation for elucidating the pathogenesis of the disease, the pathways of immune regulation which are disrupted, and

potential methods of immune reconstitution. Thus, the Laboratory of Cellular & Molecular Immunology (LCI, chief Ronald Schwartz), which studies T cell activation, the Laboratory of Host Defenses (LHD, chief John Gallin), and the Laboratory of Immunology (LI, chief William E. Paul), which conduct basic immunological research, provide a vital foundation for improving ultimate understanding of the immune system. Similarly, the Laboratory of Intracellular Parasites (LICP, chief Harlan Caldwell) and the Laboratory of Microbial Structure & Function (LMSF, chief J. Swanson) in Montana are conducting work on parasite-host interactions which may well have implications for AIDS.

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 how antigens are presented to T cells by the major histocompatibility complex (MHC) proteins, 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. This work adds further support to the contention that mammalian lentivirus-induced immunodeficiency may have an autoimmune or immune hyperactivation component.

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 and influenza viruses, woodchuck virus, hepatitis A, B and C (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 retroviruses, including 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.

Of the four laboratories in Montana, three are working on chlamydia, the lyme disease spirochete Borrelia burgdorferi, gonococcus, Campylobacter and other parasites.

The Laboratory of Persistent Viral Diseases (LPVD), chief Bruce Chesebro, works on rabies, Friend retrovirus, Aleutian disease virus, scrapie (mammalian spongiform encephalopathies), experimental allergic encephalomyelitis (EAE), equine infectious anemia virus (EIAV) and HIV cell tropism.

DIVISION OF AIDS (DAIDS)

The Division of AIDS (DAIDS), which runs most extramural AIDS programs for NIAID, is divided into 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).

The DAIDS Basic Research & Development Program (BRDP) consists of the Pathogenesis, Developmental Therapeutics, Vaccine Research + Development, and Resources + Contracts Branches (PB, DTB, VRDB + RCB, respectively). Peggy Johnston, PhD, is the newly confirmed Associate Director of the BRDP.

The Clinical Research Program (CRP) consists of the Pediatric Medicine Branch (PMB, chief Jim Balsley, MD), the Community Clinical Research Branch (CCRB, chief Bopper Deyton, MD), the Medical Branch (MB, chief Steve Schnittman, MD) and the Epidemiology Branch (EB, chief Sten Vermund, MD, PhD). The new Associate Director of the CRP is Lewellys Barker, MD, MPH.

The Treatment Research Operations Program (TROP) consists of the Clinical Research Management Branch (CRMB, chief George Counts, MD), the Operations & Data Management Branch (ODMB, chief Dennis Dixon, PhD), and the Pharmaceutical & Regulatory Affairs Branch (PRAB, chief Joe Meschino, PhD). The new Associate Director of the TROP is William Duncan, PhD.

The DAIDS Mission Statement is:

1. To discover, develop and optimize effective treatment and prophylaxis for HIV infection, opportunistic infections, AIDS-related malignancies and other complications; 2. To expedite discovery and development of an effective vaccine for HIV infection; and 3. To support basic biomedical research that increases knowledge about HIV as well as the related scientific disciplines fundamental to understanding HIV and its associated diseases. Integral to this mission is responsibility for ensuring that scientific investigation of infection with HIV

is focused on the most critical biomedical issues engendered by the AIDS epidemic.

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, bringing with him senior staff, such as Jack Killen and Susan Ellenberg. 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. Because DAIDS administers 37% of the entire NIH AIDS budget, its responsibilities are enormous. The DAIDS OD lacks strategic long-range planning staff and policy analysts. Although these functions may be conducted at the NIAID OD and in OAR, there they remain removed from day-to-day operations.

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, focused at that time on issues around Parallel Track and the ACT UP Treatment Agenda. Several BRB staff have moved on to other posts within DAIDS, such as Dennis Dixon, now chief, Operations + Data Management Branch (ODMB), TROP, and Peter Gilbert, Program Officer for DATRI. The Branch's responsibilities are crushing. It needs more staff.

BRB should work on streamlining data collection and analysis in the various NIAID clinical trials networks. This is the only way that more could be done with current, limited funds. In ACTG 019, less than 2% of the data collected were analyzed and utilized in the published manuscript. Cutting back on irrelevant data points can improve the efficiency of the ACTG and other systems.

BRB also needs a plan to help develop particularly important or promising virological, immunological and clinical markers in AIDS trials. Fewer and fewer ACTG participants are developing the "classical" CDC-defined AIDS conditions. Non-CDC-defined clinical conditions (sepsis, bacterial infections, etc.) are occurring with increasing frequency. New virologic assays such as quantitative microculture are ready for scale-up to large-scale use in efficacy trials. A new effort to develop better, cheaper immunologic assays is badly needed. BRB may be able to help develop a cross-protocol strategy to generate useful surrogates, which will make trials faster and more relevant.

Finally, BRB could help the FDA Division of Antiviral Drug Products and industry to continue working on more useful trial designs. Antiretroviral drugs like ddI and ddC are now reaching the market long before adequate information is available for their best use. Whether the nucleosides, when used early, truly confer a survival benefit is also unknown. Most ACTG participants are followed intensively for a few months or years, then dropped, when they could easily be recruited into a simple, cheap "long term follow-up" cohort to assess survival.

BASIC RESEARCH + DEVELOPMENT PROGRAM (BRDP)

The DAIDS 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.

NIAID HIV Sequence Database + Analysis Unit. NIAID supports the Energy Department's Los Alamos National Laboratory Sequence Database, which is directed by Gerald Myers. This project "tracks the variation of HIV and related immunodeficiency viruses through the compilation of genomic sequences contributed by sequence laboratories funded by the HIV Genetic Variation Program as well as by other laboratories worldwide." This program is designed to inform vaccine designers about the variation of HIV strains worldwide. WHO and the British Medical Research Council are collaborators.

Cloning + Sequencing of Immunodeficiency Viruses. The contractor is James Mullins at Stanford (formerly at Harvard). A subcontractor, Edward Hoover at Colorado State U., is looking at FIV genetic variation. "Dr. Hoover has identified 19 new FIV isolates from cats, 14 of which had clinical immunodeficiency." A subcontractor at Massachusetts General Hospital is looking at CTL clones from the peripheral blood and cerebrospinal fluid of HIV-infected individuals. NIAID also has an interagency agreement with the CDC to sequence specific HIV regions and isolates using PCR. Haynes Sheppard at the California Public Health Foundation was awarded a contract to assess and standardize panels of neutralizing antibodies to HIV for WHO and the Pathogenesis Branch. An Antibody Serological Program (ASP) sent 26 laboratories blinded samples of human and murine monoclonal antibodies (mAbs) to HIV-1 envelope proteins using mAbs which neutralized HIVMN and HIVSF2, HIVHTLV-IIIB, or both, or which failed to neutralize any of the three reference strains. A similar ASP-SIV program is now underway in 12 labs.

As is apparent from the above, the activities of the Pathogenesis Branch are rather technology-driven. What activities 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, who previously worked at the NCI DTB and came to DAIDS in 1988. At a meeting in fall 1991, Litterst 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 (17.9% of the NIH AIDS budget).

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 work has been helpful in both basic biomedical and preclinical drug development. For instance, NCDDG-HIV researchers elucidated the three-dimensional crystal structure of the CD4 molecule. They are finding out how HIV proteins like tat, rev and integrase work, and how they interact with host proteins and transcription factors. 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 both pharmaceutical companies and academic researchers. 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 compounds active against 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 (have they returned the initial investment?). In April, Fauci wrote to Abbott lamenting that:

At one time there was a fruitful collaboration between the NIH, the extramural research community, and Abbott laboratories in research on inhibitors of the HIV protease. Most significantly, this compound was discovered under a grant from the NIAID, partly as a result of direct and frequent interactions between all of the parties involved. Unfortunately, I understand that these productive relations have been severely curtailed of late.

Fauci went on to offer NIH resources and assistance. Abbott CEO Dwayne L. Burnham referred the letter to Abbott's Paul Clark, who replied:

Since we have made the decision to conduct the first studies in Europe, we have not involved the NIH... In order to keep the NIH apprised of Abbott's activities, Dr. [David] Ho has volunteered to serve as a liaison between this [Clinical Advisory] board and NIAID.

In other words: back off. As usual in America, risk is subsidized by the taxpayer while resultant potential profits are privatized as quickly as possible. In spite of all this, NIAID has the capacity, using DTB contract mechanisms, to take 1-3 compounds through the FDA-mandated "critical path" pre-clinical development process in the 5 years of the contract. NIAID could consider doing this with one of the NCDDG-funded compounds, should sponsors screw up. [What would the Competitiveness Council think of that?] Whatever the cause of Abbott's withdrawal, the episode suggests NIH has a considerable way to go in working with industry.

Many of the academic-funded NCDDGs have familiar PIs -- William Haseltine of Harvard, Evan Hersh of U. Arizona, Richard Whitley in Birmingham, Edgar Engleman at Stanford, Donald Armstrong of Memorial Sloan-Kettering, Raymond Schinazi at Emory and Jerome Groopman from Harvard. Schinazi has been particularly prolific, turning up D4T, AZdU (sorry, too toxic), FLT, and other new twists on nucleoside analogues (3TC and others must be in the pipeline too by now). The others are working on an eclectic batch of HIV protein inhibitors - nucleosides, thiosemicarbazones, myristic acid analogues, porphyrins, protease inhibitors, etc. An early NCDDG award to Biogen helped spur the rapid (but, alas, disappointing) development of rsCD4.

National Cooperative Drug Discovery Groups for the Treatment of Opportunistic Infections Associated with AIDS (NCDDG-OI). None of the original applicants for the NCDDG applied to study OIs. 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. The awards were conveniently announced the day Congress held hearings on "Drugs for Opportunistic Infections in Persons with HIV Disease." 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. At their first annual meeting, the NCDDG-OI "investigators requested a closed first meeting." This is ironic, considering how hard activists worked to force NIAID to fund OI work. The NCDDG-HIV meeting is open to community activists, and the NCDDG-OI group should follow their example. New DTB OI awards due in 1992 include NCDDGs and contracts to further study PCP, MAI, toxoplasmosis, opportunistic fungi and cryptosporidiosis.

Some of NIAID's anti-OI work is funded by the Division of Microbiology and Infectious Diseases (DMID) rather than by DAIDS. For example, DMID funds the Cooperative Antiviral Study Group (CASG), the Mycoses Study Group (MSG) and much pre-clinical work. DMID funds herpesvirus research (HSV, VZV, EBV, CMV), while DAIDS/DTB funds non-viral OIs.

Activist and Congressional pressure to increase support for studying OIs has finally begun to pay off. OI research must continue to be a top priority. In particular, better in vitro and animal models are critical to further understand and treat AIDS related opportunistic diseases.

DTB Contracts. DTB also administers a series of 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-macaques - including two awards to the University of Washington program which developed the HIV-infected Macaca nemestrina (pigtailed macaque).] Twelve contracts funded OI research, toxicology and pharmacology, including 4 PCP awards, 2 for candida and 2 for MAI.

DTB Biological Response Modifiers (BRM) Program. Six contracts funded development of immune-based therapies, using MuLV mouse models and FeLV/FIV feline models. Sandra Bridges oversees this BRM program. These contracts are due to expire in August 1992. Have they been recompeted, and will they be refunded as planned?

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). Wayne Koff, PhD, the former chief of the VRDB, has left NIAID to take a job with United Biomedical, Inc., on Long Island. 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), and $9M in unsolicited basic research.

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). Giorgi, Valentine and Bekesi were looking at discordant couples (one positive, one negative), which raise the possibility that either (1) some negative partners of HIV+ people have developed protective immunity against HIV without becoming infected (or by rejecting infection); or (2) cell-mediated HIV-specific immune responses precede seroconversion. Safai was studying the immune response of men with Kaposi's sarcoma who were long-term survivors - including some men with KS who were HIV-antibody negative. Zolla-Pazner was generating human monoclonal antibodies to HIV proteins. Engleman was studying the role of dendritic cells in HIV infection. Each of these areas 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 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. The contractors are Michael Murphey-Corb (Delta Regional Primate Research Center, Louisiana) and William Morton (Washington RPRC). The Delta center is comparing nine adjuvants in the SIV system. The Washington RPRC is titrating SIV challenge doses in male and female monkeys challenged mucosally and intravenously. A third study (modelled after the Corey group's HIVAC-1e vaccinia vector followed by rgp160 booster) will look at the results of challenge with vaccinia vectors and SIV proteins followed by booster doses of SIV peptides. This will use cell-associated and cell-free virus challenges, homologous and heterologous virus strains. In addition, Scripps, Johns Hopkins and the University of Pittsburgh have been awarded funds for an RFA entitled "Pathogenesis and Immunology of Animal Lentivirus Infection."

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): Emory, New Jersey Medical Center, U. Michigan, U. Maryland, Stanford, Rockefeller U., and the Wistar Institute. Better adjuvants may help to direct the immune response in a desirable direction (e.g., from a humoral to a cell-mediated response, or from Th2 cytokine to Th1 cytokine production). This program cost $1.3M in FY 1991 and will cost $1.5M in FY 1992.

AIDS Vaccine Evaluation Units (AVEUs). Building on a base of institutions which developed vaccines for influenza and hepatitis, NIAID set up the AVEU system in 1988. Five institutions (Johns Hopkins, University of Rochester, St. Louis School of Medicine, Vanderbilt University, U. Washington) have collectively 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 only for preliminary phase 1 safety/activity studies. Larger studies will be done by the new Vaccine Trials + Epidemiology Branch (VTEB) in high-incidence areas. AVEU funding is $7.5M this year.

Developing Collaboration for International AIDS Vaccine Studies. The VRDB is working with the NIAID Division of Microbiology + Infectious Diseases (DMID), the NIH OAR, the Office of International Health, the CDC, the Defense Department/ Walter Reed Army Institute of Research, the State Department/US Agency for International Development, WHO's Global Programme on AIDS and others to plan the HIV vaccine field trials in Africa, Asia and South America (as well as, possibly, the USA). The NIAID Plan for Developing Capabilities to Conduct Clinical Efficacy Trials of HIV Vaccines was presented (and presumably ratified) at the NIAID Advisory Council in May 1991. Legal restrictions on the ability of people with HIV to travel or immigrate to the USA are seriously impeding international vaccine development, because WHO personnel and others will not attend planning meetings in the United States. In the first quarter of 1991, the DAIDS Epidemiology Branch's Lew Schrager was seconded to the World Health Organization (WHO)'s Global Programme on AIDS (GPA) to work on plans for the international vaccine studies.

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.

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). Sample CFARs include:

* Duke. Dani Bolognesi, PI. The Duke CFAR involves 30 investigators in 4 broad topic areas: molecular mechanisms of HIV-host interaction, immunogenic HIV epitopes, cellular responses to HIV, and copathogens and their effect on HIV's pathogenicity. CFAR core resources include gene expression, peptide synthesis, retroviral biology, flow cytometry, SCID-hu transgenic mice, data management, procurement of human research materials, and protocol design. * Stanford. Thomas Merigan, PI. Coordinates basic research on animal retroviruses (Mullins), HIV replication (Herzenberg), murine CD4 (Parnes), with new laboratory and clinical facilities including an AIDS outpatient clinic. * UCLA. Irvin Chen, PI. CFAR core supported activities include a serum bank, virology core, flow cytometry, SCID-hu mice, development and seed grant, planning and evaluation, administrative and educational. * Southwest Foundation for Biomedical Research, San Antonio. Ronald Kennedy, PI. This, along with UCLA, was funded in 1991. Four cores include monoclonal antibodies, veterinary resources, human clinical resources and administrative support. "The Veterinary Resources Facility houses an infectious colony, a retirement colony of experimental animals, monkey facilities, an enormous baboon facility of approximately 3,200 animals, and a nonprimate animal facility... The Human Clinical Resources Facility [involves] the Wilford Hall USAF populations with over 1,100 HIV-infected individuals."

The RCB conducts site visits to selected CFARs and other BRDP-administered programs. Given the new limitations on NIH staff travel, sites can expect a long time before the next inspection.

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 $92 million ($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 "Bopper" Deyton). These branches are, individually and collectively responsible for the content and conduct of NIAID-sponsored epidemiological, clinical and large-scale vaccine efficacy trials. The Associate Director for CRP is Lewellys Barker, PhD.

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. Of these, 2/3 ($23M) were in solicited large-scale epidemiology cohort studies, with the remaining $10M in unsolicited basic research studies of transmission, natural history and cofactors. The EB's FY 1991 budget of $33,105,000 amounted to about 1/4 of NIH's $120.5M budget for "Population-Based Research" (Mason Category IIB).

Aside from the efforts of Robert Gallo to corral the new disease into his stable of human T-lymphotropic retroviruses, the NIH's first AIDS work consisted of epidemiology. Most of this work was carried out by the CDC, with some was done

by NCI and NIAID. 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. These were originally intended to provide epidemiological clues to help track down the still-undiscovered "putative AIDS agent" in the populations apparently at highest risk - gay men in urban areas. Since HIV had already been discovered by the time the SFMHS and MACS were actually underway, these studies provided a real-time focus on patterns of seroprevalence and seroconversion in six cities around the country (as well as a laboratory for the continued pursuit of the elusive potential "cofactors"). After several 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 ($100,000 in 1991 and $1M in 1992). 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). By the time this cooperative agreement (a mechanism similar to that by which the ACTG is funded) was issued in 1984, HIV (then known as LAV, as HTLV-IIIB or as ARV) had been identified. The four cities participating in the MACS - Baltimore (Johns Hopkins), Chicago (Howard Brown Memorial Clinic + Northwestern U.), Los Angeles (UCLA), Pittsburgh (University of) recruited 4,954 gay and bisexual men into a longitudinal, multiyear study of men both seropositive and seronegative. Men with AIDS in 1984 could not enroll. 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 is not as centralized as the ACTG. Sometimes MACS centers work autonomously, while other times they collaborate. The MACS has been quite productive, yielding 149 papers in the published literature between 1984 and March 1991, covering behavior, clinical medicine, epidemiology, immunology, neurology and virology. The UCLA MACS center virtually wrote the book on the use of flow cytometry (T cell counting with fluorescent antibodies). The MACS is divided into working groups, as the ACTG is divided into committees: Data, Clinical, Pathology/Malignancy, Health Services, Virology and Immunology. As the MACS has matured, the scope of its activities has shifted. More data are now collected on opportunistic infection (OI) incidence and prevalence, health care utilization, and the occurrence of AIDS-related malignancies.

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. Examination of the MACS and New York Blood Center (NYBC) databases revealed a small 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. The MACS has formed several working groups to consider issues of long-term survivors, and Sten Vermund has promised a meeting on this topic sometime after the Amsterdam conference with representatives from all Epidemiology Branch-sponsored studies.

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 as an incentive to enrollment.

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. Data from 2-3 CDC sites will be pooled with Newark data to shed further light on the discordant couples issue. The Brooklyn HATS 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). In 1991 the Pathogenesis and Epidemiology Branches, along with the CDC, sponsored a workshop on discordant couples. Two teams came to opposite conclusions about whether AZT lowers HIV's infectivity in semen and vaginal secretions.

Women + Infants Transmission Study (WITS), cosponsored by the NIAID EB and NICHD, was first 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. $100,000 was spent on planning for the WIHS in FY 1991, and $1M will be spent on start-up costs in FY 1992. The total cost will be $7M over 4 years starting in FY 1993. The NIAID program officers are Diana Hartel and Janice Cordell. 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 effrontery to claim that over half the participants in NIH AIDS clinical efforts are minorities.]

The ODB was set up because previous cohorts (including, at that time, the MACS), even when following HIV-infected persons, did not systematically track the incidence of opportunistic infections or the use of various treatments and prophylaxes. This information was crucial if relevant clinical trials were to be

developed, so the CPCRA, in conjunction with the AmFAR-funded Community-Based Clinical Trials Network (CBCTN), jointly developed the ODB. Originally the dataforms were truly simple, but eventually, as usual, NIAID added too many extra items, weighing down the project with the desire to collect every imaginable datapoint. If they had remained faithful to David Byar's initial 2-page form design, they would not now be forced by predictable circumstance to scale back. Random sampling (of, say, 10% of participants) might be able to get more useful detailed information on a subset, while saving resources.

The ODB is an interesting attempt to combine epidemiological and clinical (therapeutic) goals. Extension of the ODB model to participants in certain ACTG trials (especially randomized efficacy and early intervention trials) should be considered, in order to generate long-term follow-up data and possible rare but serious toxicities of trial therapy. People could be followed at 6-monthly intervals with simple two-page forms, with perhaps a telephone questionnaire (latest CD4 count, clinical developments). Such a database would also be a useful source for recruitment in future clinical trials.

International Epidemiology + Training. The DAIDS EB oversees $6 million in international programs.

ICAR. ICAR, or International Collaboration in AIDS Research, funds joint projects involving a US institution (usually academic) and the ministry of health or other public health agencies in Third World countries. Case Western Reserve U. from Cleveland is working in Uganda, the Harvard School of Public Health in Mexico, Johns Hopkins in Malawi, and Cornell in Brazil. NIAID-supported researchers are also working in Kenya, Rwanda, Zambia and Senegal. The New England Medical Center Hospitals were working in Zaire until recent civil unrest stopped the collaboration. ICAR projects include investigations of (1) what role endemic infections such as tuberculosis play in progression to AIDS; (2) variation of HIV isolates and AIDS natural history in high- and low-incidence AIDS areas; (3) epidemiology of perinatal and heterosexual HIV transmission; (4) relation between AIDS-associated diarrhea and wasting syndrome in the natural course of HIV disease. NIH internal documents reveal some weaknesses in the ICAR programs, especially in the Cornell/Brazil project and the Harvard/Senegal project looking at HIV-2. NIAID staff also participated in international AIDS conferences in Thailand and Zaire in 1990-91.

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. Approved by the NIAID Advisory Council in May 1991, this project will involve cooperative agreement research proposals focussing on epidemiology useful in future trials of vaccines for AIDS or other sexually transmitted diseases.

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 ACTG, CPCRA and DATRI trials which fall into its purview. The Medical Branch consists of 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, keeping chronological files on concept sheets, minutes from core committee conference calls and other vital but tedious functions. 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 SDAC manages the data - 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's funding grew from $20M in FY 1986 to $45M in 1987, $53M in 1988, $62M in 1989, $90M in 1990 and $92M in 1991; 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), ampligen (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-sulfamethoxaxole 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 help to guide the suggestion of 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 tuberculosis 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 all 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 opportunistic infections, immunology and neurology, have proved eager to work with activists and open to new ideas. In June 1992, the ACTG held a "leadership retreat" at which only 400 (rather than the usual 1,200) people attended. Discussions ranged from simple face-to-face meetings between committees which rarely have the chance to interact to larger meetings to improve communication, protocol development, and the notoriously nightmarish thrice-yearly ACTG meetings. Three problems rose to the surface:

* Communication. None of the research committees know what other committees are planning, and few know what the others are doing; * Coordination. None of the committees has prioritized its research agenda in line with current resources, and few take advantage of each other's work to streamline. [For instance, every protocol involves AZT resistance assays; this is unaffordable even assuming we knew AZT resistant HIV was clinically significant, which we don't.]; * Control. >85% of participants still enroll in nucleoside analogue trials run by the Primary Infection Committee; neither PI nor the Executive Committee takes other research needs (e.g., OIs, immunology, neurology) adequately into consideration.

The results of the June Retreat included:

1. Restructuring of the research committees and working groups to foster collaboration and communication at earlier stages of protocol development; 2. Restructuring the thrice-yearly ACTG meetings to foster more interdisciplinary communication and faster dissemination of exciting new results; and 3. Restructuring the Executive Committee (following its 7.1.92 meeting in Chicago) to include representatives from each research and resource committee on the EC to resolve issues of prioritization, resource limitations, and communication.

If these plans are carried out, it will represent a major victory for activists who have striven for these goals since 1989. Many other tasks remain. The ACTG's Primary Infection Committee came under repeated criticism at the June Retreat for being insular, uncommunicative and failing to take account of new resource limitations. 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 once they've given birth. 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.

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.).

Although the ACTG has developed a system to "streamline" protocol development from 417 days to 204 days, there is still no system to streamline 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) demonstrates that the system cannot accommodate more than one simultaneous NDA-directed antiretroviral. If the ACTG were to simplify data collection on its large efficacy studies, it might become efficient enough to overcome this legacy.

Simplifying and streamlining ACTG trials (especially those designed to optimize the standard of care with existing agents) is a long-term goal which neither NIAID nor the investigators nor, at least yet, SDAC and FRSTRF appear ready to

take responsibility for. Yet if the ACTG is to survive in an era of flat budgets, it must develop a plan to accomplish this.

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).

CPCRA PROTOCOLS UNDERWAY

CPCRA Regimen Sites Participants

001 Pyrimethamine vs. placebo for toxo prophylaxis (over) 17 433 (396) 003 ddI vs. ddC in people intolerant/failing AZT 17 467 005 (?) Observational Database (ODB) 18 4,497 007 (?) MTB screening + prophylaxis (ACTG 177) ? ?

The CPCRA is also planning a placebo-controlled study of fluconazole for preventing vaginal candidiasis. 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 the only currently underway treatment trial (002), 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. Rather than trying to fix the ACTG to make it more responsive, NIAID floated an RFA in 1991 for DATRI, and developed a new network of 40-50 sites willing to conduct studies under contract (many of these sites serve as ACTUs - e.g., St. Luke's Roosevelt, SUNY/Stonybrook). Interested sites submit bids to participate in a given DATRI study. DATRI cost $4.3M in FY 1991 and will cost $5.9M in FY 1992.

FIRST FOUR DATRI TRIALS

DATRI Regimen N

001 PK of rifabutin/clarithromycin + rif/azithromycin 68 002 AZT or placebo (12 weeks) in acute primary HIV infection; follow-up for >10 years 80 003 8 weeks of AZT, no Rx, or AZT/ddI, comparing HIV burden in lymph nodes + blood 32 004 Megace vs. dronabinol vs. both for wasting 60

DATRI 001 + 004 are necessary and useful studies (though there's no reason why Adria should not have conducted the first). DATRI 002 + 003 attempt to address two interesting pathogenesis questions, but the first is far too small to have any hope of showing whether 12 weeks of AZT before seroconversion to HIV but

after infection delays the onset of AIDS (of the 80 participants sought, perhaps half might progress by the year 2002, barring any dramatic treatment breakthrough in the next decade). DATRI 003 randomizes participants to stay on AZT or no therapy or to start AZT or AZT/ddI (8 per arm) with whole lymph node biopsies before and after the 8-week treatment period to assess if these two dideoxynucleosides lower viral burden in the lymphoid tissue as well as in the peripheral blood. The choice of agents for this invasive study is conservative, and more useful information could have been gathered by using more agents with fewer patients per arm, and not trying to attain some bogus compromise in the name of unattainable statistical significance. Pathogenesis-directed clinical trials are crucial, yet they need not replicate the mindless mindset of the ACTG with its exhaustive collection of meaningless datapoints. The DAIDS medical officers, who are to become principal investigators for DATRI, should do rotation at AIDS wards and ACTU sites in order to better understand the rigors of conducting AIDS clinical trials in the real world.

In sum, NIAID will need to devote considerable effort to streamlining its 4-5 clinical research networks, and to encouraging collaboration amongst them, if the current freeze on funds is not to paralyze all of their efforts. 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 clinical trial results must be accelerated. The Developmental Therapeutics Branch (DTB) needs a better liaison with the DAIDS Treatment Program. Major increases in basic, applied and clinical immunology are required if the promise of immune-based therapy is to be achieved. The ACTG must also develop new, effective links with research networks funded by other NIH institutes such as the AIDS Lymphoma Network (NCI), SOCA (NEI), Pediatric ACTG (NICHD), and the NIH Clinical Center (NIHCC). 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. Finally, 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.

Funding and Future Plans. NIAID spent $297,000 on AIDS in 1982, $9 million in 1983, $20M in 1984, $23M in 1985, $63M in 1986, $146M in 1987, $223M in 1988, $311M in 1989, $394M in 1990, $431M in 1991, $450M in 1992 and will receive $471M under the President's budget for Fiscal Year 1992. The 1991 figures 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%), an increase below the rate of biomedical 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:

NIAID AIDS AWARD RATES 1988-1993

Award Rates 1988 1989 1990 1991 1992 1993

AIDS 32.0% 39.8% 30.2% 40.2% 19.9% 21.3% Non-AIDS 33.6% 29.6% 28.5% 30.9% 26.6% 30.6

The number of AIDS grants awarded this year will also suffer.

NEW NIAID AIDS GRANTS 1987-1993

1987 1988 1989 1990 1991 1992 1993

New AIDS Grants 140 103 155 151 156 123 165

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.

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 - though no ACTU investigator can be happy about the budget cuts sustained during the recompetition.
Among 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 in additional funds for the interdisciplinary Centers for AIDS Research (CFARs) to study immunology, diagnostic methods, animal models, therapeutics, vaccines, and behavioral research (bringing CFAR total to $10M); * $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 supplying researchers worldwide with standard HIV strains and cell cultures; * $1.2M to study gut-associated lymphoid tissues (GALT) anti-HIV responses; * $5M for new studies of biological factors influencing HIV transmission including mucosal immunity; * $630,000 to develop new models for fungal skin infections; * $800,000 to "foster a broader base of basic research to foster strategies for reversal of immune suppression"; * $700,000 to develop laboratory and animal 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; * $85,000 to develop HIV particle vaccines; * $1M to develop vectors to induce mucosal immunity; * $1.5M to develop recombinant HIV peptide vaccines;

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:

* As long as OAR lacks the authority to move resources across institute boundaires, 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.

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II/2. National Cancer Institute

NCI

NCI, the largest and oldest of the NIH, was founded in 1937. Cancer is second only to cardiovascular disease as the leading killer of Americans. This became the case in the 1920s, when cancer came to notoriety:

Cancer has evoked popular fears that transcend its deadliness. Invested with feral personalities, cancers have been seen as "insidious," "mysterious," "lawless," "savage," and above all "relentless." At the turn of the century one physician described cancer as a "loathsome beast, which seized upon the breast, drove its long claws into the surrounding tissues, derived its sustenance by sucking out the juices of its victims, and never even relaxed its hold in death."

As early as 1915 in the USA, an "alliance against cancer, a slowly widening and ever more self-assured coalition of upper- middle-class groups," had taken shape. Physicians, scientists and journalists emphasized "the medical blessings of early detection, surgery and scientific research into causes and cures for the disease." The establishment of NCI by Congress was largely the fruit of a generation of activism by these middle-class, ostensibly "progressive" forces. The crusade against cancer continued to grow and culminated in President Nixon's 1971 declaration of "war on cancer," a war whose outlays promptly 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, spending $2.4 million on AIDS in 1982. For the ensuring years, NCI and NIAID split the lion's share of AIDS funds. But by 1985-86, as AIDS funds grew and NIH began planning a new clinical trials effort, NCI and NIAID faced off for AIDS leadership, as described above in the section on NIAID.

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.

Since 1986, NCI's appropriations for AIDS have been second only to NIAID at NIH. Its AIDS allocation in FY 1991 was 20% of NIH's total, and 10% of the NCI total budget. [NIAID spends 53% of the NIH AIDS total, which is half of its own total budget.] This amounted to $160,869,000 in 1991 and $169M in 1992. NCI's budget skips PHS, HHS and OMB and goes straight to the President under a special "budget bypass" provision [of the National Cancer Act]. For 1993, NCI asked Bush for $217.5M for AIDS. The President cut this by $44 million to $175.8M, a rise of just $6M or less than the rate of biomedical research inflation, meaning that NCI can barely afford to maintain current services. NCI spends more on AIDS intramurally than any other ICD (including NIAID: NCI $75M, NIAID $47M).

NCI AIDS Activities FY 1991

IA1 HIV + HIV genome $ 29,993,000 IA2 Immunology 8,774,000 IA3 Blood/blood products 358,000 IA5 Animal models 6,362,000 ID1 Drug Development 42,508,000 ID2 Drug Clinical Trials 39,177,000 IE1 Vaccine Development 15,148,000 IIA1 Surveillance: HIV associated diseases 2,348,000 IIB1a Transmission: sexual 1,631,000 IIB1c Transmission: hemophilia pop. 1,369,000 IIB1e Transmission: perinatal 914,000 IIB2 Natural history + cofactors 8,006,000

NCI AIDS TOTAL $160,069,000

AIDS Program. 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 for $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% (or four) of these will go on to clinical development, as further in vitro toxicology or animal studies will eliminate them from further consideration. The DTP's Acquisition Input Committee recommends and prioritizes agents for testing, fast-tracks those with previous demonstrated activity, monitors turnaround time from sample receipt to data reporting, and sends results to the supplier. 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 the following four compounds:

* Bryostatin, 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. The hope is to inhibit HIV entry, uncoating, reverse transcription, integration, expression, assembly, budding or other steps, or to block receptors, regulatory proteins and biochemical pathways used by HIV to infect or replicate. Here it is sometimes hard to tell where basic virology ends and drug discovery begins. NCI is also focusing on the cell cycle and its division in order to develop new cancer drugs. Much of this work takes place at the AIDS Basic Research Program at the Frederick Cancer Research Facility and in various labs at the main NIH campus in Bethesda. This work includes: 1)

structure/function studies of HIV RT, integrase, protease, etc., and the development of assays to screen for inhibitors thereof; 2) the development of gene therapy using retroviral vectors to insert TAR decoys or antisense sequences into susceptible cells, or to turn uninfected cells into secretors of soluble CD4 molecules to "soak up" HIV; 3) structure/function studies of nucleocapsid (NC) RNA binding protein which packages viral RNA into the HIV core, and development of protein processing inhibitors such as chloroquine; 4) investigations of the biochemical pathways involved in viral replication such as myristoylation, and inhibition thereof; 5) development of decoy linear polymers of the gp120 binding region of the CD4 molecule [that again?!]; and 6) studies of the mechanisms of angiogenesis in neoplastic disease including Kaposi's sarcoma and identification of angiogenesis inhibitors such as SP-PG and TIMP-2.

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 (LDDRD), 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:

* Fluorodideoxycytidine (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, building on a long history of basic and clinical work with cytokines and other biological response modifiers (BRMs):

There are several potential approaches to immune enhancement, including: 1) methods to increase CD4 lymphocytes, the principal cells killed by HIV, through blockade of HIV induced CD4 destruction or direct expansion of CD4 cells; 2) immune stimulation by lymphokine therapy; 3) blockade of HIV proteins which inhibit the immune system; and 4) stimulation of white blood cells to fight infection. Active research is ongoing to address each of these potential mechanisms.

Materials provided to us by NCI for this report listed few projects addressing the four areas of immune reconstitution discussed above. Developmental and preclinical work in this area is difficult to separate from the basic immunology supported by NCI. While several immune-based therapies are in development for cancers associated with AIDS and otherwise, NCI's BRM effort does not appear to be particularly focused on HIV infection per se.

However, one intramural lab, The Laboratory of Experimental Immunology, in the Biological Response Modifiers Program (BRMP), in the Division of Cancer Treatment (DCT), has been doing extensive work with an eye towards this goal. This lab 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. Other intramural NCI researchers are developing CD4+ cell expansion technologies that will be used in conjunction with gene therapy approaches to protect the new CD4+ cell population from infection by HIV. In addition, 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. The development of lymphokine activated killer (LAK) cells, tumor infiltrating lymphocytes (TIL), and monoclonal antibodies for the treatment of cancer is also being supported by both intramural and extramural work as part of the institute's AIDS program. 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 non-Hodgkin's lymphoma (NHL) of AIDS.

Clinical Trials. NCI spent $39M on clinical trials for AIDS in 1991 (40% of the ACTG amount). $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.

NCI Intramural AIDS Clinical Trials - FY 1991 (All Phase 1 or Pilot Studies)

Adult HIV Pediatric HIV

rCD4-IgG fusion protein ddC AZT/acyclovir, then ddI, then ddC ddC alt. w/ AZT (one week each, alternating) G-CSF +/or EPO (AZT neutropenia) rHGH vs. rIGF vs. rHGH/rIGF Continuous infusion vs. intermittent oral AZT 3TC (in children w/ encephalopathy) ddI Adult KS ddI/AZT Clarithromycin w/ AZT or ddI (HIV+/MAI+) Pentosan polysulfate rCD4, then rCD4/ddI in neonates; rCD4 alone in pregnant HIV+ women during labor/delivery 3TC

Dr. Yarchoan and Hiroaki Mitsuya MD, PhD, are also studying the development of viral resistance to the three currently approved nucleoside analogues, AZT, ddI and ddC; the effects of these drugs on macrophages; the etiology, clinical and immunological correlates of AIDS-related non-Hodgkin's lymphoma; and CD4+ cell counts as a relative hazard marker for mortality in HIV infection. NCI spent $6.8 million in contracts and grants for: (1) support services for its intramural clinical trials of and a few extramural clinical studies of immune based therapy of cancers; (2) neuropsychological testing of children and adults with HIV; and (3) the AIDS Lymphoma Network.

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). Strangely, the NCI did not send us materials related to the very important AIDS Lymphoma Network (ALN). The ARIS database listed twelve ALN awards in FY 1991, funded through R01s:

NCI AIDS Lymphoma Network Sites, FY 1991

Site PI ACTU site?

U. Miami John Byrnes Y Children's Memorial, Chicago Sharon Murphy N Loyola UMC, Maywood IL Richard Fisher Y USC, Los Angeles Alexandra Levine Y UCSD, San Diego [Ellen Feigal] Y UCSF, San Francisco Lawrence Kaplan Y Northwestern U., Chicago Leo Gordon Y NE Deaconess, Boston David Scadden Y U. Texas Cancer Center, Houston Richard Ford N Johns Hopkins, Baltimore Richard Ambinder Y Memorial Sloan-Kettering David Straus Y Emory U., Atlanta Henry Holland N

[Since the ACTG has been unwilling to allocate sufficient attention to AIDS-related cancers, it is lucky that NCI stepped in to fill the gap. The ACTG Oncology Committee has done a good job against enormous odds, but the program simply refused to allocate resources to cancer, and site principal investigators were unwilling to fund expensive lymphoma and cancer studies at the needed rate. Oncology was "optional" (e.g., dispensable) in the recent ACTG recompetition. Since 9/12 ALN sites are at ACTUs, maybe they can serve as an "oncology core".]

The AIDS Lymphoma Network supports basic and clinical research, including clinical trials of chemotherapy and radiation with and without the concurrent administration of antivirals or colony stimulating factors, MAbs and immunotoxin conjugates directed at cytokine receptors and other cell surface receptors on malignant B-lymphocytes, and bone marrow transplantation. Investigators are also studying 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; idiotype/anti-idiotype 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.

Blood + Blood Products. In 1991, NCI distributed $358,000, largely to support a biological reagents repository, and one grant for developing new immunotoxin conjugates for therapeutic use.

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; transgenic mice coinfected with HIV and CMV; CMI in MAIDS; cytokines in MAIDS; BIV pathogenesis; EIAV genes and virulence; copathogens in FAIDS; and HIV-1 genes in 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 CTL responses.

Epidemiology, Transmission, Cofactors. NCI spent $18,549,000 in 1991 on risk assessment and prevention research including surveillance studies, sexual, hemophiliac, perinatal and other transmission studies, and natural history and cofactor studies. $12.5M was extramural and $5.3M intramural.

$2.3M went for surveillance of diseases associated with HIV infection such as non-Hodgkin's lymphoma (NHL) and other high-grade lymphomas, anal neoplasia, HPV and cervical intraepithelial neoplasia (CIN), and KS. NCI funded six R01s for this work, which focused on coinfections with HIV and HTLV-I in NHL, HIV and HPV in CIN and AIN, and HIV and EBV in various lymphomas.

NCI also cofunded the NIAID-sponsored Multicenter AIDS Cohort Study (MACS), a long-term project following about 5,000 gay men, of whom about half are seropositive. NCI spent about $1M on MACS. 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. $1.3M underwrote technical and statistical support for NCI's Environmental Epidemiology Branch (EEB), which conducts epidemiological natural history studies of hemophiliacs, their sex partners and family. NCI also allocated $4.3M under the vague category "Other/Miscellaneous Transmission Studies," of which $2.8M supported extramural awards and $1.3M intramural work. $430,000 in contracts helped to support Frederick. Three contracts totalling $1.2M supported studies of HTLV-I and adult T-cell leukemia (ATLL) in Jamaica; invasive cervical cancer in Latin America; and HTLV-I and HIV-1 in the Caribbean basin. $374,030 went for intramural work on the epidemiology of HPV and CIN; heavy, moderate and ex-smokers; and renal cell carcinoma.

NCI spent $8M on studies of natural history and cofactors ($3.6M extra, $4M intra). Contracts provide statistical and technical support and biological reagents repositories for the Epidemiology and Biostatistics Program, DCE, NCI. $875,000 in grants is split between two R01s whose grantees are studying the natural history of AIN in HIV+ men and of CIN in HIV+ Senegalese women.

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.

Catalogued below are the NCI intramural AIDS projects listed by the NIH DRG CRISP system for FY 1991, along with the intramural projects listed in the NIH "Annual Report to Congress" for 1991. The projects are categorized by NCI division, program, branch and laboratory. The list is incomplete and slightly out of date.

DIVISION OF CANCER BIOLOGY + DIAGNOSIS (DCBD)

Laboratory of Pathology, Diane Solomon MD: Cytology applied to human diagnostic and research problems; Comparing the diagnostic sensitivities of bronchoalveolar lavage, sputum, transbronchial biopsy, and various culture and immunocytochemical techniques in the diagnosis of CMV in HIV-positive individuals; William Travis MD: Pulmonary and postmortem pathology; A comprehensive study of the pulmonary pathology of AIDS based on surgical and autopsy lung pathology material from PWAs seen at NIH; Lance Liotta MD, PhD: Development of TIMP-2 for the treatment of KS;

Experimental Immunology Branch: Gene Shearer PhD: Cellular immune function in AIDS and primary immune deficiencies; Studies of progressive functional defects in T helper cell function in HIV infection; 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; Development of an assay to detect HIV infection before seroconversion or PCR-positivity using the proliferative responses and IL-2 production by T-cells to HIV env peptides as a marker of exposure to the virus; Allan Weissman MD: The role of HIV gp120 in the immune response; The possible role of gp120 in immune dysfunction in HIV infection via inhibitory effects on uninfected clones.

Laboratory of Molecular Biology: Ira Pastan MD: Immunotoxin and oncotoxin therapy of cancer cells; Development of conjugates of Pseudomonas exotoxin + TGF-alpha, IL-2, IL-4, IL-6, IGF1, acidic FGF, CD4, anti-Tac (Fv), or antitransferrin (Fv) for the treatment of various cancers and HIV infection; David Fitzgerald PhD: Development of immunotoxins in cancer.

Laboratory of Biochemistry: Samuel Wilson MD: DNA synthesis in mammalian cells - Mechanism of HIV reverse transcriptase; Mechanism of action of HIV reverse transcriptase; SL Berger: Gene + protein structure and function in eukaryotic cells.

Metabolism Branch: Jay Berzofsky MD, PhD: Antigen-specific T-cell activation - vaccines for malaria/AIDS; Studies of the mechanisms by which T-cells recognize antigens presented on the surface of other cells in association with MHC-encoded molecules and the application of these principles in the design of synthetic vaccines for AIDS, malaria, and cancer. HIV+ human CTL recognize four envelope peptides in association with HLA-A2. A promiscuity of peptides for multiple MHC molecules was also observed in mice. Each peptide was presented by several MHC class I molecules. HIV RT epitopes presented by class I were also presented by

class II. Peptides spanning multideterminant gp160 regions are recognized by T cells from a large fraction of humans; David Nelson MD: Biology of the immune response; Studies performed to examine the maturation and regulation of the immune response in normal individuals and in patients with congenital and acquired immune deficiency states associated with a high frequency of cancer; Identification of elevated levels of sIL-2R in lymphoreticular malignancies and HIV infection; Establishment of an IL-6 responsive human tumor cell line that shares many features of the lymphoreticular malignancies occurring in PWAs; Approaches to diagnosis and treatment of AIDS lymphomas; Michael Blaese MD: Development and function of humoral and cellular immune mechanisms; Gene therapy for ADA deficient SCID now in use in two pediatric patients; Developing gene therapy protocols to treat AIDS in the coming year; Wiscott-Aldrich syndrome and the development of a new experimental immunosuppressive drug, succinylacetone, which has successfully prevented allograft rejection, GVHD, Ab production in animal models and has shown efficacy in treating several different autoimmune disorders.

Laboratory of Cell Biology (LCB): E. Appella: T-cell antigen recognition and tumor antigens;

Laboratory of Mathematical Biology (LMB): J.N. Weinstein: Combination chemotherapy of AIDS and cancer: Dipyridamole, a cardiovascular drug, which is also a potent inhibitor of nucleoside transport, may potentiate AZT's antiviral effects while buffering against toxicity; Computer-assisted studies of molecular structures of proteins and peptides including those of the HIV-1 envelope, HIV-1 protease inhibitors; J.V. Maizel: Molecular structure of animal viruses and cells by computational analysis; B. Shapiro: Computer analysis of nucleic acid structure; Computer-assisted studies on the structure of RNA, including the HIV RNA genome; R.P. Blumenthal: Membrane fusion mediated by viral spike glycoproteins; Structural/kinetic studies of HIV envelope proteins, cell adherence, and membrane fusion.

DIVISION OF CANCER TREATMENT (DCT)

Clinical Oncology Program: Seth Steinberg, PhD: Biostatistics and data management section; Statistical leadership and data management consultation for Clinical Oncology Program: Design, conduct, monitoring, and statistical analyses of intramural trials for AIDS; Development of new statistical designs and biometric methods related to the development and evaluation of new cancer and AIDS treatments; Robert Yarchoan MD [see list of NCI clinical trials]; Study of predictive factors for the subsequent development of NHL in PWAs and PWARCs, including CD4+ cell counts, length of time with AIDS, antiretroviral therapy; Hiroaki Mitsuya MD, PhD: The effect of DNA demethylation on HIV-1 expression in vitro: In cells without already highly-demethylated DNA, demethylation greatly enhanced viral replication. Proviral DNA was found to be highly-demethylated in cells lines which were already producing large quantities of virus. Development of resistance of HIV in patients receiving AZT, ddC or ddI: AZT therapy was found to induce AZT-resistant HIV variants as early as two months after initiation of zidovudine therapy. In some patients, AZT-resistant strains persist even a year after switching to ddI. HIV seems to develop resistance to ddI and ddC less easily than to AZT. Further studies correlating in vitro HIV drug sensitivities and clinical outcome are needed. In vitro inhibition of HIV-1 replication by C2 symmetric HIV protease inhibitors: Studies determined that C2 symmetric proteases had a potent antiviral activity against a wide range of HIV isolates including monocytotropic stains and primary isolates. Plasma HIV-1 viremia in HIV-1 infected individuals assessed by RNA PCR: The data preliminarily suggests that plasma HIV-1 virion levels determined by RNA PCR

technique represents the actual plasma HIV-1 viremia status in patients with varying stages of HIV-1 infection. Synthesis and in vitro anti-HIV activity of lipophilic dideoxynucleosides. These newly synthesized 2-amino-6-halo-ddPs and 6-halo-ddPs compounds may represent a new class of lipophilic prodrugs for ddG and ddI, respectively. These prodrugs may be useful in the treatment of HIV-associated neurological impairment.

Laboratory of Biological Chemistry: Ronald Felsted PhD: Myristoylation-dependent cell transformation and retroviral replication: N-myristoylation has been shown to play an essential role in the targeting of cytoplasmic onc-kinases and retroviral gag structural proteins to various subcellular membrane compartments. Inhibitors of this process have been identified. Further characterization is underway;

Pharmaceutical Resources Branch: Frank Quinn, PhD: The influence of molecular structure on chemical and biological properties: Various anti-HIV or anti-cancer compounds are being systematically investigated to obtain structural and electronic properties which may help to elucidate their mechanism of action and thus lead to improved analogues;

Pediatrics Branch: Philip Pizzo MD: Infectious complications of malignancy and HIV infection in children: Includes a program to evaluate the benefits of antiretroviral therapies in children with HIV infection. To date, these have focused on the dideoxynucleosides. Studies with immunoregulatory agents and with biologicals (e.g. rCD4) are also underway. Modulation of HIV infection by soluble factors release by human fetal glial cell lines and reducing agents (with Lee Helman MD, Pediatric Branch). Studies which have discovered the production of TNF-alpha by fetal glial cells in vitro which may contribute in vivo to HIV replication in the brain of HIV+ children and be responsible for the HIV-related encephalopathy seen in this patient population. These studies have also demonstrated the in vitro inhibition of TNF-alpha induced HIV expression by glutathione, glutathione ester, and NAC. Phagocytic and lymphoid immunity in children with HIV infection. Studies investigating a broad range of immunological functions in children with HIV infection, including: neutrophil abnormalities; the effects of cytokines on neutrophil function in vitro; imbalances in immunoglobulin subclasses and its relationship with the frequency of bacterial infection; the affects of antiviral therapy on the frequency of bacterial infections; and functional T-cell abnormalities. Pathogenesis of neurological disorders in HIV-infected children (with Carol Thiele, PhD, Pediatric Branch). Three models which may contribute to the neurological dysfunction evident in HIV infection are under investigation: (1) direct viral infection of neural cells; (2) the indirect effects of soluble viral products, and; (3) the indirect effect of cytokines produced in response to infection. David Poplack, MD: Clinical pharmacology: As part of the Pediatric Branch AIDS effort, the Leukemia Biology Section is studying the clinical pharmacology of antiretroviral agents in children. The CNS pharmacology of antiretroviral therapies is being systematically evaluated in a non-human primate model. In addition, they have assisted in the design of trials of antiretroviral agents in children and perform the detailed pharmacokinetic studies in these studies. Ian Magrath MB, FRCP: Biology and treatment of non-Hodgkin's lymphoma: Determinants of prognosis in pediatric NHL, develop improved combination chemotherapy, use colony stimulating factors to increasing dose intensity and ameliorating toxicity. Basic studies in small non-cleaved cell lymphoma, including: characterization of non-random chromosomal translocations associated with SNCL; elucidation of the association between EBV and SNCL; examination of biological and clinical aspects of AIDS lymphomas; explorations of other molecular abnormalities in SNCL, such as p53 mutations.

Medicine Branch: Carmen Allegra MD: Pharmacology of antimetabolite agents. An investigation of therapies for opportunistic infections, specifically focusing on the interactions of antifolate agents on the metabolic pathways in T. gondii, P. carinii and C. parvum. Cloning, sequencing and expressing relevant target enzymes for characterization and as an aide in the search for new therapeutic agents. Ivan Horak MD: Regulation of tyrosine protein kinases in hematopoietic cells. Studies regulation of TPKs in retrovirus-associated disease (ATLL) and uses TPK inhibitors to block T-cell activation signals. Charles Myers MD: Polyanions used as anti-neoplastic and anti-HIV agents. How polyanions like phosphorothioate oligodeoxynucleotides and bis-naphthalene sulfonic acids (e.g. suramin) may treat cancers and HIV.

Laboratory of Molecular Immunoregulation (LMI, Frederick), Francis "Frank" Ruscetti, PhD (codiscoverer of IL-2!): Interactions of human retroviruses with hematopoietic and adherent cells; Studies of viral expression in various cells of the lymphoid lineage. Certain cells may be deficient in positive viral expression regulators or possess negative regulators thereof. Understanding how negative regulators work may be useful in developing antiviral therapies. William Farrar, PhD: Biochemical and molecular mechanisms of growth factor modulated proliferation: IL-2, IL-3, GM-CSF, and EPO. 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, suggesting that certain pharmacological inhibitors can block HIV transcription at this level. Luigi Varesio, PhD: Molecular basis for macrophage activation and immortalization: Studies of macrophage and monocyte activation and inhibition by cytokines.

Laboratory of Molecular Pharmacology: Albert Fornace, MD: Effects of stress response genes on HIV gene expression. Examines activation of HIV-1 gene expression by DNA-damaging agents and other stresses, like UV light. Christopher Hatch, PhD: Study of the histone H2A.Z gene - investigator claims this system can be used to study how cellular proteins influence the level of transcription directed by the HIV LTR, and how in turn HIV tat may effect the level of transcription of cellular genes.

Laboratory of Biochemical Physiology: Hsiang-fu Kung, PhD: Characterize HIV infection in PBMC, study cytokine production by monocytes/macrophages persistently infected with HIV; quantitative infectious cell center (ICC) assays for detection of HIV-infected PBMC, and; characterization of monocyte/macrophage-tropic viruses; Transcriptional regulation of HIV gene expression: HIV-1 gene expression was observed in a monocytic cell line at different levels: productive infection; restricted or chronic low level expression; complete latency. The goal of the study is to elucidate the mechanisms of viral latency and low level expression of HIV genes (i.e. the downregulation of HIV gene expression). Biochemical characterization of HIV propagated in human primary cultures and the effects of drugs on growth and infectivity of the viruses: Examines growth kinetics of monocyte-, T-lymphocyte-tropic strains of HIV and strains with tropism for both types of cells. Future goals include identification of epitopes governing tropism in various viral strains; examination of possible correlation between the stability of gp120 on the virion and in virus-associated soluble forms and infectivity. Inhibition of HIV infection and replication by chinese herbs. Inhibition of HIV infectivity by chloroquine: Studies on the processing of HIV env proteins and the identification of inhibitors of glycosylation and proteolytic cleavage pathways.

Laboratory of Experimental Immunology: John Ortaldo, PhD: Natural cell-mediated immunity: biology and regulation of CD3-LGL. Studies examining the effects of IL-2 on NK and LGL gene expression and the induction of cytotoxicity and cytokine production. Natural cell-mediated mechanism of lysis. Studies examining the mechanisms of target recognition and cytolysis by NK and K cells. John O'Shea MD: Comparative study of receptor-mediated signalling in T cells and NK cells. Howard Young, PhD: Control of interferon-gamma expression. Induction of cytokine gene expression in vivo by flavone acetic acid. Molecular studies of cellular cytotoxicity. Studies identifying the genes expressed in T-cells and LGLs that play a role in the ability of these cells to kill tumor cells. The laboratory has isolated a gene for the receptor on NK cells for attachment to their targets and a gene for perforin in T-cells which can be induced and upregulated by IL-7 in CD8+ and CD4+ cells. Enhance NK and CTL activity by activating these and other genes. The effects of HIV gene expression on the NK receptor and perforin genes is also being examined as is the susceptibility of cytotoxic CD4+ cells to infection with the virus. Studies of human B-cell malignancies. Studies examining the mechanism by which certain agents (e.g. phorbol esters) can halt proliferation and induce cytokine gene expression in multiple myeloma cells. Robert Wiltrout, PhD: Chemoprotective effects of recombinant cytokines. Effects of rTGF-beta, rIL-7, and rIL-1-alpha on hematopoiesis. Antitumor effects of BRM-stimulated lymphocytes, NK cells and macrophages. Studies on the effects of flavone acetic acid on the cytokine gene expression in lymphoid cells. Investigate use of rIL-7 to stimulate T-cell function and LAK activity, and to increase lymphocyte production for AIDS and cancer treatment.

Surgery Branch: Steven Rosenberg, MD, PhD: Surgical consultation and collaborative research in surgical services at NIH; Immunotherapy of animal and human cancer (including lymphokine activated killer (LAK) cells, tumor infiltrating lymphocytes (TIL) and combinations of cytokines including IL-2, TNF, and IFN-alpha in the treatment of experimental animal tumors; transducing new genes into TILs; use adoptive immunotherapy for AIDS).

Laboratory of Medicinal Chemistry: Victor Marquez, PhD: Dideoxynucleosides as potential anti-AIDS drugs: Development of new dideoxynucleosides, including prodrugs of F-ddI and F-ddG as lipophilic molecules with potential for transport to the CNS. James Kelley, PhD: Analytical chemistry of anti-AIDS agents. Peter Roller, PhD: Polypeptides as potential anti-HIV and antitumor agents. John Driscoll, PhD: Synthesis and analytic chemistry of potential anti-HIV agents; Preclinical studies for DTP.

Laboratory of Biochemical Pharmacology: David Johns, MD, PhD: Cellular pharmacology of chemotherapeutic nucleosides: Examine enhancement of anti-HIV activity of dideoxynucleosides, such as ddI and ddG, by inosine monophosphate dehydrogenase inhibitors, such as ribavirin; anti-HBV activity of the dideoxynucleosides, and; metabolism and of ddC and its fluorinated analogues. Neil Hartman, PhD: Preclinical and clinical pharmacology of anti-HIV agents.

Developmental Therapeutics Program: John Cardellina, PhD: Investigate link between anti-HIV and phorbol receptor binding activities. Isolate and identify anti-HIV compounds from the Euphorbiaceae. J.A. Beutler: Anti-HIV sulfated polysaccharides from a marine sponge and a tunicate: Anti-HIV alkaloids isolated from Buchenavia capitata. Kirk Manfredi PhD: Lutein, a xanthophyll with anti-HIV activity; Anti-HIV dimeric alkaloids from Ancistrocladus spp.; Kirk Gustafson, PhD: AIDS antiviral plant diterpenes; James McMahon, PhD: Assays for stage II evaluations of new anti-HIV compounds. David Vistica, PhD: In vitro cellular pharmacology of new anti-HIV and antitumor drugs. Sherman Stinson PhD:

Preclinical pharmacological/toxicological evaluations of high priority compounds. Louis Malspeis: Structure-activity optimization strategies: Chemical structural modifications of promising anti-HIV and antitumor agents identified in NCI screens in order to develop structural analogues or congeners with greater in vivo efficacy than the original compounds.

DIVISION OF CANCER ETIOLOGY (DCE)

Environmental Epidemiology Branch (EEB). William Blattner, MD: Epidemiology of human lymphotropic viruses - Adult T-Cell Leukemia, AIDS and cancer. James Goedert, MD: National Surveillance and mathematical modelling: use backcalculation modeling to account for therapy and the changes in the surveillance definition of AIDS. Analyze incidence rates of NHL and KS in 2 cohort studies. Pregnant women and their offspring. Epidemiological studies of twins born to mothers with HIV infection as part of the international Registry of HIV-Exposed Twins. Epidemiological studies of children born to HIV+ women as part of the NCI-NICHD Mothers and Infants Cohort Study. AIDS surrogate marker studies. Epi cohort of IVDUs with HIV, HTLV, both or neither in Newark, NJ and Italy. HIV-1 and HIV-2 in Tanzania, Nigeria and Cape Verde.

Laboratory of Comparative Carcinogenesis: Jerrold Ward, DVM, PhD: Biology of natural and experimentally-induced tumors.

Laboratory of Experimental Carcinogenesis: Dolph Hatfield, PhD: Aminoacyl-tRNAs in HIV and other retroviral infected cells. Determine if host aminoacyl tRNAs required for decoding the frameshift signal in HIV and other retroviruses are altered from the normal cellular aminoacyl tRNAs. Initial evidence suggests they are.

Biostatistics Branch: Mitchell Gail, MD, PhD: Epidemiological consulting on the extent of treatment of HIV infection and its impact on AIDS incidence trends; publishing estimates of the numbers infected with HIV in the United States obtained by backcalculation; projecting the 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: James Lautenberger, PhD: Analysis of HIV gene expression, Scale-up purification of HIV-1 and HIV-2 recombinant env, nef, vpu polypeptides. Donald Blair, PhD: 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 controlling retroviral infections. 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. Examine activation of latent HHV-6 infection in PWAs, people with CFS, SLE and BMT. HHV-6 induces 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: Ravi Dhar, PhD: Yeast as a surrogate organism to study the function of HIV genes. Jeffrey Green, MD: Gene therapy for HIV and HTLV-I using HIV LTR-HSV thymidine kinase construct in defective retroviral vector will be used as the basis of a gene therapy approach to the treatment of HIV infection. 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: Stephen O'Brien, PhD: Identification of human genetic loci which influence susceptibility to HIV. Collaboration with epidemiological cohort studies of HIV and HBV. Immortal B-cell lines have been established from all members of the cohort and DNA is being screened using RFLP methodology. Distortion of allelic, genotypic, or linkage disequilibrium of linked human loci in clinically defined disease categories provides signal to discover disease susceptibility/resistance loci in human populations. Ulf Rapp, MD: Raf-1 activates transcription from the HIV LTR. Role of ras in raf coupling to transmembrane receptor tyrosine kinase. Gisela Fanning-Heidecker, PhD: Function of Nef protein of SIV. Raoul Benveniste, MD, PhD: Develop vaccines and antivirals against retrovirus infection in primates: Three separate recombinant or peptide vaccines have been shown to protect macaques from intravenous challenge with SIV or type D retrovirus (SRV-2). Characterize retroviruses(type D and SIV) isolated from primates. Pig-tailed macaques have been infected with a infectious and pathogenic SIV clone with an 82% homology to HIV-2. Follow changes in SIV env gene as a function of time after infection. Two regions of env, within the V1 and V4 regions, showed a 40% change in amino acids when AIDS became apparent in these animals. The region of the SIV env that corresponds to the immunodominant HIV V3 loop was conserved. Production of vaccine challenge stocks of SIV. David Derse, PhD: Transcriptional regulatory elements in equine anemia virus (EIAV). Mechanisms of the HTLV-1 and BLV rex protein. Dean Mann, MD: HLA antigens - Structure, function and disease association: Study association of HLA antigens with disease progression and outcome in individuals with HIV infection. Correlations between certain HLA phenotypes and the occurrence of KS have been observed. Individuals with HLA-DR1 had more rapid disease progression as defined by years from seroconversion to a decline in CD4+ cells below 20%, than individuals without this phenotype, while individuals with the HLA-DR7 phenotype had a less rapid CD4+ cell loss. Immunology of AIDS and AIDS-related diseases. Examines cell to cell and cell-free infection by monocytotropic and T-lymphocytotropic strains of HIV in vitro; virus-like particles seen in KS tissue biopsies from individuals in a cohort of HIV-1, HIV-2, HTLV-1, and HTLV-2 seronegative Greek men. (In some instances, reactivity to type D viruses was observed in sera from KS patients), and; the nature of the antibody response to HIV-1 proteins in infected mothers and their infants.

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. Studies on the Kaposi's sarcoma associated with HIV infection in vitro, in ovo, and in vivo which have demonstrated: (1) the growth of AIDS-derived KS cells is enhanced by corticosteroids; (2) AIDS-KS cells secrete factors, which not only induce angiogenesis, but increase vascular permeability; (3) AIDS-KS cells produce IL-6, and IL-8; (4) 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; (5) the ability of SPPG, a bacterial cell wall peptidoglycan, 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: (1) 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; (2) 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. Giardia lamblia and Entamoeba histolytica; human parasites as potential carriers of HIV-1. Marvin Reitz, PhD: Molecular biological studies of human pathogenic viruses. Investigate: (1) interactions between tat, rev, and cellular factors; (2) regulation of RNA polymerase promoters in different cell types; (3) regulation of viral gene expression at the level of RNA splicing in different cell types, in different diseases and stages of disease progression, and the effects of extrinsic factors, such as cytokines; (4) correlation of proviral structures and integration status with viral gene expression. HIV-1 envelope gene variability. Characterization of sites for neutralizing antibodies. Genetic determinants of cell tropism. Inhibition of HIV-1 replication by regulated transcription of poly-TAR RNA elements. Genoveffa Franchini, MD. Molecular approaches for development of an HIV vaccine, rhesus model. Molecular epidemiology and biological determinants of HTLV-1 infection. Mary Klotman, MD: HTLV-1 and adult T-cell leukemia, Pathophysiology of HTLV-1 infection: Only a small proportion of those infected by HTLV-1 go onto develop ATL. How do CMV, other herpes viruses and TNF-beta, affect development of ATL? Peter Nara, PhD: Characterization of the neutralization reaction with antibody against HIV-1. Immunobiology of HIV-1--Antigenic variation and vaccine development. Examine phenomenon of "original antigenic sin" in HIV infection. The investigator sheds serious doubt on the ability of vaccines eliciting a strong humoral response to protect against disease. Anti-HIV factors in animal sera and CD4 anti-receptor therapy for HIV-1 infection. International collaborative study to compare assays for antibodies that neutralize HIV. Prem Sarin, PhD: Retrovirus infection and treatment: Identify foscarnet analogues which can inhibit HIV RT and may be useful in the passage of the drug through the blood-brain barrier. In addition, chemically modified antisense oligonucleotides have been found to inhibit HIV replication without any toxic effect in vitro. Marjorie Robert-Guroff, PhD: Humoral and cellular immune response to HIV for vaccine development. Delineate immunologic response to HIV and identify viral subfragments which will elicit protective immunity to HIV-1, HIV-2, and SIV. Carl Saxinger, PhD: Immunopathogenesis of human retroviruses. Suresh Arya, PhD: Determinants of latency and pathogenicity of human retroviruses in AIDS. Genetic structure and function of a highly pathogenic (HIV-2ROD) and a weakly pathogenic (HIV-2ST) strain of HIV-2. Shuji Nakamura, MD: Vascular permeability activities produced by AIDS-associated KS-derived spindle cells; Kaposi's sarcoma in vitro and in vivo model systems: blockage of KS lesion by SP-PG, a bacterial cell wall complex. Paolo Russo, MD: Induction of CD4 in CD3+CD8+ T lymphocytes by HHV-6. Barbara Ensoli, MD: Biological Properties of tat, the transactivator gene of HIV-1.

FREDERICK CANCER RESEARCH FACILITY

ABL Basic Research Program: Stephen Oroszlan: Biochemistry and function of HIV and other proteases: HIV mutants deficient in genomic RNA. Ronald Rubin: Crystallographic studies of HIV integration protein. Alexander Wlodawer: Structural studies of retroviral proteins as a first step to rational drug design. George Pavlakis: Organization of HIV-1 genome; Study of essential regulatory factors of HIV and HTLV; Transdominant rev mutants: identification and expression in human cells. Barbara Felber: New HIV proteins: Tev. Cell tropism determinants of HIV-1 primary isolates. New antiviral approaches with

fast specific bioassays. Stephen Hughes: HIV integrase; Protease and protease fusion proteins; Structure and function of HIV reverse transcriptase. Christopher Michejda: Synthetic nonpeptide inhibitors of HIV protease.

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: Larry Arthur: Preparation of HIV challenge stocks for vaccine trials in chimpanzees. Molecular modeling of interactions between viral RNA and nucleic acid binding proteins. Development of assays to assess plasma p24 concentration in AIDS. Production of a defective murine type C virus and structural analysis of its capsid. Cellular proteins and the immune response to inactivated whole virus vaccines. Louis Henderson: Studies of the structure and function of HIV-1 gag proteins. Cellular proteins and the immune response to inactivated whole virus vaccines. Identification and analysis of proteins with anti-HIV activity. Robert Gorelick and Patricia Powell: Structural studies of the HIV-1 nucleocapsid protein.

Laboratory of Cell and Molecular Structure: Matthew Gonda: Development of a bovine lentivirus related to HIV as a model for AIDS antiviral therapy. Development of a transgenic-BIV mouse model for the testing of new antiretroviral compounds. Development of noninfectious pseudovirions as candidate vaccines for HIV and AIDS

Laboratories Unknown: Antoine Gessain: Genetic drift in vivo as a means to follow viral transmission and movement of ancient human populations; Jason Smythe: Linear polymers of CD4 as polyvalent molecular decoys.

Future plans. NCI asked for $217,500,000 for FY1993 and got $175,854,000 from the President: a 4.2% increase and barely enough to maintain current programs. NCI's budget request would have funded the following new initiatives and expansions of existing programs according to the FY1993 Wish List (in order of priority):

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 for 6 new grants 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, even though Dr. Fauci crossed it off the Wish List for FY1993.

* 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 HIV immunopathogenesis, including, but not limited to, those which would:

a. Correct 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. Depress the production of acute phase reactants and other inflammatory arachidonic acid metabolites, which may contribute the chronic inflammation associated with HIV; c. Depress the generalized immune activation which may contribute to the hypergammaglobulinemia, and even the depletion of the CD4+ cell population in HIV; d. Inhibit the indirect effects of HIV proteins (e.g. gp120 and tat) on CD4+ and other cells of the lymphoid lineage.

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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. DRS was founded in 1956 and DRR in 1962. Major NCRR programs include the General Clinical Research Centers (GCRCs) in medical schools around the USA, the seven regional Primate Research Centers, other animal colonies and non-mammalian research models. NCRR also provides support for biomedical engineering and instrumentation research and for research and training in minority institutions. The NCRR director is Robert Whitney, Jr., DVM. DRR (precursor of NCRR) spent $564,000 on AIDS related research in 1982. This rose to $11M in 1987, $28M in 1988 and $67.6M in 1989, and then fell to $47M in FY 1991.

The NCRR develops and provides resources essential to AIDS-related research -- from sophisticated instrumentation and technology, to the most appropriate mammalian or nonmammalian animal models, to clinical environments in which to conduct studies in humans. The NCRR supports research project grants to develop new technologies and animal models; resource centers that provide clinical research infrastructure, biomedical technology research and development, and laboratory animal resources and facilities; grants to improve animal facilities and provide shared instruments for research institutions; and programs for the development of research capability in minorities and minority institutions.

Intramural Research. While NCRR senior staff wrote to us that "the NCRR has no intramural AIDS-related research," the CRISP database lists three intramural research projects in the NCRR Biomedical Engineering and Instrumentation Program (BEIP), which is "dedicated to the acquisition of biomedical information previously unavailable to NIH scientists." Their three AIDS-related projects are investigating the physical chemistry of biological macromolecules, including the HIV reverse transcriptase p51/p66 heterodimer; microdialysis probe studies to develop methods of administering drugs such as AZT across the blood brain barrier; and seeking the cell membrane receptor for the HIV tat protein.

Extramural Research. In FY 1991, $22.8 million went to AIDS research at the GCRCs around the country, $19.7 million to primate research centers in the Comparative Medical Program, and $2 million to the Research Centers in Minority Institutions (RCMIs). These funds were spent on a diverse array of topics, including $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 research on HIV 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 Yerkes Regional Primate Research Center in Georgia lists 90 subprojects under its two grants (P51 RR00165 and P51 RR00165 0198), with 90 copies of the original abstract. No details are available through the CRISP abstracts. However, the ARIS list (pp. 570-581) lists 35 AIDS subprojects, all of which cost either $70,006 or $31,085. It appears that the centers (or NCRR or DRG staff) arbitrarily divide the number of subprojects by the amount of money available.

Yerkes received over $2.1 million for AIDS research in 1991. The seven RPRCs are:

* California RPRC, UC Davis CA * Tulane RPRC, New Orleans LA * New England RPRC, Harvard, Southborough MA * Oregon RPRC, Medical Research Foundation of Oregon, Beaverton OR * Washington RPRC, U. Washington, Seattle WA * Wisconsin RPRC, U. Wisconsin, Madison WI * Yerkes RPRC, Emory U., Atlanta GA

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.

New England RPRC workers looked at the role of macrophage cytokines in SIV infection. "The investigators examined cytokine influence on SIV replication in vitro utilizing simian alveolar macrophages and uncloned SIVMACMTV, a macrophage-tropic virus variant. These studies permitted quantification of viral replication on a per cell basis, which has made possible the most precise analysis to date of the role of cytokines for either HIV or SIV. The results showed that tumor necrosis factor-alpha significantly increased SIV production in macrophage cultures [emphasis added] but GM-CSF did not... Interleukin-6 increased SIV replication minimally but induced significantly greater cytopathic changes. In contrast, interferon greatly decreased replication."

California RPRC researchers "identified IgG as the principal isotype of immunoglobulin directed against SIV secreted into vaginal fluids of SIV-infected monkeys. The animals also showed a decrease in the number of IgA-secreting plasma cells in the mucosa of the vagina and a greatly increased level of serum IgG... Infected male rhesus macaques shed SIV in their semen before seroconversion. Hysterectomized female monkeys can be infected with SIV by the intravaginal route. Nonoxynol-9 spermicide preparations were shown to be partially effective in preventing genital transmission of SIV."

University of Washington RPRC investigators developed a new animal model for HIV infection, the pig-tailed macaque Macaca nemestrina. After challenge with HIV, eight of animals developed an acute primary syndrome resembling acute HIV-1 infection in humans, characterized by lymphadenopathy in six and rashes in two. It is still unknown whether these monkeys will develop AIDS, or whether, like chimpanzees, they will remain immunocompetent.

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 not [sic; presumably meant to read "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 Biological Models and Materials Research (BMMR) Program "develops and supports non-mammalian model systems - including invertebrates, cell and tissue cultures, and theoretical models - for studies of basic biological, biochemical and immunological processes related to AIDS." [FY 1991 AIDS spending: $0.]

The Biomedical Research Technology Program (BRTP) "funds ... structural studies of HIV receptors and viral components... and epidemiological computer models for the spread of AIDS." [FY 1991 AIDS spending: $?]

The Biomedical Research Support Grant (BRSG) program "provides funds for small-scale, short-term support of research projects using mechanisms that allow for rapid responses to unanticipated needs and new opportunities... In FY 1990, the BRSG Program supported 95 projects related to basic or clinical studies on AIDS. (Note: Funding was provided without AIDS dollars)." [FY 1991: $0; down 97.2% 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." [FY 1991: ($772,000) whatever that parenthesis means; -97.6% from FY 1990.] Examples of tools for which shared instrumentation (S10) grants are spent include: NMRs (nuclear mass resonance spectrometers), liquid chromatographs, mass spectrometers, automated DNA sequencers and electron microscopes for determining structure/function relationships of antiviral drugs and viral proteins, supercomputers for calculating three-dimensional crystal structures of drugs, viral or human proteins, and for conducting mathematical modelling of epidemiology, ultrasound for adult and pediatric diagnosis and treatment, etc.

The above programs have been shrinking (as far as AIDS is concerned) since 1989 [see below].

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... The centers... are present in 59 of the nation's 127 medical schools; some institutions have more than one center... Most centers... usually provide both inpatient and outpatient research facilities... Centers frequently have specialized laboratories, ... metabolic kitchens, ... research nurses and dietitians ... a biostatistician... [and] a computer systems manager.

Many of the 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. Because each GCRC is involved in a diverse array of research projects, the DRG CRISP database codes each subproject separately. This results in an enormous, unwieldy, virtually unusable database. When we received our three boxes of abstracts from OAR at the start of this project, one box was a simple, relatively brief (771 pages) list of all NIH AIDS extramural awards; one box consisted of abstracts of most projects of all ICDs besides NCRR (17 ICDs); the third box was entirely filled with the NCRR projects and subprojects coded as AIDS. This list is two feet high, and finding the AIDS-specific subprojects amidst it is like looking for a needle in the proverbial haystack. How can NCRR track its AIDS funds with such a system? How can anyone else?

To take just one GCRC as an example, the Duke University GCRC (M01 RR00030-30) went on for 108 pages, with one master abstract and 107 single-sentence, single-page subproject abstracts. Of these 9 were AIDS subprojects. Meanwhile, the list generated by ARIS listed six subprojects with different code numbers but the same drugs and designs. Funding for the projects ranged from $1,931 to $81,124, and totalled $127,486 for FY 1991. Basically, it appears that GCRC principal investigators assign random projects - e.g., a certain season's ACTG protocols - to GCRC subproject numbers, dividing the total award by the number of projects or according to some other unknown criteria.

Thus, while it is clear that GCRC's take in significant added funds for ACTG-conducted research, flaws remain. Accounting for these funds is somewhat arbitrary. The various NIH databases (DRG CRISP vs. ARIS) do not agree on how much or what GCRC's are doing for AIDS. The ARIS database needs to clean out the thousands of pages of irrelevant GCRC non-AIDS subproject abstracts. [Similar problems exist with the RPRC accounts and abstracts.]

GCRC support for the ACTG is significant but hard to track. For example, as cited above, Duke spent $127,486 in GCRC funds on ACTG trials. Mt. Sinai in New York got $1.3 million to garnish its ACTU funds; NYU got $2.1 million from NCRR. Did NIAID take these additional funds into account when judging the performance and funding needs of the ACTUs in the recent Recompetition?

Examples of GCRC-supported research which NCRR cited in 1991 reports to OAR include:

* "The macrophage mannose receptor is necessary for binding and uptake of Pneumocystis carinii by alveolar macrophages," according to GCRC investigators in Boston. "Competitive inhibitors of mannose receptor activity" reduced binding and uptake of cultured P. carinii ... by 90%." * Early detection of perinatal HIV infection with an HIV IgA assay at SUNY Downstate, Brooklyn. "At 3 and 6 months of age, HIV-IgA detected 62.5% and 100% percent, respectively, of CDC

indeterminately classified agents who were subsequently classified as infected." * Stress-related reduction of natural killer (NK) cells in HIV at UNC. "By use of multiple regression, highly significant negative relationships were found between stress and NK cell count and percentage in the HIV+ men. These stress/immune relationships were not explained by age, education, income, lymphadenopathy, depression, CD4 count, caffeine, tobacco or alcohol...". * Interactions between HIV and measles virus at the Medical College of Wisconsin. Human lung carcinoma H322 cells, which normally cannot become infected with HIV, are easily infected by HIV when preinfected with measles virus.

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 category, G12. AIDS-related RCMI awards included:

* $30,000 to Tennessee State University to study stress in blacks with HIV (RR03033-06 0020); * $509,000 to Morehouse School of Medicine in Atlanta for 6 projects involving laboratory studies of drug resistance, effects of AZT on pregnant mice, tissue culture models for ocular manifestations of AIDS, molecular analysis of paired mother/infant HIV isolates and provision of information resources for AIDS research (2 G12 RR03034-06 0024, 0025, 0028, 0030, 0034); * $100,000 to the Universidad Central del Caribe Medical Research Centers in Bayamon, Puerto Rico, for two projects studying the cellular pharmacology of ddI in monocytes and the cytotoxicity of HIV+ patients' sera against fungi (2 G12 RR03035-06 0054, 0055); * $104,000 to Texas Southern University in Houston to study antiretroviral drugs in rats (2 G12 RR03045-06 0072); * $172,000 to the Medical Sciences Campus of the University of Puerto Rico in San Juan for behavioral studies in Puerto Rican women with HIV (2 G12 RR03051-06); * $241,000 to the University of Hawaii in Honolulu for three projects involving the epidemiology of HTLV-I and HTLV-II in Vanuatu, of HIV in American/Pacific Islanders, and of enteric infections in AIDS patients (2 G12 RR03061-06 0137, 0140, 0141); * $284,000 to Tuskegee University in Alabama for two projects studying goat and mouse models for AIDS (3 G12 RR03059-04S1 0102 + 0103).

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. NCRR also supports development of "a comprehensive, culturally sensitive questionnaire (CCSQ) concerning AIDS for African-American women (AAW)."

Funding and Future Plans. NCRR AIDS spending reached a peak in 1989 at $67.6 million, which fell to $46M in 1990 and $47M in 1991. This was 14.2% of NCRR's total budget and 5.9% of the NIH AIDS research budget. AIDS funding for NCRR went down in real terms between 1990 and 1992. 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 NCRR AIDS research. Partially to compensate for recent cuts, NCRR requested a large increase for FY 1993, from $51M to $157 million. OAR trimmed this to $121M (140%); Assistant Secretary Mason cut it to $57M; and the President cut this to $51,505,000, a 2.9% increase or less than inflation. The present administration is starving the basic and clinical research infrastructure - including the AIDS

infrastructure. NCRR sought the additional $100 million (what do they think this is, 1988?) for the following programs:

* $20 million to enhance animal model programs, including rhesus and chimpanzee colonies for vaccine research. * $45.7 million to build extramural AIDS research facilities. * $8.3 million to buy sophisticated high technology machines for shared use by AIDS researchers (the BRS SIP program). * $5.2 million for new pilot studies (BRS program). * 17 million to expand the General Clinical Research Centers (GCRCs) for new clinical trials, pediatric, immunology and behavioral research. * $6.4 million for new initiatives at the Research Centers in Minority Institutions (RCMIs) for clinical trials, pediatric, virology, natural history and prevention/behavioral research in (and by) racial and ethnic minorities.

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 NCRR 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 NCRR 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 enchance AIDS research at minority institutions through RCMI awards.

* NCRR should work with NIAID and OAR to document the uses to which these funds are put, ensuring that grantees do not double bill the NIH.

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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 has five divisions: 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, which is run from the Office of the Director, functions as "the institute's technology transfer arm, relaying the results of heart, lung, and blood research to health care professionals, their patients, and the public."

NHLBI received $5,000 in FY 1982 for AIDS-related research. By 1983, NHLBI rose to third place behind NIAID and NCI in AIDS funding, with a budget of $1.2M. In

FY 1988, NHLBI dropped to fourth place among the institutes, as the AIDS budget of the National Center for Research Resources (NCRR) tripled. Since then NHLBI has consistently been the fourth biggest AIDS spender at NIH. In FY 1991, NHLBI received $46,406,000 for AIDS. Its budget dipped to $46,206,000 in FY 1992. For FY 1993, NHLBI requested $66,124,000. NIH trimmed the request to $59,151,000; PHS chopped off another $6,483,000; and DHHS slashed NHLBI's AIDS budget to $47,634,000. The President offered NHLBI $48.2M for FY 1993, which is barely above the level needed to maintain current services. NHLBI conducts and supports research on the pulmonary, hematological and cardiovascular complications of HIV infection. In addition, the institute sponsors research designed to assure the safety of the nation's blood supply. NHLBI funds research in a wide range of areas:

NHLBI AIDS Activities, FY 1991

IA1 HIV + HIV genome $ 2,331,000 IA2 Immunology 6,580,000 IA3 Blood/blood products 7,016,000 IA5 Animal models 519,000 IC2 Prevention 137,000 ID1 Drug Development 1,809,000 ID2 Clinical Trials 4,096,000 IE1 Vaccine Development 1,581,000 IIA1a Sexual transmission 3,659,000 IIA1c Hemophilia transmission 1,245,000 IIA1d Transfusion transmission 10,187,000 IIA1e Perinatal transmission 6,796,000 IIC5a Education + training centers 450,000

Extramural research. In FY 1991, NHLBI disbursed $39,544,729 for in extramural AIDS awards. According to ARIS, NHLBI supported 53 R01s, 24 N01s (R+D contracts), one P50 (Specialized Center), one P01 (Research Program Project), two K11s (Physician Scientist Awards), two K08s (Clinical Investigator Awards), and one R55 (James A. Shannon Director's Awards).

The 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.

Natural History. NHLBI sponsors two programs which are concerned with natural history of the pulmonary complications of HIV infection. Both are administered as N01s (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. Six sites were initially chartered:

1. UCLA, Jeanne Wallace, $567,126 2. Mt. Sinai, Mark Rosen, $889,422 3. NJU of Medicine + Dentistry. Lee Reichman, $0 in FY 1991. 4. Henry Ford Hospital, Detroit, Paul Kvale, $529,729 5. UCSF, Philip Hopewell, $456,937 6. Northwestern U., Jeffrey Glassroth, $328,641 An additional contract awarded for data collection and analysis and program support at the Research Triangle Institute, Research Triangle, NC (PI Kenneth Poole, $886,756). New Jersey appears to have been defunded. When and why? Descriptions of the study in the material sent from the institute and in the ARIS database do not provide a detailed portrait of the program, only saying that it is an investigation of "the types, incidence, course, and outcome of pulmonary disorders in newly diagnosed AIDS patients, ARC patients, and asymptomatic HIV-infected patients."

Since 1989, NHLBI has run the "Study of Pediatric Lung and Heart Complications of HIV Infection":

1. Cleveland Clinic, James Boyett, $453,703 2. UCLA, Samuel Kaplan, $1,316,326 3. Baylor, Houston, William Shearer, $1,193,521 4. Children's Hospital, Boston,

Stephen Lipschultz, $1,425,774 5. Mt. Sinai, NY, Meyer Kattan, $1,098,999 6. Presbyterian Hospital, Frederick Bierman, $1,236,067

The grant for the Presbyterian Hospital is listed by ARIS as being located at Columbia University in NYC. In NHLBI's "Special Focus Report on AIDS-Related Research" the institution is said to be in Philadelphia, PA. Where is it fellas? The Cleveland Clinic Foundation is the data coordination and program support center for the study. Most of the sites are cooperating with other institutions in their geographic areas serving children and pregnant women with HIV infection, including pediatric ACTUs, to enroll HIV+ infants and children. The study will chart the types, incidence, course, and outcome of pulmonary and cardiac complications of HIV infection in this population, and will also examine the pathophysiology of abnormalities in cardiac and pulmonary structure, growth and function, as well as virological and immunological parameters associated with these disorders.

Pneumocystis carinii. NHLBI funded six studies (five R01s and one K08) to investigate the pathobiology of Pneumocystis carinii pneumonia in HIV infection. Four grants are part of an NHLBI RFP "to study the fundamental mechanisms by which Pneumocystis carinii attaches to and injures host lung cells." These awards run from March 1991 to February 1996:

1. William Martin, Indiana University (R01 HL46647, Adherence mechanisms of P. carinii, $278,982). Explores the hypothesis that gp120 on the surface of P. carinii mediates attachment to alveolar epithelial cells by a fibronectin and/or surfactant protein A-dependent mechanism and that P. carinii proteases damage the epithelial cell as the organism detaches from it. Dr. Martin has another R01 to study, in vitro, the interaction of P. carinii with cultured lung cell, its mechanism of attachment and the role of inflammatory mediators. 2. Ward Rice, U. of Cincinnati (R01 HL46653, Control of type II cell function by P. carinii, $158,451). Does P. carinii interact with alveolar type II cells which synthesize and secrete surfactant-associated phospholipids and proteins which mediate PCP-associated lung dysfunction? 3. Miercio Pereira, New England Medical Center (R01 HL46659, Pathobiology of the P. carinii lectin, $234,518). Studies nature of recently discovered sugar-binding surface lectin of P. carinii which may mediate attachment of the parasite to lung alveolar epithelial cells and attempts to identify mAbs and other substances (e.g. lectin-specific saccharides) which might interfere with its binding to host cells. 4. David Phelps, Pennsylvania State University (R01 HL48006, Pneumocyte-immune cell interactions in the distal lung, $130,254). Examines role of type II alveolar epithelial cell and surfactants it produces in normal host defense function and in immunosuppressed hosts with P. carinii infection.

NHLBI is also funding a K08 Clinical Investigators Award to Jay Fishman MD of Massachusetts General Hospital who is studying the interactions between P. carinii and type I and II alveolar cells at the cellular and molecular levels. Finally, the institute is funding one R01 to study the mechanism of action of pentamidine in the therapy of P. carinii infection. The investigator, Anthony Veena of Indiana University hypothesizes that pentamidine activates alveolar macrophage function, specifically enhancing the release of toxic oxygen radicals.

Pulmonary immunology. NHLBI supports ten grants concerning the local pulmonary immune response during HIV infection. Six of the grants are R01s were issued in response to a FY 1988 RFA, "Alveolar Macrophages and Defense of the Lung in AIDS":

1. Richard Kornbluth, UCSD (R01 HL43523, $183,716), is studying the incidence and characteristic pathology of HIV infection of lung macrophages; the effects of HIV infection on macrophage function; cytokine production; the possible tropism of certain HIV strains for lung macrophages; and the effects of therapy with antiretroviral agents and cytokines on lung macrophages. 2. Ofra Weinberger, Columbia University (R01 HL43528, $174,986), is studying the effect of HIV gene expression on the function and physiology of HIV-infected lung macrophages. 3. David Weissman, University of New Mexico (R01 HL43529, $59,433), is investigating the relationships between HIV infection, alveolar macrophages and pulmonary immunity in AIDS by using KLH (keyhole limpet hemocyanin) to immunize a discrete region of the lung and assess humoral and cellular immune responses to the antigen in the HIV-infected individual. 4. Elizabeth Rich, Case Western Reserve University (R01 HL43571, $189,822) [abstract missing] 5. Paul Luciw, UC Davis (R01 HL43609, $223,889), is using SIV-infected rhesus macaques to investigate the function and phenotype of peripheral blood monocytes and macrophages and alveolar macrophages at various stages of disease; monitoring SIV replication in animals that progress from an asymptomatic to symptomatic disease state; analyzing the role of the macrophage in viral latency and replication and SIV's effects on macrophage function; and studying what role cellular activation plays in viral infection. 6. David Volsky, St. Luke's Institute for Health Sciences (R01 HL43628, $178,423), is investigating the hypothesis that HIV-1 infection of alveolar macrophages alters their function, particularly the production of IL-1, permitting the development of AIDS-associated lung disease. Whether the alveolar macrophage is a reservoir for HIV-1 will also be explored.

NHLBI is also supporting studies of the impairment of the antimicrobial function of alveolar macrophages in HIV infection, particularly their ability to phagocytose, inhibit and kill C. neoformans, MTB and MAI; a comparative study of the molecular biology of retroviral infection of the monocyte/macrophage and T cell, and; a study of pulmonary dendritic cells in HIV infection. Finally, NHLBI sponsors a program project (P01 HL43510, $1,646,584, PI Richard Rose) at Harvard University, which is investigating the abnormalities of pulmonary alveolar macrophages and the pathogenesis of lung disease in AIDS.

The Heart. NHLBI also funds a natural history study of AIDS-associated heart disease in an adult population. Although six institutions were originally funded for this program and are listed in the institute's 1991 Special Focus Report, only three are listed among the grants for FY 1991 in the ARIS-CRISP database (1991 funded sites in bold):

1. Melvin Cheitlin, UCSF, (R01 HL41495, $241,967); 2. William Lewis, U. Vermont (R01 HL41400); 3. Judith Hsia, George Washington University (R01 HL41507, $488,912); 4. Ahvie Herskowitz, Johns Hopkins (R01 HL41514, $441,059); 5. Azorides Morales, U. Miami (R01 HL41631); 6. John Craighead, U. Vermont (R01 HL41502).

The project charts the incidence and clinical course of cardiomyopathy in HIV infection and will investigate their etiology and pathogenesis. Under study are the contributions of HIV and other infections, autoimmunity and other immune-mediated factors (e.g. cytokines), and therapeutic agents towards the cardiac damage observed in AIDS. NHLBI funds one other grant on the cardiac abnormalities seen in AIDS, a study looking for the presence of HIV-1 proteins and RNA and associated morphological damage in the heart tissue of HIV-infected individuals (Jiang Gu, Deborah Research Institute, R01 HL44916, $70,971).

The Blood. NHLBI funds 25 grants studying 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.

Hematopoietic function in HIV infection. In FY 1987 NHLBI issued an RFA to study bone marrow suppression in HIV infection. The NIH 1991 "Report to Congress" says that 11 investigators and 14 grants are supported by this project; NHLBI's "Special Focus Report" lists 11 grants, of which only eight appear in the ARIS database (below in bold). There are indeed 14 grants, supporting 13 investigators, in ARIS' list. Most of these grants are unaccompanied by CRISP abstracts, making the program difficult to evaluate:

1. David Scadden, New England Deaconess, (R01 HL44851, "Mechanisms of hematopoiesis in AIDS", $253,229), is investigating the infection of progenitor and bone marrow stromal cell populations using PCR on samples taken from HIV-infected individuals. By infecting both normal and immortalized stromal cell lines with HIV, he hopes to determine the effects of HIV on hematopoietic capacity, cytokine expression, extracellular matrix and surface adhesion molecule expression, in the bone marrow. 2. Michael Linenberger, U. Washington (K08 HL02396, "Hematopoietic environment of retroviral infected marrow", $75,600). 3. Elder Pearce, St. Luke's, (K11 HL02444, "Infection of bone marrow by HIV-1", $65,146) is analyzing the frequency of HIV infection in bone marrow mononuclear cells (BMMC), viral expression and target cell types in BMMC from infected individuals; the mechanism of entry and expression in BMMC infected in vitro; and the effects of antiretroviral agents and antisense viral RNA on HIV infection in BMMC. 4. Anne Hamburger, U. of Maryland (R01 HL42069, "Pathobiology of Bone Marrow Suppression in AIDS", $144,309). 5. Michael Prystowsky, U. Penn. (R01 HL42090, "Effect of retroviral infection on bone marrow", $162,825), is using a murine retroviral model to study the effects of retroviral infection on hematopoiesis. Which cells are infected, and how do they respond to GM-CSF, IL-3, G-CSF, M-CSF, and EPO? 6. Stephen Emerson, U. Michigan (R01 HL42096, "Immune mediated hematopoietic suppression and AIDS", $166,194). 7. Dorothea Zucker-Franklin, NYU (R01 HL42103, "Effect of HIV on hematopoietic and stromal marrow cells", $165,025), is investigating the role of immune complexes, inhibitory factors and the virus itself in the damage of megakaryocyte and myeloid cells in HIV infection. 8. Brian Davis, MRI San Francisco, (R01 HL42105, "Bone marrow suppression in AIDS", $191,621). 9. David Golde, Sloan-Kettering Institute for Cancer Research (R01 HL42107, "Hematopoietic cell function in AIDS", $278,721). 10. Jerome Groopman, New England Deaconess, (R01 HL42112, "Bone marrow suppression in AIDS or ARC", $175,093). 11. Jeanette Mladenovic, SUNY/Stonybrook (R01 HL42142, "Pathogenesis of bone marrow failure in HIV disease", $159,549). 12. Howard Steinberg, Beth Israel, Boston (R01 HL42148, "Pathobiology of bone marrow suppression in AIDS", $190,4120). 13. Brian Davis, MRI SF (R0142283, "Study of HIV infection in bone marrow stem cells", $195,208), is assessing the possible role of HIV-infected hematopoietic cells in the bone marrow in: (1) the persistence of HIV infection through latent infection, (2) the transmission of HIV to T4 lymphocytes and brain cells, (3) altered hematopoiesis, and (4) the defective immune function of monocytes/macrophages. 14. Ronald Hoffman, Indiana U. (R01 HL42674, "Mechanism of hematopoietic suppression in HIV-1 infection", $171,897), is assessing the effect of HIV, CMV and human parvovirus B19 on hematopoiesis in people with AIDS. The ability of hematopoietic progenitor cells and stem cells to be directly infected with HIV, CMV and HPV-B19 and their effects on the function of these cell populations will be examined, as well as the contribution of autoimmune phenomena to the destruction of progenitor or stem cells in HIV infection.

Platelet Disorders. NHLBI funds four grants on HIV-associated platelet disorders. Three are part of an RFA released in FY 1991 and run until February 1996. Curiously, none seems to be concerned with specifically HIV-associated thrombocytopenias:

1. Timothy Crawford, Washington State U. (R01 HL46651, "Mechanisms of equine lentivirus-induced thrombocytopenia", $109,830), is studying the relative roles of direct viral infection compared to immune-mediated damage in EIAV; the nature of EIAV-associated thrombocytopenia (the grantee hopes to determine if lack of production or shortened platelet survival time is implicated in this disorder); whether immune mediated damage is involved; if so, the target antigens will be defined and the role of antibodies in cellular injury will be determined; and the involvement of megakaryocytes in the etiology of the thrombocytopenia. 2. Clark Anderson, OSU (R01 HL46652, "Platelet Fc receptor in HIV thrombocytopenia", $187,022), is investigating the fundamental mechanism by which antibodies activate platelets. While not particularly concerned with the platelet disorders of HIV infection, this work may increase our understanding of ITP associated with platelet-bound immune complexes and anti-platelet antibodies in AIDS. 3. Jerome Groopman, New England Deaconess, (R01 HL46668, "HIV infection of human megakaryocytes", $236,934).

The remaining grant on platelet disorders in HIV infection is a Shannon award to Cindy Leissinger of Tulane University (R55 HL46670, "Retrovirus induced immune platelet abnormalities", $50,000). Shannon grants are special awards given to R01, R03, or R29 applicants whose grants fall below an institute's funding range ("below the payline") and are highly meritorious, "but perhaps a bit risky". An institute's program staff nominates a particular application for a Shannon award, which is reviewed by a panel of senior extramural NIH scientists, and then passed on to the NIH director for final approval.

AZT myelotoxicity. NHLBI funds three grants costing $681,262 on the toxicity of AZT and other antiviral therapies to the bone marrow. None of these abstracts are available in the ARIS-CRISP system, and no descriptions available in the NHLBI materials.

Hemophiliacs. NHLBI funds three grants on the manifestations of HIV infection in hemophiliacs, a natural history study of HIV-positive hemophiliacs and their spouses, which is also looking at the contribution of cofactors to the pathophysiology of the disease, and two immunological investigations. Of particular interest is a study of the immunological defects observed in hemophiliacs receiving large donor pool commercial factor VIII concentrates. The PI, John Sullivan of the U-Mass. Medical School, hypothesizes that the immunoregulatory dysfunction may be attributable to reactivation of EBV and CMV infections following the bombardment of the immune system with large doses of alloantigens which are contained in the factor VIII preparations. While HIV infection is not under consideration here, the possibility that alloantigens and herpesviruses may accelerate the course of immune deficiency in hemophiliacs and other populations has been proposed by at least one other investigator.

Safety of the nation's blood supply. NHLBI devotes a fat portion of its extramural resources to programs to assure the safety of our nation's blood supply. Its earliest AIDS work was in this area, beginning with the Transfusion Safety Study (formerly the Association of Blood Product Use with Immune Function Study) in 1983. 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.Blood Screening. In FY 1986, NHLBI issued an RFA entitled, "The Development and Evaluation of New Screening Tests for HTLV-III Antigens, Antibodies, or Nucleic Acids". The program "developed and evaluated procedures used in the screening and monitoring of individuals who are carriers of HIV-1." Although many contracts were originally supported by this study, by FY 1991 only one contract was still being funded. However, a new RFA was announced in FY 1989 to develop diagnostic procedures for detecting retroviruses other than HIV, which is included among the institute's AIDS program. The participating investigators are:1. Frederick Kramer, Public Health Research Institute of the City of New York (R01 HL43521, Extremely sensitive assays for human retroviruses, $337,551);2. Kary Mullis, Specialty Laboratories, Inc. (R01 HL43532, Mass screening strategy--detection of human retroviruses, $96,754);3. Mark Manak, Biotech Research Laboratories, Inc. (R01 HL43560, Combined assay for HIV-1 and HTLV-1 using PCR, $228,331);4. Tun-hou Lee, Harvard University (R01 HL43561, Assays for screening HIV-2 and HTLV-1 antibodies, $211,219);5. Raphael Viscidi, Johns Hopkins University (R01 HL43586, Protein-gene sequence specific retrovirus diagnosis, $298,328);6. Edouard Cantin, City of Hope National Medical Center (R01 HL43594, Development of universal PCR assay for retroviruses, $118,176);7. Bernard Poiesz, Syracuse University (R01 HL43602, Development and evaluation of new screening tests, $345,833).Epidemiology and natural history. NHLBI supports two epidemiological studies one largely to determine the prevalence of HIV infection in blood donors and the other to assess the factors influencing the risk of transmission of the virus by contaminated blood and the rate of progression to AIDS in transfusion recipients. The Epidemiological Studies of Human Retroviruses in Volunteer Blood Donors program began in FY 1989. Six institutions, including Westat, Inc., which functions as a coordinating center, participate in the program:1. UCSF, Edward Murphy (N01 HB97077, $677,223);2. Oklahoma Blood Institute, Ronald Gilcher (N01 HB97078, $710,678);3. American National Red Cross (ANRC), Alan Williams (N01 HB97079, $969,603);4. ANRC Angeles, Steven Kleinman (N01 HB97080, $839,374);5. ANRC Michigan, AW Shafer (N01 HB97081, $888,654);6. Westat, Inc., George Schreiber (N01 HB97082, $4,414,468).These studies are intended to (a) determine retrovirus seropositivity in first-time blood donors; (b) determine the rate of seroconversion in repeat blood donors; (c) determine the risk factors for seropositive donors; (d) characterize the demographics of the blood donor population by geographic location, age, sex, race, ethnicity, and donation history and to correlate these parameters with seroprevalence, seroconversion incidence, and risk factors; (e) identify recipients of retrovirus-positive blood and to conduct clinical and laboratory follow-up of this population to determine the transmissibility of these pathogens via transfusions, and; (f) establish blood specimen (from donors and recipients) repositories for future testing. The Transfusion Safety Study began in FY 1983 as the Association of Blood Product Use with Immune Function Study and is one of NHLBI's earliest AIDS efforts. The project began before the discovery of HIV and was originally designed "to characterize the immune function in heavily transfused patients and determine the relation of these alterations to AIDS." After HIV was discovered, the program set up a cell and serum repository to study HIV-infected transfusion recipients with a focus on the correlates of transmissibility and clinical progression. The clinical centers are located in Los Angeles, New York, Miami and San Francisco.Blood Supply Protection. NHLBI supports several programs designed to improve the safety of our nation's blood supply. The first is part of the National Blood Resource Education Program (NBREP), which is run by the Office of Prevention, Education and Control. NHLBI funds a contract with the University Research Corp. of Chevy Chase, to help develop and evaluate its smoking, high blood pressure, cholesterol and blood resource education programs. The second study is assessing why autologous blood donation for elective surgery is not more widely used, and is targeting an education program towards surgeons (who can order predonation).

NHLBI funds another study "to determine the behavioral factors involved in blood donation to investigate why donors with risk factors continue to donate blood and why low-risk donors refrain from donating blood." Two other studies are attempting to improve the safety of our nation's blood supply by two very different means. One assesses whether older Americans (63-70), whose HIV incidence is relatively low, can give blood 4-5 times a year without a risk to their own health. The other assesses the feasibility and utility of using bovine and human hemoglobin as oxygen carriers in health care delivery procedures. NHLBI supports work to inactivate HIV, hepatitis, and other viruses in blood products.Specialized Center for Research in Transfusion Medicine. This multidisciplinary program is devoted to:
(1) increasing the efficiency of transfusion practice by evaluating current US transfusion practice;
(2) assessing the adequacy of the nation's blood supply;
(3) developing better diagnostic tools to screen blood for HIV-1, HIV-2, and HTLV-II;
(4) identifying defects in antigen-triggered CD4+ cell activation in children with AIDS, and; (5) elucidating cellular and viral factors which determine HIV tropism for cells of the myeloid and lymphoid lineages. A cohort of people with AIDS and their sexual partners, children with AIDS and hemophiliacs with AIDS has been established.Other extramural research. NHLBI runs several other eclectic programs. 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. NHLBI supports 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. Finally, the institute funds a grant to study impairment of the cytotoxic ability of natural killer cells in HIV infection.Intramural research. In FY 1991, NHLBI appropriated $5,571,000 for intramural research on AIDS. Some recent projects include:* Laboratory of Molecular Cardiology, Robert Adelstein: Myosin expression in cells infected with HTLV and HIV-1;* Laboratory of Chemical Pharmacology, Michael Beaven: Rat basophilic leukemia exocytosis signaling pathways;* Clinical Hematology Branch, Takashi Shimada: Development of antisense RNA sequences to inhibit HIV-1 replication;* Laboratory of Biochemistry, Rodney Levine: Mechanism of inhibition of a HIV-1 fusion protein;* Molecular Hematology Branch, W. French Anderson: Gene therapy for HIV infection: retroviral vectors encoding sCD4, IFN-alpha, transdominant rev mutants or HIV-inducible diptheria toxin;* Pulmonary Branch, Ronald Crystal: a clinical trial of aerosolized IFN-alpha and glutathione in patients with HIV-infection and their effects on the pulmonary macrophage;* Laboratory of Chemistry, James Ferretti: Structure of various env glycoprotein peptides;* Clinical Hematology Branch: Etiology of anemia caused by bone marrow failure in HIV infection; IVIG in the treatment of parvovirus induced anemia. Future Plans. NHLBI asked for approximately $20 million in new funds for FY 1993 to support a large collection of new initiatives:1. $1,2M for 6 new RPGs (research project grants) to investigate the basic mechanisms involved in the proliferative patterns of vascular cells in Kaposi's sarcoma;2. $3M for 5 new contracts for HIVIG clinical trials to prevent vertical transmission during the third trimester;3. $310,000 for intramural work on anti-HIV gene therapy;4. $1M for 5 new RPGs to study the etiology and mechanisms of non-infectious pulmonary complications of HIV infection;5. $1M for 5 new RPGs 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 for 5 new RPGs to investigate whether transfusions from CMV-negative donors reduces the incidence of active CMV infection in people with AIDS;8. $1,2M for 5 new RPGs to study the viral etiology of myocarditis and dilated cardiomyopathy in children with AIDS;9. $1,2M for 6 new RPGs to study lung macrophages and T-

lymphocytes in pulmonary disease in children with AIDS;10. $4M for 7 new contracts to extend the Pulmonary Complications of AIDS natural history study.11. $1M for 5 new RPGs 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 for 5 new RPGs 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 draconian AIDS 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 revise its "Special Focus Report on AIDS-Related Research" to indicate which participants in a given program are actually currently funded, otherwise: (1)those programs seem bigger than they really are; (2)when programs are scaled back, it isn't noticed;* NHLBI should add RPGs to investigate MTB in HIV infection and Congress should give them the money to do it;* NHLBI should add RPGs to investigate lymphoid interstitial pneumonia in children with HIV;* NHLBI's program on thrombocytopenia purpura in HIV infection should be expanded to include projects that more closely deal with of the immune thrombocytopenia purpura observed in HIV infection. Current grants on EIAV induced thrombocytopenia, the normal interaction between antibodies and platelets, and the infection of megakaryocytes are worthwhile, but studies directly investigating the etiology of the disorder in people with HIV should be carried out as well.* NHLBI should add RPGs to investigate the particular cardiac complications of HIV infection seen in injecting drug users.* NHLBI should broaden its work on the other opportunistic infections affecting the lung in HIV infection.* NHLBI should initiate a PCP Prophylaxis Education Campaign through its Office of Prevention, Education and Control, for HIV+ individuals who may not know this OI is preventable.Contact: Elaine Sloand Special Assistant to the Director AIDS Coordinator, NHLBI * II/5. National Institute of Child Health + Human Development NICHDCreated in 1962 by act of Congress (P.L. 87-838), NICHD now consists of five major 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 (3entific Review Program. Since 1986 the NICHD Director has been Duane Alexander, MD.NICHD support for AIDS research began with $1.4 million in 1986, rising rapidly to $32.6 million in FY 1991. $30 million went for 70 extramural awards supporting a diverse range of activities from basic virology and immunology ($193,776), diagnostic studies and animal models ($4.9 million), neuroscience ($109,000), preclinical ($111,087) and clinical drug development ($8 million), research training ($109,627), studies of sexual, perinatal and other modes of transmission ($14 million), epidemiology ($2.7 million) and health education and risk reduction ($2.4 million). Staff costs for supporting this research amounted to $1.2 million.Basic research. NICHD spent $1.3 million on various intramural AIDS research programs, including 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 receptor structure and function and T cell receptor 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. Several grantees are trying to develop 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 too participated in this study through the pediatric AIDS Clinical Trials Units (ACTUs). The study was controversial because of the use of an intravenous placebo. In 1991, the study was published, showing a statistically significant decrease in the rate of serious bacterial infections in the treatment group. [It is unknown, however, whether the hospitals which treat most children with HIV infection can afford IVIG, which is costly.] Further follow-up and analysis of the IVIG study are ongoing. 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 (ACTG 051, 128 and 138) to date.NICHD is also nesting a neurodevelopmental study within ACTG 152. In conjunction with NIAID and NHLBI, NICHD is developing 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, ACTG 185, is projected to enroll 800 women and infants.Children with HIV. NICHD is supporting research into the effects of being born to HIV-infected womenon 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.Initial studies demonstrated that a nonoxynol-9 containing contraceptive gel and foam provide partial protection against vaginal transmission of SIV... Initial monkey studies have demonstrated that administering the spermicide 5 days a week does not result in overt irritation as observed by colposcopy... A study is under way to determine whether female monkeys administered progesterone may be more susceptible to infection... RNA PCR development is under way to determine whether sperm themselves are virus carriers.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.. Proposals responsive to a new RFP, "Development and Testing of New Spermicides," were received in March 1992 and are presumably now under review.Vertical transmission. Several 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 spent $32.6 million on AIDS in FY 1991, 6.5% of its total budget and 4.3% of the NIH AIDS total. NICHD is still flush with new funds from Congress' pediatric earmark of 1991; its budget is rising by 6.1% in the President's budget request to $38.2 million. Thus, NICHD is one of the few institutes whose AIDS budget is rising faster than inflation (4.5%).

Nonetheless, NICHD had requested an increase to $64.7 million to fund the following projects:* $10 million in new funds to double the pediatric clinical trials network and 10 new FTEs.* $3 million to double funds for current studies of risk behavior and create databases to model HIV transmission.* $6 million to study of adolescent risk behavior and HIV infection, the American Teenage Study.* $1 million to develop monkey models for mucosal immunity and $1.3 million to develop and test new virucidal spermicides. * $1 million for behavioral studies of AIDS prevention in high-risk teenagers.* $1 million to add to NIAID's RFA on "Mothers + Infants: Early Diagnosis + Correlates of Immunity."* $2.4 million to train pediatricians and adolescent health providers to address sexual development and behavior, and adapt these "for use in inner cities."* $1.3 million for behavioral intervention studies.* $500,000 for epidemiological studies of HIV-infected adolescents.* $1 million to develop transgenic mice in which to screen for antiretroviral drugs.* $1.4 million 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 transmission in vitro.* $650,000 to supplement a comparative study of growth in HIV+ and HIV- children with hemophilia.* $400,000 to support a National Academy of Sciences panel on international issues and behavioralresearch.* $775,000 to study whether vaginal insertion products cause abrasions which raise the risk of HIV transmission in women.* $575,000 for a prospective observational 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 3-year studies of HIV+ women to assess the effects of oral contraceptives on the rate of progression.The breadth and ambition of NICHD's requests stands out among the ICD's wishlist for FY 1993. Perhapsthis is because funding patterns for pediatric AIDS research have not yet suffered the plateau which hasafflicted adult AIDS research funds. It is notable how many of the questions NICHD seeks to address relateto 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'soriginal request of $78 million; Mason cut $22 million more (to $42,466,000); Sullivan cut $4 million to thefinal President's request for $38 million. NICHD how has 28 AIDS FTEs and wanted to add 25 for a total of53.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. *Contacts: Duane Alexander, MD Director, NICHD Bldg. 31, Rm. 2A03 301/496-3454 301/402-1104 Sue Van Lenten 301/396-1877 * II/6.National Institute of Neurological Disorders and Stroke NINDSNINDS originated in 1950 as the National Institute of Neurological Disorders and Blindness (NINDB). In1960, the joint intramural research program of NINDB and NIMH was divided into two separate intramurallaboratory programs. In 1968, NINDB's blindness program became the core of the new National EyeInstitute (NEI), and the NINDB's became NINDS. In 1975, the institute had yet another name change to theNational Institute of Neurological and Communicative Disorders and Stroke (NINCDS). In 1988, thecommunicative disorders program became the nucleus of the new National Institute of Deafness and OtherCommunication Disorders (NIDCD) and NINCDS became NINDS once again. Dr. Murray Goldstein is theDirector of the NINDS.NINDS has six divisions: (1) Convulsive, developmental, and neuromuscular disorders; (2) Demyelinating,atrophic, and dementing disorders; (3) Fundamental neurosciences; (4) Stroke and trauma; (5) Extramuralactivities; and (6) Intramural research.NINDS was one of the original seven NIH institutes to receive appropriations for AIDS research in 1982,when it received $310,000. Its AIDS

funding wavered over the next few years, rising to $1,510,000 in 1984,dipping to $1,168,000 in 1985, jumping to $3,685,000 in 1987. Its AIDS budget dramatically increased in1988 to $12,342,000 and has continued to grow steadily since then. In FY 1991, NINDS received$16,651,000 for AIDS-related activities. For FY 1993, NINDS requested a doubling of its budget to$34,751,000. The NIH trimmed the request to $32,651,000; PHS cut the figure to $25M, DHHS to $19.8M;and the President to $18.6M. While substantially below the amount the institute originally requested (andlike most other institute's budgets, barely over the amount needed to maintain current services) NINDS'spercentage increase over 1992 is the highest among all institutes and centers at NIH at 7.9%.
NINDS'sextramural research is all funded under Mason category IB: Neuroscience and Neuropsychiatric Research. The institute funds a mix of R01s, R29s (First Independent Research Support and Transition [FIRST]Awards) and P01s (Research Program Projects). NINDS supports basic and clinical research on theneurological complications of HIV infection, including, but not limited to, AIDS dementia complex and theopportunistic infections affecting the nervous system, and investigations of potential therapies for theseconditions. According the 1991 NIH "Annual Report to Congress," the goals of the NINDS's AIDS programare:* 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 enable clinicians to predict the onset and severity of neurological symptoms in HIV-positive individuals;* 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 insure the inclusion of 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 25 R01s, 4 R29s and 7 P01s.Opportunistic Infections. Two grants supported diagnosis of the neurological OIs of AIDS. Onecorrelated the presence of JC virus DNA in the CSF with PML. The other was an investigation of the use ofNMR to distinguish CNS toxoplasmosis from CNS lymphoma in AIDS.Primary HIV Infection of the Nervous System. 26 of NINDS's 29 basic AIDS research grants (R01s andR29s) go to the study of the neuropathogenesis of HIV infection, including the pathogenesis and naturalhistory of AIDS-related encephalopathy; peripheral neuropathy and myopathy; the development of animalmodels for the neurological effects of HIV; and potential therapeutic approaches.14 grants studied the pathogenesis of CNS involvement in AIDS, including identification andcharacterization of neurotropic variants of HIV; identification of receptors for HIV in the brain; the extent anddistribution of cortical atrophy; the role of macrophage or astrocyte produced cytokines in mediating CNSdamage; 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 dysfunctionand degeneration, as well as immunosuppressive neuroendocrine responses; the effects of HIV and itsproteins (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 HIVinfection in children (3 grants) and gay men (1 grant). NINDS-supported researchers are also investigating the pathogenesis of other lentiviral infections in otherspecies (visna virus, CAEV, FeLV and borna disease) as animal models for HIV infection. Two grants areinvestigating the gene expression of the visna virus. One is studying the molecular biology of borna virusand interestingly implicates the veterinary pathogen in selected human neuropsychiatric diseases, includingAIDS

encephalopathy. Another is a broad immunological study of visna and CAEV infections, looking at,among other things, virus-macrophage interactions, the induction of a novel interferon by these ruminantpathogens, and the etiology of the acute episodic lesions in the CNS occurring in the disease. Only twogrants are specifically concerned with the neurologic pathology of lentiviral infections. The first is a study offeline leukemia virus (FeLV) and feline lentivirus (FIV), characterizing the specific cellular tropism,pathogenicity, and genotype of neurotropic strains of the viruses. The second is a study of the mechanismof the neuroinvasiveness and neurovirulence of visna virus focusing on viral gene expression in brainmacrophages and subsequent cytokine production and CNS damage.Finally, two grants are investigating therapies for the neurological effects of HIV infection. One grantee isinvestigating the use of probenecid and salicylic acid to alter the distribution of AZT between the CNS andthe plasma, in the hope of achieving higher levels in the brain. The other is investigating myopathy in HIVinfection, both HIV-associated and AZT-associated, comparing corticosteroid therapy with AZT withdrawalin the treatment of this condition.One R01 stands out from the crowd of NINDS grants. It is a psychoneuroimmunological study of theeffects of Pavlovian conditioning on mucosal immunophysiology in normal and infectious and inflammatorystates.AIDS Dementia Centers and other P01s. Seven NINDS-supported research projects are studying AIDSDementia Complex and other neurological complications of HIV infection:1. AIDS Dementia Center, UNC, Chapel Hill, NC, PI Colin Hall ($958,736, 2 P01 NS26680-04A1), supports longitudinal neurological studies of HIV+ adults, adolescents, and hemophiliacs. Neurological, neuropsychological, psychiatric, CSF and hematological examinations are conducted every six months. Neuroexams include routine and quantitative EEG; visual, brainstem, auditory, P3 cognitive and somatosensory evoked potentials; nerve conduction and fiber density studies; MRI and spectroscopy. Participants enroll in multicenter trials of antiretroviral agents for the prevention and treatment of HIV-associated neurological disease. 2. Research Centers for AIDS Dementia and other Retroviral Neurological Disorders, Johns Hopkins U., Baltimore, MD, PI Opendra Narayan ($1,525,732, 5 P01 NS26643-04), examines the clinical manifestations, cellular pathology, and pathogenesis of the neurological complications of HIV infection. Part of the project includes longitudinal studies of both CNS and PNS disease in gay men, IVDUs, and HIV+ infants. Through various morphological methods, peripheral nerve abnormalities, the involvement of the dorsal root and autonomic ganglia, and the cellular pathology of vacuolar myelopathy and HIV encephalopathy will be studied. Immunopathogenic mechanisms potentially responsible for neurological damage in HIV infection are also being investigated. The phenotype of inflammatory cells, their state of activation and the production of cytokines in specific regions of the CNS will be correlated with the presence of viral antigens and RNA. The effects of HIV on macrophages and monokine production are under examination as well. Several animal models are being employed in the project, including cats with FIV and transgenic mice expressing genes for specific retroviral proteins which are being studied for the effect of the individual gene products on neurologic pathology.3. Neurologic Complications of HIV, U. Miami, Miami, FL, PI Joseph Berger ($911,991, 5 P01 NS25569-04), conducts four studies: 1) a longitudinal study of asymptomatic, HIV+ adults from various demographic groups and matched seronegative controls to determine the frequency and nature of neurological disease in HIV infection, identify predictors, immunological and virological correlates of neurological disease; 2) in vitro assessment of virus-CNS cell interactions; 3) a longitudinal controlled (as above) natural history study of CMV-induced neurological disease. 4) a longitudinal controlled study of autoimmune phenomena in AIDS-related neurological disease, specifically attempting to correlate the presence of brain reactive antibodies with dementia. 4. AIDS Dementia Complex, U. Minnesota, Minneapolis, MN, PI Richard Price ($991,156, 5 P01 NS25701-05), runs three cohort studies which are attempting to

collectively develop a more precise characterization of AIDS Dementia Complex, its neurological and neuropsychological features, natural history and epidemiology, and the immunological, virological and neuroradiological correlates of the condition. The three cohort studies are longitudinal investigations of the following populations: 1) PWAs with ADC and PWAs at high risk of developing ADC; 2) HIV seropositive individuals without AIDS who are at moderate risk of developing ADC, along with a group of seronegative controls, and; 3) HIV seropositive blood donors from the New York Blood Center. In addition, U-MN is using positron emission tomography (PET) and fluorodeoxyglucose to define the metabolic anatomy of the disorder, its severity and progression, and response to antiretroviral therapy. Another part of the project is attempting to characterize and localize HIV infection of the brain and identify and characterize neurotropic variants of the virus. Finally, the sixth part of the project is attempting to characterize the cell types expressing the CD4 surface receptor and their distribution in the brain and develop a mouse model of AIDS and ADC. 5. Molecular and Cellular Biology of HIV Encephalopathy, U. Penn., Philadelphia PA, PI Neal Nathanson ($569,655, 5 P01 NS27405-03), is conducting in vitro studies of the pathogenesis of HIV encephalopathy. The first project is an investigation of HIV infection of cultured human neural cells comparing the level of replication in different glial and neural cell lines and assessing the mechanism of viral entry, latency and activation. The next is a study of HIV infection of cultured human fetal neural tissue investigating the nature and localization of the CD4 surface protein and related molecules in the fetal nervous system. This project is also examining the effects of monokines from HIV-infected cells on fetal neural tissue. The third study is an investigation of HIV infection in cultured human monocytes looking at replication patterns of monocyte-tropic and T-lymphocyte-tropic variants (and recombinant mixes) and the toxic and trophic effects of monocyte secretions on human neural and glial cell populations. The last project is an investigation of the mechanisms of HIV neurotoxicity which is seeking to isolate and identify the toxic products of infected or uninfected monocytes and determine the nature of their deleterious effects (biochemical, biophysical) on CNS cells.6. Comprehensive AIDS Research Center, U. Maryland Professional School, Baltimore, PI Gerald Cole ($1,002,542, 5 P01 NS26665-04), focuses on perinatal and pediatric HIV infection with a particular emphasis on three major areas: 1) humoral and cellular maternal immune response to HIV and their effect on vertical transmission; 2) the risk factors and mechanism responsible for neurological complications in pediatric HIV infections, and; 3) immunological approaches for treatment or prevention of HIV infection in perinatal and pediatric populations. As part of the program on the neurological aspects of HIV infection, the U-MD center is conducting a prospective longitudinal study of infants born to HIV seropositive mothers to determine the natural history of AIDS Dementia in pediatric patients. The study includes neurological, developmental and psychological examinations, including neuroimaging and neurophysiologic studies, as well as immunological studies of the CSF and serum. Finally, investigators at the center are also looking into the contribution of herpesviruses to the development of AIDS Dementia, specifically examining the effects of the transactivating genes of the herpesviruses on HIV expression.7. AIDS Encephalopathy Multidisciplinary Program, USC, Los Angeles, CA, PI Leslie Weiner ($1,005,695, 5 P01 NS26991-02), consists of five research projects investigating: 1) the role of T-lymphocytes in CNS HIV infection, specifically assessing cytokine (TNF-alpha, IFNs, IL-4) production in the CNS and characterizing the population of T-cells involved in the CNS immune response to the virus; 2) the molecular basis of HIV-1 gene expression, specifically examining tat gene expression and its effect in the developing nervous system of transgenic animals; 3) viral and host protein synthesis and their interactions in different neural cell types; 4) the development of novel protein molecules

that can be used as protective vaccines against HIV. This involves the construction of hybrid virus-HLA class I molecules designed to elicit a CTL response against the virus, which will be evaluated in a mouse model, and; 5) the development of retroviral constructs with HIV antisense gene inserts, which will be introduced into mouse hematopoietic stem cells and transplanted into irradiated mice.Intramural Research. NINDS's extramural AIDS budget for 1991 was $11,939,027, leaving the remainderof the AIDS budget for that year, $4,711,973 for intramural research and administrative costs. What followsis a list of the intramural laboratories at NINDS and the projects being pursued in each: Laboratory of Viral and Molecular Pathogenesis: Recombinant Chimeric Glycoproteins andRecombinant Pseudotype Viruses for the Study of HIV Replication and HIV Receptors; Studies of HIV-1Neuropathogenesis; JC Virus Induced Demyelination, Progressive Multifocal Leukoencephalopathy, in theImmunodeficient AIDS Patient; HIV-1 Infection of the CNS in the Pediatric AIDS Patient; Neurotropism ofHIV-1; Viral Gene Therapy for HIV Infections Using Defective Interfering HIV ParticlesLaboratory of Molecular and Cellular Neurobiology: Investigation of the Molecular Pathogenesis ofDemyelination and Myelin Abnormalities in the Central and Peripheral Nervous System of AIDS PatientsMedical Neurology Branch: Neurological Dysfunction and Neuroimmunological Profile in HIV-Positive,Asymptomatic Individuals: A Longitudinal Study; Investigation of the Neuromuscular Diseases Associatedwith HIV Infection; Investigation of Dorsal Root Ganglia in HIV-Positive Patients with and withoutNeuropathy; Characterization of Viral and Cellular Immune Responses in HIV-Related InflammatoryMyopathy; Susceptibility of Human Muscle to HIV Studied in vitro; The Role of HIV Infected Lymphocytesand Macrophages in the Pathogenesis of Human Inflammatory Myopathy; Examination of the Myotoxicity ofAZT in vitro; Screening of Tissue Specimens from Patients with Polymyositis, Dermatomyositis, andInclusion Body Myositis for Retroviruses; Longitudinal Studies on Patients with HTLV-1 Myopathy and T-CellLeukemia; Myotropism for HTLV-1; Distinction of AZT-Induced Myopathy from That Due to HIV; AnimalAZT myotoxicity studies.Laboratory of Central Nervous System Studies; Epidemiology and Virology of Tropical SpasticParaparesis (TSP) and other HTLV-1-Caused Diseases in the Western Pacific; Retrovirus Antibodies inJamaican Schizophrenics; Studies on HIV Positive Chimpanzees Immunized with a Killed HIV Immunogen;Animal Models for AIDS: Investigations of HIV Infected Chimpanzees; Studies on Lower Primates Infectedwith HIV; Hairy Cell Marker in Retrovirus Infected Macaques; Flow Cytometry of SIV Infected Macaques;Studies on HTLV-1 in Rabbits; Development of Simian Model of Neuro-AIDS (project terminated 2/92);Maternal Transmission of SIV (project terminated 2/92); Murine Model of HTLV-1; Isolation andCharacterization of HTLV-1-Related Retroviruses from Remote Population Groups in Melanesia; Detection,Isolation and Characterization of Human Lymphotropic Viruses (HTLV) Among Semi-Isolated AmerindianPopulations of Columbia; Prevalence of Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy(TSP/HAM) in Chile; Isolation of HTLV-1 from Blood and CSF specimens of TSP/HAM and PolymyositisPatients; Immunovirological Studies on HTLV-1 and HTLV-2 in the Pathogenesis of Neurological andSystemic Diseases Other Than TSP/HAM, ATLL and Polymyositis; Detection of the Cytokines, TNF-alpha,TNF-beta, and IL-6 in Lymphocyte Cultures From TSP/HAM and HTLV-1 Associated Polymyositis Patients;Prevalence of TSP/HAM in Columbia and Cuba; HTLV-1 DNA Sequences in Central Nervous SystemTissue of a Patient with Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (TSP/HAM); HTLV-1Infection of Rabbit Monocytes/MacrophagesDevelopmental and Metabolic Neurology Branch: Synthesis of Inhibitors of Protein MyristylationNeuroimmunology Branch; Clinical and Immunological Studies in TSP; Evidence of Retrovirus Etiologyfor Multiple Sclerosis; Cellular Immune Response as Well as Biochemical nd Molecular Analysis of HTLV-1Envelope Gene Products; Assessment of Cellular Immunology Function in TSP, Multiple Sclerosis andRelated Disorders; Assessment of Cellular Immune

Function in Individuals Infected with HTLV-2.Future plans. NINDS had quite a hefty little tome for its FY 1993 wish list, including: Significant expansions* $2.1M for 5 new RPGs (and 2 new FTEs) to study neuro-AIDS in adults and children;* $2.1M for 5 new RPGs (and 2 new FTEs) to study neurovirulent strains of human retroviruses, cofactors affecting the growth of these variants, opportunistic infections, CNS control of the immune response, and viral alterations of nerve cells;* $400,000 for 1 new RPG on HIV's role in neuronal damage, including the effects of cellular toxins, lymphokines and HIV proteins on the nervous system;* $300,000 for 2 new FTEs for intramural research on the neurovirulence of certain viral strains and the mechanism of their molecular control in the nervous system;* $700,000 for 2 new FTEs for intramural research on neurotoxins produced by HIV+ cells in the CNS, mechanisms of action and treatments for neurological HIV manifestations;* $1.8M for 1 new FTE for intramural research ($1,000,000) and to further support cooperative clinical research ($800,000) on the assessment of 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;* $300,000 for 1 new RPG to identify other retroviruses which affect the central and peripheral nervous systems and define clinical, pathological and immunological parameters; New Efforts* $1M for 3 new RPGs to study HIV's effects in the developing CNS and its role in the pathogenesis of pediatric AIDS;* $1M for 3 new RPGs to work with the ACTG to identify and evaluate treatments for the neurological aspects of AIDS and assess the neurological side effects of new drugs;* $1M for 3 new RPGs to study prevention and control of neurological disease in kids with AIDS;* $400,000 to develop better animal neuro-AIDS models;* $800,000 for 2 new RPGs to study effects of HTLV-1 on the CNS, including the function of infected T-cells, and to molecularly characterize viral genetic sequences and expression;* $3M for 3 new RPGs to support centers studying large populations of PWAs, with a particular emphasis on children and people of color; longitudinal studies will assess early neurological effects and the effects of maternal immune response on transmission to neonates;* $1M for 6 new FTEs for intramural research, 3 on neuroimmunological response to retroviral infection and 3 on HIV-1 products in neural (and lymphoid) cells, to develop new assays and reagents to detect low levels of HIV infection in CNS cells;* $400,000 for one new contract to develop a better non-human (non-chimpanzee) primate and smaller animal models for the study of HIV and other human retroviruses in the brain.With a 7.9% budget increase for FY 1993, NINDS may be able to fund only a fraction of these programs.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-associated and drug-induced neuropathies and myopathies, as well as 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;* NIND S has proposed a novel way of funding new initiatives in AIDS and other diseases. Most I nstitutes fund many large gran ts which run for several years. Therefore, research monies are locked into research projects funded several years earlier. This prevents the rapid allocation of funds to new, cutting edge areas. The NINDS has recently implemented a policy to cap large research grants at $750,000. While this new policy has many (potentially) negative ramifications, it does

allow more money each year to fund cutting edge projects. For this reason, the NINDS must be commended for attempting to preserve quality, relevant research in a time of drastic funding cut-backs. * Again, the NINDS has lead the way for the other Institutes by implementing a collaborative neuro-AIDS research project with the NIAID. The NINDS is independently funding neurologists within NIAID's ACTG system to perform scientifically integr ated, but financially autonomous, projects. This should serve as a model for other Institutes.Contact: Carl Leventhal, MD Director Division of Demyelinating, Atrophic and Dementing Disorders NINDS, NIH * II/7. National Institute of General Medical Sciences NIGMSEstablished in 1963, NIGMS It supports 6 extramural basic biomedical research and training programs [ithas no intramural research of any kind]: Cellular and Molecular Basis of Disease Program; GeneticsProgram; Pharmacological Sciences Program; Biophysics and Physiological Sciences Program; MinorityAccess 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 directorof the NIH Office of Research on Women's Health. NIGMS first awarded $180,000 for AIDS in 1987, andnow provides over $15 million in extramural research and training awards. The NIGMS program of AIDS-related research focuses on efforts to design drugs for the treatment of HIV infection on the basis of knowledge of the three-dimensional structures of various viral proteins. This approach relies on the field of structural biology, in which the relationship between the form and function of biologic materials is studied by use of the sophisticated techniques of X-ray crystallography and theoretical chemistry directed toward molecular modeling. Additionally, the NIGMS supports training programs in structural biology.The NIGMS extramural FY 1991 AIDS obligation of 81 awards totalling $15,548,253 was divided into $9.7Mfor "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 readingunless you are a synthetic chemist. 30 abstracts for awards totalling $9 million are on-line in CRISP forR01 and P01 awards. Six P01 awards (Research Program Projects) totalling $5,191,352 and involving atleast 21 subprojects in which heavy duty high-tech molecular biology is brought to bear on the problem ofelucidating the shape of HIV proteins in their native forms and when bound to substrates, and developingpharmacological agents to inhibit viral enzymatic activity. 17 R01 awards (traditional research projects) andone 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-raycrystallography, 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 ofboradeoxyribonucleosides (in which boron replaces carbon in deoxyribonucleosides), synthetictransmembrane anti-HIV agent carriers, comparison of antigenicity of differentially glycosylated peptides byT- and B-cells, glycosidation inhibitors, synthesis of avarol derivatives, and the role of the "zinc finger"amino acid sequences of retroviral gag proteins. 51 abstracts are missing for $6 million in training awardsand interagency agreements. Because these abstracts are missing, and their listed titles uninformative, itis unclear how, if at all, these awards - especially the training awards - relate to AIDS. Abstracts are not available in electronic form (DRG CRISP system) for Activity Codes that begin with F and T. These are Fellowship and Training respectively... Descriptions may be available from the individual ICD [No, they are not].NIGMS and OAR should make efforts to put these abstracts on-line. The training awards are intended tohelp fill the gap in qualified basic researchers: The issue of research training as related to the problem of AIDS is simply the issue of providing sufficient numbers of

adequately trained personnel to conduct the basic and clinical research needed by this country... The skills required are in the areas traditionally supported by NIH in cell biology, immunobiology, molecular biology, etc. In particular, the field of structural biology was identified as being of special importance for the AIDS effort due to its central role in developing the capabilities for targeted drug design, and because of the shortage of manpower relative to demand in this area of research... A similar shortfall has since been recognized in the areas of synthetic organic chemistry, mechanistic chemistry and physical chemistry as applied to biological systems...3 S06 Minority Biomedical Research Support (MBRS) Grants are not among the ARIS-listed grants,though they are in the abstracts. These grants are intended "to strengthen the biomedical research andresearch training capability of ethnic minority institutions," and are in this case supporting work at FiskUniversity, at Rio Piedras in Puerto Rico and somewhere unknown. Two subprojects are AIDS-related.Recent Progress. NIGMS held its Sixth Meeting of Groups Studying the Structures of AIDS-RelatedSystems 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-pseudomonasexotoxin as an antiretroviral agent, gag proteins, integrase, tat, rev and protease. Eddy Arnold presentedthe 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 drugdesign and related structural biology in FY 1992, and $10.8 million in FY 1993. $5.825 million will be spenton these training grants in FY 1992 and FY 1993. NIGMS requested $14,500,000 in new funds for FY1993, but the President awarded just $912,000. The 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. *Contact: Marvin Cassman, PhD Deputy Director NIGMS, WB/909 301/496-0186 301/402-0019 FAX * II/8. Office of the NIH Director ODThe NIH Director "gives overall leadership to NIH activities and maintains close liaison with the DHHSAssistant Secretary for Health in matters relating to medical research, research training, health professionseducation and training, manpower resources, and biomedical communications... He [sic] also maintainsclose communications with other constituents of DHHS in order to provide more effective programrelationships. The current NIH Director is Bernadine Healy MD, who took office in April 1991. After hergraduation from Harvard Medical School in 1970, Dr. Healy completed her internship at Johns Hopkins,where she joined the faculty in 1976. She remained at Johns Hopkins until 1984, practicing and conductingresearch in cardiovascular disease. She directed the JHU Coronary Care Unit and served as assistantdean for postdoctoral programs and faculty development. Dr. Healy became deputy director of WhiteHouse Office of Science and Technology Policy (OSTP) from February 1984 to November 1985. Beforecoming to NIH, Dr. Healy was chairperson of the Research Institute of the Cleveland Clinic Foundation.The NIH has three Deputy Directors, including one each for Intramural and Extramural Research, andseven Associate Directors for Disease Prevention, AIDS Research, Clinical Care, Research Services,Science Policy + Legislation, Administration and Communications. Anthony S. Fauci, MD, became the firstAssociate Director of the NIH for AIDS Research in 1988. Previously (since 1985), he had been the NIHAIDS Coordinator. In 1988, the Office of AIDS Research (OAR) was established within the Office of the NIHDirector and Dr. Fauci became Director of the OAR as well. He has been

chief of the Laboratory ofImmunoregulation, NIAID since 1980 and Director of NIAID since 1984. One man, four hats.For FY 1986, its first year of AIDS funding, the NIH Office of the Director (OD) received $73,000 for AIDS-related activities. Since then the OD's AIDS budget has grown considerably, though it is currently slowing. In FY 1991, the OD received $11,737,000 for AIDS. This will rise to $13.7M in 1992. The OD requested$14,677,000 for AIDS activities in FY 1993. The NIH actually increased the OD's request to $17,361,000before sending it on to PHS. No other ICD had its budget request increased by NIH. It's good to be thedirector, isn't it? However, by the time the budget got back from the Oval Office, the OD is offered$14,372,000, just a small increment over current services. The OD ranks 8 among the NIH ICDs in AIDS:NIH OD AIDS Expenses FY 1991 ID1 Drug Development $10,126,000 IF1 Training 1,924,000 IIC4a3 Treatment trials info. services 1,193,000 OD AIDS Total $13,243,000AIDS Programs. The OD's AIDS budget supports the Office of AIDS Research (OAR), the Intramural AIDSTargeted Antiviral Program (IATAP), the Protein Expression Laboratory (PEL) and personnel within otherOD divisions who work on on AIDS-related activities.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 is Jack Whitescarver, PhD. Thefunctions and responsibilities of the OAR 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 informationstrategies with interagency collaboration to inform the public of NIH and PHS AIDS research activities; torecommend solutions to ethical/legal issues; to foster national and international information exchange withgovernment, industry, and academia concerning AIDS research; to manage the NIH Loan RepaymentProgram for AIDS researchers.The OAR coordinates the meetings of the AIDS Program Advisory Committee (APAC) which advises theHHS Secretary, the Assistant Secretary for Health, the NIH Director and the Associate Director for AIDSResearch on short- and long-term planning needs for AIDS research. 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 ofMedicine. A November 1991 DRAFT "Strategic Plan" was presented to the APAC, then revised and sent tothe Directors, AIDS Coordinators and intramural scientists at the 18 ICDs for comment and review. Furtherrevisions will take place this summer.OAR has also developed the AIDS Research Information System (ARIS), a database containing informationon all NIH AIDS research projects funded since FY 1989. This report could not have been written withoutthe information centralized and made accessible through ARIS and its able creators, Stan Katzman andLinda Reck.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) toresearchers recruited to conduct intramural AIDS research. Thirty-four researchers have participated in theprogram, including physician/scientists from NIAID, NCI, NINDS, NICHD, NIDR, NEI, NHLBI and the ClinicalCenter. OAR estimates that 20 new participants will enroll in the LRP in FY 1992 and 20 more in 1993.The OAR has been extremely helpful to TAG in our efforts to analyze the NIH's AIDS research programsand policies. Gregg Gonsalves, Mark Harrington and Derek Link of TAG first met with Dr. Whitescarver inFebruary 1992 to discuss the AIDS budgetary and research policy development process at NIH. Meetingswere also held at that time with Stan Katzmann and Linda Reck of the OAR, who introduced us to the ARISsystem. Since then they have sent us all of the grants for AIDS research at NIH and other supportingmaterial for this report and have expedited our contacts with the Institute AIDS coordinators.The OAR, although vested with the responsibility to coordinate AIDS research at NIH, has not been giventhe power or developed a mechanism for doing so. The only real power lies in the hands of those who

setbudgets, who are the Institute Directors. Healy has an additional $20 million discretionary fund (nowrenamed "high priority" fund), but OAR itself has no direct power to reallocate programs or resourcesacross institutes. While the forthcoming "Strategic Plan" may be a step in the right direction, the drafts circulated thus far area catalogue of NIH's current efforts without any analysis of how the program can be improved, whereresources need to be increased, where new initiatives are necessary, what evaluation measures should beused, or what timelines should be imposed. Although OAR coordinates several advisory committees, none seems to be concerned with detailedevaluations of existing programs. Broad research priorities are legislated or pressured by Congress and theExecutive branch (e.g. pediatrics, opportunistic infections, vaccines) or by crises that can't be ignored anylonger (e.g. tuberculosis). Although the budget process passes through the OAR, the institutes retaincontrol over appropriations when the money is disbursed.While it is an old and maybe tiresome complaint, Dr. Fauci's many responsibilities are unlikely to leave himmuch time to concentrate on the responsibilities of the OAR. Dr. Fauci's stature in the research communityand his position as director of NIAID, however, give the OAR a legitimacy which it might not enjoy with alesser figure at its helm. As director of NIAID, Dr. Fauci also has a theoretical conflict of interest since hecuts the AIDS budgets of other institutes. At the same time, though, he has no authority to compel anyinstitute other than the NIAID to change its budget priorities once money is disbursed. The ARIS system is new and can be improved upon. Mason categories, while useful in budgetaryadminstration, do not accurately categorize NIH programs for research policy review. There is a great needto track projects with keywords, to generate more flexible and user-friendly formats, and, perhaps, togenerate an annual "NIH AIDS Resource Book" summarizing its AIDS Programs in a more accessibleformat. Moreover, OAR should work with NLM to develop a system to track the productivity of NIH AIDSgrantees by cross-referencing researchers with their recent publications in the peer-reviewed literature. Finally, ARIS should be available to all users on-line.Intramural AIDS Targeted Antiviral Program (IATAP). The IATAP supports basic research on thestructure and function of HIV. Currently, 49 teams from 12 institutes are supported by IATAP. Usingstructural biology and molecular biochemistry techniques, IATAP researchers are attempting to elucidatethe structure of HIV proteins, the molecular mechanisms of action of viral enzymes, the mechanisms ofviral DNA integration, proviral activation and gene expression, and the cellular processing and modificationof viral peptides necessary to assemble complete functional virions. This may help in the design of newtherapies to block various steps in the viral life cycle. This work may also identify new molecular targets forantiviral agents and new methods for drug screening. Recent accomplishments of intramural IATAPresearchers include:* 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;* Development of a simple assay for the activity of the HIV integrase, which can be used to screen inhibitors of the enzyme;* Discovery of additional mechanisms for the high rate of error in HIV reverse transcription;* 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 inbringing highly-talented NIH researchers into AIDS research for the first time is a notable achievement aswell. This model should be duplicated for other AIDS research areas, especially those which lack thealready high level of support and scientific interest that molecular and structural biology have. A similarprogram should be created for research on the immunopathogenesis of HIV infection, the etiology andtreatment of the wasting syndrome, and numerous other "orphan" research topics.The Protein Expression Laboratory (PEL). The Protein Expression Laboratory was established under theaegis of the OD to support the work of the IATAP and is staffed by two senior NIH scientists, threetechnicians and a

secretary. The purpose of the PEL is to provide highly purified HIV proteins, includingRNase H, reverse transcriptase, rev, tat, protease and integrase, for the IATAP's structural, physiochemicaland pharmocological studies.Personnel. The OD's AIDS budget supports 42 FTEs. Twenty-one are within the OAR. The remaining 21FTEs work for:* Protein Expression Laboratory (PEL) - 6 FTEs;* Division of Financial Management - 1 FTE [tracks AIDS budget];* Division of Legislative Analysis - 2 FTEs ["so that's what Senator Metzenbaum wanted!"];* Division of Contracts + Grants - 5 FTEs [oversees expedited award of AIDS-related contracts + grants];* Division of Personnel Management - 5 FTEs [recruits for AIDS positions NIH-wide];* Office of Protection from Research Risks (OPRR) - 2 FTEs [reviews human subjects protections and certificates of confidentiality for all AIDS projects.]Future Plans. The OD does not contribute to the wish lists for annual budget requests - they review thewishes of the ICDs. The small increase in the OD's budget for FY 1993 will be used to maintain currentprograms and services.Recommendations. Aside from the comments above, recommendations for the OD will largely reflect therecommendations made for the NIH as a whole in our final report.Contacts: Dr. Jack Whitescarver, PhD Deputy Director OAR, OD, NIH 301/496-0357 Linda Reck Senior Program Analyst OAR, OD, NIH 301/496-0358 Stan Katzmann ARIS, OAR, OD, NIH Wendy Wertheimer Program Analyst OAR, OD, NIH * II/9. National Institute of Dental Research NIDRThe Public Health Service created a Dental Hygiene Unit in 1931. The PHS DHU pioneered the study offluoride on tooth decay, leading to widespread and controversial fluoridation of drinking water in the US. In1948 the National Dental Research Act (P.L. 80-755) created the NIDR. Currently NIDR studiesperiodontal and soft tissue diseases, craniofacial anomalies, pain control, behavioral research, caries,restorative materials, bone research, immunology, salivary function, and microbial ecology. The currentNIDR Director is Harald Loe, DDS, DO, who was designated an honorary Knight of Danebrog in 1972 bythe Queen of Denmark. NIDR's support for AIDS research dates back to 1982, when it provided $25,000. This rose to $1.7 million in 1986 and to $6.2 million in 1991. NIDR researchers spent $2.6 million onintramural research and program support in 1991. NIDR supports investigation in the following areas:* Investigating parallels and differences between Sjogren's syndrome and HIV-associated salivary gland disease. Salivary secretions from HIV-1 positive patients with salivary gland enlargement (HIV-SGD)... were analyzed. Higher elevations of salivary IgA, lactoferrin, and IgA rheumatoid factor (RF) were present in HIV-SGD patients than in HIV-1+ patients without SGD. However, the saliva from patients with Sjogren's syndrome had much higher levels of salivary IgA, lactoferrin, and IgA RF. 44% of patients with HIV-SGD also had salivary autoantibodies that recognized the cytoplasm of a salivary epithelial cell line, but the autoantibodies were not anti-SS-A, anti-SS-B, or anti-DNA... HIV-1 proviral sequences were found in 50% of whole saliva samples from HIV-positive patients...* Cloning the HIV genome into transgenic mice to determine the role of various viral proteins on murine cells and tissues; * NIDR's Laboratory of Immunology is 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 NIDR grantees have found that different fractions of saliva exhibit varying degrees of anti-HIV activity: Submandibular/sublingual saliva has a greater inhibitory effect than did parotid saliva... HIV inhibitory activity was present even at a 1:32 dilution of the original sample, and an increased inhibitory effect was seen with submandibular saliva as the time of exposure was increased from 2 to 60 minutes.NIDR

researchers are also examining other vital bodily fluids: Tears and saliva alike exhibited modest 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.In 1991, NIDR spent $3.7 million on 18 extramural awards. These included six epidemiological studies ofthe oral manifestations of AIDS (totalling $1,773,710, including two in monkeys, one in the Army and one inhemophiliac children), six studies of antiviral (anti-HIV, HSV, CMV, EBV) factors in human saliva($1,172,064), four studies ($506,008) of candidiasis, and one study each of monocytes ($183,955) and oforal drug delivery systems ($21,183). The epidemiological studies are intriguing. Increased levels of treponemes and mycoplasmas are found in [periodontal pockets of] the HIV group... The variance in the types of bacteria found in individual subjects is three times greater than that of the noninfected group, indicating the presence of more species of bacteria in the sites tested. Two newly named species of lactobacilli uniquely associated with the oral cavity are found in significantly higher numbers and represent 5 to 7% of the total cultivable flora. Attempts are under way to determine whether mycoplasmas are prevalent in the oral soft tissue lesions.Three months later, additional progress was reported. All plaque samples from HIV-infected subjects with gingivitis and moderate periodontitis have now been processed... The oral lesions of HIV-infected subjects... are being screened for common viruses, oral bacteria, and fungi. Bacterial samples are being processed by the Department of Anaerobic Bacteriology at Virginia Polytechnic Institute and State University... The NIDR oral health research facility at [Walter Reed] has completed its second year of operation. More than 525 of an anticipated 1,000 HIV+ subjects have volunteered for the study to date. Approximately 375 subjects have received their initial oral examinations and approximately 125 of these have received one or more 6-month follow-up examinations... Oral candidiasis occurred in 16% of subjects and oral hairy leukoplakia in about 14%... Candidiasis was also associated with current tobacco use. Erythematous gingival banding was present in 49% of the subjects... Papillary destruction was present in 25% of subjects and was more extensive in earlier stages of infection...Funding + Future Plans. NIDR ranks 9 of 18 ICDs at NIH, spending $6,214,000 on AIDS in FY 1991 -4.4% of its total budget (and 0.8% of the NIH AIDS budget). Of this, $3.7M went for 18 extramural awardsand $2.6M for intramural programs. Of the extramural awards, $3.3 million went for immunology studies,and $310,313 for studies of natural history and cofactors. NIDR's AIDS budget for FY 1992 was $6.538M. 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 requestfor FY 1993 were the following new programs:* $2.9 million 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.* $530,000 for intramural studies of how virus-host interactions involving infected T cells, HIV genes and host tissues may lead to Kaposi's sarcoma, central neuropathology and nephropathy. This would support 3 new FTEs.* $480,000 for new intramural and contract studies of the neuroimmunologic manifestations of AIDS, including the possible role of monocytes/macrophages in neuropathology and AIDS CNS dysfunction. This would support 4 new FTEs.* $420,000 to develop new antiretroviral therapies by using cell surface antigens to target infected cells without damaging uninfected tissue. This would support 2 new FTEs.Recommendations:* Congress should replace the missing $2 million 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 a clinical trial of thalidomide for aphthous ulceration. Contact: Ms. Joan Wilentz, NIDR NIH Building 31, Room 2C36 301/496-6705 FAX: 301/496-9988 II/10.National Institute of Diabetes + Digestive + Kidney Disorders NIDDKNIDDK began in 1950 as the National Institute of Arthritis and Metabolic Diseases (NIAMD) and wasoriginally chartered to investigate rheumatic diseases, diabetes and other metabolic, endocrine andgastrointestinal illnesses. In 1972, it became the National Institute of Arthritis, Metabolism and DigestiveDiseases (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 Diseasesspun off to form NIAMS. NIDDK's Division of Intramural Research supports investigations of a wide varietyof diseases, including diabetes, other inborn errors of metabolism, endocrine disorders, mineralmetabolism, digestive diseases, nutrition, urology and renal disease, and hematology. The NIDDK DIRstudies biochemistry; nutrition; pathology; histochemistry; chemistry; physical, chemical and molecularbiology; pharmacology; and toxicology. NIDDK's extramural research is administered by four subdivisions:(1) Diabetes, Endocrinology and Metabolic Diseases; (2) Digestive Diseases and Nutrition; (3) Kidney,Urologic and Hematologic Diseases; and (4) Extramural Activities.NIDDK spent $495,000 in its first year of AIDS research in 1987. In 1988, its AIDS budget grew over sixfoldto $3.33M, and it has grown steadily since then. In FY 1991, NIDDK received $6,290,000 and this year$6,382,000. For FY 1993, NIDDK asked for approximately $10M in new funds. The DHHS cut the requestto $6.7M, and the President offered $6.8M. While the final appropriation is drastically below what wasrequested by the institute, NIDDK is one of the few ICDs to obtain an AIDS budget increase over the rate ofinflation (it's 7%). Only NIDR and NINDS received higher percentage increases for FY 1993. NIDDK'swork focuses on immunology ($5.2M in FY 1991) and preclinical drug development ($1 million). NIDDKsponsors a range of studies of endocrine, metabolic, gastrointestinal, renal, urologic and hematologicalcomplications of HIV and AIDS. The wasting syndrome receives more attention from the NIDDK than fromany other ICD. NIDDK also conducts and supports studies on basic mechanisms of HIV infection, thestructure of HIV and the development of antiviral therapies.Extramural Research. In FY 1991, NIDDK funded 33 research project grants, all R01s, at a cost of$5,243,679. All the grants were classified as immunology. Since 1987, NIDDK issued 6 AIDS RFAs: * Pathogenesis of Intestinal Dysfunction in AIDS; * Effects of HIV Infection on the Kidney and in Dialysis and Renal Transplant Patients; * Genitourinary Tract Manifestations of HIV; * Pathobiology of Bone Marrow Suppression in AIDS and ARC; * Endocrine Aspects of AIDS; Endocrine Basis of Wasting in AIDSNutrition + Wasting. Some grantees are investigating diagnosis, etiology and treatment of HIV-relatednutritional and metabolic disorders, measuring body composition, caloric intake, energy expenditure, andmetabolism in adults and children with HIV: Body composition is being measured using neutron activation analysis, whole body potassium 40 counting, and assessment of total body water, as well as intracellular and extracellular compartment water. These studies have demonstrated that AIDS patients have a greater loss of body cell mass than would be predicted by their degree of weight loss alone. The results of body composition analysis are being correlated with parameters reflecting immune function... Elevated resting metabolic rates have been reported in AIDS patients.

Hypertriglyceridemia has been found and may precede weight loss. In studies of caloric intake and nutritional status in an HIV-infected population free of confounding gastrointestinal problems, researchers found a relative caloric deficiency in HIV-infected patients. These studies show a somewhat worse nutritional status for AIDS patients than for HIV-infected patients without AIDS but a greater caloric intake in the AIDS group. A strong relationship between nutritional status and immunological function suggested that dietary intervention should be considered early in the disease. NIDDK researchers are also investigating the nutritional and metabolic disorders found in HIV infection,including abnormalities in intestinal enzymes, perturbations of normal intestinal flora, endocrine andcytokine dysregulation as contributing factors to wasting and other metabolic disturbances: Most HIV-positive children with gastrointestinal symptoms have evidence of disaccharidase deficiency and/or bacterial overgrowth as evidenced by breath hydrogen analysis. Dietary modification, after evaluation of gastrointestinal function and nutritional status, has resulted in improved growth for these children... Impaired adrenal function may occur in 5-10% of AIDS patients. Adrenal pathology is common at autopsy and hypothalamic pituitary involvement is likely. Several groups are conducting carefully controlled prospective studies of adrenal function at various stages of HIV infection to elucidate the pathogenesis of adrenal dysfunction. In addition, HIV and AIDS patients have been found to have a unique pattern of thyroid function tests. Usually T3 levels are low in patients with serious illness and rT3 levels are increased. However, this pattern is not seen in HIV+ and AIDS patients, in whom inappropriately depressed rT3 and failure to decrease conversion of T4 to T3 have been reported. The researchers postulate that cytokines or other immune mediators may have direct effects of thyroid hormone metabolism with the net result that, in HIV and AIDS patients, a mechanism to spare metabolic demands in time of stress may be impaired... NIDDK-supported researchers examining the possible role of cytokines in mediating AIDS-associated weight loss and metabolic disturbances found significantly elevated levels of interferon-alpha in AIDS patients, as well as a significant correlation between interferon alpha and triglyceride levels. This study suggests that interferon alpha, which is known to moderate lipid metabolism, may be responsible for elevated triglyceride levels that are characteristic of AIDS.NIDDK grantees are also working on nutritional interventions for AIDS and evaluating parenteral nutritionaltherapy.In September 1990, the PHS "Strategic Plan for HIV/AIDS" called for an increased research emphasis onwasting and other nutritional deficiencies associated with AIDS. The NIH's AIDS Program AdvisoryCommittee (APAC) echoed the recommendations of the PHS on this matter. In FY 1991, seven NIDDKgrants were funded for research on wasting and other metabolic and nutritional disorders at a total cost of$1,160,983. For FY 1993, NIDDK put research on wasting at the top of its wish list and asked for money tofund 13 new grants in this area. PHS and DHHS cut NIDDK's budget request back to funding levels only2% above the scientific inflation rate of 5%. This is lip service at its worst. First the PHS recognizesresearch on wasting as a priority and then refuses to fund it. Let's have a big glass of TNF and IFN-alphafor Mssrs. Mason, Sullivan and Darman. Drink up, boys.In 1991, NIDDK grantees also conducted studies on how TNF and IL-1 contribute to metabolic dysfunctionin 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 opportunisticsequelae in the digestive system. This work has focused on studies of GI cell infection by HIV, thephysiological basis of AIDS enteropathy, the pathogenesis of cryptosporidiosis, and liver damage: Human gastrointestinal (GI) cells may serve as a primary replication site or reservoir for HIV. In recent studies, researchers infected cultured epithelial and submucosal (SM) cells from

human colon and small intestine with four strains of HIV. All four strains could replicate in the GI cells, but susceptibility and infective potential varied depending on the host cells and the virus tested. Preliminary findings from the epithelial cell cultures indicate that HIV infection can alter membrane transport and cell growth and differentiation. Findings from studies to assess angiogenesis in SM cell cultures suggest that HIV infection of the SM cells mimics several features of Kaposi's sarcoma. The SM model has potentially important clinical implications, since the GI tract is a common site for Kaposi's sarcoma in AIDS patients... NIDDK grantees have been conducting studies on the intestines in patients with AIDS enteropathy. AIDS enteropathy has been attributed to the wasting and chronic diarrhea of HIV-infected persons who have no identifiable enteric organism. To better understand the mechanism of intestinal diseases associated with HIV infection, investigators have studied the level of stomach acid production in HIV infected individuals, since acid is protective against bacteria. In their study, AIDS patients with diarrhea all had low gastric acidity associated with high gastric bacterial counts and also opportunistic enteric pathogens. The cause of the hypoacidity is not yet known, but the implication is that this may contribute to the enhanced susceptibility to enteric pathogens due to loss of the "gastric barrier..." NIDDK grantees are also studying various microbial agents that may be involved in the diarrhea associated with HIV infection. For example, investigators are developing a pig model for the study of diarrhea caused by the ileal infection with the parasite Cryptosporidium parvum. They have found that, in this model, the diarrhea appears to be a malabsorptive disease associated with tissue damage rather than with impairment of the absorptive mechanism. Because the neutral sodium chloride absorptive mechanism was fully intact in infected ileum but the sodium-coupled glucose transport was impaired, studies were conducted in an attempt to stimulate sodium chloride absorption. Glutamine, which had been shown to stimulate neutral sodium chloride absorption in pig jejunum, was added to indomethacin-treated Cryptosporidium-infected ileum tissues. Mucosal addition of glutamine increased net sodium absorption to a much greater extent than could be achieved with addition of mucosal glucose in the infected tissue. Thus, glutamine may be a useful oral therapy for rehydration in this disease... A prospective study was undertaken to define the pathology, course, and pathogenesis of liver disease in rhesus monkeys after intravenous inoculation with simian immunodeficiency virus (SIV). The data indicate that the liver is involved early during the course of SIV infection. Infection is followed by persistent changes until the terminal stage of the disease. The findings suggest that the liver damage in SIV-infected monkeys is similar to that observed in AIDS patients.Despite the voluminous documentation above, the actual work supported in 1991 on the effects of HIV andOIs on the GI system amounted to just two grants costing $331,992. The two grants, "HIV Infection ofIntestinal Epithelium" (5 R01 DK40582-04, $164,932, M. Kagnoff-UCSD) and "CD4 Cell Deficiency andIntestinal Immune Responses" (5 R01 DK42418-02, $167,060, J. Cowdery-U Iowa), are investigating,respectively, the interactions between cytokines, HIV, and the intestinal epithelial cell in the pathogenesis ofAIDS related diarrhea; and IgA loss and CD4+ cell depletion in the gut.NIDDK wanted to award ten new grants in FY 1993, but the expansion of their programs was rebuffed byPHS, DHHS and OMB. If these additional funds were forthcoming, studies of the gastrointestinal mucosalimmune response in HIV infection, the dynamics of retroviral infection in the gut, the mechanisms of AIDSenteropathy, and malabsorption, could be funded. Additionally, more funding would allow studies in thefollowing critical areas: * Microsporidiosis; * Enteropathic/enteroadherent E. coli infection * Herpes virus 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 tractEndocrinology. In 1991, NIDDK funded 11 grants on the neuroendocrine-immune interactions in HIVinfection: * POMC peptide synthesis by normal and AIDS leukocytes, $141,829, D. Orth, Vanderbilt U., Nashville, TN (5 R01 DK41043-03); * Effects of androgens on the thymus, $96,361, N. Olsen, Vanderbilt U., Nashville, TN (5 R01 DK41053-03); * Steroid hormones, HIV-infected cells and HIV genes, $142,419, B. Thompson, U-TX, Galveston, TX (5 R01 DK41058-03); * Neuropeptide interactions with HIV-infected macrophages, $103,074, J. Mills, UCSF, San Francisco, CA (5 R01 DK41059-03); * Feline retrovirus associated endocrine dysfunction, $117,515, J. Rojko, Ohio State U., Columbus, OH (5 R01 DK41066-03); * Monokines in control of hypothalamic-pituitary axis, $138,582, S. McCann, U-TX, Dallas, TX (5 R01 DK409994); * Adrenocortical control in patients with HIV infection, $41,166, J. Findling, Medical College of WI, Milwaukee, WI (5 R01 DK41015-03); * Immune-adrenal axis in AIDS, $217,330, J. Melby, University Hospital, Boston, MA (5 R01 DK41016; * Prenatal viral infection and neuroendocrine development, $105,169, M. O'Grady, U-South Florida, Tampa, FL (5 R01 DK41025-03); * Effects of HIV on the immune and neuroendocrine axis, $141,659, E. Smith, U-TX, Galveston, TX (5 R01 DK41034) * Regulation of neuro-immuno-endocrine cells, $135,461, M. Melner, Medical Research Foundation of Oregon, Portland, OR (5 R01 DK41035-03).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 endocrineabnormalities. NIDDK support of this research is commendable. NIDDK wanted to fund an additionaleleven grants in this area for FY 1993, but of course can not in the current fiscal climate. There is an urgentneed for more work on this topic. Specifically, further research is necessary on the role of the thymus, theeffects of neuroendocrine hormones and peptides on lymphocyte development and function, and on theregulation of the immune response in HIV infection.Kidney + Urologic Disease. NIDDK is supporting research on HIV infection of the genitourinary tract andthe renal complications of AIDS: A team of grantees has determined recently that men whose blood is positive for HIV may excrete the virus in their semen during early HIV infection. Furthermore, while HIV was isolated from the semen of only one third of men whose blood showed HIV infection, its presence in the semen could not be predicted by factors such as whether the men had symptoms of disease or whether they were receiving zidovudine therapy... Results of studies of renal biopsies form HIV-infected patients suggest that HIV infection of kidney tissue may be an important determinant of the pathogenesis of glomerulonephritis, a disease process that damages the kidney's filtering system. Findings indicate that the glomerulonephritis in HIV-infected patients may be associated with in situ HIV immune complex formation, perhaps secondary to modification of cellular protein after viral infection. Other grantees are attempting to establish a relevant animal model for the study of the principal renal lesion associated with HIV infection: focal and segmental glomerulosclerosis with endothelial tubulorecticular inclusions. Their studies focus on comparative nephrology in human and simian AIDS... Grantees are also seeking to identify potential surface cell markers for HIV in various renal cell subpopulations. They hope to identify glomerular cell populations infected with HIV, correlate HIV infectivity and surface cell receptors, and use blocking antibodies to study the role of surface cell receptors in HIV infection... Studying a population of infants and children of HIV-positive mothers, other investigators are examining the occurrence of proteinuria and hyponatremia, assessing renal histology, determining glomerular volume, and searching for viral particles in renal tissue.NIDDK grantees are also studying the effect of cytokines on glomerular epithelial cell pathology, the effectof vasectomy on transmission of HIV, and the results of kidney transplants among patients with HIV.In 1991, NIDDK funded five awards for genitourinary and kidney AIDS research at a cost of $1,386,469. NIDDK wanted to add two new grants in 1993 to study HIV transmission and the genitourinary

tract,elucidate the sites of virus replication and transmission and the factors which affect transmissibility andviability of the virus. However, the money needed to conduct these studies was cut from the NIDDK'sbudget. Another topic worthy of support and not currently part of NIDDK's portfolio is the renal toxicities ofmany drugs currently in use in HIV infection. Of interest and deserving of further investigation are theeffects of kidney transplant on HIV infection (NIDDK currently support a grant on the effects of HIV onkidney transplants [abstract not supplied]). What, if any, effect does the immunosuppressive therapy usedin transplantation have on the course of HIV infection?Hematopoiesis. NIDDK supports several grants which are looking into hematopoietic function in HIVinfection and the effects of antiretroviral therapy with AZT on the bone marrow: Now, it has been demonstrated that megakaryocytes - the cells that produce platelets - can become infected [with HIV]. This finding could explain the severe decrease in blood platelets common in patients with AIDS. Investigators are attempting to infect normal megakaryocytes with HIV in the laboratory to learn at what stage in development the infection occurs. Other studies are under way to determine the pathway of the infection... Grantees are studying the effects of HIV infection of mononuclear phagocytes, which regulate hematopoiesis and through production of several growth factors. AIDS patients commonly exhibit disorders of hematopoiesis, and investigators hypothesize that the disorders are the direct result of infection of mononuclear phagocytes by HIV. Other studies are under way to investigate the alteration of gene expression caused by HIV infection of myeloid cells, the effects of drugs in the modulation of HIV expression in those cells, and the mechanism of HIV-mediated suppression of myeloid cell growth.NIDDK's work in this area for 1991 largely focussed on the pathogenesis of 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 progenitorcells. Other work focused on the effects of AZT, acetaminophen, and other drugs on the production anddifferentiation of myeloid and erythroid progenitor cells. NIDDK supported eight grants in this area inFY1991 at a total cost of $1,083,670. For 1991, NIDDK requested $741,000 for three additional grants onbone marrow function in AIDS. While NIDDK's efforts should be applauded, since the institute has a smallAIDS budget, it might be wiser to leave support of studies in this area to the larger institutes sponsoringinvestigations 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, whichhave little support outside of NIDDK.Other Work. NIDDK listed some accomplishments for 1991 which were not listed in that year's awards: NIDDK grantees have discovered a new brain hormone which activates neuronal and pituitary cell membrane adenyl cyclase, stimulating production in these cells of an important chemical messenger, cyclic AMP. Cultured brain cells treated with this hormone were shown to be protected from infection with HIV... In collaborative studies with the NIAID, an NIDDK grantee has found that chemical compounds called thiols can suppress the activity of HIV. [...] The investigators found that pretreatment of these cells with the thiols - glutathione, glutathione ester, or N-acetylcysteine - suppressed in a dose-dependent fashion the induction of HIV expression mediated by the known inducers. The thiols suppressed HIV reverse transcriptase activity, induction of total HIV protein synthesis, and the accumulation of HIV mRNA.Intramural Research. In FY 1991, NIDDK allocated $1,046,000 for intramural AIDS research. For FY1992, NIDDK is lowering its intramural AIDS budget to $757,000, with a slight rise to $812,000 in FY 1993. NIDDK's intramural efforts are largely focused on elucidating the structure of HIV, expression of its genes,the function of its proteins, and the development of antiretroviral agents. "No NIDDK intramuralinvestigators work uniquely on AIDS-related questions; rather, they apply the expertise of their laboratoriesto

specific AIDS-related problems." Non-AIDS funds for the intramural laboratories at NIDDK probablysupport a significant portion of the intramural AIDS work, considering the size of the AIDS program and thesmall amount of financial support it receives. The following laboratories are involved:Laboratory of Chemical Biology: Transcriptional regulation by tat-protein and LTR of HIV in vitro;Laboratory of Chemical Physics: Structural studies of AIDS proteins by NMR; Investigations ofmacromolecular structures and dynamics by NMR;Laboratory of Bioorganic Chemistry: Mechanistic enzymology of HIV proteins; Halogenated biogenicamines in biochemistry and pharmacology;Laboratory of Molecular Biology: Studies on the mechanism of retroviral DNA integration; AIDS relatedproteins - structure and function; Study of the potential use of catalytic antibodies against AIDS;Genetics + Biochemistry Branch: CD4 receptor structure/function project; Target ribozymes to HIVsequences;Laboratory of Molecular and Cellular Biology: Function of DNA virus genomes in animal cells;Regulation of HIV by AAV;Laboratory of Medicinal Chemistry: Analogues of nucleic acids and their components as potential anti-AIDS agents.Some of the accomplishments of these laboratories include: 1) identification of two glycosylation sites onthe CD4 molecule required for proper protein folding and transport to the cell surface; 2) identification of theprotein necessary for integration of HIV into the host genome and the development of an assay to screenfor inhibitors of this enzyme; 3) preliminary evidence that shows that the human parvovirus AAV rep geneblocks growth of infectious HIV by inhibiting the function of the HIV tat gene; 4) 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 isdisappointing. Work of this kind is heavily subsidized elsewhere and NIDDK's efforts don't particularly standout from the crowd, except for the research on the HIV-1 integrase and the negative regulatory properties ofthe AAV rep gene. It would be nice to see NIDDK's intramural Clinical Endocrinology, Clinical Hematology,Digestive Diseases, Metabolic Diseases, Molecular, Cellular, and Nutritional Endocrinology branchessupplement NIDDK's extramural research.For FY 1993, NIDDK wanted to double its AIDS FTEs from 10 to 20 for intramural research projects. Ifmoney were available, NIDDK should not simply double its efforts in the area of molecular virology anddrug design, but should also attempt to involve intramural researchers in projects on wasting and relatedmetabolic disturbances, gastrointestinal infections and abnormalities, neuroendocrine and immune systeminteractions, thymic pathology, hematopoietic dysfunction, and renal complications of AIDS.Future Plans. Items on NIDDK's wish list for FY 1993 appeared above. Since there will be but a scantbudget increase for NIDDK, the wished-for initiatives and expansions are unlikely to occur.Recommendations:* NIDDK's request for an additional $10M for FY 1993 should be honored and funded by Congress. NIDDK's research portfolio represents many areas given little attention or financial support to date, most notably wasting and metabolic disorders, and neuroendocrine and immune system interactions in HIV infection;* NIDDK's contribution to the NIH "Annual Report" did not accurately or clearly portray its research commitments for 1991. Some projects described therein were not part of the 1991 grant portfolio. NIDDK needs to track and document its programs on AIDS in a better way. Perhaps the institute could prepare a description of its grants on AIDS-related research for each fiscal year with brief abstract of each project and its accomplishments [NHLBI does this]. * 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.). NIAID could use the resources and expertise of NIDDK to strengthen its program in these areas. [There is now a precedent for this: the NINDS plans to fund a neuro-AIDS supplement for the ACTG.]Contacts: Dr. Judith Fradkin, NIDDK Ms. Dee LeRoy Office of Program Planning and Evaluation NIDDK II/11. National Eye Institute NEIBackground. NEI

was established in 1968 (P.L. 90-489) to support "basic and applied research, includingclinical trials, related to the cause, natural history, prevention, diagnosis, and treatment of disorders of theeye and visual system." Carl Kupfer, MD, is its first and hitherto only director. NEI's Intramural ResearchProgram includes a Clinical Branch, Laboratories of Immunology, of Mechanisms of Ocular Diseases, ofMolecular and Developmental Biology, of Retinal Cell and Molecular Biology, and of SensorimotorResearch. NEI also runs a Biometry and Epidemiology Program, Extramural/Collaborative Programs, andan Office of International Program Activities. AIDS Programs. NEI's commitment to AIDS started with $33,000 in 1982 and has risen steadily since thento $5.68 million in FY 1991. Most NEI AIDS funds go to the SOCA program (see below) and to anintramural clinical trials program, with much smaller extramural awards in diagnostic methods, animalmodels, neuroscience and diseases related to HIV (principally CMV, toxoplasma and microsporidia-relatedretinitis).Basic research. Of the 11 non-SOCA extramural awards, two involve developing mouse models for CMVretinitis; one small training grant targets ocular manifestations of SIV in primates; two are attempting todevelop new methods to diagnose HIV, HHV-6 and CMV in people with AIDS; three are looking at othermechanisms of HIV- and/or CMV-induced optic neuropathy; and one each is looking at ocular toxoplasmosis and ocular microsporidiosis in AIDSIntramural clinical trials. NEI conducted intramurally the pivotal study which led to FDA approval offoscarnet for CMV retinitis. In FY 1991 NEI spent about $1 million on its intramural clinical trials,developing a surgical implant to deliver ganciclovir directly to the eye over a period of months (hopefullyavoiding the toxicity of systemic ganciclovir and the dangers of intravitreal injection); this trial will begin inmid-1992. The trial will randomize participants to immediate vs. deferred treatment for CMV retinitis, whichis impractical and widely believed to be unethical.NEI's Laboratory of Immunology is jointly carrying out epidemiology on the ocular manifestations of AIDS inchildren with the NCI Pediatrics Branch, following 150 children. They have recently identified VZV retinitisas a new opportunistic infection in these children. These conditions are a diagnostic challenge, sincechildren - especially infants - are less likely to report visual problems.In addition, NEI studied the ocular toxicity of ddI in children, about 6% of whom appear to develop areversible form of dose-dependent optic neuritis. This side effect has not been noted in adults. Four of ninety-five children with symptomatic (CDC class P2) HIV infection ... developed peripheral atrophy of the retinal pigment epithelium (RPE) during ddI therapy.NEI also 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 HIVinfection. 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 issupported 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 U01supports the Fundus Photograph Reading Center in Madison, Wisconsin, where retinal photographs areanalyzed to determine retinitis progression. The entire SOCA system is subcontracted and administeredfrom Hopkins. [Imagine the ACTG funded as a series of subgrants from Harvard and Stanford and you'llget the picture.] Thus, the $2.8 million which supports the 11 clinical centers around the country is allfiltered through Curtis Meinert's Coordinating Center at Hopkins. [Each SOCA unit, with the exception ofBaylor College in Houston, also receives ACTU funds.] Meinert is an internationally recognized clinicaltrials methodologist. The SOCA took a radically different approach from the ACTG. Rather than trying to do everything, theSOCA tried to do one thing well. In this case, SOCA took on the most pressing single question about CMVretinitis -- which treatment is better, foscarnet or ganciclovir? -- and answered it in just 18

months. Beforethe trial was started, many AIDS researchers were skeptical about its usefulness. At the 8th ACTG meetingin March 1990, one ACTG investigator said: Foscarnet is going to have to prove itself much better than DHPG, or else people are going to continue using DHPG.Ironically, Foscarnet did prove itself better than ganciclovir - not in terms of CMV progression or preservingsight but in terms of survival. People randomized to foscarnet lived an average of 3-4 months longer thanthose assigned to ganciclovir. The study was stopped in October 1991 due to the significant survivaldifference; a clinical alert was released within two weeks; and the manuscript was published in January1992. Follow-up continues until October 1992.Yet, so far at least, the standard of care appears to have shifted only slightly from ganciclovir to foscarnetas first-line therapy for CMV retinitis. This is probably in part due to the fact, which Bozzette pointed out,that the grade 3 toxicities of the former are lab toxicities (leukopenia), while those of the latter are clinical(seizures, kidney failure). It is also due to the fact that the cost of foscarnet is twice that of ganciclovir: At my institution an induction course of 2-3 weeks with foscarnet costs US $1,694-2,541 and maintenance therapy is US $21,900 per year. A similar induction course with ganciclovir costs US $840-1,260 and maintenance therapy is US $10,950 per year.The SOCA, like the ACTG, the CPCRA, and AmFAR's Community Based Clinical Trials Network (CBCTN),wanted to follow up on its success by conducting a three-arm, two-drug trial of oral ganciclovir (Syntex) vs.oral BW256u87 (Burroughs-Wellcome) vs. placebo for CMV prophylaxis. Syntex, however, has beenconsistently unwilling to contribute drug for such a study.Thus SOCA's plans for the immediate future include the "CMV Retinitis Retreatment Trial." Patients whohave completed 28 days of induction/maintenance for retinitis, yet who relapse, will be randomized to either1) continue on their current treatment, or 2) switch to the alternative (PFA or DHPG).Discrepancies. It is striking, in looking at accrual into the SOCA study, that ACTG funded sites accountedfor 193/240 (80%) of the participants. Each of the ACTUs participating is also a SOCA-funded site, withthe exception of UCSD, whose ACTU receives a separate $73,419 award to conduct retinopathy studies(which are said to involve cotton wool patches, hemorrhages and microvascular abnormalities as well asretinitis proper). Only two sites are listed as SOCA and non-ACTU - the Bascom Palmer Eye Institute(affiliated with the University of Miami) and Baylor College in Houston. It is hard to believe that enrolling theremaining 47 SOCA participants, plus data management, costs the $2.9 million awarded to Hopkins in FY1991 to coordinate SOCA. The total NEI costs for the study [SOCA 001/ACTG 129] ... was [sic] $9.0 million. The total NIAID costs for the study are estimated to be $4.4 million.How could NEI incur twice the expenses of NIAID, while ACTG funded sites provided 80% of participants,and SOCA funded ones only 20%? How are the SOCA sites funded? Is there double-dipping by sites? Does SOCA pay the site by number of participants enrolled?? Coordination. SOCA gives credit to the ACTG in its journal article, but the collaboration has been adifficult one. Personality issues and turf wars were frequent, and ACTG investigators felt locked out of theprotocol development process. While SOCA worked effectively with AIDS activists to develop the originaltrial, it lacks a formal, ongoing mechanism to incorporate community input into its efforts. NEI should workwith SOCA and the Viral Diseases Pathogen Study Group of the ACTG, in conjunction with communityactivists, to improve communication and cooperation.Funding and Future Plans. NEI's AIDS program spent $5,680,000 in FY 1991, 2.2% of its total budgetand 0.7% of the NIH AIDS total. [NEI ranks 11 of the NIH.] This rose incrementally in FY 1992 to $5.9million. NEI requested a major 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 [in a study which would have complemented or duplicated, depending on your outlook, Syntex' ongoing three such studies]; * $3

million in new funds to study CMV prophylaxis, perhaps by comparing oral ganciclovir with anti-CMV monoclonal antibodies [for prophylaxis?]; * $1.4 million to triple current funds to study animal models of the ocular complications of AIDS. Recommendations * NEI should enhance its extramural programs, and initiate intramural ones, to elucidate 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, using BW256 or oral ganciclovir. * 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 clarify how it separates its funds from those of the ACTG, and how it funds its sites. * SOCA should improve relations with the ACTG Viral PSG and should include community activists on its protocol steering committee(s). * NEI should report more regularly to the OAR's Institute AIDS Science Report, instead of providing the same summary about SOCA every three months. * OAR should list the NEI and SOCA projects in the section of the Strategic Plan concerning treatments for opportunistic infections. *Contacts: Richard L Mowery, PhD Chief, Collaborative Clinical Research Branch NEI, Bldg 31, Rm. 6A48 301/496-5983 FAX: 301/402-0528 Judith A Stein, MA Chief, Scientific Reporting Section Office of Science Policy & Legislation NEI, Bldg. 31, Rm 6A32, 301/496-5248 * II/12. Fogarty International Center for Advanced Studies in the Health Sciences FICBackground. FIC was established in 1967 as a memorial to Rep. John E. Fogarty (Rhode Island). FIC,the focus for international aspects of biomedical and behavioral research at NIH,* Facilitates the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of health sciences internationally;* Provides research programs, conferences, and seminars to further international cooperation and collaboration in the life sciences;* Provides postdoctoral fellowships for research training in the United States and abroad and promotes exchanges of senior scientists between the United States and other countries;* Coordinates the activities of the NIH concerned with the health sciences internationally; and* Receives foreign visitors to NIH.FIC sponsors two international AIDS programs: * International Training in Epidemiology Related to AIDS; and* International Postdoctoral Research and Training in AIDSFIC also funds some special projects and several fellowship programs supporting scientists who wish topursue collaborative research projects outside their home country. FIC has no AIDS-related intramuralprograms. FIC is the NIH's principal liaison to international health science organizations, including WHO,PAHO and the European Medical Research Councils. Funding. FIC spent $4,505,000 for AIDS-related activities in FY 1988, the first year of the center'sprograms in this area. In FY 1991, the FIC's AIDS budget was $5,351,000. For FY 1993, the FIC asked for$8,489,000. The President cut this down to $5,849,000, which is barely enough to maintain current (FY1992) services.Although FIC's expenditures on AIDS-related programs ranks twelfth in size among the eighteen institutesand centers at NIH, almost a third of FIC's total budget is devoted to AIDS. The International Training inEpidemiology Related to AIDS program is funded through D43 grants; a unique activity code specificallycreated for the program. The International Postdoctoral Research and Training in AIDS program is fundedthrough T22 grants, which are institutional research fellowships "to

support an institution with an approvedpreceptor for a number of postdoctoral research training fellowships in a limited number of specifiedshortage biomedical science areas." For FY 1991, the FIC allotted its AIDS budget in the following Masoncategories: FIC FY 1991 Activity by Mason Category Code Activity Amount IA1 HIV + HIV Genome $ 514,161 IA2 Immunology 514,161 IA3 Blood/Blood Products 514,161 IA4 Diagnostic Methods/Reagents 514,161 IIB1A Transmission Sexual 385,621 IIB1B Transmission IVDU 385,621 IIB1D Transmission Blood Recipient/Donor Studies 385,621 IIB1E Transmission Perinatal Infection 385,621 IIB1G Transmission Other/Miscellaneous 385,621 IIB2 Natural History + Cofactors 1,157,445 FIC AIDS Total $5,351,000For FY 1992-1993, the FIC is planning to redirect its efforts toward vaccine development: FY 1991 FY 1992 FY 1993 Biomedical Research $2,140,000 $1,119,000 $1,169,000 Vaccine Development + Trials 0 2,798,000 2,925,000 Transmission, Natural History, Cofactors 3,211,000 1,680,000 1,755,000This transfer of resources away from prevention and natural history-directed epidemiology to vaccineinfrastructure development is a major development in the NIH's AIDS program which has, hitherto, receivedlittle attention or broad discussion. What is the impact in developing countries of cutting back on preventionand epidemiology? Are the vaccine products to be tested promising enough to justify the expense? Arelocal communities involved? Will the vaccines, if proven effective, be distributed in the countries where theywere tested?The AIDS International Training and Research Program (AITRP) was initiated in 1988 in response toCongressional pressure to address the international scope of the epidemic. Its goals are:* To increase the capacity of foreign scientists to deal with AIDS epidemic through epidemiological research, clinical trials and other prevention programs;* To support collaborative research between US and foreign scientists in the epidemiology, diagnosis and treatment of AIDS; and* To stimulate cooperation and sharing of research knowledge by scientists combatting AIDS worldwide.The AITRP is an integral part of the NIH's strategy for developing an infrastructure for future HIV vaccinetrials. Other emphases include the prevention and treatment of opportunistic infections and the uniqueproblems of women and children with HIV infection. FIC's efforts are coordinated with other internationalAIDS research efforts administered by the NIH and other federal agencies, as well as those supported bythe World Health Organization's Global Programme on AIDS (WHO/GPA). As the program nears the end of its first five-year cycle, FIC is re-examining its mission, particularly theextent to which it should support the development of an infrastructure for clinical trials of HIV vaccines andantiretroviral therapies abroad. FIC is also discussing the extent to which its future efforts should bedevoted to assisting the more developed countries of Central and Eastern Europe. Other long-rangepossibilities being considered by FIC include broadening its program to focus on other international healthconcerns, in the unlikely event that the AIDS epidemic is brought under control and an increased emphasison tuberculosis and the opportunistic infections associated with AIDS.In FY 1991 the AITRP was expanded and now involves scientists from the USA and over 50 other nations. It operates through grants to US institutions, which then select participating scientists. Since 1988, theprogram has trained nearly 400 American and foreign health professionals in the USA, and has providedover 100 in-country training courses for foreign health professionals. In 1991, it began to admit participantsfrom Central and Eastern Europe. The AITRP's two components are the International PostdoctoralResearch and Training in AIDS, and the International Training in Epidemiology Related to AIDS programs.The International Postdoctoral Research and Training in AIDS Program supports collaborativeresearch and training for US and foreign scientists who want to expand their capabilities in theepidemiology, diagnosis, prevention and treatment of AIDS. While AIDS researchers from any country andcareer level may apply through this program, priority is given to those from developing countries. Four USinstitutions conduct the program:1. UCSD, San Diego. Dr. Dennis Carson.

Most participants are from the industrialized countries of Europe and Japan, with two from China and India. Research areas include: the role of TGF-beta and HIV's tat protein in the pathogenesis of AIDS; interactions between HIV and macrophages; the role of Ig V gene polymorphisms in pathogenesis; the role of the HIV rev gene in the establishment or termination of viral latency; the HIV-infected neonatal SCID mouse as a model for pediatric AIDS; the interactions between HIV and human CMV in the CNS.2. UCLA, Los Angeles, Center for Interdisciplinary Research in Immunology and Disease. Dr. John Fahey. Its original participants were drawn from Pacific Rim and Latin American developing countries, but now include scientists from Eastern Europe and the former USSR. Research areas include immune dysregulation in HIV infection; the role of IL-6 in B-cell lymphoma; the diagnosis of HIV-related neurological diseases; the epidemiology and case management of HIV infection in Brazil; pediatric clinical trials.3. University of Washington, Seattle. Dr. Joan Kreiss. The UW program largely sponsors US scientists doing collaborative research in Africa, but also hosts participants in Seattle from China and Kenya. The emphasis is on the epidemiology of HIV infection and STDs, including heterosexual and IVDU transmission. Other areas of research include HPV and cervical dysplasia; the interaction between HIV and malaria; the pharmacokinetics of ddI; and an evaluation of a condom marketing program in the Central African Republic.4. University of Miami, Dr. Gwendolyn Scott. Miami's guests have come largely from developing African, South American and Caribbean nations, with a focus on Haiti, Zambia and Brazil. Some researchers from Germany and Romania have also enrolled. U. Miami's program specializes in pediatric AIDS. Research areas include the epidemiology of lymphoid interstitial pneumonia (LIP), maternal risk factors, breast milk transmission and materno-fetal transmission of HIV; the immunological response to vaccine antigens in HIV-infected children; pediatric studies of AZT and other antivirals; congenital toxoplasmosis; early diagnosis of neonates; PCP in neonates; early diagnosis of syphilis and neurological impairment in neonates; CTL responses in neonates.Each of these programs is at a NIAID-funded AIDS Clinical Trials Unit (ACTU) site, allowing for a broadfocus in AIDS research.The International Training in Epidemiology Related to AIDS Program. program is designed to increaseforeign scientists' expertise in epidemiological research related to AIDS and its use in clinical trials andprevention research. Five types of training are available through the program:* Training in epidemiological concepts, methods, field studies and research related to AIDS that will lead to the MS or PhD degree for individuals with previous field experience;* Training in epidemiological field studies and research related to AIDS that will lead to the MS degree for individuals without prior field research experience;* Short-term comprehensive courses in epidemiology with an emphasis on AIDS for health professionals;* Training in laboratory procedures and research techniques related to AIDS for individuals with an MS or PhD;* Practical and applied short-term training related to AIDS conducted in the foreign country for professionals, technicians, and allied health professionals.The program also provides support for US faculty to conduct collaborative research with trainees after theyhave returned to their home countries. Long-term training is based in the US while short-term training isprovided in the US and elsewhere. Ten institutions carry out the program across the US and each has alimited set of countries with which it collaborates:1. Tulane, Dr. William Bertrand: Zaire;2. Emory, Dr. Philip Brachman: Cote d'Ivoire, Thailand, Caribbean lands;3. UCLA, Dr. Roger Detels: Brazil, China, Philippines, Singapore, Thailand;4. Harvard AIDS Institute + Department of Cancer Biology, Dr. Myron Essex: China, Mexico, Senegal, Taiwan, Zaire;5. Johns Hopkins University, Dr. Harvey Fischman: Brazil, Columbia, Haiti, Malawi, Rwanda, Thailand, Poland, ex-USSR;6. U. Miami, Dr. Marianna Fordyce-Baum: Argentina, Caribbean lands, Ecuador, Haiti, Honduras, Mexico, Peru;7. Case Western Reserve U., Dr. Harold Hauser: Uganda;8. Cornell U., Dr. Warren Johnson:

Brazil, Haiti, China;9. U. Washington, Seattle, Dr. Joan Kreiss: Kenya, Mozambique, Senegal, Thailand, Zimbabwe;10. UC Berkeley, Dr. Arthur Reingold: Brazil, Dominican Republic, ZimbabweFuture plans. The FIC wanted to expand both the International Training in Epidemiology Related to AIDSand the International Postdoctoral Research and Training in AIDS programs for FY 1993by adding additional institutions and increasing the funding for the currently participating sites, in order to: Provide greater emphasis on training related to the international testing of candidate AIDS vaccines and research in the areas of pediatrics and HIV-infected women, following the Secretary's trip to Africa.FIC wanted an additional $1.3 million for supplementary funds for the International Training in EpidemiologyRelated to AIDS program, and an additional $200,000 for the International Postdoctoral Research andTraining in AIDS program. FIC also wanted to add three sites to the former and one to the latter at a cost of$250,000 per new site ($1M total). Finally, the FIC wanted to add one FTE to its current number of four forFY 1993. Of course, the FIC received little more for FY 1993 in the President's budget than it was allottedfor 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": "It is evident that 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 UCSD center, for instance, draws most participants from industrialized countries in Western Europe and Japan. Perhaps, UCSD could recruit additional participants from India, Thailand, Singapore and other countries in Southeast Asia, which are underrepresented in the program as a whole and where the epidemic will rapidly worsen soon.* 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 clinical trials training and development program unless extra money is specifically allocated for that purpose. With an effective vaccine probably many years away, the developing world's best bet on controlling the epidemic is the expanded development of risk assessment and prevention programs, the infrastructure of which the AITRP is currently helping to construct. 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 little extra money for the endeavor. At

the FIC this means pitting risk assessment and prevention, and basic scientific training against the search for a vaccine. When DHHS or Congress presses NIH to begin a new initiative or expand its efforts in a specific area without appropriating additional funds, it is intolerably destructive to existing programs.* The FIC stands out among all the other 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.Contact: Kenneth Bridbord Chief International Studies Branch FIC, NIHPublicationsof interest: FIC, Third Year Progress Report, AIDS International Training and Research Programs, Executive Summary and Appendix, October 1991 * II/13. National Institute of Environmental Health Sciences NIEHSBackground. The Division of Environmental Health Sciences was established in 1966 at ResearchTriangle Park, North Carolina, where it became the NIEHS in 1969. Its mission is to investigate "the effectsof chemical, physical and biological environmental agents on human health... [supporting] training inenvironmental toxicology, pathology, mutagenesis, epidemiology and biostatistics."AIDS Programs. NIEHS started funding AIDS research in 1987, with $216,000, rising to $3.8M in 1988 andmore slowly thereafter. NIEHS is part of the National Toxicology Program (NTP). Its AIDS toxicologyprogram is supervised by the Systems Toxicity Branch of the Division of Toxicology Research andTesting. By the end of 1991, this program had evaluated the effects of acute and chronic administrationof AZT, ddC, ddI, d4T, alpha interferon, and pentamidine isethionate on mice and rats, measuring "effectson body weight, survival, food and water consumption, hematology, clinical chemistry, organ weights andhistopathology". NIEHS is carrying out 2-year mouse studies of single drug and combination (AZT/IFN)carcinogenicity in rodents. Since in vivo exposure of mice to rHuIFN-alpha A/D suppressed T and B lymphocyte responsiveness, rHuIFN-alpha A/D was evaluated in vitro for its effect on a T cell-dependent, antigen-specific B lymphocyte differentiative response... the ability of antigen-specific B lymphocytes to produce anti-TNP was suppressed at therapeutic concentrations of rHuIFN-alpha A/D.A new 5-year award cycle started in September 1991 measures reproductive and developmental toxicityand carcinogenicity in rodents given single, 28-day, 90-day and 6-month doses of single drug andcombination therapies. NIEHS scientists demonstrated that fetal deformities [in pregnant female mice given ddC] occur even at doses at which the mother did not exhibit signs of overt toxicity. The number of litters with any malformation, the number of litters with one or more malformed fetuses, and the percentage of malformed fetuses was significantly increased, and the average fetal body weight was significantly decreased among groups that received 1000 or 2000 mg/kg of ddC. Malformation (micrognathia, open eyelids, cleft palate, and bent tibia, fibula and/or femur) were observed at 400 mg/kg, but the numbers were significantly increased at 1000 mg/kg. At 2000 mg/kg developmental malformations were present in 25% of the litters and, in addition to the above, included tail, limb and vertebral defects. Therefore, exposure to ddC during the period of major organogenesis [days 6-18 of gestation] resulted in fetal/developmental toxic effects but no overt toxic effect to the dam.NIEHS rodent studies use both male and female rodents. They are also looking at toxic interactionsbetween mouse retroviruses and anti-retroviral agents, and at nucleoside neurotoxicity (myopathy andneuropathy) in rodents. The NIEHS intramural program is examining molecular structure of HIV proteins such as reversetranscriptase and protease. One intramural collaboration is with Brendan Larder of Wellcome UK todetermine the "Fidelity of Retroviral Reverse Transcriptases", an issue with broad significance for viralmutation, pathogenesis, and the generation of drug-resistant HIV mutants.Gary Rosenthal in the Systems Toxicity Branch is examining the effects of pentamidine and its analogueson lung macrophages Laboratory results have demonstrated an inhibitory effect of pentamidine (15 mg/kg IV) on serum IL-6 and TNF levels following LPS-induced inflammation. Concomitant to this is a pentamidine-induced normalization

of thermal regulation.Studies carried out in New Mexico showed that 30 days of dapsone therapy resulted in A selective modulation of B lymphocyte function, manifested by increased antibody-forming cell activity...Funding. NIEHS spent $4,516,000 on AIDS programs in FY 1991, 1.9% of its total budget and 0.5% of theNIH AIDS total. [Its comparable budget in FY 1992 went down to $4.320M.] Of the $4.514M, $3,929,252went for 12 extramural awards all related to toxicological studies of AIDS drugs (Mason Category 1D1,Therapeutic Agents - Development). Of the remainder, $587,000 went for intramural researchFuture Plans. For FY 1993, NIEHS requested an increase to $7.106M, 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 atotal of 20; they will be lucky to add three with the President's budget.NIEHS would like to initiate studies of how "'substance abuse' drugs affect the action of AIDStherapeutics," but how it will do so in the absence of new funding is unclear.Other program requests for FY 1993 included:* Doubling funds for an intramural program to hire a second FTE to study the cellular molecular biology of Kaposi's sarcoma ($143,000 total)* $1 million for a nuclear molecular resonance 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, and their effects on reproduction;* $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 BW, BMS + HLR!].* NIEHS should coordinate its projected studies of substance use drugs and AIDS drugs with NIDA.* NIEHS should expand its studies of the effects of various OI drugs on immune cells and cytokine expression.Contact: Janet Guthrie, Program Analyst, NIEHS PO Box 12233, Research Triangle Park, NC 27709 919/541-4258, 919/541-4075 FAX * II/14 National Center for Nursing Research NCNR.Background. NCNR was established in 1986. Its current director is Ada Sue Hinshaw, PhD, whosegraduate training was in both nursing and sociology. NCNR supports research and training in three majorareas: (1) health promotion and disease prevention, (2) understanding and ameliorating the effects of acuteand chronic illness, and (3) improving patient care and the environment in which it is delivered. NCNR alsosupports pre- and post-doctoral research training and career development for nurse-scientists and otherexperienced investigators. NCNR's small intramural research program is devoted almost entirely to HIVinfection and AIDS. With the National Advisory Council on Nursing Research and others in the field, NCNRhas developed a National Nursing Research Agenda. Among the agenda's priorities are: * Low birth weight: mothers and infants; * HIV infection: prevention and care; * Long-term care for older adults; * Symptom management; * Health promotion for children and adolescentsFunding. NCNR began funding research on HIV infection and AIDS in FY 1988 with $602,000. By FY1991, NCNR's AIDS budget had grown to $2,545,000. For FY 1993, NCNR requested $6,786,000 forAIDS-related programs, but this figure was cut at PHS and then again at DHHS to $3,172,000 which wasbelow funding levels for FY 1992. Finally, the President's budget offered NCNR $3,337,000, which is stillbelow the level necessary to maintain current services. NCNR's AIDS programs in 1991 included: NCNR AIDS ACTIVITIES FY 1991 I. BASIC BIOMEDICAL RESEARCH IA2 Immunology $400,000 IC1 Behavior/change 260,000 IC2 Prevention 163,000 IF1 Training 267,000 II. RISK ASSESSMENT + PREVENTION IIB1a Transmission - Sexual 200,000 IIB1f Transmission - Occupational 74,000 IIB2 Natural history + cofactors 75,000 IV. CLINICAL HEALTH SERVICES RESEARCH + DELIVERY IVD Research 1,106,000 NCNR AIDS TOTAL $2,545,000AIDS Program. NCNR's AIDS program focuses on four major areas: (1) physiological aspects of nursingcare, (2) psychosocial aspects of nursing care, (3) delivery of nursing

care and (4) prevention oftransmission. Research on HIV infection has been designated a priority in the National Nursing ResearchAgenda. In FY 1991, AIDS research occupied about 7% of the NCNR's resources. NCNR has identifiedseveral demographic groups of special concern in its efforts: sexual partners of infected individuals, womenof childbearing age, sexually active young adults and people of color.Extramural program. For FY 1991, NCNR funded twenty awards in AIDS research:I. Physiological aspects and delivery of nursing care:* Nursing--Self Care and HIV Disease;* AIDS Care - Nurse Retention and Patient Satisfaction(2);* Quality of Nursing Care of People with AIDS;* Effects of Nurse Care Managed Home Care for HIV Patients;* Caring Environment of Persons With AIDS;* Nursing Care of People With AIDSII. Psychosocial aspects of nursing care:* Coping Response in HIV Infection--Panel Analysis;* Psychoimmunological Patterns in HIV-Infected Individuals;* Meaning-Making in Chronic Illness;* Coping Among Persons With HIV Disease;* Ethical Problems Experienced by Persons With AIDS;* Stress and Coping in Caregivers of AIDS ChildrenIII. Prevention of transmission:* Women's Subjective Assessment of HIV Risk;* AIDS Lay Caregivers: Potential AIDS Educators;* Genital Herpes & Risk of HIV Adapting To Chronic Disease;* A Nursing Intervention to Prevent AIDS;* Preventing AIDS Transmission in At-Risk Youth;* Modification of High-Risk Behavior in Young Women;* Predictors of Glove Usage by Health Care WorkersMany of these programs are difficult to evaluate because the abstracts for many of the awards are notavailable in the DRG, OAR, CRISP databases [training grants are not abstracted in these databases]. TheNCNR was among the more refractory of the institutes in terms of information sharing during this project.In the area of physiological aspects and delivery of nursing care, NCNR's programs are generallyevaluations of existing care systems for people with AIDS and HIV infection which are then used to improveon the current structures or develop new models of nursing care. Both hospital, home and self based careare under consideration.NCNR's prevention and education programs are geared towards women, adolescents and young adults. One program, in particular, Genital Herpes & Risk of HIV Adapting To Chronic Disease, is problematic.The program is an investigator-initiated grant (R01), given to Janice Swanson of Merritt College in Oakland,CA, which calls for the use of a control group in the investigation of the efficacy of psychoeducationalintervention in reducing sexual health risks in young adults, 18 to 35 years of age, with genital herpes. While controlled experiments are an important scientific tool, withholding educational counseling as acontrol in this case, may put these individuals at higher risk of HIV infection and is unethical. Somebehavioral studies are not worth doing at all, rather than doing them this way. How do you administer"informed consent" when telling your charges they may be randomized not to know or be taught how toprevent HIV?Psychological and social pressures on people with HIV and their caregivers is also being studied by NCNR,with a view towards developing interventions to ameliorate their effects.In conjunction, with NIA, NICHD and USAID, NCNR is participating in an international behavioral researchprogram. As part of this effort, NCNR has funded a grant to develop an AIDS prevention program in Chileutilizing Chile's network of primary and secondary health care clinics.Intramural program. NCNR runs a small intramural program in collaboration with NIAID and the NIHClinical Center to assess the physiological and psychological effects of HIV infection. Studies completed orcurrently 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 peoplewith 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 existingprograms 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 extramural project grants on symptom management and quality of life for $1.1 million;4. An extra $201,000 for nursing research training initiatives;5. $264,000 for a new RPG to evaluate the efficacy of universal precautions as well as other methods of avoiding exposure to infection with HIV for healthcare providers;6. $1.1M to fund four research project grants studying high-risk behavior and educational interventions in women and people of color; and7. 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:* Besides for the one questionable risk assessment and education grant described above, 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.Contacts: Dr. Martha Ann Carey Dr. Jan Heinrich Department of Extramural Programs, NCNR Dr. Mary Ropka Department of Intramural Research, NCNR Dr. Ada Sue Hinshaw Director, NCNR II/15. National Institute of Arthritis and Musculoskeletal and Skin Diseases NIAMSBackground. The NIAMS goes back to 1950 with the foundation of the National Institute of Arthritis andMetabolic 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 theNIDDK (P.L. 99-158), with NIAMS to focus on arthritis, musculoskeletal diseases, muscle biology + skindisease.NIAMS' Intramural Research Program consists of a Laboratory of Physical Biology and the Arthritis andRheumatism Branch. Its four extramural branches are: 1) Rheumatic Diseases; 2) MusculoskeletalDiseases; 3) Skin Diseases; and 4) Muscle Biology and Training. There is also an Epidemiology/DataSystems Program and the three Centers programs: a) Multipurpose Arthritis and Musculoskeletal DiseasesCenters (1974); b) Specialized Centers of Research (1987); and c) Skin Diseases Research Centers(1988).The NIAMS Director is Lawrence E Shulman, MD, PhD "an internationally recognized [rheumatologist]...who has made major contributions especially in the areas of SLE and scleroderma. A recent discovery waseosinophilia fasciitis (also called Shulman's disease)."AIDS program. NIAMS spent $1,633,000 on AIDS in FY 1991; of this, $1,240,120 went for 5 extramuralAIDS awards, all filed under Mason Category 1A2, Immunology. An additional $142,880 went forintramural AIDS research, and $251,000 for extramural research management + support. 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 conducting a "StructuralAnalysis of HIV Proteins by Electron Microscopy and Image Processing," with particular focus on gp160,gp120, gp41 and rev.[It is a pity that the NIAMS leadership, with its experience in autoimmune diseases such as lupus, is notfurthering the study of the intriguing parallels between AIDS and lupus intramurally.]We wrote to Stephen P Heyse, MD, MPH, Director, Office of Prevention, Epidemiology + ClinicalApplications, for NIAMS' perspective on its AIDS research. He referred our inquiry to Dr. Stanley Pillemer"who conducts our AIDS program for a reply," and he indeed responded on 3 June 1992.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 [impressive array of skin] manifestations ... in US Army and Navy personnel. Approximately 600 individuals

[now over 680have been evaluated... Preliminary estimates of the prevalence of the more common skin disorders have been made.NIAMS would like to extend these studies to hemophiliacs and community-based populations. Dendritic cells and autoimmune skin phenomena. NIAMS issued two program announcements forAIDS-related research in FY 1991: * "Association of arthritis, inflammatory muscle diseases, and other rheumatic manifeatations with HIV positivity and AIDS," (PA-91-82, 8.2.91); * "Cutaneous manifestations of HIV infection and AIDS," (PA-91-63, 5.31.91)In response to these PAs, NIAMS awarded three AIDS-related basic research grants in 1991, and one sofar in 1992. These projects focus on skin and joint disorders in AIDS; the role of dendritic cells and skincytokines; the possible role of autoimmune phenomena in HIV-related psoriasis, arthritis and Reiter'ssyndrome [PARS]; and parallels between AIDS and lupus: * Robert Winchester at Columbia received $445,366 to study "Cutaneous and Articular Manifestations in HIV Diseases" [7 RO1 AR39626-04]; * Brian Nickoloff at Ann Arbor received $282,739 to study "Dermal Dendrocytes and AIDS-related Psoriasis" [1 R01 AR40488-01A1]. He will be attempting to verify the following model: HIV -> T cell -> lymphokines -> dermal dendrocytes -> IL-1, GM-CSF, TNF-alpha, bFGF -> psoriasis. * Madeline Duvic at the University of Texas, Houston, received $62,015 to study "Pathogenesis of AIDS/HIV Related Psoriasis" [5 R01 AR39915-03] and its possible links to immunogenetics (e.g., HLA associations with progression or protection). * Steven Rich at the NYS Department of Health, Albany, received a grant to study "Human lupus-type inclusions in SLE and AIDS" [1 R01 AR41619-01].These four investigators are studying questions which go to the heart of several unresolved issues ofAIDS pathogenesis. The Columbia investigators have hypothesized that persons developing another AIDS-related autoimmune complex, DILS (diffuse infiltrative lymphocytosis syndrome) may progress much moreslowly. Elucidation of the mechanisms of PARS and DILS, and development of treatments if necessary, isa 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, macrophagesand dendritic cells, and of primary and secondary immune responses occurring in situ as well as inperipheral lymphoid organs, should help to further elucidate the pathogenesis of AIDS.Funding. NIAMS spent $1.633M on AIDS in FY 1991, comparable to $1.727M in FY 1992. This amounts to0.8% 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 $86,000increase (5%) to $1.813M. NIAMS has 4 AIDS FTEs and would have added 2 more next year.Future plans. The ICD Directors' Wishlist for FY 1993 included: * $848,000 to double the current R01 program investigating skin and joint disorders in AIDS. * $576,000 triple the existing $353,000 program studying the role of Langerhans/dendritic cells as potential reservoirs or accessory cells in HIV infection, and to study lymphokine modulation of DCs in HIV. [NIAMS' next two requests were listed on a missing page 59 of the Wishlist.] * $360,000 to expand epidemiological studies of the rheumatic and skin manifestations of HIV in military populations, minorities and children with HIV. This would have funded 2 new interagency agreements.These new initiatives are infeasible without more support. The elucidation of the role of dendritic cells in HIVdisease is a central current issue of pathogenesis. 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. * Epidemiological studies of cutaneous and autoimmune (PALS, DILS) manifestations of HIV should be expanded. * Studies of the pathogenesis and treatment of HIV-related (and AZT-related) myopathy should be initiated. *

Pathogenesis of these manifestations should be elucidated - is there an autoimmune element? - how do AIDS-autoimmune phenomena resemble SLE or GVHD? - is it HLA-linked as appears likely? - is it mediated primarily through CD8+ cells or are autoantibodies also involved (anti-collagen, etc.)? - how significant are LC/DC as reservoirs of HIV [Knight/Haseltine differ w/ others]? - how significant is impaired APC function of LC/DC in leading to clinical immunodeficiency? - how feasible is cytokine manipulation in the skin + joints? - further studies of treatment of psoriasis, cutaneous KS, etc., appears warranted. * Skin infections due to Molluscum are common in people with AIDS and significantlyu affect quality of life and comfort. The NIAMS should begin an initiative to seek effective therapies for this viral infection. Contacts: Stanley Pillemer, MD Office of Prevention, Epidemiology + Clinical Applications NIAMS, Bldg. 31, Rm. 4C13 Bethesda, MD 20892 301/496-0434 II/16. National Institute on Aging NIABackground. NIA was founded in 1974 following the 1971 recommendation of the White HouseConference on Aging, and was given responsibility for "biomedical, social and behavioral research andtraining related to the aging process and diseases and other special problems and needs of the aged." The current [acting] NIA Director is Dr. Gene Cohen. NIA runs a Gerontology Research Center inBaltimore, MD, where most of its intramural research is conducted. The NIA Laboratory of Neurosciencesconducts basic and clinical research at the NIH Clinical Center. NIA runs eight intramural laboratories inClinical Physiology, Behavioral Sciences, Personality and Cognition, Cellular and Molecular Biology,Biological Chemistry, Molecular Genetics, Cardiovascular Sciences, and Neurosciences. NIA's ExtramuralDivision has eight subdivisions: Biomedical Research and Clinical Medicine, Molecular and Cell Biology,Geriatrics, the Neuroscience and Neuropsychology of Aging, Behavioral and Social Research, AdultPsychological Development, Social Science Research on Aging, and demography and PopulationEpidemiology.Funding. NIA started funding AIDS-related projects in FY 1987 with $184,000. Its FY 1991 AIDS budgetwas $985,000 and FY 1992 is $1,081,000. For 1993, NIA requested a substantial increase to $3,058,000,which was cut by the powers that be to $1.046M, an amount less than that needed to maintain currentservices ($1.128M). NIA's recent activities fell into the following Mason code categories: NIA AIDS Activities FY 1991-1992 BASIC SCIENCE RESEARCH FY 1991 FY 1992 IA1 HIV + HIV Genome $187,000 $190,000 IA2 Immunology 534,000 641,000 IC1 Behavior/change 198,000 250,000 IE2 Vaccine clinical trials 35,000 0 RISK ASSESSMENT + PREVENTION IIB1a Transmission - sexual 17,000 IIB1b Transmission - IVDU 9,000 IIB1e Transmission - perinatal 5,000AIDS Program. NIA AIDS research focuses on the biomedical, clinical and behavioral aspects of HIVinfection in middle-aged and older individuals. NIA is concerned with how aging and its associated immunechanges affect the course of HIV disease and response to treatment in these populations. NIA places aspecial emphasis on behavioral research focused on AIDS-related behaviors and behavioral change in themiddle and later years, the impact of a diagnosis of AIDS on families and social networks, and the impact ofAIDS on health care of older individuals. In addition, NIA, in collaboration with NICHD, NCNR andUSAID, supports an international behavioral research program. NIA's contribution to this program involvesa AIDS education program for women in Botswana.Extramural research. In FY 1991, NIA supported three extramural projects at a cost of $385,000,including:1. A Y01 interagency agreement with CDC to support part of a study on "Social and Behavioral Aspects of AIDS" (X Y02 AG80124, $10,000) run by CDC's Gary Noble;2. A study on "the Effect of Age on Retrovirus Disease and Immunosuppression in Mice" (5 R01 AG08659, $187,000), which uses a mouse model to study the more rapid progression to symptomatic disease which has been seen in older HIV-infected humans, hoping to elucidate potential differences in susceptibility to retroviral disease and immunosuppression based on age and the mechanisms of retrovirally induced immunosuppression in mammals of all ages.3. A collaborative grant for behavioral

research and intervention conducted with NCNR, NICHD and USAID, NIA supports a grant, examining the use of nurse-managed peer group supports to reduce the transmission of AIDS in Botswana women (5 R01 AG10499, $188,000). After conducting interviews to identify (1) the most important behaviors contributing to HIV transmission for women in Botswana; (2) the potential of existing community leaders and groups to serve as peer group leaders; and (3) the changes in a peer education model need to make it suitable for the culture and resources of Botswana, a pilot peer education program will be designed, implemented and evaluated in a single urban area.Intramural research. 3/5 of NIA's AIDS budget is for intramural research. In FY 1991, NIA spent $600,000 on this. These studies were carried out at the Laboratory of Clinical Physiology (LCP) in the Clinical Immunology Section (CIS): The CIS 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 LCP's major AIDS-related findings include: * Serum levels of gp160 are elevated in AIDS patients, but not in asymptomatic HIV infected individuals or individuals with ARC. The gp160 appears to be complexed with the CD4 protein and anti-gp160 antibody; * Faster progression of HIV infection in older patients is related to a more rapid loss of CD4+ cells in that group. The loss may be due to a progressive age-related inability to generate functional T cells to replace those lost due to HIV [and those lost or disabled during aging];* As HIV infection progresses as determined by a loss of CD4+ T cells, there is a loss of antibody to the HIV core proteins but no change in the amount of antibody to the envelope proteins. This may be due to a progressive loss of an ability too disrupt infected cells due to a loss of cytotoxic T cells. With less cell disruption there would be less core protein released;* Individuals infected with measles or influenza virus make antibodies which complex to HIV associated antigens on western blot analysis.The Clinical Immunology Section, LCP, also collaborated on a trial of HIV gp160-vaccinia recombinantvaccine with investigators at Johns Hopkins. Two additional clinical trials, one of human growth hormoneand the other of arginine (which stimulates endogenous production of HGH), were conducted to investigatethe immunomodulatory effects of these agents in non-HIV-infected subjects. No effect on immunologicalparameters was observed at the doses administered.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 for a new initiative to expand AIDS information and risk behavior studies to individuals of 55 years of age and older;* Five new AIDS FTEs for a total of ten.As mentioned above, NIA's request for an increased allocation was denied. For FY 1994, NIA will againrequest 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 HIVinfection in older individuals is a valuable program. The other basic immunology conducted by the ClinicalImmunology Section, LCP, on lymphocyte activation, growth factors and cytokines and their interest inboosting the immune response of the older individual are useful and applicable to AIDS. The budgetincreases requested by NIA, a modest amount - only $1.5M - should be honored in full.Contact: Dr. Samuel Korper PhD Associate Director, NIA * II/17. National Library of Medicine NLMBackground. NLM originated from the Library of the Office of the Surgeon General in 1836, and waschartered in its present form by the NLM Act of 1956, which mandated an NLM to collect, preserve anddisseminate the world's published medical information. Since 1964, NLM has initiated several on-linecomputerized medical information databases, including

MEDLARS and MEDLINE.In the Health Omnibus Program Extension (HOPE) act of 1988 [P.L. 100-607] Congress directed the NLMto develop several AIDS-related research databases. The AIDSLINE database was created within theNLM's MEDLARS information retrieval system. AIDSLINE is updated with over 800 citations monthly, whichare also available in its printed periodical AIDS Bibliography. Additional databases are being added toAIDSLINE, including AVLINE, BIOETHICSLINE, CANCERLIT, CATLINE, HEALTH and POPLINE. Online access is charged at MEDLINE rates average ($2-$5 per search)... It 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 TrialsInformation System, 1-800-TRIALS-A). These databases contain more information on publicly fundedclinical trials than on those sponsored by industry. [In this respect, AmFAR's and many local or regionaldirectories may be both more complete and more timely than the ACTIS/NLM system.]NLM also runs the database DIRLINE, which "contains descriptions of approximately 2,000 organizationsand other types of information resources in the AIDS arena... provided to NLM by the National AIDSClearinghouse... The online databases are available 24 hours a day, seven days a week."The DRAFT "NIH Strategic Plan" assigns NLM roles in "Information Dissemination," where NLM issupposed to help "expedite the dissemination of the latest information on state-of-the-art therapies, healthcare and prevention techniques" through its on-line databases, by 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 inAIDSTRIALS information about international clinical trials," and by publishing "full text of abstracts frommeetings, where available, online..."Since NIAID has no system to expedite analysis and publication of its AIDS clinical trials, many ACTGstudies (especially opportunistic infection trials, drug-company sponsored studies, and early phase studies)remain inaccessible years after their completion. Funding. NLM spent $519,000 on AIDS related activities in FY 1991, 0.6% of its total budget. Thisamounts to 0.1% of the NIH AIDS budget. The comparable amount this year (FY 1992) is $1,057,000. NLM requested an increase to $3,821,000 in FY 1993, but the President cut this back by $2.73 million to$1.1 million (a $44,000 rise over FY 1992, or 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.Future plans. NLM requested a budget increase of $2.7 million in FY 1993 to enhance the support of itsAIDS information systems and to develop a "single point user initiated online access (gateways) program tomerge databases to avoid duplication of existing databases." (ICD Wishlist FY 93).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 and the NIH OD should concern themselves with the still relatively slow rate of analysis and publication of NIH clinical trials, especially those dealing with AIDS. A top-down approach to resolving this could make NLM's programs more timely and more useful. * 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). Such analyses should be made available to Study Sections when reviewing grant applications, as well as to NIH extramural research management and support staff and to OAR, for use in assessing and improving the overall productivity of NIH-supported efforts. *Contact: Henry M. Kissman, Ph.D. Associate Director Specialized Information Services NLM, NIH Bethesda, MD 20894 * II/18. National Institute on Deafness + Other Communication Disorders NIDCDBackground. NIDCD was

formed in 1988 (P.L. 100-553) after developing as a Division within what is nowNINDS. James D. Snow Jr., MD, is the first and so far only NIDCD Director. According to its missionstatement, the 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 languageFunding. NIDCD first funded AIDS-related research in FY 1991, funding projects in the Mason category of"Animal Models and Related Studies" at a cost of $495,189, or 0.5% of the institute's overall $135M annualbudget. NIDCD is doubling its AIDS program in FY 1992 to $985,000. For 1993, NIDCD requested$1.98M. The President's FY 1993 budget offers NIDCD a tiny increase [4.5%] for FY 1993, raising its AIDSallocation to $1,029,000. NIDCD has just one AIDS FTE.AIDS program. NIDCD claims its AIDS-allocated research focuses on aspects of HIV infection that mayinvolve impairment of hearing, balance, smell, taste, voice, speech, and language:* A Clinical Research Center for Communicative Disorders at Yeshiva University in New York, NY (5 P01 DC00223-08, $206,821), with the aim of better detection, treatment and prevention of childhood communicative disorders;* A small study of auditory processing in hearing-impaired children at the Baylor College of Medicine in Houston, TX (5 R29 DC00421-03, $29,551);* A study of congenital CMV infection and auditory pathology at UCSD (5 R01 DC00386-05, $258,817). None of these appears on its face to have any direct AIDS-related application.NIDCD provides otolaryngic and audiological consultation and care to people with AIDS participating inresearch 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 asMeniere's disease, perilymphatic fistulae, sudden onset hearing loss, and hearing and balance disordersemerging in people with AIDS. NIDCD wants $1.865M to support 6 new research grants in this area.Recommendations* Although small, NIDCD should direct its program towards more specifically AIDS-related projects. Possible impairment of hearing, balance, smell, taste, voice, speech, and language in HIV+ persons should be studied.* 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 these findings, since the reported phenomena fall within its mission. * Studies of other serious otolaryngological manifestations of HIV disease, such as severe recurrent otitis media in children with AIDS, could also be studied. * 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's current budget increase will not allow it to fund any new initiatives. Its request for $1,98M should be honored.* 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! *Contact: Dr. James B. Snow Dr. Amy Donahue Director, NIDCD AIDS Program Director, NIDCD Ms. Pat Sparks Budget Officer, NIDCD *