The AIDS Research Program of the National Institutes of Health

Committee to Study the AIDS Research Program of the National Institutes of Health

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The AIDS Research Program of the National Institutes of Health

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AIDS Activities

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.
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Committee To Study the AIDS Research Program of the National Institutes of Health

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Preface

This report on the acquired immune deficiency syndrome (AIDS) research program of the National Institutes of Health (NIH) and the study on which it is based were requested by NIH's Office of AIDS Research (OAR). In only a short time, NIH has mounted a large, wide-ranging, complex program of AIDS research activities that involve every component of the agency. Because of the program's fast growth, scientific and public health importance, and high public expectations, James B. Wyngaarden, then director of NIH, asked Anthony S. Fauci, associate director for AIDS research and director of OAR, to oversee an evaluation of the program's research directions, management, and resources. OAR in turn asked the Institute of Medicine (IOM) to conduct an objective, unbiased review of the program, giving particular attention to its scope and content, management, results, and levels of budgetary and administrative support.[1] IOM agreed to undertake the study beginning in August 1989 and to make recommendations for strengthening current efforts as well as for the program's future directions.

The president of IOM, with the concurrence of the president of the National Academy of Sciences, appointed a 15-member study committee to prepare the report. Individuals were selected for their knowledge and expertise in the areas of virology, immunology, neuropathogenesis, epidemiology, infectious diseases of adults and children, nursing, health behavior, drug and vaccine development, clinical trials, animal models development, research program administration, and health program evaluation. Academia, private industry, and the patient advocacy perspective were all represented. In addition, a special effort was made to appoint a chairman and a majority of members who were neither directly involved in NIH-supported AIDS research nor members of major NIH advisory groups overseeing AIDS research (such as the AIDS Program Advisory Committee, the executive committee of the AIDS Clinical Trials Group, and the national advisory councils to the institutes). Several committee members involved in AIDS research activities provided the grantee perspective on the NIH AIDS research effort, however. Adel A. F. Mahmoud and Howard M. Temin, members of the National Advisory Allergy and Infectious Diseases Council and the National Cancer Advisory Board, respectively, attended an early meeting of the committee.

The committee met five times between October 1989 and September 1990 to define its task, develop a study plan, receive information, analyze the issues, and develop recommendations. The charge from NIH focused on questions of program balance, organization, management, and

[1] Appendix A lists specific issues of program organization, management, staffing, and funding to be addressed in the study.

resources. Included in the charge was a review of the appropriateness of the scope and content of NIH's AIDS research program. This phrase might have justified a detailed evaluation of the AIDS research agenda, but the committee decided against doing so. Such an effort would require a large-scale consensus development process involving groups of experts from many scientific fields and medical disciplines, a project beyond the resources and time available for the study. The group concluded instead that, given the long-term nature of the epidemic of HIV and AIDS, it would be most useful to review and make recommendations for improving NIH's institutional capacity to develop and implement an appropriate AIDS research agenda in the coming years. Thus the study emphasized programmatic issues, with the intent of advising NIH on ways in which it might improve its ability to identify and pursue the most important research questions. The committee did assess the appropriateness of the current NIH role and scale of effort in each area of research and addressed the appropriate balance among the areas and the potential impact of AIDS research on other research areas.

At the first several meetings, the committee heard presentations by NIH officials from the Office of AIDS Research (Anthony S. Fauci), the National Institute of Allergy and Infectious Diseases (Daniel F. Hoth, H. Clifford Lane), the National Cancer Institute (Bruce A. Chabner), the National Heart, Lung, and Blood Institute (Elaine M. Sloand), the National Institute of Child Health and Human Development (Antonia C. Novello), the National Institute of Neurological Disorders and Stroke (Carl M. Leventhal), the National Center for Nursing Research (Ada Sue Hinshaw), and the Division of Research Grants (Bruce Maurer, Gilbert W. Meier). The committee also benefited from presentations by the following: James R. Allen, Director, National AIDS Program Office, Public Health Service; Frank E. Young, Deputy Assistant Secretary for Health/Science and Environment, Department of Health and Human Services; Robert Wittes, Executive Vice President for Cancer Research, Bristol-Myers Squibb; Lawrence Corey, Professor, Department of Laboratory Medicine, University of Washington; and Edward M. Connor, Associate Director, Department of Immunology and Infectious Diseases, University of Medicine and Dentistry/New Jersey Medical School. Corey and Connor, respectively, chair the Executive and Pediatric Committees of the AIDS Clinical Trials Group. Committee members and staff also learned much from attending meetings of the AIDS Clinical Trials Group, the NIH director's AIDS Program Advisory Committee, the NIH AIDS Executive committee, and the National Institute of Allergy and Infectious Diseases' (NIAID) AIDS Division advisory committee.

The committee invited testimony from AIDS-related groups, and representatives of many of them testified at a hearing held by the committee in conjunction with its second meeting on December 4-5, 1989. Others submitted written statements. The following organizations responded to the committee's invitation: National Organizations Responding to AIDS, American Association of Physicians for Human Rights, Project Inform, National Association of People with AIDS, Physicians Association for AIDS care, American Nurses' Association, National Minority AIDS Council, National Organization for Rare Diseases, AIDS Treatment Registry, and the Pediatric AIDS Foundation. The committee also monitored testimony from these and other groups, as well as from federal AIDS officials and academic researchers, at congressional hearings on AIDS and before the National commission on AIDS.

In addition to presentations and testimony, the committee reviewed a series of reports on AIDS research by previous IOM committees, the Presidential commission on the Human Immunodeficiency Virus Epidemic, NIH advisory groups, and NIH itself. It also reviewed current internal NIH planning and budget documents and the documents justifying NIH's budget request to Congress for fiscal year 1991. The staff then synthesized information on the NIH AIDS research program and the AIDS activities of other Public Health Service (PHS) agencies (Centers for Disease Control; Alcohol, Drug Abuse, and Mental Health Administration; and Health Resources

and Services Administration) in a series of background papers that were discussed at committee meetings and formed the basis for the report's findings. These papers reflected not only pertinent documents and program data but also more than 150 interviews, primarily with NIH officials, program managers, and researchers, and with other PHS officials, university-based researchers, community-level clinician-researchers, and congressional staff (see the list in Appendix B).

Rather than offering a lengthy description and analysis of all facets of NIH's large, rapidly changing AIDS research program, the committee chose to present its conclusions and recommendations in a brief report that addresses the major issues of research and management. The report concentrates on the broad content areas of NIH's program, on the balance among those program areas, and on the overall management system needed to plan, set priorities, coordinate, and monitor a research effort being implemented in every institute, center, and division of NIH. Although the committee chose not to organize the study specifically around the nine study issues suggested by NIH, each of the issues is addressed in the report at some point (see Appendix A for the list of study issues and the report sections that address them). The report does not comprehensively review AIDS-related activities of other PHS agencies but only presents those activities in their relation to NIH and its research mission.

During the preparation of this report, the committee was constantly reminded that it was assessing a moving target: NIH continues, appropriately, to add to and revise the AIDS program. Consequently, this report presents the committee's evaluation as of September 1990. Important developments since then are noted in footnotes at appropriate points in the report. The number and detail of the committee's conclusions and recommendations vary with its judgment of the importance and complexity of the issues raised. Thus, for example, the committee spent a great deal of time assessing the AIDS clinical trials program and made a number of recommendations because the program is large, important, and controversial and because at the time of the study it was undergoing several major changes.

The committee concluded that, because of the scientific opportunities and the importance of controlling the burden of illness, it is wise to increase substantially the funding for AIDS research. The source of these additional funds remains an issue, however. Research on AIDS is part of and dependent on the total biomedical research enterprise. Given the current serious shortage of funds for new and competing research project grants, it would be unwise to shift funds from other areas of biomedical research and risk setbacks in the orderly development of the nation's research effort. Maintaining the total biomedical research effort must be a high priority for all those concerned with specific diseases.

Important among the AIDS-related issues that lie outside the purview of NIH is financing of care for AIDS patients. The health care burden of AIDS is large and still growing, and it has already begun to impose severe stresses on America's health care system. Moreover, human immunodeficiency virus (HIV) infection and disease are spreading rapidly among those who have inadequate or no insurance. Much-needed research is difficult among these groups because many of them have no regular source of care and hence are difficult to enroll and retain in research protocols for new treatments or therapies. The committee is further concerned that inadequacies in the health care system will slow or prevent some populations from adopting the products of AIDS research, for instance, new drug therapies or early interventions that might delay the development of disease in presymptomatic HIV-infected individuals. The committee could only flag the problems associated with health care financing for persons infected with HIV and recommend that the administration and Congress resolve them.

The committee wishes to thank the many individuals and organizations that advanced its work, many of whom are named already in this preface (or listed in Appendix B). Special thanks go to Jack Whitescarver, deputy director of the Office of AIDS Research, and Marc Horowitz, of the OAR staff. As project officers for the study, they facilitated the committee's access to people, documents, and data at NIH. Donna Adderly of the Division of Financial Management answered many requests for budgetary and program data with unfailing cheer, as did Linda Jackson, administrative officer of the Office of AIDS Research. John James, Bruce Maurer, and Gil Meier, all of the Division of Research Grants, provided data about grant applications and awards. The committee also deeply appreciated the support of its capable, hard-working staff, who conducted scores of interviews and reduced mountains of scattered data to a manageable form. Finally, I should like to thank the other committee members for their time and effort. Their contributions are an important element in the effort to address a problem that will continue to challenge NIH and all of society for at least the next decade and probably well beyond.

WILLIAN D. DANFORTH

CHAIR, COMMITTEE TO STUDY THE AIDS RESEARCH PROGRAM OF THE NATIONAL INSTITUTES OF HEALTH

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THE AIDS RESEARCH PROGRAM OF THE NATIONAL INSTITUTES OF HEALTH

Summary

AIDS: THE RESEARCH CHALLENGE

In the 1980s the National Institutes of Health (NIH[1]) faced an unprecedented challenge in responding to the epidemic of human immunodeficiency virus (HIV) infection and the acquired immune deficiency syndrome (AIDS), modern biology's first pandemic of a new, deadly infectious disease. Once the magnitude of the epidemic became clear-especially once HIV was identified as the causal agent-NIH was given the mandate and resources to develop a large, multifaceted AIDS research program to understand the virus's pathogenesis, discover and test therapies, and develop prevention strategies and a vaccine. Research supported and conducted by NIH has led to rapid increases in basic knowledge about HIV and its replication, the molecular and behavioral aspects of transmission, the human immune response to HIV infection, and the clinical course of AIDS. Researchers have discovered and developed some partially effective therapies, and recent advances in vaccine research have convinced many scientists that an effective vaccine may someday be available. Meanwhile, however, the epidemic continues to grow and spread to new areas and populations, trends that argue for a well-planned, well-organized long-term research program leading to the control and eventual eradication of the disease.

The committee concludes that NIH should continue to give AIDS research high priority because HIV infection and AIDS constitute a major public health threat and because they provide substantial opportunities for greater scientific understanding of the human immune system and of other viral diseases. The size and long-term nature of the threat call for an institutionalized response by NIH.

Recommendation 1.1: NIH should complete its building of the AIDS research program as a comprehensive, long-term effort. The shaping and implementation of such a program will require a series of steps that are described in the remainder of this report.

These steps should have several positive results: strengthened management structures and processes for planning, coordinating, evaluating, and reallocating the AIDS research activities supported by the various NIH components and for ensuring their quality and cost-effectiveness; fuller development of some promising research areas; an increased overall level of support for

[1] See Appendix D for a complete list of abbreviations and acronyms.

AIDS research; and increased personnel and facilities resources to enable NIH to conduct and manage an effective, efficient AIDS research program.

Although the committee was not asked to address health care issues, it could not avoid the finding that NIH-sponsored research on HIV infection and AIDS has been hampered by inadequate participation in clinical trials of some high-incidence groups whose members are not insured for and are unable to pay for treatment or associated medical care. This lack of coverage of some high-incidence populations is part of the larger problem of health care delivery and financing for persons with AIDS, a problem that looms ever larger as more and more individuals acquire the disease in the near future. The committee believes that NIH's mandate is to facilitate the discovery and clinical evaluation of therapeutic, diagnostic, and preventive agents and not to assure health care. This problem must be addressed at more appropriate levels of the federal health policy-making establishment.

Recommendation 1.2: The Health Care Financing Administration (HCFA) should make its reimbursement policies consistent with NIH assessments of promising treatments so that when treatments have moved beyond phase 1 testing, their associated medical care costs (and the costs of the treatment if the sponsor is unable to provide it free of charge) are covered for Medicare and Medicaid beneficiaries.

Changing HCFA policies to cover treatment and other medical care costs associated with research is only part of the solution to the problem of caring for HIV-infected persons. A more comprehensive approach to financing such care will be needed to eliminate barriers to participation in AIDS/HIV clinical research and to ensure that the improved therapies that emerge from federally supported research are available to those who need them.

Recommendation 1.3: The administration and Congress should immediately address and resolve financial barriers to the receipt of appropriate medical care by persons with HIV infection.

MANAGING THE NIH AIDS RESEARCH PROGRAM

HIV and AIDS are not solely challenges faced by physicians and scientists. The management of NIH has also been presented with an unprecedented task in developing, implementing, coordinating, and evaluating a rapidly growing, complex set of AIDS research activities that now involve every NIH institute, center, and division.

AIDS research at NIH is unusual in that it is not organized under an institute as are, for example, cancer research, vision research, and research on cardiovascular diseases. Instead, NIH is managing the AIDS research program as an "institute without walls," operating the AIDS program from the Office of the NIH Director but using organizational elements analogous to those of the institutes. These elements include a director (the associate director for AIDS research), a national advisory council (the AIDS Program Advisory Committee), an executive committee of senior program officials (the NIH AIDS Executive Committee), and an executive office for staff support (the Office of AIDS Research, or OAR). The committee believes these organizational arrangements and associated administrative processes for managing AIDS research should be strengthened, as an alternative to creation of a separate AIDS institute, and institutionalized as a major long-term program at NIH.

Strengthening Planning and Evaluation

Planning

Because of the large size and organizational complexity of NIH's AIDS research enterprise, the committee believes program management as well as program effectiveness would be improved by the development of an overall long-range research plan. The plan should set out the program's goals and assign priorities. It should define the resources required and the mechanisms to be used and identify the results that are expected over specific time periods. The plan also should be flexible to allow prompt adaptation to unanticipated events that alter prior assumptions. Consequently, it should be subject to periodic review and should be revised annually through a formal decision process.

Recommendation 2.1: NIH should develop a five-year plan to identify AIDS-related research needs and opportunities, set priorities, assess program balance, identify research areas that need stimulation, determine the resources required to carry out the program, and evaluate progress. The plan should be developed under the auspices of the AIDS Program Advisory Committee (after the committee is expanded and oriented as recommended below), with the input of outside experts as well as OAR staff, and it should be reviewed and updated annually. The annual plan review should occur in time to guide the preparation of the regular annual budget so that responsibilities and resources can be shifted if appropriate.

Evaluation

Until recently the rapid budgetary growth of the AIDS program has driven the planning process, rather than the reverse. Most of NIH's AIDS research activities were hurriedly launched by limited staff in the mid-1980s, years of substantial budget increases. As the program matures, however, attention is turning appropriately to the relevance, effectiveness, and efficiency of ongoing activities. Until now, NIH has relied on its time-honored method of evaluation and quality control: peer review of research applications by study sections of independent experts. Many AIDS grants, however, involve large, multidisciplinary projects, centers, and cooperative groups that are closely related to an institute's categorical mission. Scientific review of these projects is essential, but insufficient, because administratively they pose quite different questions of efficiency, effectiveness, and productivity than projects involving an individual investigator in a lab. The situation calls not only for stronger program planning but for stronger evaluation efforts and close linking of planning and evaluation results to the budget allocation process.

Recommendation 2.2: AIDS program evaluation processes should be strengthened and linked closely to planning and budgeting processes to ensure that, first, questions of the highest priority are addressed adequately at all times; second, all studies being supported are still relevant and are as productive and efficient as possible; and third, resources are redeployed, sometimes across institutes, in response to research advances and breakthroughs or as time and experience indicate that some programs are more and some less successful than others in achieving their goals. The Office of AIDS Research should work closely with the Division of Planning and Evaluation in the NIH Director's Office to coordinate evaluations of AIDS research programs in the various institutes. In turn, evaluation results should be considered in program planning and budgeting.

Strengthening External Advisory Processes

One of NIH's strengths is its ability to incorporate external advice from scientists and the public in its planning and operations. As in its other research programs, NIH has established advisory groups at every level of the AIDS research program; many of these groups include patient advocates and members of the general public as well as scientists and researchers. The associate director for AIDS research should routinely reevaluate the need for such committees as the AIDS research program is institutionalized as a long-term activity over the next several years. Not in question is the need for a high-level advisory function, and the committee urges NIH to strengthen its processes for external advice on overall issues of level of effort, balance among research areas and mechanisms, and research opportunities and needs in the AIDS research program. This high-level advisory function, which national advisory councils fulfill in relation to the institutes, should be the role of the AIDS Program Advisory Committee (APAC). APAC has a critical role to play in providing broad advice and overall program oversight; it should also oversee development of the long-term AIDS research plan and ensure extensive external input.

Recommendation 2.3: The AIDS Program Advisory Committee should take a larger role in providing broad policy advice and program oversight and should include among its activities the development of the five-year AIDS research plan and annual updates. It should also conduct an annual review of the programs and budgets developed to implement the plan. This expanded role will require additional staff support and a larger committee to ensure that all AIDS-related areas of expertise are represented, including the behavioral and social sciences and public health authorities. It may also require the establishment of additional subsidiary committees and the recruitment of additional outside experts to review the various research areas (e.g., basic, behavioral, epidemiological).

Strengthening Staff Support

The expanded roles of the associate director for AIDS research and the AIDS Program Advisory Committee in planning, evaluation, and budgeting will require some additional staff support by the Office of AIDS Research and related units in the Office of the NIH Director. In most areas of the AIDS research program, the associate director for AIDS research and the OAR will coordinate activities that are actually carried out by the institutes, centers, and divisions; in other areas-planning, implementing, and evaluating certain cross-cutting functions such as training and construction programs—they should play a larger role. In addition, as recommended later, OAR should review and approve (in accordance with assigned priorities in the overall plan for research) AIDS-related requests for applications (RFA) and requests for proposals (RFP) initiated by the individual institutes.

Recommendation 2.4: The capacity of the Office of AIDS Research should be increased so that it can function adequately as the staff arm of the associate director for AIDS research in his or her role as leader and coordinator of the AIDS program. In particular, OAR will need some additional planning and evaluation staff, including several senior-level scientists who can assist the associate director for AIDS research and the AIDS Program Advisory Committee in monitoring the AIDS research agenda, assessing progress, identifying scientific gaps that need to be addressed, and coordinating the review of institute research initiatives.

Strengthening Executive Authority and Flexibility

The AIDS program is the first major research program to be managed by the Office of the NIH Director rather than by a single institute. The committee considered and rejected the option of creating a separate National Institute of AIDS Research because it believes that the involvement of multiple institutes in addressing the complexities of AIDS will speed scientific progress. Most, if not all, of the advantages of putting the program under one institute—improved communication, management, priority setting, and accountability—can be achieved by the adoption of the strengthened management system, based in the Office of the Director, that is recommended in this report. Thus, in addition to comprehensive, long-range planning and evaluation of AIDS research, the capacity of the NIH Director's Office to implement and coordinate AIDS research activities should be augmented.

Recommendation 2.5: The director of NIH should be given an adequate annually renewed discretionary fund of at least $20 million along with additional authority to transfer up to 1 percent of each NIH appropriation account to increase the agency's flexibility in responding to future emergencies or research opportunities. These resources could be used to exploit important scientific breakthroughs arising in AIDS or non-AIDS research that could not be anticipated in the regular budget process or to address major epidemics or other public health problems that suddenly emerge.

The committee is convinced that an important component of the current strength and success of the NIH AIDS research program is the unique leadership provided by Anthony Fauci, associate director of NIH for AIDS research and director of the National Institute of Allergy and Infectious Diseases (NIAID). Having the same person as director of NIAID, which receives nearly half the NIH AIDS budget, and associate director for AIDS research is administratively unorthodox, because it poses potential conflict of interest problems when questions of interinstitute coordination, budget allocation, and program jurisdiction arise. Each of the positions is also extremely demanding, an aspect that, in the case of the position of associate director for AIDS research, will only intensify if the AIDS program structure is strengthened and institutionalized, as recommended in this report. In this instance the arrangement has worked well because of the energy, knowledge, even-handedness, and prestige of the incumbent.

Recommendation 2.6: The current arrangement of the same person holding the positions of both associate director for AIDS research and director of NIAID is working well. Nevertheless, because of the already substantial and still growing workload of each position, and the potential for bias in mediating conflicts among institutes, the committee believes that the joining of these positions should be reconsidered at such time as the current incumbent steps down.

ELEMENTS OF THE NIH AIDS RESEARCH PROGRAM

In Chapter 2, the committee's main concern was to review the structures and processes for managing the NIH AIDS research program—how it is planned, implemented, coordinated, and evaluated—to ensure that all high-priority scientific questions are being addressed without gaps or overlaps, that programs are well designed and effective and efficient in achieving their goals, and that administrative support by NIH is adequate. The committee believes these questions are especially pertinent at this time, as the program shifts to a long-term managerial mode in response to the size, complexity, and endurance of the HIV/AIDS epidemic, the large size and complexity of the NIH AIDS program itself, and the overall constraints on the federal budget. In Chapter 3,

the committee reviews the components of the NIH AIDS research program in light of the shift to an institutionalized, long-term research effort. Where appropriate in the following sections, it also offers specific conclusions and recommendations regarding the mission, design, size, and management of each component.

Basic Research

The 1980s have seen several major advances in research on AIDS-for example, identification of the causal agent, HIV; development of diagnostic tests for HIV infection; and progress in vaccine and drug development. Such advances have been, and will continue to be, based on fundamental knowledge and methods derived from basic, undifferentiated research that predates the advent of the AIDS pandemic. The committee believes that a strong basic research program is critical in supporting such applied activities as drug and vaccine development. Basic research on HIV and the diseases it causes will in turn produce new knowledge and methods that may contribute to progress against other diseases.

Recommendation 3.1: Greater investments should be made in basic research in such areas as immunology, virology, and molecular biology as part of NIH's long-term research program on AIDS. These basic research advances are critical not only to progress against AIDS but also as a contribution to the base of fundamental knowledge that will be needed to deal with other diseases of the present and future .

Vaccines

Recent advances in HIV vaccine research give considerable cause for optimism about prospects for an HIV vaccine, although many scientific obstacles remain to be overcome. This progress, given the enormous benefit of a successful vaccine for prevention of HIV infection, warrants vigorous expansion of the HIV vaccine program. In order to pursue as many promising research avenues as possible, including those not fully explored by the individual investigator-initiated mechanism, strong support of RFAs and RFPs is appropriate.

Recommendation 3.2: NIH should expand its vaccine research program and furnish strong support for agents that show promise of efficacy and for RFAs and RFPs that target the essential unanswered immunological questions.

The committee considered and rejected recommending a centralized approach to vaccine research because it is premature to focus on a particular approach. The many remaining scientific obstacles to an AIDS vaccine argue for support of diverse research efforts such as those currently being pursued by the various institutes within NIH, together with a mechanism to preclude the inefficient use of resources.

Recommendation 3.3: NIH should create an agencywide vaccine research advisory panel of top extramural scientists to identify research needs, establish priorities, and determine the resources and facilities required for a successful program. In addition, the panel should perform an oversight function to ensure that institutes supporting diverse lines of simian immunodeficiency virus (SIV) and HIV research use resources effectively and in a complementary manner. The committee further recommends that this advisory panel outline a mission for NIH's AIDS vaccine research that complements vaccine research being conducted by the pharmaceutical industry.

If and when attractive candidates for vaccines emerge, the clinical trials that must be conducted to establish their efficacy will be logistically difficult, requiring considerable planning. Problems include liability concerns, developing criteria for placing an HIV vaccine candidate into phase 3 efficacy trials, and selecting trial participants.

Recommendation 3.4: NIH should begin immediately to plan the trials (especially phase 3) that eventually will be required to test a viable vaccine candidate. This process should include the development of criteria for entering a vaccine candidate into human efficacy trials. The committee further recommends that NIH work with Congress to evaluate plans to provide liability coverage for the development of vaccines that pharmaceutical companies otherwise may hesitate to evaluate.

Other major barriers to producing a viable candidate vaccine are a shortage of animal models (especially nonhuman primates), a lack of suitable containment facilities (i.e., facilities rated at biosafety levels 2 and 3) for housing animals and conducting HIV or SIV vaccine research, and a lack of reagents. Recent studies demonstrating protection against infection with the SIV model are cause for optimism regarding an HIV vaccine and warrant increased support for further animal-model studies (see recommendations 3.28 and 3.29). The long lead time necessary for breeding animals highlights the urgent need to plan ahead for adequate resources so that when a candidate vaccine is ready for preclinical testing, scientific progress will not be hindered by inadequate supplies of animals or by substandard facilities or unavailable reagents.

Recommendation 3.5: NIH should provide the support needed to ensure an adequate supply of nonhuman primates, especially chimpanzees and rhesus monkeys, for preclinical development and testing of HIV and SIV vaccine candidates. NIH should also pursue the development of other animal models that might be cheaper and easier to use in vaccine development. Finally, through the associate director for AIDS research, NIH should coordinate the research plans of the various categorical NIH institutes investing in vaccine development with the long-term plans of the National Center for Research Resources for developing and supporting animal models.

NIH officials and extramural researchers were unanimous in asserting that poor access by investigators to high-quality reagents has hindered HIV vaccine research. They also said that investigators do not always provide other scientists with access to reagents developed with NIH support.

Recommendation 3.6: NIH should strongly support a full-scale reagent repository and implement the recommendation from *Confronting AIDS: Update 1988* that "all investigators receiving NIH funds must make their AIDS-related reagents available to a distribution center, and thereby to all qualified investigators, after publication of their research." NIH should enforce this policy by making further funding contingent on cooperation with a reagent pooling program.

Epidemiology

NIH conducts and supports a number of epidemiological studies that in the past have provided invaluable knowledge about the natural history, transmission, clinical markers, and cofactors of HIV infection and the advent and course of AIDS. Information from these studies provided the foundation for a range of NIH AIDS research efforts, including the design and conduct of clinical trials of therapeutic agents against HIV and associated opportunistic infections

(OI) and cancers. In the future, epidemiological studies will be especially important in identifying populations suitable for large-scale vaccine efficacy trials. Yet as the disease changes (e.g., in the appearance of opportunistic infections, in the groups affected) and responds to new treatments, the additional insights to be gained from existing cohorts may not justify the costs of data collection and analysis. NIH's epidemiological AIDS research component should be routinely evaluated for continued relevance and adjusted to the changing course of the epidemic as, for example, more and more members of older cohorts progress to AIDS, members of younger cohorts become infected, and new risk groups are identified.

Recommendation 3.7: NIH should reassess its epidemiological research priorities; evaluate ongoing research, discontinuing less productive or redundant studies and expanding studies in groups experiencing higher rates of HIV infection; and reassess the size of the total NIH epidemiology program in light of fiscal constraints and other emerging research needs. This reassessment should involve external advice.

To maximize the use of resources and prevent the initiation of cohorts of insufficient size to enable meaningful statistical analysis, NIH should also identify opportunities for collaboration, both among institutes and with other Public Health Service (PHS) agencies involved in epidemiological research (the Centers for Disease Control [CDC] and the Alcohol, Drug Abuse, and Mental Health Administration [ADAMHA]).

Recommendation 3.8: NIH should pursue collaborative efforts among its institutes and with other PHS agencies sponsoring epidemiological research to address all first-priority epidemiological issues, avoid duplication, and ensure adequate sample and cohort sizes.

Behavioral Research

The HIV/AIDS epidemic is both a biological and a behavioral phenomenon, and efforts to contain its spread must look to both biomedical and behavioral sciences for interventions. The committee believes NIH has neglected AIDS-related behavioral research. Lack of knowledge regarding patterns and determinants of sexual and drug-using behaviors in the general public, as well as in groups at particular risk for HIV infection, has hampered public health efforts to develop health education interventions for the prevention of AIDS. The committee considers increased attention and funding to be warranted, given the lack of scientific data on behaviors related to HIV infection, the seriousness of the HIV/AIDS epidemic, available research opportunities in the field, and the potential public health benefits such research could realize.

Recommendation 3.9: The NIH AIDS program should increase its support for behavioral research, especially for basic behavioral research (e.g., research designed to understand the etiology or underlying causes of behaviors and evaluate the effectiveness of interventions to modify particular health-related behaviors) on behaviors relevant to the transmission of HIV, including but not limited to human sexual development and practices and (in coordination with ADAMHA) drug addiction and abuse.

The AIDS epidemic has highlighted the need for up-to-date data that are representative of the general population and that can provide a sound basis for designing, implementing, and evaluating education and intervention programs to stop the spread of HIV. In an effort to expand this data base, the National Institute of Child Health and Human Development (NICHD) has

proposed a national survey of health behaviors and AIDS risk prevalence, but plans for the survey have not been approved by the Department of Health and Human Services because of concerns about the survey's scope and content.

Recommendation 3.10: The pretest questionnaire for NICHD's National Survey of Health and AIDS Risk Prevalence should be finalized and released, and the study should be allowed to proceed immediately.

Nursing Research

The committee believes that high-quality care of persons with AIDS, and management of the side effects of AIDS therapeutics, will be essential to ensure a reasonable quality of life for persons who are living with HIV infection. The committee also believes that the knowledge base in this area must be improved if adequate care is to be provided to the thousands of HIV-infected persons who will be flooding the health care system by the mid-1990s.

Recommendation 3.11: Support should be substantially increased for nursing research on the care of people with HIV-related illness.

Preclinical Drug Development

Preclinical drug development of anti-HIV agents and agents for related opportunistic infections is supported by both NIH and the pharmaceutical industry. The different groups that have shown interest in developing anti-HIV drugs possess varying levels of resources for conducting the critical studies required by the Food and Drug Administration (FDA) for an investigational new drug (IND) application to permit use of the drug on a broad scale. The National Cancer Institute's (NCI) long experience in developing therapies in collaboration with drug companies and academic health centers has provided valuable lessons for organizing the development and clinical testing of new AIDS drugs. The committee believes NIH should focus its AIDS-related drug development resources on promising drugs that would not otherwise be developed by the pharmaceutical industry, and on assistance for drug sponsors that do not possess adequate resources to complete the studies required for submission of an IND application.

Recommendation 3.12: The optimal role for NIH's preclinical drug development program should be to facilitate drug development by all sectors—governmental, academic, and private—and to develop drugs whose development is not likely to be supported by the pharmaceutical industry.

Both biochemical and cell-based drug screens are necessary to identify agents with differing mechanisms of action against HIV as well as agents active against discrete components of the HIV life cycle. NIH support for mechanism-of-action studies is particularly important because such studies are unlikely to be conducted by industry.

Recommendation 3.13: NIH should develop and support a range of screening tests for anti-HIV drugs. In addition, NIAID and its Division of AIDS should establish contract-based screening capabilities, and NIH should expand its intramural or dedicated extramural resources for mechanism-of-action studies for anti-HIV agents.

An underdeveloped basic science knowledge base and lack of suitable animal models for many of the OIs that commonly occur in people with AIDS have hindered drug development efforts. Support by the pharmaceutical industry for basic science and animal model studies related to OIs is unlikely. The committee concludes that NIH should have the capacity to conduct this research and all critical path studies required by the FDA for submission of an IND application for drugs for opportunistic infections.

Recommendation 3.14: NIH should increase its support for basic and applied research in the area of opportunistic infections. NIH should also facilitate the development of promising drugs for opportunistic infections through all the steps necessary to secure the IND application.

Clinical Trials

Once the federal government recognized the urgent nature of the AIDS epidemic, and the enormous challenge the disease presented, it began to increase substantially its support of AIDS-related research, the NIH therapeutics programs, and especially the NIAID clinical trials program. NIH was charged with developing the organization for a new, comprehensive drug evaluation program at the same time it was enrolling thousands of patients in clinical trials. Despite these formidable tasks, the short history of the NIH clinical trials program records several notable accomplishments:

- determination of the efficacy of zidovudine (AZT) in the treatment of children with AIDS;
- establishment of a national clinical trials program capable of testing new anti-HIV and anti-OI therapeutic agents;
- recruitment of many talented investigators into AIDS clinical research;
- extension of the use of AZT for persons with early and asymptomatic infection and a better understanding of the drug's most effective and safe dosage ranges; and
- initiation of dozens of important clinical trials that promise to provide essential information about treatment with a wide array of antiviral and anti-OI drugs.

Mission

The committee strongly believes that the rapid growth of the NIH clinical trials program, and its undertaking of a much larger number of trials than were originally envisioned, involving thousands of patients, necessitate a reevaluation of the NIH clinical trials system to ensure that it functions both efficiently and cost-effectively. To begin with, NIH must define the AIDS Clinical Trials Group's (ACTG) mission more clearly with a realistic statement of its scientific goals.

Recommendation 3.15: The ACTG should focus its mission more narrowly and tailor the number of trials it conducts to that new mission, to currently available staff, and to the capacities of the local AIDS clinical trial units.

In redefining the ACTG's primary mission, NIH must distinguish the tasks to which it is best suited and the tasks that are better left to the pharmaceutical industry, the other major resource for AIDS clinical trials in this country.

Recommendation 3.16: The ACTG should assume primary responsibility for trials that are important to the public health and that are unlikely to be conducted by the pharmaceutical industry. These include trials of drugs in combination, trials that compare drugs made by different companies, trials of drugs for small patient populations such as those with particular opportunistic infections or AIDS-related cancers, and, in rare instances, phase 4 or postmarketing trials that may not otherwise be conducted. However, the pharmaceutical companies should be encouraged to take responsibility for phase 4 trials of their products, especially those that expand the indications for already approved drugs.

Interviews with many NIH officials and representatives of the pharmaceutical industry indicated that the ACTG and the industry have not yet established a consistently constructive, complementary relationship. Given that the supply of trial participants and qualified researchers is finite, it is essential that the two primary vehicles for conducting trials (i.e., the pharmaceutical industry and NIH) clearly define their missions and roles and meet regularly to resolve conflicts. The committee believes that NIH-industry collaborations are appropriate and can benefit the development of anti-HIV and anti-OI drugs.

Recommendation 3.17: NIH should ensure maximum coordination of its clinical trials with the pharmaceutical industry by meeting regularly to resolve conflicts over rights to data ownership and access to patients and investigators at AIDS clinical trials unit (ACTU) sites. NIH should also negotiate with pharmaceutical companies for supplemental financing of NIH-conducted trials (e.g., postmarketing studies) that clearly benefit the industry sponsor.

Efficiency Within the ACTG

NIH's initial goals of erecting a clinical trials system and enrolling patients as quickly as possible is giving way to a new stage in which the ACTG evaluates its performance and reassesses its administrative procedures and clinical goals. The committee recognizes and endorses the ongoing effort at the Clinical Research Management Branch of NIAID's Division of AIDS to develop a mechanism and criteria for evaluating individual ACTUs as a basis for planning future trials and for ACTU refunding in 1991 and 1992.

Recommendation 3.18: NIH should conduct an annual, systematic evaluation of each ACTU. The results of these evaluations should be reviewed by an extramural group authorized to advise corrective action and recommend defunding of sites that do not meet expected performance standards.

At present, the ACTG develops protocols by a multistep consensus process in which ACTU investigators develop a concept and send it through multiple ACTG committees and the Division of AIDS program office for revisions and approval. The committee believes that the large number of ACTG trials has combined with the multiple revisions and steps required in its protocol development process to overload the ACTG system and slow the opening of important new trials.

Recommendation 3.19: NIH should simplify the ACTG protocol development process while retaining incentives for individual investigator contributions. Small groups of ACTG investigators should assume the decisive role in designing protocols, and NIH should establish a mechanism by which they can receive frequent informal comments and advice from an active, participatory FDA on the data needed for regulatory

approval. If the ACTG Executive Committee rejects a protocol that has been so designed, a simple appeals process should be available to resolve the dispute.

To address and resolve the many problems involved with protocol design, the ACTG established a protocol evaluation subcommittee.

Recommendation 3.20:. The committee strongly endorses the work of the ACTG's protocol evaluation subcommittee and recommends that its guidelines on optimal protocol design be made available to all ACTG investigators and used as part of NIH's evaluation of proposed protocols.

Accrual

The committee considers it essential that NIH improve its recruitment of minority populations, women, children, and intravenous drug users for clinical trials. The committee recognizes NIH's efforts to engage health professionals in outreach activities among populations that are currently underrepresented in the trials (with the goal of hastening trial accrual) and encourages further measures, such as less stringent entry criteria, that might speed trial accrual among all infected populations.

Recommendation 3.21: The committee believes NIH should increase participation of currently underrepresented populations (i.e., minorities, current and former users of intravenous drugs, women, and children) in AIDS drug trials. To achieve this goal, NIH should (1) examine entry criteria for clinical trials and, where appropriate, make them less stringent, and (2) improve outreach and the provision of ancillary services to underrepresented populations.

Coordination

Interinstitute sponsorship of clinical trials can bring a wide variety of expertise and resources to bear on difficult scientific questions. However, the interinstitute conflict that frequently accompanies such sponsorship may hinder NIH's ability to maximize its resources. Instances of unresolved conflicts surrounding the sponsorship and funding of trials highlight NIH's need for a stronger mechanism to resolve interinstitute disputes and implement necessary changes, as recommended in Chapter 2. In the case of interinstitute coordination of pediatric AIDS clinical trials, the committee believes unresolved conflicts have prevented a fully operational merger of NIAID's and NICHD's pediatric trial systems.

Recommendation 3.22: NIH should complete the merger of the NICHD and NIAID pediatric trials systems to unify their management and funding and ensure maximal use of the two institutes' resources. The merger should include sufficient funding to allow enrollment of NICHD's large pool of patients.

The committee believes that the intramural clinical trials programs at NCI and NIAID possess excellent researchers and resources that have allowed them to achieve important advances in the development of new AIDS therapies. Moreover, the close proximity of intramural laboratories to clinical programs at the NIH clinical center promotes rapid in vivo testing of in vitro results.

Recommendation 3.23: NIH should continue to provide strong financial support for AIDS research efforts of the intramural clinical trials programs.

The committee is concerned, however, that NIH does not have a clear track for bringing a drug through all stages of clinical testing and has not sufficiently capitalized on its intramural program for the execution of certain trials.

Recommendation 3.24: NIH should establish a mechanism for better coordination of extramural and intramural clinical trials and consider shifting more responsibility for phase 1 studies to the intramural program.

Information Dissemination

The extreme sense of urgency surrounding the results of AIDS clinical trials has placed great pressure on the agency to obtain and release usable trial data rapidly. The committee believes NIH has an obligation to publish all such results, whether the trial has a positive, negative, or indeterminate conclusion, because the publication process is the primary means for expanding the knowledge base. The committee strongly endorses the use of expeditious peer review and publication as the best method of information dissemination but recognizes that alternative, faster means may be needed for certain clinically relevant trials.

Recommendation 3.25: The ACTG should institute a comprehensive policy requiring submission of trial data to a peer-reviewed journal within a specified time after completion of the trial or a major protocol change, and timely submission of results should be linked to ACTU evaluations. In addition, NIH should develop a mechanism for public reporting of data with clinical urgency soon after trial completion and prior to journal publication.

Some concerns have been raised that the early release of trial results might lessen the imperative felt by investigators to publish full scientific papers in peer-reviewed publications. An interim publication in no way lessens NIH's responsibility and that of its investigators to publish their data in full.

Recommendation 3.26: The ACTG should establish a working relationship with scientific journals to ensure rapid interim and full publication of high-priority trial results.

Research Resources

Research resources, a public "good" for which federal support is especially suited, are investments in the infrastructure of biomedical science that help researchers do their work quickly and economically. The importance of such resources increases as the AIDS research program becomes a long-term effort.

Training

Research training is an integral part of NIH's multi-institute AIDS research program. Planning and implementation of training activities should be administered centrally by the associate director for AIDS research with staff assistance from the OAR.

Recommendation 3.27: Support should be increased for pre- and postdoctoral training to a level (about 3 percent of the budget) comparable to other training programs within NIH-in a wide range of AIDS-related disciplines: for example, molecular biology, virology, cell biology, immunology, epidemiology, behavioral sciences, infectious diseases, and clinical medicine. Increases should also be made in the number of predoctoral slots supported by the National Institute of General Medical Sciences (NIGMS) and the postdoctoral training grants supported by NIAID.

Animal Models

The lack of a single good animal model of HIV infection and disease progression is still a major impediment to research on AIDS pathogenesis, treatment, and prevention. NIH is currently underwriting development of several promising models including HIV in transgenic and severely immunodeficient mice, SIV in macaque monkeys, and HIV in chimpanzees. For example, as discussed earlier, recent demonstrations of prophylactic and postinfection protection from disease in the SIV-macaque model hold considerable promise for the development of an effective vaccine against HIV. An expanded effort to exploit the SIV model, however, requires better understanding of the immune system of rhesus monkeys and a larger supply of them for future vaccine research. NIH should also support the development of other animal models.

Recommendation 3.28: NIH should develop a plan that addresses animal resource needs for future research, especially vaccine research. For example, the rhesus monkey population available for research should be increased to the level required to support the expanded program of studies on SIV. This should include not only an expanded breeding program but also a larger program of research on the biology of rhesus monkeys and the construction of additional biocontainment facilities.

Facilities

Inadequate facilities will hinder scientific efforts and could pose unnecessary dangers for AIDS researchers. In the committee's view, support for upgraded facilities and equipment is an appropriate element in a balanced, long-term AIDS research program, especially during initial expansion years.

Recommendation 3.29: The associate director of NIH for AIDS research should plan and oversee the implementation of a program for developing an adequate physical infrastructure for AIDS research. The actual administration of the program could be delegated to the National Center for Research Resources or to other NIH operational units.

Communication of Research Results

In addition to the dissemination of trial results, NIH supports an extensive AIDS communications program for scientists, health providers, patients, and the general public. (Research advances with implications for prevention, diagnosis, and treatment are raising new and urgent questions about early dissemination, which were addressed in the section on clinical trials [recommendations 3.25 and 3.26].) The committee commends this work but encourages NIH to solicit input from the

public and the scientific community on its efforts and periodically to review its programs in this area.

SUPPORTING THE NIH AIDS RESEARCH PROGRAM

The success of the NIH AIDS research program depends critically on adequate, high-quality resources to support the program's efforts. These resources include funds for the research itself, in the form of grants, contracts, and intramural projects, and for research infrastructure—research training programs and facilities and equipment grants. Research resources also include NIH's apparatus for reviewing research grant and contract applications and proposals for technical merit and program need, as well as the agency's own staffing and facilities.

Funding of AIDS Research

The committee reviewed carefully the size and composition of the NIH AIDS budget, aware of a general perception that the epidemic is receding and that the current level of effort is adequate. The committee finds, however, that the epidemic of HIV infection and AIDS remains a severe global public health emergency that is causing a growing burden of illness and death and placing severe stresses on the nation's health care system. At present there is no cure for the disease and no vaccine. Containment, therefore, must be a high national priority, and more effective interventions are urgently needed.

As a comprehensive, long-term effort, the NIH AIDS program must respond in a balanced way to knowledge gaps, emerging scientific opportunities, changes in the epidemic, and other, unforeseen contingencies. The question of program balance is thus an evolving one that should be addressed through the planning and priority-setting process recommended in this report. For example, promising scientific developments in vaccine research urge additional studies, which will require more funds for grants and research resources. In addition, a balanced, long-range program should invest more in undirected individual investigator-initiated research, given the lack of basic knowledge about HIV infection and AIDS. The benefits to be derived from such research often go well beyond those applicable strictly to HIV/AIDS. Scientific advances in AIDS research also will continue to have important spinoffs that contribute to progress against other diseases and provide a base of knowledge that will be useful in dealing with epidemics of the future.

The committee concluded that other areas of AIDS-related research are relatively under-developed and should be expanded; these include behavioral research, nursing research, development and testing of therapies for AIDS-related OIs and cancers, and research training. On the other hand, greater efficiency may be possible in some of the large-scale programs that have been running for several years or more, such as epidemiology and clinical trials. In the opinion of the committee, increased management efforts and program activity in a number of areas would not be adequately accommodated within the present level of effort. The net effect of the committee's recommendations could increase costs on an order of magnitude of 25 percent, a rough estimate that might be lowered (if there were significant savings in existing activities) or raised (if there were major breakthroughs that required exploiting).

The committee is aware that many people consider the NIH budget as a whole to be inadequate and that there is an immediate crisis in funding a sufficient number of competing grants this fiscal year and next to maintain the nation's biomedical research momentum. The committee is also aware that advances in containing and controlling AIDS rest on the overall strength of the

NIH units. Taking resources from other pans of the agency to expand the AIDS research program would impede overall progress in biomedical research and the AIDS program itself, which is an integral part of and dependent on a wide range of NIH activities.

Recommendation 4.1: Implementing the long-term AIDS research program recommended by this committee will require a larger budget to ensure that the most promising basic science opportunities are supported, that underdeveloped areas of research are expanded, and that research resources are adequate to support the planned level of research effort. These opportunities and needs could justify an immediate increase of as much as 25 percent in NIH's budget for AIDS research; the exact timing of the increase should be an integral part of the long-range plan recommended by the committee. It is essential that any such budget increases be new funds and that they not be derived at the expense of ongoing NIH programs.

In the past, NIH defined AIDS research narrowly to encourage well-established researchers to leave research in other areas for studies on AIDS. This goal has now been achieved, and the artificial distinction between AIDS research and AIDS-related basic research has outlived its usefulness.

Recommendation 4.2: NIH should adopt NIAID's recent redefinition of AIDS research (to include closely related basic research in immunology, virology, molecular biology, cellular biology, and other related areas) for use throughout its institutes.

Grants Policy and Administration

The committee has carefully examined NIH's organizational and procedural arrangements for reviewing and awarding AIDS-related research grants and concludes that currently they are adequate. AIDS research project grant applications and awards have increased in number and improved in quality, as measured by peer-review scores. The share of the AIDS budget going to research project grants has increased to about 40 percent, and the proportion of those solicited by RFAs has decreased. The committee recognizes the need for solicited research and directive mechanisms in building a fast response to a public health emergency but believes that a long-range AIDS research program warrants greater reliance on grants, especially individual investigator-initiated grants.

Recommendation 4.3: NIH should continue to increase its use of research grants, especially traditional individual investigator-initiated and related grant mechanisms, to carry out the expanded research effort recommended by the committee, in particular, the increased effort in basic research.

RFAs and RFPs at NIH are usually initiated by program staff who identify gaps in research and propose mechanisms for soliciting grant applications to address those gaps. After approval at the institute and advisory council levels, proposed RFAs and RFPs receive an administrative review in the Office of the NIH Director and are circulated to the other institutes for comment and to minimize duplication of effort. The committee believes that central review of RFAs and RFPs should be coordinated with the research planning effort recommended in Chapter 2 of the report to identify and remedy gaps in AIDS research.

Recommendation 4.4: The NIH associate director for AIDS research and the AIDS Program Advisory Committee should review all RFAs and RFPs for AIDS research to

ensure coordination and avoid duplication. They should also have the authority to recommend RFAs and RFPs in the case of gaps in the NIH AIDS research program that are not being addressed by individual institutes.

Administrative Support

The effectiveness and success of the NIH AIDS extramural and intramural research programs depend in part on the adequacy of the administrative support they receive in the form of staffing and facilities.

Staffing

Until recently, NIH operations were hampered by arbitrary personnel ceilings imposed by the Office of Management and Budget (OMB). These ceilings had a significant effect on the AIDS research program because the number of scientists and science administrators could not increase as quickly as the scientific opportunities for intramural AIDS studies or the amount of funding for extramural AIDS grants and programs. Chronic understaffing thus has constrained NIH's ability to conduct AIDS research and adequately plan, administer, and evaluate its extramural AIDS programs. Now, however, OMB and the Department of Health and Human Services (DHHS) have delegated increased authority to PHS agencies to set personnel levels. NIH in turn must determine appropriate program staffing and develop a plan to achieve it.

Recommendation 4.5: The committee strongly opposes arbitrary restrictions on NIH staffing levels that are established without regard to program requirements because they hamper effective, efficient management. Personnel ceilings should be abandoned permanently, and future staffing decisions should be part of the strengthened program planning and budgeting processes recommended in Chapter 2 and coordinated by the Office of the NIH Director. Adjustments in staffing levels should be made carefully over several years to achieve appropriate balances between AIDS and non-AIDS programs, between the elimination of past deficits and the needs of new initiatives, and between the budgets for extramural grants and contracts and for staff to administer those grants and contracts.

The committee also supports efforts to maintain NIH staff excellence by addressing broader personnel problems, both those relating to compensation and those stemming from inflexible or sluggish policies and procedures of government personnel systems. The committee endorses as well special efforts to solve problems specific to the AIDS program, such as recruitment and retention of medical officers in the NIH AIDS treatment research (clinical trials) program.

Facilities

NIH-wide space limitations and inadequacies have affected the AIDS research program disproportionately because it is a relatively new and fast-growing set of activities. Congress's appropriations over the past several years for buildings and facilities have greatly reduced the backlog of needs for adequate, appropriate space and equipment for AIDS research, but much of this capacity is in off-campus sites. The committee believes that the scattered locations of AIDS activities hamper communication and collaboration between AIDS basic and clinical researchers and between AIDS and non-AIDS researchers involved in related studies; they also impede administra

tive coordination of extramural AIDS and AIDS-related research programs in the different institutes, centers, and divisions.

Recommendation 4.6: As part of its long-range building and facilities program, NIH should consolidate AIDS research and research administration on the NIH campus. This consolidation will facilitate communication between the intramural and extramural programs and coordination of the multiple institutes, centers, and divisions involved in AIDS research activities. The committee endorses NIH's effort to take a systematic, sustained approach to upgrading and maintaining the campus infrastructure, which will benefit the AIDS program as well as non-AIDS research.

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AIDS: the Research Challenge

This report examines the AIDS research program that NIH, the nation's foremost biomedical research institution, has developed in response to the epidemic of HIV infection and its most serious clinical manifestation, AIDS. The report focuses on the challenges facing NIH in the present struggle to understand, manage, and control the disease and presents conclusions and recommendations regarding the present status of the program and its future directions. Because the epidemic will continue to grow, NIH is now faced with institutionalizing its many AIDS research activities and melding them into a well-planned, well-managed research program that takes a comprehensive, long-range view of the epidemic. This report addresses the tasks that must be completed to accomplish that mission. First, however, this chapter discusses the reasons why NIH should continue to make AIDS research a high priority and convert it into a long-term program. It also reviews the latest epidemiological trends and discusses the problems for NIH's clinical research effort caused by inadequacies in the nation's health care delivery and financing system. The rest of the report examines program-wide (Chapters 2 and 4) and specific (Chapter 3) adjustments recommended by the committee for the future of the program, given present scientific opportunities and public health needs.

UNIQUENESS OF THE EPIDEMIC

AIDS is the first major life-threatening infectious disease epidemic faced by the United States in decades. It is also the first such epidemic since the advent of modern biology and the growth of the national biomedical research enterprise. Caused by the human immunodeficiency virus, AIDS is a fatal disease for which there is no known cure or vaccine. Those affected remain infectious for years, during both a symptomatic stage as well as an asymptomatic phase that precedes manifestation of the disease. Because HIV specifically targets and kills certain critical cells of the body's immune system, the immune response of infected individuals eventually fails. They cannot eradicate the virus that infects them, and they become chronically susceptible to life-threatening infections by a myriad of other microbes, generally succumbing eventually to one of these opportunistic invaders or to certain forms of cancer to which they are also especially susceptible.

At the beginning of the epidemic, AIDS was especially prevalent among socially stigmatized members of society—homosexual men and users of intravenous drugs. A decade into the epidemic, the disease is slowly moving into a new subpopulation—inner-city minorities who also live on the margins of mainstream America. Many observers have attributed the slowness of the initial federal

response to AIDS to the fact that it appeared to be a sexually transmitted disease confined to these socially marginal subpopulations. The marginality of these groups has also affected other aspects of the nation's response. Because many of those currently infected are among the poorest in the nation, with limited access to primary health care, clinical trials to assess drug efficacy are enormously complicated. These circumstances, and the basic unpredictability of the disease's future course, make the AIDS epidemic a challenge of unprecedented magnitude and complexity for both NIH and the nation. The committee's concerns about the inability of the health care delivery and financing system to respond adequately to the epidemic, and its effects on NIH's capacity to conduct research, are addressed later in this chapter.

In the midst of such concerns, however, it is wise to remember that some positive notes have been sounded as well. As the disease has become better understood, behavioral changes among some of the groups most at risk have slowed the advance of infection. In addition, new forms of therapy for those affected have begun to alter the course of the disease, making it more of a chronic than an acute condition. Yet these promising changes are making only modest inroads toward changing the epidemic's course. It is clear that initially afflicted groups are still represented among new cases and that the epidemic is spreading into hitherto untouched populations.

NIH'S RESPONSE TO THE EMERGING EPIDEMIC

In response to the epidemic, NIH has developed an extensive program of AIDS research that involves every institute at the agency and every type of activity traditionally supported by NIH, ranging from basic research to clinical trials to public information campaigns. In fact, the AIDS program constitutes an unprecedented attempt to address a disease with an NIH-wide program rather than through a single institute. If all AIDS research funds at NIH were allocated to a single institute, it would be the third largest in terms of budget and staff.

NIH's role in responding to the emerging epidemic was, and continues to be, only one element of the federal government's AIDS activities. CDC, another PHS agency and the government's lead agency for investigating disease outbreaks, carried out a significant part of the government's early efforts. In 1981 and 1982, CDC officials investigated case reports of *Pneurnocystis carinii* pneumonia (PCP) and Kaposi's sarcoma, two of the diseases now known to be characteristic of AIDS, and the results of those investigations prompted the initiation of epidemiological studies. In contrast to the CDC focus, NIH launched studies probing the biological basis of the disease, began admitting patients to its clinical center, and began developing requests for grant applications to investigate clinical and scientific aspects of AIDS. Since AIDS was first identified, CDC, like NIH, has greatly expanded its HIV/AIDS program and continues to make significant contributions to controlling the epidemic by its surveillance and education initiatives. The other PHS agencies have also become involved.

- ADAMHA, through its three institutes (the National Institute of Mental Health [NIMH], the National Institute on Drug Abuse [NIDA], and the National Institute of Alcohol Abuse and Alcoholism [NIAAA]), supports a substantial amount of research on HIV infection. NIMH supports research on neuroscience, neuropsychiatric, and behavioral aspects of HIV infection and AIDS; NIDA and NIAAA focus on the connection between drug use and HIV infection, development of more effective pharmacologic agents to treat drug addiction (increasingly a risk factor for HIV infection), and development of effective behavioral interventions to prevent or stop drug abuse.

- FDA has regulatory responsibility for ensuring the safety and effectiveness of therapeutic agents, vaccines, diagnostic reagents/test kits, blood and blood products, and medical devices related to HIV infection, AIDS, and associated infections.
- Another PHS agency, the Health Resources and Services Administration (HRSA), supports several service delivery and education programs, including adult and pediatric service delivery demonstrations, regional AIDS education and training centers, an AZT reimbursement program, and AIDS services in community migrant health centers.
- The Agency for Health Care Policy and Research (formerly the National Center for Health Services Research) gathers and analyzes data on the costs, quality, delivery, availability, and financing of HIV-related services for different risk groups, geographic locations, stages of illness, treatment modalities, and treatment settings.
- The Indian Health Service (IHS) supports reservation-based prevention programs, HIV testing and counseling through IHS facilities, and monitoring and surveillance in coordination with the CDC and state health officials.
- The National AIDS Program Office (NAPO), in the Office of the Assistant Secretary for Health, coordinates PHS activities related to HIV infection and AIDS; it also provides leadership in developing PHS policy related to the epidemic, reviews PHS agency budget requirements, and sponsors a wide range of conferences and forums on AIDS issues.

The structure of the NIH AIDS research program evolved incrementally as the agency responded to emerging scientific opportunities, and it reflects NIH's role as a biomedical research agency. In the early years of the epidemic, individual intramural scientists and extramural investigators became involved in AIDS research because they were motivated by the scientific challenges of AIDS; an organized response by NIH did not occur, however, until 1985 when the NIH Director's Office initiated expedited procedures and coordinating activities for AIDS-related research.

Several factors impeded NIH from moving quickly during the epidemic's first few years. Initially, there was uncertainty about where to look for the causes of AIDS until CDC-sponsored epidemiological studies determined in late 1982 that it was most likely an infectious virus. Moreover, the Reagan administration would not allow NIH to request increased funding for AIDS research for several years, during which time the agency had to reprogram resources from ongoing programs. NIH was also hampered by its own standard operating procedures and decentralized organizational structure, which were oriented toward support of long-range basic research rather than swift, coordinated action on a complicated disease that cut across the traditional missions of the 14 major NIH research units that existed in 1981-1982. (That number has grown to 18 with the addition of the arthritis and deafness institutes and the centers for nursing research and human genome research.)

By 1985 NIH had deemed its standard practice of waiting for investigators to submit high-quality proposals too slow for the exigencies of the AIDS epidemic. Under substantial congressional pressure to expand AIDS research, NIH quickly increased its intramural efforts. Extramurally, it expedited grant reviews, used RFAs and contracts to stimulate research in specific areas, funded some applications with relatively low peer-review scores, and employed cooperative agreements and contracts.

To manage and coordinate the interdisciplinary, interinstitute program that had begun to evolve, NIH developed a special administrative system for AIDS activities. The NIH AIDS executive committee was established in 1984 (superseding several working groups created in 1982 and 1983); its membership consisted of representatives from each institute, center, and division involved in AIDS efforts. In 1985 NIH designated NIAID the lead institute and named the NIAID

director the NIH AIDS coordinator. It also established the AIDS Program Advisory Committee of outside experts in 1987 to advise the director on AIDS issues. In 1988 NIH created the Office of AIDS Research, located in the Office of the Director, to coordinate intramural and extramural AIDS research, centralize AIDS-related policy and operating functions, and represent the director on matters related to AIDS. At the same time, the NIAID director became associate director for AIDS research throughout the agency.

The committee concludes that NIH faced an unprecedented challenge in responding to the epidemic of HIV infection and AIDS, the first pandemic of a new deadly infectious disease to occur in the era of modern biology. Once the magnitude of the epidemic became clear—especially once HIV was identified as the causal agent—NIH was given the mandate and resources to develop a large, multifaceted AIDS research program to understand HIV's pathogenesis, discover and test therapies, and develop prevention strategies and a vaccine. AIDS research supported and conducted by NIH has led to rapid increases in basic knowledge about several aspects of the disease: HIV and its replication, the molecular and behavioral aspects of transmission, the human immune response to HIV infection, and the clinical course of AIDS.

Recent projections indicate that the epidemic is still growing and spreading and that its scientific challenges may be changing. Initial scientific inquiries focused on the discovery of the etiologic agent and on understanding the natural history and epidemiology of HIV infection. Once HIV had been identified, however, new scientific opportunities abounded and continue to arise. The major research challenges now are to develop methods to slow and halt transmission of the virus and improve the effectiveness of therapies for those infected. The most promising approaches to controlling transmission are through behavioral change and development of a vaccine. The challenges in developing better therapies focus on the development of pharmacological agents for HIV and for prevention and control of opportunistic infections. Another substantial challenge is the development of more effective ways of providing care for infected individuals.

To achieve these goals, much must be learned about the virus itself and its effect on its human host. Major scientific questions remain to be answered in many fields, including immunology, virology, biochemistry, epidemiology, and behavior. Some partially effective therapies have been discovered and developed, and recent advances in vaccine research have convinced many scientists that an effective vaccine may someday be available. Meanwhile, however, the epidemic continues to grow and spread into new areas and populations. HIV infection is a lethal infectious disease that warrants a well-planned, well-organized long-term research program leading to the control and eventual eradication of the disease.

The committee concludes that NIH should continue to give AIDS research high priority because HIV infection and AIDS constitute a major public health threat and because they provide substantial opportunities for greater scientific understanding of the human immune system and of other viral diseases that affect mankind. The size and long-term nature of the threat call for an institutionalized response.

Recommendation 1.1: NIH should complete its building of the AIDS research program as a comprehensive, long-term effort. The shaping and implementation of such a program will require a series of steps that are described in the remainder of this report.

These steps should have several positive results:

- strengthened management structures and processes for planning, coordinating, evaluating, and reallocating AIDS research activities supported by the various research components of NIH and for ensuring their quality and cost-effectiveness;
- fuller development of some promising research areas;
- an increased overall level of support for AIDS research; and
- increased personnel and facilities resources to enable NIH to conduct and manage an effective, efficient AIDS research program.

DEMOGRAPHICS AND PROJECTIONS OF THE EPIDEMIC

AIDS was first recognized as a syndrome in 1981 (CDC, 1981; Gottleib et al., 1981), and HIV was identified as the etiologic agent in 1983 (Barre-Sinoussi et al., 1983; Gallo et al., 1984). The World Health Organization (WHO) estimates currently that 8 to 10 million people worldwide are infected with HIV (WHO, 1990a) and that more than 283,000 persons have developed AIDS (WHO, 1990b). WHO also predicts that, by the year 2000, 15 to 20 million persons will have been infected with HIV and that approximately nine times as many adults will develop AIDS during the 1990s as during the 1980s.

HIV is transmitted through sexual contact, infected blood or blood products, contaminated needles or syringes, and transplanted tissue or organs from an infected donor, as well as from mother to fetus. HIV is a retrovirus that inserts its genetic material into various types of human cells, which then produce copies of the virus. It invades and eventually destroys T4 lymphocytes, white blood cells that are part of the body's immune system. As infected persons' T4 cells are depleted, they develop AIDS; that is, they develop clinical symptoms and usually die from one of a number of opportunistic infections or cancers that are able to establish themselves because of the body's weakened immune system.

The epidemic of HIV infection and AIDS is still growing and has been steadily rising in the national rankings of causes of death. In 1989 the PHS estimated that between 800,000 and 1.2 million persons were infected with HIV in the United States and that although projections indicate that the overall rate of increase has slowed, the incidence of HIV infection is still increasing (CDC, 1990a). As of August 31, 1990, reported AIDS cases totaled 146,746 (CDC, 1990b: Table 1), and CDC estimated that between 390,000 and 480,000 new cases of AIDS would be reported between 1989 and 1993 (CDC, 1990a: Table 2). Also as of the end of August 1990, deaths in the United States from AIDS totaled 89,761 (CDC, 1990b: Table 8). As the annual deaths from AIDS increased from 6,540 in 1985 to 15,026 in 1987, its ranking among causes of death for adults moved from 19th to 15th (National Center for Health Statistics, 1990b: Table 24). The disease will continue to move up in the rankings as the annual number of deaths from AIDS increases from about 32,000 in 1989 to between 53,000 and 76,000 in 1993 (CDC, 1990a: Table 2; Figure 1.1[1]).

AIDS' impact ranks higher in terms of years of potential life lost (YPLL) before age 65 because HIV infection and AIDS disproportionately affect the younger segments of the population. More than two-thirds of AIDS patients are less than 40 years of age at the time of diagnosis. In 1988 AIDS ranked sixth in YPLL before age 65 (CDC, 1989b). If actual deaths from AIDS reach

[1] Tables and figures appear at the end of the text of each chapter.

CDC's midrange estimates, the YPLL before age 65 could reach fifth place in 1991 and third place in 1993 (Table 1.1).

The composition of the AIDS population is changing both by geographic area and risk group. Although AIDS is still most prevalent among homosexual and bisexual men and in large metropolitan areas, the epidemic is spreading rapidly among users of intravenous drugs and their sexual partners, minority individuals whose behaviors place them at risk, women, and children. The epidemic is also spreading beyond the urban centers where HIV first made an impact and into less populated areas of the country. For example, prior to 1985, well over half of all reported AIDS cases were in the "first wave" metropolises of New York, San Francisco, Miami, and Newark. More recent data show increased numbers of AIDS cases in the central region of the country. As of 1988 the percentage of total cases for first-wave cities had dropped to 36 percent; new cases in the rest of the United States rose from 22.1 percent to 37.8 percent of all cases. In addition, 15 other standard metropolitan statistical areas (SMSA) increased their representation from 19.3 to 26.2 percent of all cases (CDC, 1989a).

Certain minorities are disproportionately represented among AIDS cases, in part because of higher prevalence among certain groups of illicit drug users and subsequent transmission of the virus to their sexual partners and children (Curran et al., 1988). The pattern of distribution of sexually acquired AIDS parallels the distribution of other sexually transmitted diseases, which are also more frequent among black and Hispanic inner-city populations (Holmes et al., 1990). Blacks constitute 12 percent and Hispanics 7 percent of the U.S. population, but they account for 28 and nearly 16 percent, respectively, of all AIDS cases (CDC, 1990b). Age-adjusted death rates (deaths per 100,000 persons in the resident population) for AIDS in 1988 were 25.4 for black males and 8.3 for white males (the overall age-adjusted rate for deaths from AIDS was 5.5 deaths per 100,000). In 1988 the death rate for black women (10.3 per 100,000) was nine times the rate for white women (1.2 per 100,000; Chu et al., 1990).

Intravenous (IV) drug users are increasingly represented among reported AIDS cases. Since 1981 the percentage of AIDS cases ascribed to the use of IV drugs has risen from 11 percent in 1981 to 23.2 percent at the end of 1989 (Table 1.2). CDC estimates that more than one-quarter of all AIDS cases are associated with IV drug abuse (PHS, 1988:66). The PHS also estimates that in communities with large illicit-drug-using populations, such as New York City, the prevalence of HIV infection is between 30 and 40 percent among IV drug users aged 15 through 24 (PHS, 1990a:479). According to CDC estimates, there are 1.1 to 1.3 million IV drug users in this country, all of whom are potentially at risk for HIV infection, as are their sexual partners and children (PHS, 1988:66).

Women and children are beginning to account for more and more cases of AIDS and HIV infection. Although the number of women with AIDS (13,807 cases reported through August 1990) is relatively small in relation to the total number of cases, the incidence rate among women has been steadily increasing, from 7 percent of reported cases during 1985 to 11 percent during 1989 (3,931 of 35,238 cases reported; PHS, 1990b). Between 1985 and 1988 the death rate from HIV/AIDS for U.S. women between 15 and 44 years of age quadrupled (from 0.6 to 2.5 per 100,000), and by 1987 HIV/AIDS had become one of the 10 leading causes of death for that age group (Chu et al., 1990). CDC estimates that, of the approximately 1 million Americans who are currently infected, about 100,000 are women, most of whom (79 percent) are in their peak childbearing years—between 13 and 39 (U.S. DHHS, 1988:7,13). As a result, HIV disease is also rising rapidly as a leading cause of death among children in the United States. As of September 1990, CDC reported 2,525 diagnosed cases of AIDS among children and 1,328 deaths (CDC, 1990b). By 1987 AIDS was the ninth leading cause of death among children 1 to 4 years of age

and the seventh for young people between the ages of 15 and 24; it is expected to be one of the top five leading causes of death among children by 1990 or 1991 (U.S. DHHS, 1988:7). Approximately 83 percent of all AIDS cases in children under 13 are perinatally acquired (CDC, 1990b: Table 4). Among the AIDS cases in adolescents and young adults aged 13 to 24 reported between 1981 and 1988, the most common mode of transmission among males was homosexual/bisexual contact (65.8 percent); the most common mode among females was heterosexual contact (41.6 percent; U.S. DHHS, 1988: Chart 15).

HIV infection and AIDS disproportionately affect those who are disenfranchised not only from the health care system but from society as well. All projections indicate that the trends noted above will continue. Therefore, unlike other diseases such as heart disease and cancer, which also pose a significant yet historically stabilized burden of disease, the burden of disease created by the HIV epidemic is still climbing with no end yet in sight.

HEALTH CARE FINANCING

As noted earlier, the shift in demographics in the HIV/AIDS epidemic also represents a shift toward populations who have poor access to the health care delivery system and thus already carry a disproportionately heavy burden of ill health and disease—to which AIDS is being added. The committee is very concerned that inadequacies in the financing of health care in the United States threaten the research program at NIH, in particular, the conduct of clinical trials for AIDS therapies, as discussed later in this section. Although the state of the nation's health care delivery system was not within its direct charge, during the course of the study the committee found it impossible not to confront the serious deficits of this system and their deleterious effects on NIH's research efforts. The provision and financing of care for persons with HIV infection are major problems that must be addressed not by NIH but by higher levels of the federal health policymaking establishment.

HCFA has estimated that 25 percent of AIDS costs are funded through Medicaid and that 40 percent of all patients with AIDS are served under Medicaid (Winkenwerder et al., 1989:1600). In general, AIDS patients are less likely than the general population to have their health care financed by Medicare or private insurance and more likely to rely on Medicaid or to be uninsured (Figure 1.2). Indeed, recent evidence shows that the proportion of AIDS patients who are covered by private health insurance has declined over time and that payment responsibilities are shifting increasingly to the public sector, primarily to Medicaid (Arno, 1987; Green and Arno, 1990). Several factors account for this trend: (1) the changing demographic face of the epidemic, in which increasing proportions of AIDS cases are occurring among populations (e.g., IV drug abusers, minorities) who are less likely than earlier groups with high incidence (i.e., gay men) to be covered by private insurance and more likely to be covered by Medicaid; (2) the increasing proportion of people with AIDS who have lost their private insurance and have become eligible for Medicaid; and (3) the growing number of private insurers that avoid AIDS cases by selective underwriting of policies (Baily, 1989).

Previous Institute of Medicine (IOM)/National Academy of Sciences (NAS) committees (IOM/NAS, 1986, 1988a), an IOM/NAS white paper (IOM/NAS, 1988b), the National Commission on AIDS (1989, 1990), the Congressional Research Service (1989), and health policy researchers (Baily, 1989; Green and Arno, 1990; Makadon et al., 1990; Thorpe, 1990) have all noted that problems with the health care system—particularly the problem of access to care—have especially negative effects on persons with HIV infection. In the United States, health care is financed through a mix of private initiatives and public programs, with most persons gaining access to the

medical care system through health insurance (Congressional Research Service, 1988). Approximately 64 percent of the population have employment-related coverage; only about 10 percent rely solely on public coverage (Short et al., 1988). This patchwork arrangement leaves between 31.1 and 37 million Americans with no health insurance (Moyer, 1989). The uninsured are not, however, a representative cross-section of the United States; they are more likely than the insured population to have low incomes, to work part-time or in a small firm, to be under the age of 30, and to be black or Hispanic (Congressional Research Service, 1988). There is, therefore, an overlap between the uninsured population and the groups expected to have increased future incidence of HIV infection (Baily, 1989).

The committee believes that facilitating economic and geographic access to health care falls beyond NIH's purview. Agencies and programs outside NIH have the lead responsibility for (1) establishing health care reimbursement policies, (2) financing health care, and (3) providing geographic access to health care. For example, policies established by the Health Care Financing Administration for Medicare and Medicaid affect virtually all elements of the health care system but fall far short of a comprehensive national program for ensuring the delivery and financing of care for poor and minority patients with HIV infection or AIDS. The problem of access to care is beyond the scope of this study. The committee nevertheless concludes that the growing number of AIDS patients, their increasing length of survival after diagnosis, the efficacy of early intervention, and the costs of current and future therapies have implications for the health care system that require urgent attention.

The lack of insurance coverage and access to primary health care experienced by many of the populations most at risk for HIV/AIDS seriously impedes NIH's ability to conduct quality clinical research. On one level, it is much more difficult to recruit patients for participation in clinical trials when those patients do not normally receive health care from the hospitals conducting the trials; as a result, certain patient groups are excluded from trials because they lack health insurance or access to a tertiary care center. On a second level, once a patient who lacks health insurance or a primary care provider is recruited for a trial, he or she places great demands on the clinical trials staff for social work services and health care that are often not directly related to the trial protocol. These patients can pose financial burdens either by limiting the overall number of patients a trial site can manage (owing to demands on staff time), or by increasing the level of the hospital's uncompensated care. The NIH clinical research budget of $164 million is only a fraction of what would be needed for comprehensive AIDS care for the more than 60,000 people with AIDS and the estimated 800,000 to 1.2 million persons infected with HIV. **The committee believes that NIH's mandate is to facilitate the discovery and clinical evaluation of therapeutic, diagnostic, and preventive agents and not to assure health care**.

Another serious financial burden facing NIH clinical research centers is the lack of third-party reimbursement for inpatient care for persons participating in clinical trials. Public and private insurers, including Medicare and Medicaid, exclude payment for state-of-the-art care associated with a trial, even when such care is customary and within the normal scope of care that would be provided if the patient were not participating in the trial (Fauci, 1990; McGuire, 1990; Sande, 1990). This practice is based on a traditional policy under which payers do not cover the costs associated with experimental treatments.

The issues surrounding third-party reimbursement for necessary and appropriate patient care costs associated with approved clinical trial protocols have been studied by a previous IOM panel, the Committee to Study Resources for Clinical Investigation, and by the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS (also known as the Lasagna committee). The IOM committee concluded that "it is wholly inappropriate for third

party payers to deny reimbursement for all appropriate and necessary patient care costs (not marginal costs owing to investigational intervention) that would have been incurred in any case simply because a patient is on an investigational protocol" (IOM/NAS, 1988c:7). The committee thus recommended that third-party payers, both governmental and nongovernmental, pay the necessary and appropriate patient care costs for beneficiaries enrolled in approved clinical investigation protocols; they also recommended that the marginal costs related to the clinical investigation be borne by the agency sponsoring the research (IOM/NAS, 1988c:7-8). The Lasagna committee looked at the approval process for new drugs for life-threatening diseases for which existing therapies are inadequate, including AIDS, and concluded that the medical care costs associated with such research should be covered by Medicare, Medicaid, and private insurers (NCI, 1990:14-15). The Lasagna committee also recommended that investigational drugs, marketed drugs prescribed for unlabeled indications, and ancillary medical care costs be covered by insurers if they were approved by expert government agencies for therapeutic use (such as NCI approval of Group C cancer drugs and FDA approval of drugs under treatment INDs) or included in authoritative medical compendia (such as the three intended for use under the Medicare Catastrophic Coverage Act of 1988; NCI, 1990:13).

This committee concurs with these recommendations—that third-party payers should cover the costs of medical care of beneficiaries in approved AIDS clinical trial protocols, costs that would be incurred whether or not the patient were in a clinical trial, and that they should pay for promising investigational drugs for HIV infection and associated infections and cancer. NIH should support the additional costs related to the conduct of the clinical research. Adoption of these recommendations will require a clarification in current Medicare regulations of the definition of medically necessary care.

The committee believes these steps are necessary to remove financial barriers to participation in investigational protocols and thus sped advances in AIDS therapeutics. They will also serve to extend and improve the quality of life of those infected by HIV.

Recommendation 1.2: The Health Care Financing Administration should make its reimbursement policies consistent with NIH assessments of promising treatments so that when treatments have moved beyond phase 1 testing, their associated medical care costs (and the costs of the treatment if the sponsor is unable to provide it free of charge) are covered for Medicare and Medicaid beneficiaries.

Changing HCFA policies to cover treatment and other medical care costs associated with research is only part of the solution to the problem of caring for HIV-infected persons. A more comprehensive approach to financing such care will be needed to eliminate barriers to participation in HIV/AIDS clinical research and to ensure that the improved therapies that emerge from federally supported research are available to those who need them. An earlier IOM/NAS white paper, *HIV Infection and AIDS* (1988b), based on the work of the IOM/NAS AIDS Activities Oversight Committee, recommended that the Secretary of Health and Human Services "take the lead in developing a comprehensive national plan for delivering and financing care for needy HIV-infected and AIDS patients." In the meantime, steps should be taken to provide financing for persons who participate in NIH research, either through one of the existing federal health financing programs, such as Medicare or Medicaid, or through a special categorical grant program. Additional actions by NIH to increase participation in clinical research by women, children, minorities, and persons using IV drugs are described in the section on clinical trials in Chapter 3.

Recommendation 1.3: The administration and Congress should immediately address and resolve financial barriers to the receipt of appropriate medical care by persons with HIV infection.

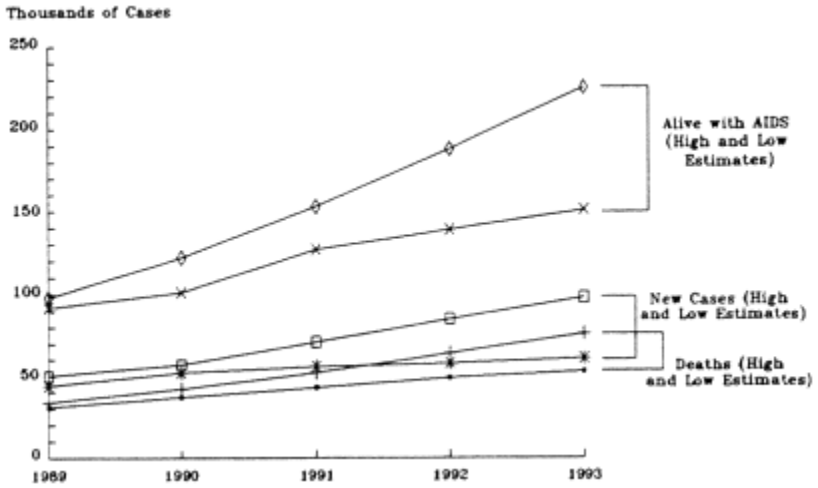

Figure 1.1
Projected annual number of AIDS cases, deaths attributable to AIDS, and living persons with AIDS, United States, 1989-1993. Projections were adjusted by CDC for unreported diagnoses of AIDS by adding 18 percent to projections obtained for reported cases.
Source: CDC, 1990a.

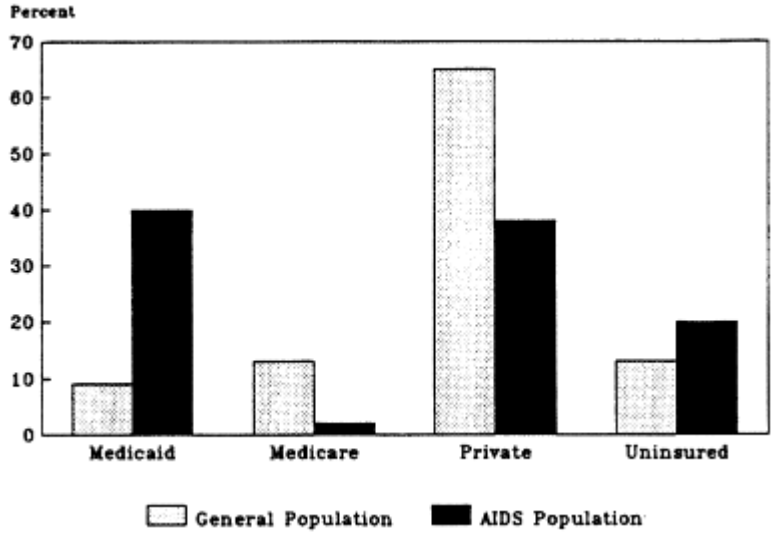

Figure 1.2
Distribution of payers for AIDS and non-AIDS medical care, 1989.
Source: Thorpe, 1990: Figure 4.

TABLE 1.1 Estimates of Years Potential Life Lost (YPLL) Before Age 65 for HIV/AIDSYear

Year	YPLL	YPLL Estimate (Lower)	YPLL Estimate (Upper)
1987[a]	363,494		
1988[a]	472,800		
1989[b]	562,602		
1989[c]		848,000	930,000
1990[c]		1,012,000	1,149,000
1991[c]		1,176,000	1,423,000
1992[c]		1,341,000	1,751,000
1993[c]		1,450,000	2,079,000

NOTE: Footnotes give sources of the mortality data used to compute YPLL estimates.
[a] CDC, 1990c.
[b] National Center for Health Statistics, 1990a: Table 10.
[c] CDC, 1990a: Table 2.
SOURCE: The table was prepared by James W. Buehler, Chief, Special Projects Section, Surveillance Branch, Division of HIV/AIDS, Centers for Disease Control, September 27, 1990.

TABLE 1.2 Distribution of Reported Cases (percentage) by Year of Diagnosis and Exposure Category

	Adults								Pediatric					
Year of Diagnosis	Male Homo-Bisexual	IVDU[a]	Male Homosex. +IVDU	Hemo-philiac	Hetero-sexual	Pattern II[b]	Trans-fusion	Other[c]	Hemo-philiac	Risky Mother[d]	Trans-fusion	Other[c]	Total	*N*
1981	64.9	11.0	7.1	0.5	0.5	6.0	0.5	4.5	0.0	4.5	0.0	0.5	100	382
1982	60.7	16.9	9.4	0.6	1.1	5.1	0.8	2.9	0.2	1.7	0.4	0.3	100	1,076
1983	61.4	17.8	9.4	0.5	1.0	3.5	1.5	2.3	0.1	2.0	0.3	0.0	100	2,933
1984	64.3	16.7	8.7	0.9	1.5	2.2	1.7	2.1	0.1	1.5	0.3	0.0	100	5,926
1985	64.1	17.5	7.5	1.0	2.0	1.6	2.5	1.8	0.1	1.5	0.4	0.0	100	11,038
1986	62.9	18.2	7.8	0.9	2.5	1.4	2.7	2.1	0.1	1.3	0.2	0.0	100	17,777
1987	60.5	20.1	6.8	1.0	3.2	1.2	2.9	2.7	0.1	1.4	0.2	0.0	100	25,987
1988	56.9	22.8	6.3	1.0	4.1	1.1	2.5	3.7	0.1	1.3	0.1	0.1	100	29,761
1989[e]	55.3	23.2	5.8	0.7	5.0	1.2	1.9	5.3	0.1	1.2	0.1	0.1	100	22,901
Total	59.5	20.6	6.9	0.9	3.4	1.4	2.4	3.3	0.1	1.4	0.2	0.1	100	117,781

[a]IVDU: intravenous drug user.
[b]The cases assigned to this category involve individuals from those countries in central, eastern, and southern Africa and some Caribbean countries in which the majority of AIDS cases have been ascribed to heterosexual transmission, the male-to-female case ratio is approximately 1:1, perinatal transmission is more common than in other areas, and intravenous drug use and homosexual transmission occur at a very low level.
[c]This category includes cases currently under investigation for which no history of exposure has yet been reported and cases for which no exposure mode could ever be determined.
[d]Mother with, or at risk for, HIV infection.
[e]The 1989 figures include only those cases reported through December 31, 1989. All data shown in this table are subject to delays in reporting. Therefore, counts of cases diagnosed in a particular year may understate the number that will ultimately be reported. This type of understatement is particularly likely for cases diagnosed in 1988 and 1989.

SOURCE: National Research Council, 1990:Table 1.1. Computed from CDC's AIDS Public Information Data Set for AIDS cases reported through December 1989.

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Managing the NIH AIDS Research Program

In the nine years since the epidemic of HIV infection and AIDS emerged, NIH has created a vigorous research program that has achieved several notable successes. Researchers have identified HIV as the viral agent, made progress in understanding the epidemiology, natural history, and pathogenesis of the disease, and developed several therapeutic and prophylactic drugs that are partially effective against HIV and some of the opportunistic infections and cancers associated with it. These advances, among the most rapid in the annals of medical history, attest to the underlying strength of American biomedical research and NIH responsiveness, once the agency was provided with resources to mount a major AIDS research program. Much remains to be done, however; the burden of AIDS-related disease continues to grow, and many important scientific and practical questions have yet to be answered.

The challenges presented by HIV and AIDS are not limited to those involving actual research. NIH has also faced unprecedented management demands to develop, implement, coordinate, and evaluate a rapidly growing, complex set of AIDS research activities that now involve every NIH institute, center, and division. In response to rapid program differentiation and growth, NIH has evolved a special administrative system, based in the Office of its Director (OD), for coordinating and managing the AIDS research program. The overall NIH AIDS management structure is depicted in Figure 2.1.

As NIH ends a decade of rapid growth of its AIDS research programs, it is well to ask whether the management arrangements that worked during that period are appropriate for the 1990s and beyond. The agency's overall goal remains the same, that is, to achieve an understanding of HIV infection and related diseases so that they can be prevented, cured, or controlled through the development of new therapies, vaccines, and programs of behavioral change. What needs to be reviewed now are the adequacy and appropriateness of the structures and procedures NIH has evolved to ensure that (1) the most important scientific questions are being pursued and the highest priority programs are in place, (2) gaps in knowledge are filled and duplication of effort is avoided, and (3) generally, the multiplicity of activities being carried out by the various units and subunits of NIH add up to a coherent strategy. Such a reassessment should consider the changes needed in the current program structure as AIDS research matures and becomes more integrated with regular NIH activities. Reassessment is also needed as research advances and breakthroughs require reallocation of resources from existing to new programs (and perhaps from one institute to another) and time and experience indicate that some programs are more and some less successful than others. As the AIDS research enterprise matures, NIH must shift from an entrepreneurial

to a management mode of program operations. This shift will require strengthened management systems for planning, coordination, and evaluation in the NIH Director's Office.

ORGANIZATIONAL STRUCTURE

NIH is a highly decentralized organization, a structure appropriate to a basic research enterprise. The agency comprises 13 research institutes, 5 research centers, 2 divisions, the National Library of Medicine, and the Office of the NIH Director, all of which conduct AIDS-related activities (Figure 2.2). Organizationally, NIH is further decentralized by the separation of the grants review process from extramural program management. All research grant applications receive a first-level review for scientific merit by independent disciplinary study sections of extramural experts, after which the applications are sent to the appropriate institutes for decisions on funding. Organizational analysts consider this interplay between the categorical institutes and the disciplinary study sections to be the genius of NIH's organization: "The primarily disease-based institutes enable Congress to understand, appreciate, and support the research accomplishments of the institutes, and also to express concerns and priorities about the need for further research. The study sections, on the other hand, cut across institute lines and ensure that appropriate scientific talent and ideas are brought to bear on the problems" (IOM/NAS, 1984:1). As a result, NIH has been able to sustain high-quality research, address public scientific concerns, as defined by Congress, and support basic biomedical research on which future advances will surely depend. It is evident, however, that this decentralized structure is not designed to respond as swiftly and efficiently as a more hierarchical organization to situations that require a coordinated, agency-wide response.

Within this highly decentralized organization, the NIH director and a small staff are expected to provide leadership in the interplay between the public and the scientific community. They must also coordinate programs that cross institute lines (but not micromanage the research programs of the institutes) and oversee common housekeeping functions for the institution as a whole. In the case of AIDS, each institute manages its AIDS activities as part of its overall program, involving the institute's staff, senior leadership, board of scientific counselors (which oversees the intramural program), and national advisory council (which discusses policy and program issues, reviews program concepts, and approves each grant). In most cases, AIDS activities are carried out within the institute's regular organizational structure; only NIAID, because of the large size of its AIDS program (53 percent of NIAID's budget in fiscal year 1990), has set up an organizationally separate AIDS activity. At the same time, AIDS-related efforts within the institutes are subject to an unprecedented (for NIH) degree of coordination and direction by the NIH Director's Office. The goals of this oversight are many: ensuring that information is shared and advances communicated to NIH's various publics, identifying and exploiting research opportunities, filling gaps in the research program, avoiding duplication of effort, and seeing that the overall program is adequate and balanced.

Historically, large new research programs on health problems of major public concern have usually been handled organizationally at NIH by creating a new institute or center. The committee considered and rejected the option of creating a national AIDS institute. The arguments for such an institute are that it would

- upgrade the status and visibility, and therefore the funding, of the research area;
- accelerate research progress by focusing research efforts in an integrated program (comprising, for example, basic, clinical, epidemiological, nursing, and behavioral research) and giving attention to such related activities as communications, training, and research resources; and

- provide a familiar, tested management structure for setting priorities and coordinating activities, including a director and administrative staff for planning and evaluation, and strong extramural oversight through a national advisory council.

The report of the IOM Committee for a Study of the Organizational Structure of the National Institutes of Health reviewed these arguments in 1984 and concluded that the results of institute creation were mixed. That committee also cited the costs of establishing new institutes, centers, or divisions (IOM/NAS, 1984:20), in particular noting that the costs of the new administrative superstructure are not always covered by increased appropriations. In addition, the increased number of institutes adds to the problems of effective program coordination by the NIH director. (Two institutes and two centers have been created since 1984, although this increased structural complexity is partially offset by the merger of two divisions.) Another problem that can arise is that the new structure fragments the scientific effort and diminishes effective communication among key scientists in the various institutes. These potential drawbacks led the 1984 committee to suggest several criteria for assessing the need for a new institute. The new entity should, for example, increase the prospects of scientific progress in a research area, and the new organizational structure should, on balance, improve communication, management, priority setting, and accountability (IOM/NAS, 1984:22-23).

Because of the profound immune deficiency caused by HIV infection, affected individuals are vulnerable to many different diseases that often involve multiple organ systems. This committee found the arguments for program decentralization compelling in that a decentralized structure allows NIH to draw on the strengths of its various institutes. (Even if there were an AIDS institute, the scope of HIV infection and AIDS is such that the NIH Director's Office would have to have a significant planning and coordination capacity.) The involvement of multiple research areas in the various institutes will better address the complexities of AIDS, thus speeding scientific progress more effectively than might be accomplished by a single institute. Most if not all the advantages of a single-institute program—improved communication, management, priority setting, and accountability—could be achieved by implementing the committee's recommendations regarding the AIDS program management system (based in the Office of the Director), increased budgetary resources, and flexibility.

The organizational elements that have evolved in the OD for administering the multi-institute AIDS research program provide a good foundation for stronger overall planning and evaluation processes and program coordination. These elements are discussed in the sections below.

Associate Director for AIDS Research

Program coordination and direction are assigned to a high-level NIH official, the associate director for AIDS research, who advises the NIH director on all aspects of the AIDS program. Anthony S. Fauci, the current incumbent and a leading AIDS researcher, was NIH's AIDS coordinator before being appointed associate director for AIDS research when the position was created in 1988. He chairs the NIH AIDS Executive Committee and represents NIH at the meetings of the PHS Executive Task Force on AIDS. He is also executive secretary of NIH's AIDS Program Advisory Committee and director of the Office of AIDS Research.

AIDS Program Advisory Committee

APAC was established by the NIH director in 1988 to provide a formal channel for external advice on AIDS research, a function previously carried out on an ad hoc basis (e.g., the Extramural Ad Hoc Consultants to the NIH AIDS Executive Committee, which issued the report, *Future Directions for AIDS Research*, in November 1986; the meeting of the NIH Advisory Committee to the Director on the topic, "The Role of Biomedical Research in Combating AIDS," in November 1987). According to its charter, APAC provides advice on all aspects of AIDS research (OAR, 1987). In particular, the committee identifies opportunities to further research on AIDS and recommends initiatives; it also advises the agency on research directions and identifies areas of research that require additional effort.

When APAC was first established, the NIH director chaired the group; it is now headed by a member of the committee "to enhance the committee's sense of self-direction" (NIH, 1988:2). APAC originally had eight members, six of whom were authorities in the fields of molecular biology, immunology, virology, neurology, pediatrics, vaccine development, antiviral development, clinical care, animal model research, retrovirology, structural biology, or epidemiology. There were also two members of the general public. The membership now has been expanded to nine authorities in the fields listed above and four public members, appointed to overlapping four-year terms.[1] There is no requirement for an authority in the behavioral or social sciences or public health (although one of the current members is a behavioral scientist). As noted in the previous section, the associate director for AIDS research serves as the committee's executive secretary, and part-time staff support is provided by the OAR.

At APAC's first meeting in February 1988, NIH director James Wyngaarden stated (1988:13):

> This advisory committee will play a vital role in providing advice and counsel on the difficult research and science policy issues that we face as we move towards our goal of eradicating AIDS. These meetings will serve as an effective stage from which we can review our AIDS research activities in a comprehensive fashion and examine the direction, composition, and management of our efforts.

Initially the committee was to meet for two days three times a year, issue summaries of each meeting, and prepare an annual report on its activities and recommendations during the year (Wyngaarden, 1988:14). After the first year, the meetings were reduced to two a year, and subcommittees on vaccines, therapeutics, and biosafety were established. Proceedings for each meeting have been published, but the committee has issued no annual reports. Meeting topics were as follows: introduction and overview of the NIH AIDS research program (February 1988), obstacles and opportunities in the development and testing of HIV vaccines (July 1988), development and evaluation of therapeutics for AIDS (December 1988), special considerations in the treatment of HIV infection for children and minorities (June 1989), recent developments in clinical trials, epidemiology, and central nervous system disease (December 1989), and emerging issues in drug and vaccine development and immunopathogenesis research (June 1990).

So far, APAC has provided valuable input on specific issues but has not addressed overall priorities and balance in NIH's AIDS research effort. Neither has it contributed to the preparation of annual program plans and budgets. The meetings consist largely of presentations by panels of AIDS researchers and agency officials, followed by committee discussions and, sometimes,

[1] Appendix C lists the current membership of APAC.

recommendations to the NIH director. For example, the committee at its June 1989 meeting made a series of recommendations concerning access to clinical trials, reimbursement for AIDS drugs, and coordination among NIH, the Health Resources and Services Administration, and the Health Care Financing Administration; the recommendations were then sent by NIH to the Secretary of Health and Human Services. At its second meeting the committee reviewed and commented on a draft of NIH's plan for AIDS vaccine development and evaluation.

NIH AIDS Executive Committee

In July 1982, NIH director James B. Wyngaarden asked his special assistant to set up an interinstitute coordination group to track AIDS activities and exchange information and to attend meetings of the PHS task force on AIDS (Gordon, 1983). When Wyngaarden discovered that NIAID and CDC, which were collaborating with French researchers to identify the AIDS virus, were unaware of similar efforts in Robert Gallo's NCI laboratory (U.S. Congress, Office of Technology Assessment, 1985:28), he established an NIH AIDS executive committee in May 1984. The committee, which Wyngaarden chaired, was composed of representatives from the institutes conducting AIDS research (NCI, NINDS [National Institute of Neurological Disorders and Stroke], NICHD, and NIAID).

When Anthony Fauci was appointed AIDS coordinator in 1985, NIH reconstituted the NIH AIDS Executive Committee (NAEC) to include the directors of each institute involved in AIDS research or high-level alternates with the authority to make decisions on behalf of their organizations. The strengthened committee advised the NIH director on allocation of the $70 million for AIDS research that had been appropriated to the OD for fiscal year 1986; it was also given the assignment of "providing guidance and direction for NIH-wide scientific, planning, and resource allocation decision-making and for ensuring effective coordination' (Wyngaarden, 1985). NAEC was supported at first by the Office of Program Planning and Evaluation and later by the OAR, after it was established. In recent years, the AIDS coordinators rather than the directors of the various institutes have attended the meetings. The committee originally met twice a month, after the meetings of the PHS Executive Task Force on AIDS, to receive updates on developments and provide advice on NIH's contributions to PHS AIDS policy development. Usually, one of the institutes would also give a presentation on its AIDS activities. Recently, meetings were changed to a monthly basis because, according to Fauci (1990), "[t]he original purpose of the NAEC was to serve as an in-house advisory committee to the NIH Director on matters of NIH AIDS research policy and budget. As the NIH AIDS research program has matured, with much interaction between the individual ICDs [institutes, centers, and divisions] and the Office of AIDS Research, the NAEC meetings no longer serve that purpose to the same degree."

Office of AIDS Research

Staff work on AIDS matters initially was conducted by analysts in the OD's Office of Program Planning and Evaluation (now the Office of Science Policy and Legislation; Rodriguez, 1989). OAR was created in April 1988 to handle the workload created by AIDS budget increases of 111 percent in fiscal year 1986, 94 percent in 1987, and 81 percent in 1988, and the establishment of AIDS research programs in every institute, center, and division of NIH. OAR coordinates NIH intra-and extramural AIDS research, represents the NIH director on AIDS-related matters, and centralizes certain AIDS-related policy and operating functions, such as the development of the NIH annual budget request for AIDS and an AIDS research information system (PHS, 1989a:274).

Specifically, according to NIH's statement of organization and functions (*Federal Register*, April 28, 1988:15290), OAR

> (1) [a]dvises the Director, NIH, and senior staff on the development of NIH-wide policy related to AIDS research, and coordinates NIH intramural and extramural AIDS research activities; (2) provides the Chairperson for the NIH AIDS Executive Committee and represents the Director, NIH, on all outside AIDS-related committees requiring NIH participation; (3) provides staff support to the NIH AIDS Executive Committee and the NIH AIDS Advisory Committee; (4) recommends intramural/extramural AIDS research priorities to the Director, NIH; (5) develops an NIH annual plan and budget for AIDS research; (6) develops policy on laboratory safety for AIDS researchers and monitors the AIDS surveillance program; (7) develops and maintains an information data base on intramural/extramural AIDS activities and prepares special or recurring reports as needed; (8) develops information strategies to assure that the public is informed of NIH AIDS research activities; (9) recommends solutions to ethical/legal issues arising from intramural/extramural AIDS research; (10) facilitates cooperation in AIDS research between government, industry, and universities; and (11) fosters and develops plans for NIH involvement in international AIDS research activities.

In November 1988, OAR was established legislatively through the Health Omnibus Program Extension Act (P.L. 100-607) to provide administrative support to the NIH director. It accounts for 19 of the 29 full-time equivalent (FTE) AIDS positions and $3.4 million of the $12.1 million allocated to AIDS in the OD budget for fiscal year 1990.[2]

OAR's day-to-day operations are supervised by deputy director Jack Whitescarver, who was appointed to the position in August 1988. The office is organized by function (e.g., program analysis, budget analysis, data management, legislative analysis; Figure 2.3). As of October 15, 1990, the office had 16 full-time employees in 19 approved positions and was requesting three more slots, for a total of 22 (Table 2.1). One of the vacant positions is that of a high-level health science administrator with AIDS research experience.

The OAR budget for fiscal years 1988-1991 is shown in Table 2.2. The OAR budget also supports the costs of the AIDS Program Advisory Committee (about $170,000 a year, including $36,000 in OAR staff support). If the President's budget request for fiscal year 1991 is funded, the OAR budget will increase $2.3 million (65 percent) to $5.7 million. More than half the increase ($1.3 million) is for AIDS programs (technology transfer meetings and loan repayments for NIH AIDS researchers) rather than for increased interinstitute program planning and coordination capacity. The increase assumes a staffing level of 22 FTEs.

Much of the work of OAR staff involves collecting and compiling information on the AIDS activities conducted by the various components of NIH for administrative and congressional reports and to satisfy numerous ad hoc requests. For example, OAR staff provided information on AIDS

[2] The other FTEs (whose support totals $522,000) are located in central administrative services offices, such as the Division of Contracts and Grants and the Division of Personnel Management, where they handle some of the extra workload caused by AIDS activities. The remaining $8.1 million in OD AIDS funds support extramural AIDS activities in the Research Centers for Minority Institutions (RCMI) program of the NIGMS (all RCMI funding will be transferred to NIGMS in fiscal year 1991), intramural basic research projects on the structure and function of HIV, and a project conducted by NIH's Protein Expression Laboratory to isolate and purify proteins encoded by the HIV virus for research purposes (the last two activities are administered by the Office of Intramural Research).

for the so-called Moyer Report on annual research accomplishments that was prepared for appropriation hearings (PHS, 1989b), the annual report on AIDS activities mandated by the Health Omnibus Program Extension Act of 1988 (P.L. 100-607), and the quarterly *Institute AIDS Science Report* on new research findings from intramural and extramural activities. The OAR's information compilation capacity will be greatly increased as the automated AIDS Research Information System comes on-line over the next year. The staff also coordinate NIH's responses to information requests or policy development initiatives from the PHS Executive Task Force on AIDS.

The development of NIH's annual budget request for AIDS is another activity to which OAR staff contribute. This process, under the leadership of the associate director for AIDS research and the NIH director, is much more intensive than the NIH director's review of other NIH activities, which come under the purview of the individual institutes. The director's review of non-AIDS budgets focuses on aggregate numbers of projects and dollars by mechanism (e.g., how many new and competing research project grants will be funded, how many center grants will be supported); the review of the AIDS budget, however, extends to the examination of individual studies and projects at each stage of the budget process (Mahoney et al., 1990). The authority to approve budget requests gave the director and associate director for AIDS research influence over the shape and direction of AIDS research during the years when the budget was increasing quickly, even though Congress appropriated funds directly to the individual institutes and not to the director of NIH. Use of budget formulation authority to influence the AIDS research program will have less and less effect as the program matures and the rate of budget growth slows.

OAR participates in several coordination efforts among the institutes and between NIH and other agencies (OAR, 1990; PHS, 1989a:274-277). For example, OAR

- coordinated the development of AIDSTRIALS, the centralized information system for AIDS clinical trials involving NIAID, the National Library of Medicine, and the Food and Drug Administration;
- oversaw development of NIH's policies for the medical management of employees exposed occupationally to HIV infection, in conjunction with the NIH clinical center, the NIH Division of Safety, and CDC (subsequently, OAR was involved in the development of a PHS-wide policy published by CDC [1990]);
- coordinates NIH responses to congressional requirements, such as the plan to double the capacity of the outpatient AIDS programs of NCI and NIAID as called for in the Health Omnibus Program Extension Act of 1988 (P.L. 100-607) and a section of the Comprehensive AIDS Resources Emergency Act of 1990 (P.L. 101-381); the plan authorizes $20 million for demonstration projects to coordinate NIH clinical trials with health care delivery programs of the Health Resources and Services Administration to increase the participation of women, children, IV drug users, and other groups that are underrepresented in AIDS clinical research; and
- participates in efforts to increase international information sharing, exchange visits, and research collaboration to increase knowledge and support the development of the infrastructure needed to conduct international clinical trials of vaccines.

Last year, OAR began to develop an NIH AIDS plan, an effort that was subsumed by the development of a PHS-level strategic plan for HIV/AIDS activities. Currently, OAR is coordinating and editing NIH's contribution to the plan, which delineates the areas NIH and the other PHS agencies will emphasize over the next several years, including key actions and outcomes to be achieved (PHS, 1990).

STRENGTHENING MANAGEMENT OF THE NIH AIDS RESEARCH PROGRAM

As an 'institute without walls," NIH's AIDS research program is managed from the Office of the NIH Director (instead of being organized under a particular institute). The elements of the program's organizational structure are analogous to those of the various institutes: a director (the associate director for AIDS research), a national advisory council (the AIDS Program Advisory Committee), an executive committee of senior program officials (the NIH AIDS Executive Committee), and an executive office for staff support (the Office of AIDS Research). The committee believes these organizational arrangements and associated administrative processes for managing AIDS research should be strengthened as an alternative to the creation of a separate institute and institutionalized as part of a major, long-term program at NIH.

Strengthening Planning and Evaluation

Planning

AIDS program planning at NIH has been a by-product of the budget process and is based on expected resources rather than on program goals and scientific opportunities. Currently, it comprises two major events. In January each institute conducts a half-day briefing for the director and OD staff in preparation for appropriations hearings. An additional half day is devoted to a briefing on the AIDS program, which is attended by the NAEC representatives from each institute. (The January 1990 briefing, for example, covered major cross-cutting areas of research: pediatrics, vaccines, treatment, and underserved populations.) The second event is the development of an agenda and background materials for a November meeting between the NIH director and the assistant secretary for health to launch the annual budgeting process.

In contrast, the institutes each develop their own annual plan using a process that reviews goals, objectives, and research strategies; evaluates program progress; assesses scientific opportunities; sets priorities; and modifies program directions and emphases accordingly, all with the involvement of the institute's national advisory council and the scientific community (through various advisory committees and panels). In the past the AIDS program never developed a formal, detailed program plan that encompassed the above steps but instead launched initiatives as needs became apparent. Now, however, limited resources and competing demands are constraining AIDS research initiatives. Given the large size and organizational complexity of NIH AIDS research, the committee believes program management as well as program effectiveness would be improved by the development of an overall long-range research plan. The plan should set out the program's goals and assign priorities. It should define the resources required and mechanisms to be used and identify the results that are expected over specific time periods. Rather than a blueprint that specifies how investigators should proceed, the plan should be a roadmap that identifies goals but permits multiple routes. It should allow a significant amount of basic, undirected research initiated by investigators with good ideas, because historically this has been the method used to produce many important scientific advances. The plan should also be flexible to allow prompt adaptation to unanticipated events that alter prior assumptions. Accordingly, the plan should be subject to periodic review and revision through a formal decision process. The overall plan should be issued annually in light of accumulated revisions. Because some work products may be available in less than a year while some may not be available for more than five years, formal interim and endpoint reviews should be part of the plan.

Recommendation 2.1: NIH should develop a five-year plan to identify AIDS-related research needs and opportunities, set priorities, assess program balance, identify

research areas that need stimulation, determine the resources required to carry out the program, and evaluate progress. The plan should be developed under the auspices of the AIDS Program Advisory Committee (after the committee is expanded and oriented as recommended below), with the input of outside experts as well as OAR staff, and it should be reviewed and updated annually. The annual plan review should occur in time to guide the preparation of the regular annual budget so that responsibilities and resources can be shifted if appropriate.

Evaluation

Most of NIH's AIDS research activities were hurriedly launched by limited staff during the years of rapid budgetary growth. As the program matures, however, attention is appropriately turning to the relevance, effectiveness, and efficiency of ongoing activities. There are several evaluation mechanisms already in place. The associate director for AIDS research relies on NIH's time-honored method of evaluation and quality control—peer review of research applications by study sections of independent experts. The Division of Planning and Evaluation in the OD's Office of Science Policy and Administration also coordinates a formal evaluation program of "discrete, circumscribed studies and analyses of selected aspects of the NIH mission," using a 1 percent evaluation set-aside fund ($4.5 million in fiscal year 1990; NIH, 1989:1). But AIDS research presents several unique problems. Many AIDS grants involve large, multidisciplinary projects, centers, and cooperative-group efforts that are closely related to an institute's categorical mission. Scientific review of these projects is essential but insufficient, because administratively they pose quite different questions of efficiency, effectiveness, and productivity than projects involving an individual investigator in a lab. Evaluation of an AIDS clinical trials unit, for example, involves issues of accrual rates, data-gathering accuracy and efficiency, timeliness of reporting, and protocol compliance of patients and providers—in addition to issues of scientific excellence in the research design and data analysis plan. These features of AIDS research call not only for stronger program planning but for stronger evaluation efforts and close linking of planning and evaluation results to the budget allocation process.

Recommendation 2.2: AIDS program evaluation processes should be strengthened and linked closely to planning and budgeting processes to ensure that, first, questions of the highest priority are addressed adequately at all times; second, all studies being supported are still relevant and are as productive and efficient as possible; and third, resources are redeployed, sometimes across institutes, in response to research advances and breakthroughs or as time and experience indicate that some programs are more and some less successful than others in achieving their goals. The Office of AIDS Research should work closely with the Division of Planning and Evaluation in the NIH Director's Office to coordinate evaluations of AIDS research programs in the various institutes. In turn, evaluation results should be considered in program planning and budgeting.

Strengthening External Advisory Processes

One of NIH's strengths is its ability to incorporate external advice from scientists and the public in its planning and operations. As in its other research programs, NIH has established advisory groups at every level of the AIDS research program; many of these groups include patient

advocates and members of the general public as well as scientists and researchers.[3] Most of these advisory groups address specific technical aspects of the AIDS research program; because of their number and specificity, the committee could not evaluate each group's appropriateness and usefulness. The associate director for AIDS research should routinely reevaluate the need for such committees as the AIDS research program is institutionalized over the next several years as a long-term effort.

Not in question, however, is the need for a high-level advisory function, and the committee urges NIH to strengthen its processes for external advice on overall level of effort, balance among research areas and mechanisms, and research opportunities and needs in the AIDS research program. For the institutes, this role is played by the national advisory councils; for the AIDS program, this function should be the role of the AIDS Program Advisory Committee. APAC should review annual program and budget plans and oversee development of the five-year AIDS research plan recommended above with extensive external input-for example, as the National Advisory Eye Council prepares five-year national vision research plans. This responsibility would require substantially increased staff support (rather than the part-time staffing now provided by the OAR).

APAC's goal should be a research program that focuses on acquiring fundamental knowledge about HIV and its transmission and pathogenesis and on developing and testing new agents and programs to prevent and treat HIV infection and AIDS. APAC's guiding policy should include optimum use of all possible resources toward these ends; thus the program should take into account the contributions of other government agencies, as well as private organizations and companies.

Although recently APAC membership was increased from 8 to 13, including 4 members of the general public, the committee believes the group should be enlarged further to ensure that all areas of AIDS research and AIDS research policy and administration are adequately represented. National advisory councils to the institutes typically have 18 members, 12 with health and science expertise (including public health and the social and behavioral sciences) and 6 public members with backgrounds in public policy, law, economics, and management. APAC's base of expertise could also be expanded by naming additional non-APAC members to the committee's subcommittees.

Recommendation 2.3: The AIDS Program Advisory Committee should take a larger role in providing broad policy advice and program oversight and should include among its activities the development of the five-year AIDS research plan and annual updates. It should also conduct an annual review of the programs and budgets developed to implement the plan. This expanded role will require additional staff support and a larger committee to ensure that all AIDS-related areas of expertise are represented, including the behavioral and social sciences and public health authorities. It may also require the establishment of additional subsidiary committees and the recruitment of additional outside experts to review the various research areas (e.g., basic, behavioral, epidemiological).

[3] In November 1990 NIAID announced that the ACTG was adding patient and community representatives to its executive committee and each of its research committees (e.g., primary infections, pediatric AIDS, etc.).

Strengthening Staff Support

The expanded roles of the associate director for AIDS research and the AIDS Program Advisory Committee in planning, evaluation, and budgeting will require some additional staff support by the Office of AIDS Research and related OD units-the divisions of financial management and planning and evaluation, for example. Fortunately, OAR receives excellent budgeting support from the OD's financial management division and is developing the computer-based AIDS Research Information System, which will support these expanded planning, budgeting, and program evaluation efforts.

In most areas of the AIDS research program, the associate director for AIDS research and the OAR will coordinate activities that are actually carried out by the institutes, centers, and divisions; they should play a larger role, however, in planning, implementing, and evaluating certain cross-cutting functions—for example, training and construction programs (see Chapter 4). In addition, as the committee recommends later in this report, the OAR should review and approve AIDS RFAs and RFPs initiated by the individual institutes in accordance with their priority in the overall plan for AIDS research.

As it did for other governmental units, the Office of Management and Budget established an FTE ceiling for fiscal year 1991 for the OAR, restricting its staff to the 16 positions already assigned to it. When the restriction was eased in early 1990, OAR immediately added 3 positions and requested funding for 3 more in fiscal year 1991 to accomplish its current workload. The additional work called for in this report will require additional personnel, some with high-level science training and AIDS-related research experience.

Recommendation 2.4: The capacity of the Office of AIDS Research should be increased so that it can function adequately as the staff arm of the associate director for AIDS research in his or her role as leader and coordinator of the AIDS program. In particular, OAR will need some additional planning and evaluation staff, including several senior-level scientists who can assist the associate director for AIDS research and APAC in monitoring the AIDS research agenda, assessing progress, identifying scientific gaps that need to be addressed, and coordinating the review of institute research initiatives.

Strengthening Executive Authority and Flexibility

The AIDS program is the first major research program to be managed by the Office of the NIH Director rather than by a single institute. The committee believes, therefore, that the OD's capacity to implement and coordinate AIDS research activities should be strengthened, in addition to the enhancement of its long-range planning and evaluation capabilities, as recommended above.

Past evaluations of the structure and performance of NIH have noted the loss of influence of the NIH director within the Department of Health and Human Services and the Office of Management and Budget on the one hand, and the individual institutes on the other (White House, 1965; U.S. Department of Health, Education, and Welfare [U.S. DHEW], 1976; IOM/NAS, 1984, 1988; Singer, 1990). These evaluations concluded that, although decentralized authority is good for a basic research organization, the NIH director needs clear authority and specifically allocated resources to ensure a coordinated response to scientific opportunities or public health emergencies. For example, once Congress approves the NIH budget, the director has power only over the OD budget, which is 1.4 percent of the overall agency appropriation; the rest of the funds are

appropriated directly to each institute, center, and division, and the director does not now have authority to reallocate them in response to contingencies that may emerge during the fiscal year. Review groups have regularly recommended several steps to strengthen the director's position within the agency.

- The NIH director should have greater discretion over resource allocation to allow flexible responses to health emergencies (such as the AIDS epidemic) and exploitation of emerging scientific opportunities.
- Advisory groups to the director should be strengthened to identify problems facing NIH and help build political consensus for solutions.
- The director should have a discretionary fund 'for correcting imbalances, for exploiting new scientific opportunities, and for contingencies" (U.S. DHEW, 1976:16) or "to be used to address emerging issues and special inter-institute research opportunities" (IOM/NAS, 1988:138).
- The director should have authority to transfer funds (up to 0.5 or 1 percent) across institute lines to meet contingencies (White House, 1965:16; IOM/NAS, 1984:32; Presidential Commission on the Human Immunodeficiency Virus Epidemic, 1988:41; Singer, 1990).

The recent report of the IOM Committee to Study Strategies to Strengthen the Scientific Excellence of the NIH Intramural Research Program recommended that Congress appropriate no less than $25 million annually to be used by the NIH director to address emerging issues and special interinstitute research opportunities (IOM/NAS, 1988:138). The administration's budget request for fiscal 1991 included $20 million for an NIH director's discretionary fund, "an important mechanism that would allow the NIH to respond more effectively to unforeseen changes in research direction and emerging research opportunities" (PHS, 1989a:Vol. 6, p. 263) and authority to transfer up to 1 percent of NIH appropriations "to high priority activities the Director may so designate" (U.S. PHS, 1989a:Vol. 6, p. 252). Congress recently approved the 1 percent transfer authority and $20 million "as a director's reserve for high priority needs of the NIH" (U.S. Congress, 1990:21), but it is not clear that it is a revolving fund that will be automatically replenished each year.

Recommendation 2.5: The director of NIH should be given an adequate annually renewed discretionary fund of at least $20 million along with additional authority to transfer up to 1 percent of each NIH appropriation account to increase the agency's flexibility in responding to future emergencies or research opportunities. These resources could be used to exploit important scientific breakthroughs arising in AIDS or non-AIDS research that could not be anticipated in the regular budget process or to address major epidemics or other public health problems that suddenly emerge.

The committee is convinced that an important component of the current strength and success of the NIH AIDS research program is the unique leadership provided by Anthony Fauci, associate director of NIH for AIDS research and director of NIAID. Having the same person as director of NIAID, which receives nearly half the NIH AIDS budget, and associate director for AIDS research is administratively unorthodox, because it poses potential conflict of interest problems when questions of interinstitute coordination, budget allocation, and assignment of program jurisdiction arise. Each of the positions is also extremely demanding, an aspect that, in the case of the position of associate director for AIDS research, will only intensify if AIDS program management is strengthened and institutionalized, as recommended in this report. In this instance the arrangement has worked well because of the energy, knowledge, even-handedness, and prestige of the incumbent.

Recommendation 2.6: The current arrangement of the same person holding the positions of both associate director for AIDS research and director of NIAID is working

well. Nevertheless, because of the already substantial and still growing workload of each position, and the potential for bias in mediating conflicts among institutes, the committee believes that the joining of these positions should be reconsidered at such time as the current incumbent steps down.

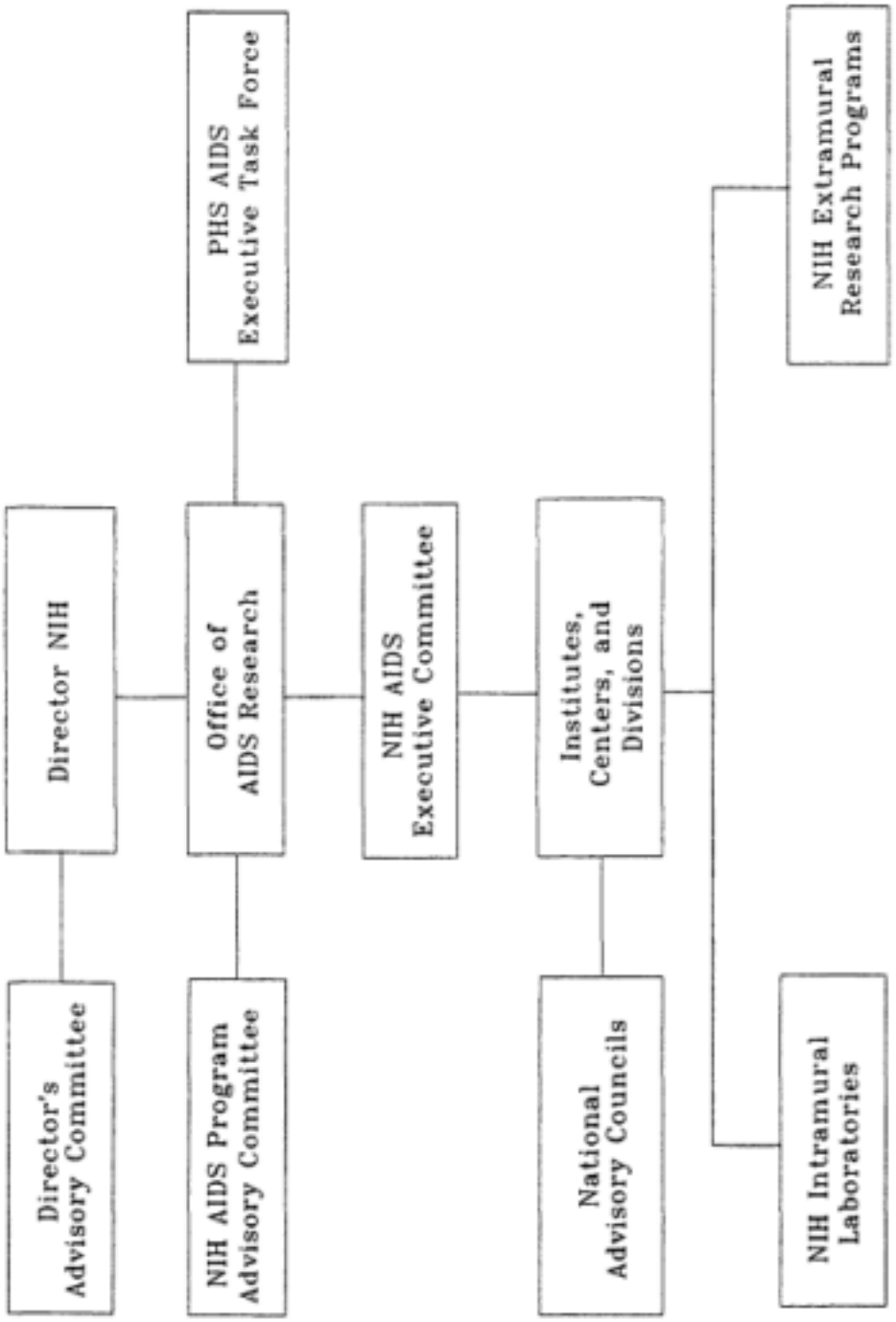

Figure 2.1
Management structure of the AIDS research program of the National Institutes of Health.
Source: Based on NIH documents and interviews.

Figure 2.2
Organizational structure of the National Institutes of Health, 1990.
Source: Based on interviews and information in the NIH Almanac: 1989 (NIH Publication No. 89-5, May 1989, Bethesda, Md.).

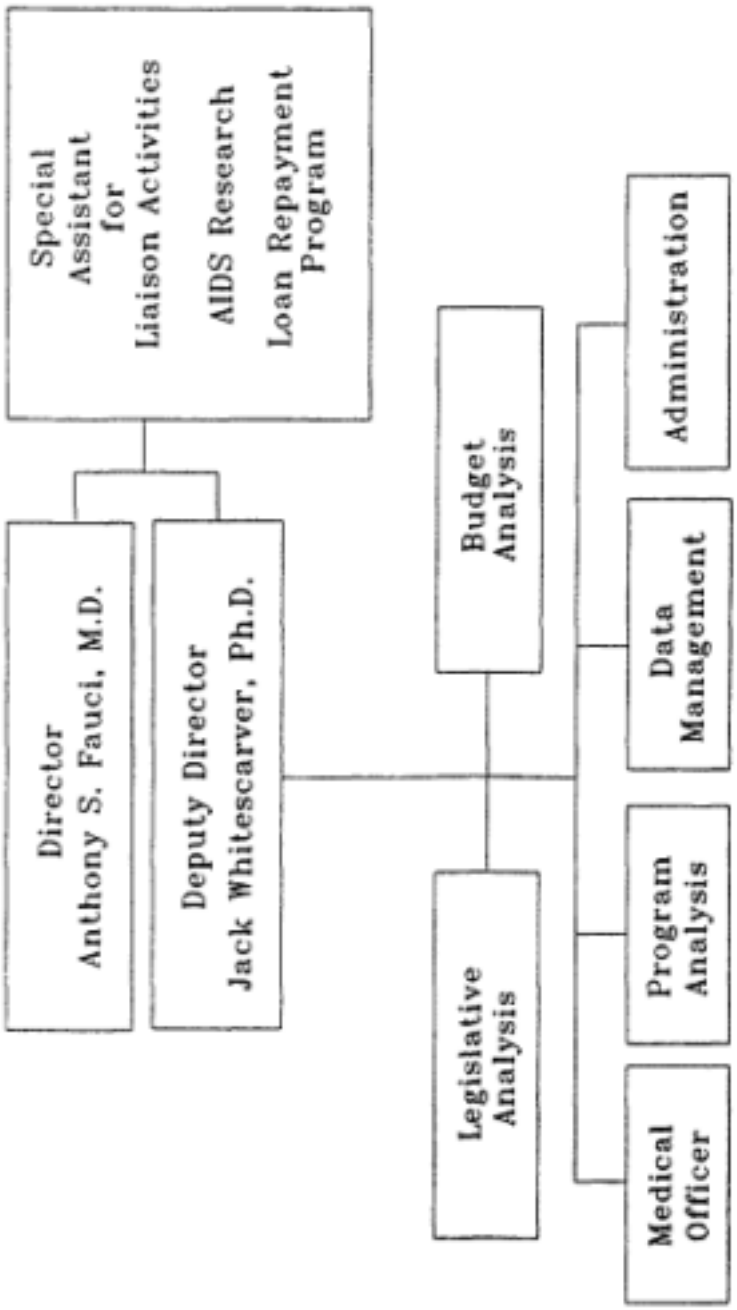

Figure 2.3
Position chart of the Office of AIDS Research, National Institutes of Health, 1990.
Source: NIH Office of AIDS Research, September 29, 1990.

TABLE 2.1 Office of AIDS Research Staff Slots

	Fiscal Year 1989		Fiscal Year 1990
Position or Unit	Filled	Vacant	Projected
Deputy director	1		1
Loan repayment	1	1	2
Legislative analysis	2		2
Budget analysis	1		1
Medical officer	0	1	1
Program analysis	4	1	5
Data management	2	1	3
Administration	5	2	7
Total	16	6	22

SOURCE: Administrative Officer, Office of AIDS Research, October 19, 1990.

TABLE 2.2 Budget (in thousands of dollars) of the Office of AIDS Research (OAR), Fiscal Years 1988-1991

Activity	1988	1989	1990[a]	1991[b]
Administrative services				
Office of AIDS Research	454.7	1,069.0	1,353.0	1,841.0
Office of Science Policy Legislation[c]	-[d]	62.0	77.0	55.0
Division of Financial Management[c]	-	23.0	55.0	58.0
Subtotal	454.7	1,154.0	1,485.0	1,954.0
OAR programs				
Loan repayment	-	-	989.0	2,000.0
AIDS Research Information System	-	-	500.0	1,000.0
Technology Transfer Regional Meetings	-	-	480.0	750.0
Subtotal	-	-	1,969.0	3,750.0
Total	454.7	1,154.0	3,454.0	5,704.0

[a] Estimated.
[b] president's budget.
[c] The persons assigned to AIDS research in legislative analysis (Office of Science Policy Legislation) and financial analysis (Division of Financial Management) sit in those offices but work for and are paid by OAR.
[d] Dashes indicate no funds allocated.
SOURCE: Administrative Officer, Office of AIDS Research, October 12, 1990.

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3

Elements of the NIH AIDS Research Program

In Chapter 2, the committee's main concern was to review the structures and processes for managing the NIH AIDS research program—how it is planned, implemented, coordinated, and evaluated—to ensure that all high-priority scientific questions are being addressed without gaps or overlaps, that programs are well designed and effective and efficient in achieving their goals, and that administrative support by NIH is adequate. The committee believes that these questions are especially pertinent at this time, as the program shifts to a long-term managerial mode in response to the size, complexity, and endurance of the HIV/AIDS epidemic, the large size and complexity of the NIH AIDS program itself, and the overall constraints on the federal budget. In this chapter, the committee reviews the components of the NIH AIDS research program in light of the shift to an institutionalized, long-term research effort. Where appropriate in the following sections, it offers specific conclusions and recommendations regarding the mission, design, size, and management of each component.

BASIC RESEARCH

Basic research is research that increases knowledge and understanding about basic biological processes (e.g., research in the fields of immunology, virology, or molecular biology) and causes of diseases (i.e., pathogenesis) but that may not be intended to have an immediate practical use. The NIH AIDS research program devotes a smaller proportion of resources to basic research than do most other NIH research programs. The percentage of AIDS-related basic research[1] has decreased since fiscal year 1983, when basic research funding was approximately 43 percent, to its fiscal year 1990 level of 31 percent. To date, the NIH AIDS program has been more oriented toward applied research—that is, research aimed at exploiting existing knowledge and techniques to improve diagnosis and treatment as quickly as possible. Typically, institutes devote about 60 percent of their budget to basic research, through extramural grants and projects in their intramural laboratories, on the premise that in the long run knowledge gained from such research will serve as a foundation for progress in the research effort against disease.

[1] The functional categories used by the Public Health Service for classifying the AIDS budget do not allow a clear distinction between basic and applied research. For the purposes of this study, basic research encompasses the following Charlottesville functional categories: virology, etiologic agent and cofactors, immunologic studies, simian AIDS, and vaccine development.

- National Institute of Allergy and Infectious Diseases—NIAID finances the largest portfolio of AIDS-related basic research of all the NIH institutes. NIAID's basic research goals are to examine HIV entry mechanisms, cell types (host and virus), reservoirs, and latency; study the mechanisms of cellular immunity; assess the role of autoimmunity in AIDS pathogenesis; research the role of other viruses as cofactors in AIDS; understand HIV gene regulation; define the vital components responsible for infectivity, syncytia formation, CD4 receptor binding, and immune response elicitation; and determine the mechanism of T-cell killing. NIAID's AIDS-related basic research is conducted in many venues, including universities, independent laboratories and research centers, and its intramural laboratories. The Pathogenesis Branch in NIAID's Division of AIDS (DAIDS) administers most of the institute's AIDS basic research grants. Its mission is "to discover the mechanisms by which HIV causes immune deficiency, produces other pathological disorders, and avoids immune surveillance" (NIAID, 1990). The branch's extramural grants support research on the biological properties, molecular biology, and host response to HIV infection and on the development of an animal model for HIV infection. The branch administers Programs of Excellence in Basic Research on AIDS (PEBRA), which are five-year grants to support clusters of long-term investigations of biological processes related to AIDS. PEBRAs were awarded to five sites in 1988.

  DAIDS also funds nine centers for AIDS research using core grants to investigators who have a record of proven excellence in AIDS research and are already receiving NIH funds. The grants provide core support for central research and support services and also include some money for salaries for junior-level investigators and for renovation and upgrading of facilities. Intramurally, NIAID's researchers are conducting a range of research on the nature of the etiologic agent (HIV) and its pathogenesis in addition to a considerable program of vaccine and drug development studies. Selected research includes studies focused on the immunopathogenic mechanisms of HIV infection and opportunistic infections, animal retroviruses, and how the CD4 receptor recognizes the HIV envelope protein.
- **National Cancer Institute**—NCI supports the next largest basic AIDS research program at NIH, much of it intramural. Its efforts focus on HIV and the mechanisms of pathogenesis, including the following major areas: regulation of HIV gene expression, the mechanism of HIV infection, virus cofactors in pathogenesis, regulation of the CD4 receptor, mechanisms of loss of T-helper cell immune function, processing of HIV proteins, the role of cytokines and immunity in HIV pathogenesis, and research on the structural biology of HIV for the purpose of devising therapeutic agents.
- **National Institute of Neurological Disorders and Stroke**—NINDS supports the third largest NIH program of basic AIDS research, the primary goal of which is understanding the relationship between HIV and the human nervous system. NINDS-supported research falls into two main scientific areas: how HIV damages nervous system cells and how it crosses the blood-brain barrier. In support of these research endeavors, NINDS funds both extramural and intramural basic research. Extramural research focuses on HIV subtypes that enter the brain, methods to improve the transport of drugs into the central nervous system, and the role of metabolites in the pathogenesis of AIDS dementia. In contrast, intramural research examines a number of key scientific questions including SIV neurologic disease, analysis of the effect of HIV gene products on nervous system cells, the pathogenic mechanism of AIDS dementia, and differentiation of HIV- and zidovudine (AZT)-induced neuropathies.
- **National Heart, Lung, and Blood Institute**—NHLBI conducts a wide range of AIDS research from the very basic to the clinical, focusing on the cardiac, pulmonary, and hematologic consequences of HIV infection. The institute's basic AIDS research includes the following major areas: chronic processes of cardiac and pulmonary pathology in AIDS, HIV-related viruses, the pathogenesis of cardiac and respiratory problems unique to the pediatric population, the HIV disease process in the lung (particularly to understand cell injury caused by *Pneumocystis carinii*

pneumonia), the pathogenesis of cardiac complications, and the causes of the numerous blood deficiencies induced by HIV infection.

Despite the support by the above institutes of basic science research related to HIV infection, many critical gaps remain in current understanding of the basic biology of HIV and its associated opportunistic infections and cancers. The committee notes that most of the progress in understanding and treating HIV infection and related diseases has been based on knowledge generated from basic, undifferentiated research that predates the advent of the AIDS pandemic. To date, the NIH AIDS research program has emphasized directed research, primarily in large-scale collaborative studies, in an effort to develop a quick cure from existing knowledge. It is now evident that a cure or vaccine is years away and that their development will come from a better basic understanding of HIV infection and pathogenesis. The committee believes that a strong basic research program is critical in supporting such applied activities as drug and vaccine development. Basic research on HIV and the disease it causes will in turn produce new knowledge and methods that may contribute to progress against other diseases.

Recommendation 3.1: Greater investments should be made in basic research in such areas as immunology, virology, and molecular biology as part of NIH's long-term research program on AIDS. These basic research advances are critical not only to progress against AIDS but also as a contribution to the base of fundamental knowledge that will be needed to deal with other diseases of the present and future.

VACCINE RESEARCH AND DEVELOPMENT

As recently as early 1989, many AIDS researchers expressed considerable pessimism about the possibility of developing an effective HIV vaccine. In the past year, however, a more hopeful outlook about vaccine development has begun to prevail, largely based on some recent successful experiments with rhesus macaques. SIV and the infection it causes in rhesus monkeys constitute a valuable model for HIV and AIDS. For example, the SIV genome is similar in organization to that of HIV, and, like HIV, the simian virus also infects host cells through their CD4 surface receptor. In addition, infection is persistent and eventually leads to T-cell immunodeficiency with an AIDS-like syndrome and death. Two recent trials of immunization of rhesus monkeys with formalin-fixed whole killed SIV have led to a substantial level of protective immunity against the virus. Although crude, inactivated whole virus may not be the final acceptable form of the vaccine because of its risks (i.e., virus inactivation approaches 100 percent but generally leaves residual trace amounts of infectious material), its demonstrated effectiveness provides a valuable target for systematic comparison with various purified HIV antigens and synthetic epitopes. Further systematic exploitation of the SIV-rhesus monkey model may bring additional progress.

Although recent developments give considerable cause for optimism about the prospects for an HIV vaccine, the difficulties that must be overcome remain formidable (Bolognesi, 1989).

- The critical components of an HIV vaccine, as well as the relative importance of humoral versus cellular immunity, have yet to be determined.
- There is still no agreement on the clinical goal of a vaccine. Should it completely block infection? Prevent disease? Or delay the onset of disease? Answers will probably come from empirical approaches in which vaccines that elicit powerful antibody or T-cell responses will be tested on various populations under diverse conditions.
- The available animal models are still limited. Chimpanzees can be infected with HIV but do not develop disease; rhesus monkeys, on the other hand, develop an AIDS-like disease from SIV

but are unaffected by HIV. The SCID-hu mouse shows some promise as a model for testing new drugs, but it has not yet been shown to respond immunologically to HIV antigens.

- A major obstacle to tests of the efficacy of any HIV vaccine is the lack of consensus on specific immunologic end points that correlate with immunity. Should the end point be the production of neutralizing antibodies? Other antibodies? CD4 T cells? Or CD8 T cells?
- The consequences of HIV genetic variation on immunologic responses have not been thoroughly evaluated, although they may render a vaccine ineffectual in some patients.
- From general experience with experimental and clinical vaccines it is clear that one or more adjuvants[2] are likely to be critical components of an HIV vaccine. The mechanism of action of adjuvants is still far from clear, however, and only a few of them are available for use in humans.

Overcoming these obstacles and taking advantage of the opportunities presented by recent successes will require a concerted effort by all sectors involved in vaccine research and development. The following sections describe the NIH vaccine program and propose a role for NIH in the overall scheme of HIV vaccine development.

NIH Vaccine Research Program

In fiscal year 1990, NIH allocated $78.6 million for HIV vaccine-related research; the fiscal year 1991 budget projects a 10 percent increase in that amount, bringing the total to approximately $86.1 million. The bulk of NIH vaccine research is sponsored by NIAID and NCI.

National Institute of Allergy and Infectious Diseases

NIAID's Vaccine Research and Development Branch (VRDB) located in the Division of AIDS acts as NIH's primary arm for planning and funding vaccine research. The President's 1990 budget allotted $51.2 million to NIAID for vaccine research; of that amount, the VRDB received $32.1 million for 1990 with the remainder divided among intramural research and research support contracts. The VRDB is divided into three sections that span basic research, preclinical science, and clinical testing. Through each of these sections, NIAID funds a variety of grants, cooperative agreements, and contracts for extramural vaccine researchers.

NIAID officials identified several major VRDB efforts:

- identifying gaps in AIDS-related basic immunology research in order to target program resources;
- developing a preclinical capacity in extramural locations for testing candidate agents in vitro and in animal models;
- developing a capacity for assessing vaccines in human trials;
- continuing coordination with WHO so that once there is a promising candidate, phase 3 efficacy trials can begin as soon as possible; and
- monitoring the progress of candidate HIV vaccines through preclinical testing and evaluating selected vaccines in phase 1 and 2 trials at the AIDS vaccine evaluation units supported by NIH.

[2] An adjuvant is a substance that enhances the effectiveness of a medical treatment; in immunology it is generally a nonspecific stimulator of the immune response.

NIAID's basic research program consists largely of a mixture of grants and contracts that support extramural investigators in studies of the role of HIV genetic variation, the immunology of a protective response, and lentiviruses in a variety of animal models. NIAID's preclinical development section constitutes the core of its vaccine efforts. In this area, NIAID funds 11 national cooperative vaccine development groups (NCVDG), each of which is a consortium of industry and academic scientists that collaborate on preclinical vaccine development—for example, immunologic research, evaluation in animals, and production of reagents needed to conduct human trials. For example, the NCVDG program funds the two primate centers in Boston and New Orleans that recently demonstrated successful protection by a whole-killed-SIV vaccine in macaques. The fiscal year 1990 funding for the NCVDG program is $13.2 million. In addition to the NCVDGs, the preclinical section funds 16 cooperative groups that study HIV vaccine adjuvants and supports an HIV vaccine repository program to provide quality-controlled reagents to any NIH-sponsored researchers.

In early 1990 NIAID's clinical development section awarded five-year contracts to five AIDS vaccine evaluation units (AVEU), four of which already have a long record of testing vaccines for various infectious diseases. All five of the AVEUs have experienced investigators on staff who are capable of conducting phase 1/2 testing of candidate HIV vaccines. AVEUs are an important component of NIH's vaccine program that provide a capability to conduct early clinical testing of vaccines on a small number of patients. The NIAID clinical section also supports the AIDS Vaccine Selection Group of senior scientists charged with setting guidelines for trial eligibility of candidate vaccines and recommending which candidates NIH should evaluate.

National Cancer Institute

NCI recently established the AIDS Vaccine Task Force, which is pursuing the development of an effective AIDS vaccine. In 1991 NCI will receive approximately $19.1 million for vaccine research, most of which supports intramural studies in two areas: identifying HIV peptides that can raise a protective immune response and determining how to combine synthetic peptides to produce a more effective vaccine than one based on a single HIV protein. NCI researchers favor the combined peptide approach because of the possibility of transmitting infectious particles in a whole-killed-virus vaccine.

The Role and Mission of NIH

Until now, NIH's primary functions have been to fund investigator-initiated extramural and intramural research, develop reagent and animal model resources, and promote information exchange among researchers. Each of these functions is valuable and well suited to NIH's traditional role of facilitating scientific research, but the recent breakthroughs in vaccine studies have raised the question of whether NIH should invest additional resources in vaccine research and assume a greater role in coordinating its next stage. The committee believes NIH can make significant contributions in vaccine research that would complement efforts in the private sector by continuing to identify research needs and provide research resources, continuing to facilitate scientific exchange among researchers, increasing its support of basic science research, and increasing its leadership role for the planning of trials of vaccine candidates. Therefore, NIH should increase the scale of its vaccine research program and define a clear mission that is coordinated with ongoing efforts in industry and in the academic and international sectors.

As previously discussed, the field of vaccine research is progressing rapidly, yet many scientific obstacles remain to be resolved before an effective HIV vaccine can be developed. The committee commends NIH's funding of a wide range of research approaches but notes that the lack of new NIH resources for extramural research has prevented qualified investigators outside of the ongoing NCVDGs from acquiring NIH support. Given the large number of scientific opportunities and the availability of investigators, the committee believes NIH should expand its funding to support investigators able to address the most pressing questions in the search for a vaccine against HIV/AIDS. Increased support of investigator-initiated research can make a significant contribution to overcoming the scientific obstacles that stand in the way of a vaccine against AIDS. Given the tremendous public health benefits of an effective vaccine, it is important to pursue as many promising research avenues as possible, including those that may not be fully explored or that may be bypassed by traditional investigator-initiated funding mechanisms. To pursue research opportunities adequately, the committee believes that an increase in RFAs and RFPs is appropriate.

Recommendation 3.2: NIH should expand its vaccine research program and furnish strong support for agents that show promise of efficacy and for requests for applications and requests for proposals that target the essential unanswered immunological questions.

The committee considered and rejected recommending a centralized approach to vaccine research, that is, a centrally directed, narrowly focused program that would devote a large amount of money to bringing together the major vaccine researchers and conducting a coordinated attack on the essential questions in AIDS vaccine research. Researchers interviewed by the committee were divided in their views of the wisdom of a centralized program. In its support, several NIH officials emphasized the need for rapid performance of the critical experiments required to follow up the recent SIV studies and their view that NIH was the only institution capable of assembling all of the researchers necessary to develop and execute a coordinated plan. They also noted that a more directed approach would increase data sharing among researchers, lessen the risk of duplication, and encourage pooling of limited reagents and resources. Extramural vaccine researchers argued that central planning would not work at this stage because scientists lack the base of knowledge needed to plan a centralized approach; in particular, agreement is lacking on a limited number of specific questions as the top priorities for investigation. The committee believes that a centralized approach to HIV vaccine development would be warranted when experts in this field reach near-unanimous consensus that only a few clearly defined research questions stand in the way of developing a vaccine. AS there is presently no such consensus, the committee believes it necessary and appropriate for NIH at this point to pursue a wide range of scientific leads.

Interviews with NIH officials indicated that NIAID and NCI, the two lead institutes at NIH for vaccine research, run relatively independent research programs with different scientific priorities. NIAID has put substantial resources into expanding the SIV model on the hypothesis that whole-virus research is essential groundwork for development of an effective human vaccine. NCI research, on the other hand, concentrates on identifying specific subunit epitopes of HIV that may confer protection. As with many other aspects of the NIH AIDS research program, the committee believes that expertise and input from multiple institutes strengthen the vaccine research program. The relative lack of direction within NIH vaccine research is also consistent with the agency's traditionally decentralized approach to research. In this case, however, the committee is concerned that the two institutes' efforts are inadequately coordinated, which may lead to the inefficient use **of** scarce resources.

Recommendation 3.3: NIH should create an agencywide vaccine research advisory panel of top extramural scientists to identify research needs, establish priorities, and determine the resources and facilities required for a successful program. In addition, the panel should perform an oversight function to ensure that institutes supporting diverse lines of SIV and HIV research use resources effectively and in a complementary manner. The committee further recommends that this advisory panel outline a mission for NIH's AIDS vaccine research that complements vaccine research being conducted by the pharmaceutical industry.

Many NIH and pharmaceutical industry representatives interviewed for this study asserted that drug manufacturers' liability concerns about developing an HIV vaccine, particularly whole-killed-virus types, have slowed some areas of vaccine research. Some observers believe that these liability fears may be a deterrent to industry vaccine development. NIH, on the other hand, as a component of the federal government, has a responsibility to advance as many promising vaccine approaches as possible, despite legal or financial concerns. In its history, NIH has often taken on scientific tasks that offer little incentive to pharmaceutical companies; one example is NCI's cancer clinical trials program of combination drug regimens that appear to have a public health benefit but offer little financial promise to the pharmaceutical industry. Because of the liability issues surrounding whole-virus vaccine research, the committee believes NIH could serve the public interest and contribute greatly to an understanding of protective immunity by increasing its support of research in this area.

In addition to liability concerns, when and if attractive candidates for vaccines emerge, the clinical trials that must be conducted to establish their efficacy will be logistically difficult (IOM/NAS, 1988:145). One unresolved dilemma centers on developing criteria for placing an HIV vaccine candidate into human efficacy trials. Another major problem involves potential trial populations. The trials will have to enroll sufficiently large numbers of subjects at sufficiently high risk of infection that any decrease in the number of infected persons attributable to the experimental vaccine will be statistically significant. (For this reason, the sites for large-scale efficacy trials will most likely include African and other developing countries.) For ethical reasons, those who receive the vaccine must be counseled about behavior changes that reduce the risk of HIV infection, which will increase the number of trial participants required. The deliberate seroconversion of seronegative individuals will also raise difficult ethical issues. The committee notes that NIAID's Vaccine Research and Development Branch has begun to address the issues surrounding deliberate seroconversion, and it commends these efforts.

Recommendation 3.4: NIH should begin immediately to plan the trials (especially phase 3) that eventually will be required to test a viable vaccine candidate. This process should include the development of criteria for entering a vaccine candidate into human efficacy trials. The committee further recommends that NIH work with Congress to evaluate plans to provide liability coverage for the development of vaccines that pharmaceutical companies otherwise may hesitate to evaluate.

Confronting AIDS: Update 1988 (IOM/NAS, 1988) noted that the development of a small, well-understood animal model, such as the mouse, would greatly enhance vaccine development. The committee is particularly concerned that NIH does not support adequate facilities for the growing number of animals needed for vaccine testing; this shortage continues at present despite agency officials' assertions that increased isolation and holding space in primate facilities are critical to preventing further delays in research. The committee believes NIH needs to provide funding

for new facilities with suitable containment areas (rated at biosafety levels 2 and 3[3]) for its own campus and for extramural academic sites, which would enable expanded use of potential animal models such as the rhesus monkey and SCID-hu mouse. The long lead time necessary for breeding animals highlights the urgent need to plan ahead for adequate resources so that when a candidate vaccine is ready for preclinical testing, scientific progress will not be hindered by inadequate supplies of animals, substandard facilities, or unavailable reagents.

Recommendation 3.5: NIH should provide the support needed to ensure an adequate supply of nonhuman primates, especially chimpanzees and rhesus monkeys, for preclinical development and testing of HIV and SIV vaccine candidates. NIH should also pursue the development of other animal models that might be cheaper and easier to use in vaccine development. Finally, through the associate director for AIDS research, NIH should coordinate the research plans of the various categorical NIH institutes investing in vaccine development with the long-term plans of the National Center for Research Resources for developing and supporting animal models.

NIH officials and extramural researchers were unanimous in asserting that poor access by investigators to quality-controlled reagents has hindered HIV vaccine research. Reagents that were identified as particularly important were supplies of purified HIV proteins, various strains of SIV, and T- and B-cell lines. NIH officials reported that extramural researchers frequently do not share reagents they have developed with NIH grants because such sharing may lessen the credit given for the original finding. The committee believes NIH has a responsibility to ensure that reagents developed with NIH funds are made available to the entire scientific community. The committee commends NIAID's efforts to establish a reagent repository program for vaccine research as an excellent example of how NIH can facilitate the research process from a neutral position.

Recommendation 3.6: NIH should strongly support a full-scale reagent repository and implement the recommendation from *Confronting AIDS: Update 1988* that Mall investigators receiving NIH funds must make their AIDS-related reagents available to a distribution center, and thereby to all qualified investigators, after publication of their research.'' NIH should enforce this policy by making further funding contingent on cooperation with a reagent pooling program.

EPIDEMIOLOGICAL RESEARCH

NIH conducts epidemiological research to improve understanding of the natural history of HIV infection, which aids the development of treatments and vaccines for HIV disease. Natural history studies seek to describe the sequence of clinical manifestations and biological processes that occur throughout the course of infection; these studies provide the foundation for a range of other AIDS research efforts at NIH, including clinical trials of therapeutics and vaccines and development of clinical practice guidelines.

Within NIH, nine institutes support epidemiological studies on AIDS and HIV infection (Table 3.1), with each institute sponsoring studies related to its particular mission. The sections below briefly discuss these programs. Total funding for NIH-supported HIV-related epidemiological

[3] A summary of biosafety level definitions and recommendations of the Centers for Disease Control and the National Institutes of Health may be found in the April 1, 1988, *Morbidity and Mortality Weekly Report*, Vol. 37 (suppl. S-4).

research in fiscal year 1990 was approximately $125 million, or about 17 percent of NIH's AIDS budget.

National Institute of Allergy and Infectious Diseases

NIAID studies account for more than half of NIH's AIDS epidemiology budget. Among NIAID's major initiatives are four large, prospective natural history studies of HIV infection: the Multicenter AIDS Cohort Study (MACS), the San Francisco Men's Health Study (SFMHS), the Women and Infants Transmission Study (WITS), and the Heterosexual HIV Transmission Study (HATS). The MACS is a prospective study of HIV infection that follows more than 4,000 homosexual male volunteers every four to six months to assess virologic, immunologic, clinical, behavioral, and neurological status. The SFMHS is a prospective study of the natural history and epidemiology of HIV infection in a cohort of 1,034 single men aged 25-54. Unlike the MACS, participants were recruited using a population-based sampling strategy, which results in the inclusion of both homosexual and heterosexual men. The WITS, a collaborative effort with NICHD, investigates the effects of HIV infection on pregnant women, perinatal transmission, the impact of pregnancy on the course of HIV infection, and pediatric outcomes. HATS examines factors related to HIV transmission in persons without histories or evidence of male homosexual behavior or intravenous drug use, and in couples discordant for HIV status (i.e., one partner is infected and the other is not). NIAID also collaborates with the U.S. Army on the Newark Perinatal Study, which involves women at risk for HIV infection, and maintains a specimen repository as a resource for its other studies.

A range of internationally focused epidemiology studies are another aspect of NIAID's epidemiological program. The institute initiated collaborative efforts with the Pan American Health Organization to facilitate the development of epidemiological research in Latin America and the Caribbean on HIV and associated infections. NIAID also supports the International Collaboration for AIDS Research program, which provides research grants to U.S. universities to foster collaborative epidemiological studies with investigators in foreign countries (currently, Uganda, Mexico, Brazil, Malawi, and Zaire). The third major international initiative is Project SIDA. This project supports a series of epidemiological, clinical, and laboratory science studies in Kinshasa, Zaire; prospective studies there include workers, women and children, and couples.

National Heart, Lung, and Blood Institute

NHLBI sponsors epidemiological studies focusing on transfusion safety and the identification of HIV in blood products. It also sponsors several major studies that have made significant contributions to an understanding of HIV prevalence and transmission. For example, the Transfusion Safety Study established in 1983 is a multicenter study to evaluate factors that influence the risk of transfusion-associated AIDS. A study of human retroviruses in volunteer blood donors, another NHLBI effort, examines the prevalence of retrovirus seropositivity in first-time blood donors, the rate of retrovirus seroconversion in repeat blood donors, and risk factors for antibody-positive donors. In their study of the effectiveness of screening for retroviruses, NHLBI researchers are evaluating the effectiveness of present screening efforts to identify HTLV-I, HTLV-II, and HIV in infected whole blood units, blood components, and Factor VIII concentrates. The institute has also established the Serum Repository, which seeks to facilitate the identification of seropositive donors and of recipients of blood products from these donors.

National Cancer Institute

NCI supports HIV-related epidemiological research to generate and test hypotheses about the role of pathogenic human viruses **in the** etiology of cancer and to expand the AIDS epidemic knowledge base, focusing on cancer in particular. To this end the institute supports a broad range of efforts, including large and modestly sized prospective studies, collaborative studies, and an international registry.

- Among NCI's largest initiatives is a study of hemophiliacs and their female sexual partners, which involves a multicenter cohort (16 domestic and 4 foreign sites) of 1,219 subjects with hemophilia or related disorders. The study is both retrospective and prospective and designed to define rates, markers, and cofactors of HIV infection and AIDS. It uses samples from NHLBI's hemophilia centers, which were established and operational prior to the HIV epidemic.
- A study of parenteral drug users, conducted in collaboration with the National Institute on Drug Abuse, evaluated 1,766 parenteral drug users for HIV and HTLV-I and HTLV-II infection.
- In 1982, NCI established a cohort of 249 gay men, recruited from the New York City and Washington, D.C., metropolitan areas. At the time of its initiation, this study was unusual in that it focused on the cohort rather than the disease.
- In a study of mothers and infants, a collaborative effort with NICHD, researchers are examining the effects of HIV infection on pregnancy, the factors associated with vertical transmission, and the effect of HIV disease on the health status of the newborn.
- In a prospective study of heterosexual transmission of AIDS, spouses and long-term partners of patients in various clinical stages of HIV infection are being studied to gain a better understanding of risk factors for acquiring HIV and its sequelae; both behavioral and serologic factors are considered. (Children of the index cases [i.e., the infected individuals] are also enrolled in the study.)
- To study the relationship between AIDS and cancer, in particular, Kaposi's sarcoma, and identify risk factors, researchers are analyzing a case-control study of homosexual men with the condition recruited from New York City.
- NCI has established an international registry of persons with AIDS who have documented dates of HIV seroconversion to evaluate cofactors and trends in risk for HIV infection. Thirty-eight investigators from three continents have contributed 1,115 subjects for analysis.

National Institute of Child Health and Human Development

NICHD conducts several epidemiological and natural history studies related to HIV, as well as research on associated risk factors in pregnant women, mothers, infants, children, and adolescents. Its perinatal natural history study focuses on the neurodevelopmental outcomes of children exposed to and infected with HIV. The study is conducted at three centers and is a component of the collaborative NICHD/NCI study on vertical transmission noted above. NICHD also collaborates (by means of interagency agreements) with the Department of Defense in a study of the epidemiology of HIV among pediatric and perinatal patients from military families. Additional research includes a study of the natural history of HIV infection in hemophiliac children. This investigation is a multicenter study of 263 children conducted in collaboration with the Office of Maternal and Child Health of the Health Resources and Services Administration, which funds a network of comprehensive health centers for hemophiliacs. The study compares developmental, neurological, and immunologic outcomes of HIV-infected hemophiliac children with outcomes of uninfected hemophiliac controls and uninfected male siblings. Finally, an NICHD-sponsored seroepidemiological study of HIV prevalence among childbearing women uses routinely

collected, paper-absorbed samples of newborn blood to examine trends in HIV infection among women. The study gathers data on about 80,000 births per year in the northeastern United States and North Carolina.

Fogarty International Center

A collaborative effort by the Fogarty International Center (FIC) and NIAID established the International Network for AIDS Research and Training, which links the major international AIDS programs of NIH, the Centers for Disease Control, the U.S. Agency for International Development (USAID), the World Health Organization's Global Programme on AIDS, and the Pan American Health Organization. The network is intended to facilitate the coordination of research and training needs, identify emerging research opportunities and appropriate responses, and minimize duplication of effort among NIH institutes and between U.S. organizations and the programs of other governmental and international organizations.

Other NIH Epidemiological Studies

Studies supported by the remaining four institutes-the National Institute of Dental Research (NIDR), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Aging (NIA), and National Center for Nursing Research (NCNR)-account for less than 3 percent of the NIH HIV epidemiology budget. Each institute supports initiatives related to its mission: NIDR supports research on the oral complications of HIV infection, NIAMS studies skin disorders associated with HIV infection, NIA investigates the prevalence of HIV in the over-50 population, and NCNR conducts studies on the nursing needs of HIV-infected persons.

Results

Information provided by NIH-sponsored epidemiological studies includes the following:

- NHLBI's Transfusion Safety Study provided definitive evidence that HIV is not transmitted by casual but rather by sexual contact with infected persons and from infected mothers to their babies.
- Data gathered by the MACS showed a marked increase in the risk of contracting *Pneumocystis carinii* pneumonia (PCP) when an individual's CD4+ cell count dropped below 200 per cubic millimeter (mm^3) of blood. This information became the foundation for the Public Health Service's recommendation that HIV-infected persons with CD4+ cell counts below 200/mm^3 receive prophylactic therapy against PCP.
- A neuropsychiatric substudy of the MACS demonstrated that neurologic or psychiatric complications of HIV infection are rarely seen prior to the onset of other HIV-related symptoms. This information refuted earlier assertions that neuropsychiatric deterioration may be among the first manifestations of HIV infection.
- The SFMHS, studying neutralizing antibodies to HIV, demonstrated that a patient's ability to neutralize his or her own HIV isolates does not correlate with the progression of HIV infection.

- The MACS and SFMHS determined the risk of occurrence of opportunistic infections,[4] and NCI-sponsored studies recently discovered an increase in non-Hodgkin's lymphoma, among HIV-infected persons.
- A study sponsored by NCI and NICHD demonstrated that mothers who did not transmit HIV to full-term babies had antibody reactivity to a specific epitope of gp120; the majority of mothers of babies who became infected lacked antibodies to gp120.
- The MACS has studied surrogate markers of HIV disease, particularly those that might predict progression to AIDS by an asymptomatic person. Data generated by the MACS showed that CD4+ cell counts, neopterin levels, and soluble beta-2-microglobulin, taken as an aggregate, are more predictive of progression to AIDS than CD4+ cell counts alone.
- Using polymerase chain reaction and vital culture techniques, NIAID investigators determined that HIV infection may be present for up to 42 months before seroconversion.
- NIAID-sponsored epidemiological studies of the immunopathogenesis of HIV infection provided important information on antibody-dependent cellular cytotoxicity and the responses of natural killer cells, lymphokine-activated killer cells, and alpha interferon and their role in moderating the effects of HIV. Data on alterations in Iymphocyte blastogenesis and gamma interferon production have also been gathered.

NIH's Role in Epidemiology Research

Within the PHS, HIV epidemiology studies are conducted by CDC and ADAMHA, as well as NIH.[5] The research perspectives represented by these three agencies are fundamentally different, and they support varying proportions of epidemiological studies. ADAMHA funds only a small fraction of PHS initiatives in this area (less than 10 percent), focusing on the role of drug use as it relates to HIV infection; this leaves the vast majority of studies to be supported by CDC and NIH. NIH epidemiological research focuses on the underlying biological processes of HIV infection; in contrast, CDC studies focus predominantly on the identification of disease patterns in populations and the risk factors associated with HIV infection. In fiscal year 1990, CDC supported more than 87 percent of PHS HIV-related surveillance and NIH supported 8.2 percent. In contrast, NIH supported 66.3 percent of PHS efforts in population-based research (which includes natural history studies), compared with 21.6 percent supported by CDC. These figures reflect the traditional missions and capabilities of the two agencies. CDC has the capacity, through its Epidemiological Intelligence Service, to respond quickly and flexibly to emergencies, whereas NIH's strength is its capacity to conduct large, detailed, long-term studies. The two agencies also have different constituencies: CDC interacts primarily with state and local health departments, and NIH works with basic and clinical researchers.

Establishing Epidemiological Research Priorities

The committee believes that in the area of epidemiological research NIH should clearly identify those scientific questions that are most important to its mission of finding treatments and a vaccine for HIV infection. The natural history of HIV infection is changing dramatically as the virus affects populations other than homosexual men and the effects of treatment are taken into

[4] Currently, CDC-sponsored epidemiological studies record a person's presenting condition and, where possible, cause of death. In contrast, NIH-sponsored epidemiological studies, as a result of extensive data gathering on clinical parameters and their prospective study design, allow an understanding of the sequence of occurrence of opportunistic infections.

[5] Although ADAMHA's and CDC's HIV epidemiology efforts have contributed significantly to an understanding of the epidemic, they are addressed in this report only in terms of their relation to NIH's HIV epidemiology efforts.

account. For example, preliminary studies indicate that the types and patterns of opportunistic infections experienced by women and IV drug users are significantly different from those experienced by homosexual men. In addition, data characterizing the effects of treatments and prophylaxis are incomplete; research has not yet determined, for example, whether PCP prophylaxis extends life in HIV-infected persons. Data describing HIV incidence and prevalence are also incomplete, a critical gap for efforts to identify suitable populations for vaccine trials and promising avenues of investigation for therapeutics; these data are also essential for planning, developing, and assessing prevention programs. Continued epidemiological research is thus essential to an understanding of the emerging profile of HIV disease.

Given the many scientific questions yet to be answered, and the need to use available resources efficiently, the committee considers this an appropriate time for NIH to reassess its priorities for epidemiological research, including a review of ongoing research and careful planning for future epidemiological studies. As part of the priority-setting process, NIH should identify the key scientific questions that are most important to its mission. Moreover, this evaluation of the size and focus of the present program should involve outside advice, either through an ad hoc outside review group of epidemiological researchers selected by the NIH director (similar in nature to the committees established by NIAID to review the WITS and HATS studies) or by the epidemiology subcommittee of the APAC (described in Chapter 2). Over the longer term, the planning and evaluation of AIDS epidemiology efforts, including the epidemiology component of the five-year plan recommended in Chapter 2, could be overseen by the epidemiology subcommittee of APAC.

The committee is concerned that some epidemiological studies may be maintained to a point of diminishing scientific return compared with other studies that might be supported. There is an understandable reluctance to disband long-standing cohorts that are still producing information. However, given the emerging research opportunities and current fiscal constraints, NIH must carefully assess whether the data produced by long-running studies are still worth the investment. Epidemiological research should be routinely evaluated for continued relevance and adjusted to the changing course of the epidemic as, for example, more and more members of older cohorts progress to AIDS, members of younger cohorts become infected, and new risk groups are identified. NIH must also identify emerging research opportunities in the international arena and their potential value for future trials of therapeutics and vaccines.

Recommendation 3.7: NIH should reassess its epidemiological research priorities; evaluate ongoing research, discontinuing less productive or redundant studies and expanding studies in groups experiencing higher rates of HIV infection; and reassess the size of the total NIH epidemiology program in light of fiscal constraints and other emerging research needs. This reassessment should involve external advice.

Coordination of Studies

The committee believes that the types of epidemiological studies supported by the various PHS agencies provide different but equally important kinds of information that contribute to a full understanding of the epidemic. Epidemiological research is unique in that much of it depends on the maintenance of large cohorts of human subjects over an extended period of time, and the data serve to identify promising avenues of investigation for a number of research areas including vaccines, drug development, clinical trials, nursing, behavioral sciences, and epidemiology itself. Because of its unique character and indispensable role in providing direction for other programs, it is essential that studies be carefully planned and coordinated within NIH, with other PHS

agencies, and with outside agencies to reach consensus on the appropriate epidemiological research agenda and ensure that high-priority research questions are being addressed and that data are shared. At present, some mechanisms exist for identifying research needs and facilitating coordination; these include agreements between NIH institutes, clearance of proposed RFAs through the NIH Office of Extramural Programs, the FIC-sponsored International Network for AIDS Research and Training, informal discussions between researchers, and, until it was recently dissolved, the NAPO-sponsored Epidemiology and Surveillance Subcommittee of the PHS Executive Task Force on AIDS. These mechanisms have resulted in the collaborative studies previously noted in this section, but despite these successes, some unproductive overlap has also occurred. For example, out of a laudable desire to quickly establish cohorts to investigate perinatal transmission, several PHS agencies established cohorts that were too small to have sufficient statistical power to answer key research questions. Although interorganizational coordination is always difficult and requires constant effort and attention, NIH must continue to work to identify opportunities for collaboration between institutes and with other PHS agencies to ensure that gaps are identified or addressed, duplication is avoided, and cohorts are of sufficient size to enable meaningful statistical analysis. There should also be a coordinating mechanism at the PHS level to include NIH, CDC, and ADAMHA.

Recommendation 3.8: NIH should pursue collaborative efforts among its institutes and with other PHS agencies sponsoring epidemiological research to address all first-priority epidemiological issues, avoid duplication, and ensure adequate sample and cohort sizes.

BEHAVIORAL RESEARCH

The epidemic of HIV infection and AIDS is both a biological and a behavioral phenomenon, and efforts to contain its spread must look to both biomedical and behavioral sciences for interventions. Since the discovery of the virus and its modes of transmission, there have been significant advances in treatment for HIV disease. Historically, however, the discovery of effective chemotherapies and vaccines has not guaranteed success in controlling sexually transmitted diseases (STD) or other types of infection. For example, although penicillin has been an important and effective part of the campaign against syphilis for more than 40 years, this sexually transmitted disease persists and in fact today is on the rise (Rolls and Nakashima, 1990). Outbreaks of childhood measles also still occur, despite the availability of a safe, effective vaccine. Disease prevention, then, often requires more than biomedical technologies. HIV infection is an example of an incurable but preventable disease that is amenable to behavioral intervention.

The committee believes NIH has neglected AIDS-related behavioral research, the results of which are inadequate funding and an underdeveloped knowledge base (compared with such disciplines as immunology and virology), absence of a behavioral research infrastructure (including a paucity of Ph.D. level professionals), and lack of understanding of the behaviors central to the transmission of HIV. Lack of knowledge regarding patterns and determinants of sexual and drug-using behaviors in the general public, as well as in groups at particular risk for HIV infection, has hampered public health efforts to develop health education interventions for the prevention of AIDS. The committee considers increased attention and funding to be warranted, given the lack of scientific data on behaviors related to HIV infection, the seriousness of the HIV/AIDS epidemic, available research opportunities in the field, and the potential public health benefits such research could realize.

In fiscal year 1989 the Office of the Assistant Secretary for Health (OASH) reported that NIH spending for behavioral research was $5.7 million. Of this amount, funding for human behavioral research was $4.6 million (0.76 percent of the total NIH research budget); the remaining $1.1 million went to the Animal Resources Program in the Division of Research Resources to support the use of chimpanzees in studying HIV infection. OASH estimates for behavioral research in fiscal years 1990 and 1991, respectively, are $3.4 million and $3.2 million, or 0.45 and 0.39 percent of the total NIH research budget. Thus, funding for human behavioral research has decreased since fiscal year 1989 both in total amount and as a percentage of the total NIH AIDS research budget.

Behavioral research spans a broad spectrum. It can include the use of epidemiological techniques to identify the distribution of behavioral risk factors, and basic research designed to understand the etiology, or underlying determinants, of behavior. Such research may include, for example, studies of the physiological, psychological, and social mediators that influence and modify behaviors relevant to the transmission of HIV. It also includes efforts to evaluate the effectiveness of interventions intended to modify behaviors. This may include design and assessment of strategies to prevent the initiation of high-risk behaviors, reduce recidivism, or test the efficacy of culturally specific behavioral strategies to reduce risk behaviors for HIV infection.

Significant research opportunities exist in the field of behavioral research. For example, very little is known about the prevalence of sexual behaviors, especially in minority groups, the adolescent population, women, the over-50 age group, and prostitutes (male and female); even less is known about their etiology. As an illustration of a significant data deficit, estimates of the number of men who engage in same-gender sex figure prominently in calculations of HIV prevalence; yet the figures used by the PHS in those calculations were derived from Kinsey's studies on male sexual behavior from the period 1938-1948 (Turner, 1990). The precision of two methods currently used to forecast the AIDS epidemic, trend analysis and back calculation, is also hampered by a lack of information about the basic determinants of HIV incidence; for example, little information is available about the average number of sexual contacts within certain population groups and the probability that these contacts are made with uninfected individuals (Hellinger, 1990). Data are scarce on initiation into early sexual activities and the influence of family and peer groups on sexual behavior and contraceptive use (CDC, 1990b). It is also unclear how much of the sexual activity of adolescence is motivated by sexual desire and how much results from the desire for peer acceptance and other nonsexual motives (Turner et al., 1989).

Significant gaps also exist in understanding intervention strategies. It is known that, for behavior to change, individuals must recognize a problem, be motivated to act, and have the knowledge and skills necessary to perform the action. However, data on how best to present information, instill and maintain motivation, and inform individuals remain incomplete. For example, studies have shown that information is necessary but often insufficient by itself to effect behavioral change; the association between knowledge and attitudes on one hand, and behavior on the other, however, remains unclear (Turner et al., 1989). The effectiveness of fear as a motivating element in AIDS prevention messages also is not well understood; nevertheless, PHS-sponsored information and prevention and treatment programs for sexually transmitted diseases often employ fear-evoking messages. Research has shown that, to be effective, information must be delivered in a manner that is comprehensible, convincing, and relevant to the audience it is intended to reach. Achieving this goal will require a much greater understanding of the perspectives and culture of the various ethnic, racial, social, age, and sexual orientation groups that currently make up the national population (Turner et al., 1989). Also necessary is a better understanding of the effects of different intervention strategies among different populations. For example, although some strategies have been effective in certain populations (i.e., gay men), it is not known whether the

same approaches would successfully solicit cooperation and motivate change in other populations such as adolescents, minorities, women, or prostitutes.

The public health consequences of continued neglect and inadequate funding of behavioral research could be severe. Effective interventions require an understanding of the behaviors that place a person at risk for acquiring HIV/AIDS, especially in view of the fact that modification of risky behavior is the only currently available way to prevent HIV infection. Getting ahead of the epidemic requires foresight to limit the spread of infection in populations and regions that currently have a low prevalence of AIDS and HIV infection; such opportunities should not be overlooked, for, once lost, they cannot be recaptured. Adolescents are generally recognized as a population for which prevention activities could have a great impact. The large and growing middle-aged and older segments of the population also deserve attention to forestall any possibility that the epidemic may become established in the more than 60 million people aged 50 and older. Currently, women of childbearing age still have a low HIV prevalence rate overall and also represent an excellent opportunity to avert the spread of HIV infection. Yet before intervention strategies can be designed to prevent the spread of HIV to those who are not yet infected, it is essential to know which behaviors to target, in whom they occur, and how they can be modified.

Given the lack of understanding of behaviors related to HIV infection and of ways to change them, the committee believes that there is a role for ADAMHA, CDC, and NIH in supporting behavioral research. All three agencies currently conduct behavioral research, but the type and focus vary significantly according to each agency's respective mission. ADAMHA's mission is to find scientifically based solutions to alcohol, drug, and mental health problems and to promote effective strategies to deal with the health problems associated with the abuse of alcohol and drugs and mental illness (ADAMHA, 1990). The agency sponsors research that principally addresses the neuropsychological changes encountered after HIV infection occurs and the etiology and role of drug abuse (including alcohol) in HIV infection. The ADAMHA HIV/AIDS program has a unique focus in that the agency combines research on the biological, behavioral, and psychological aspects of HIV infection with intervention research and the provision of clinical services. In contrast, CDC's mission is to prevent unnecessary disease, disability, and premature death, and to promote healthy lifestyles (CDC, 1990a). To this end CDC supports mainly applied behavioral research that is directly related to the implementation and assessment of broad-scale education and prevention programs. NIH's mission is to conduct and support research on the causes, diagnosis, prevention, and cure of diseases in humans (NIH, 1987). In keeping with this mission, NIH supports a small amount of basic behavioral research on the determinants of HIV-related behaviors based on the institutes' specialized constituencies and research interests. For example, investigators at NICHD are studying developmental components of sexual behavior, whereas NIAID researchers are incorporating interventional behavioral research into clinical research on sexually transmitted diseases. Thus, ADAMHA supports basic and applied research; CDC focuses on programs of disease surveillance and control, with mainly applied research examining behavioral change interventions (particularly in high-risk groups) as part of specific efforts in disease prevention and health promotion; and NIH supports mostly basic research, whose findings provide the basis for the design of actual interventions by CDC and other public health agencies.

As the government's principal biomedical research organization, NIH sponsors behavioral research in areas other than AIDS in which the disease burden to society is significant, such as cancer and heart disease. For example, NCI's Cancer Prevention and Control Program supports behavioral research on a range of topics from nutrition to smoking cessation. In fiscal year 1990, NCI spent 5 percent of its budget on behavioral research. NHLBI also devotes substantial funding to behavioral research and interventions in areas such as hypertension and cardiovascular disease, the institute spent approximately 3.3 percent of its budget on behavioral research. Overall, NIH

devotes approximately 3.1 percent of its funding to behavioral research (Raub, 1988). The comparable figure for AIDS behavioral research was 0.45 percent. (This is not to say that the proportion of NIH resources devoted to behavioral research has been optimal; indeed, the Senate Committee on Appropriations directed NIH to establish a comprehensive 10-year plan for steadily increasing its funding of health and behavioral research [U.S. Congress, Senate, 1989].)

CDC has been making a large investment in applied behavioral sciences research with regard to AIDS. This fact, however, does not relieve NIH of its responsibility to support and conduct such research; indeed, other committees (e.g., Turner et al., 1989) have noted particularly pressing needs for behavioral research on AIDS and strongly recommended an NIH role. This committee believes that, similar to its work in heart disease and tobacco use, NIH can play a key role in supporting basic research to understand the etiology of sexual and drug-using behaviors and in initiating demonstration projects to evaluate intervention strategies. This research may also benefit efforts to prevent transmission of other sexually transmitted diseases and the initiation and continuation of illicit drug use. The committee commends present NIH efforts (i.e., NIAID's efforts to integrate behavioral research with biomedical research through its Sexually Transmitted Diseases Cooperative Research Centers and NICHD's research on adolescents) but considers more research to be needed.

Recommendation 3.9: The NIH AIDS program should increase its support for behavioral research, especially for basic behavioral research (e.g., research designed to understand the etiology or underlying causes of behaviors and evaluate the effectiveness of interventions to modify particular health-related behaviors) on behaviors relevant to the transmission of HIV, including but not limited to human sexual development and practices and (in coordination with ADAMHA) drug addiction and abuse.

As behavioral research becomes a greater part of the NIH and PHS research portfolio, it will require careful planning and coordination to develop appropriate research agendas and clearly define agency roles. At present PHS has mechanisms in place to designate responsibility for research areas and prevent unproductive duplication; these include agreements between NIH institutes, clearance of proposed RFAs through the NIH Office of Extramural Programs, posting of proposed RFAs on a computerized bulletin board for review by other NIH and ADAMHA components, and informal discussion among researchers. These mechanisms, however, do not provide for early-stage coordination and lack high-level PHS oversight. At one point, the PHS Executive Task Force on AIDS had several subcommittees focusing on specific components of behavioral research (e.g., addiction and behavior), but these committees have been disbanded in preparation for a reshaping of all task force committee structures. This committee believes that the PHS should sponsor conferences, involving appropriate NIH, CDC, and ADAMHA officials and behavioral scientists, to identify promising areas of behavioral research, develop a PHS behavioral research agenda, and make recommendations on methods to improve coordination among PHS agencies sponsoring behavioral research.

AS noted earlier in this section, the AIDS epidemic has highlighted the need for current data that are representative of the general population to guide the design of behavioral interventions on sexual behavior. To fill this data gap, NICHD proposed a national survey of health behaviors and AIDS risk prevalence that included questions on sexual relationships, partner characteristics, sexual behaviors with partners, and behaviors such as drug use that put people at risk for AIDS. The survey was also intended to provide a research basis for designing, implementing, and evaluating education and intervention programs to stop the spread of HIV. Despite the value of such information, however, the survey has not as yet been performed. NICHD sought to conduct

a pretest to refine the questionnaire and identify possible design problems and sent the pretest survey questionnaire to OMB in December 1988. Since then it has undergone multiple reviews by OMB, the NIH Director's Office, the Office of the Secretary of Health and Human Services, and OASH, which has been holding the revised pretest since July 1989. Currently, negotiations continue regarding the content and design of the questionnaire, and the future of the full survey is uncertain. The committee believes that these protracted delays have had an injurious effect on the scientific process and on the progress of behavioral research on sexual behavior. The committee believes that the National Survey of Health and AIDS Risk Prevalence will provide invaluable information for efforts to prevent the spread of AIDS and HIV infection and should go forward as soon as possible.

Recommendation 3.10: The pretest questionnaire for the National Institute of Child Health and Human Development's National Survey of Health and AIDS Risk Prevalence should be finalized and released, and the study should be allowed to proceed immediately.

NURSING RESEARCH

High-quality nursing care of persons with AIDS, in conjunction with advances in medical therapy, is an essential component of ensuring a reasonable quality of life for persons who are living with HIV infection. Owing in part to improvements in treatment, the number of persons alive with AIDS continues to grow. CDC estimates that by 1993 between 151,000 and 225,000 persons will be alive with AIDS, compared with 48,000 in 1988, more than a threefold increase in five years (see Figure 1.1). NIH's stated goal is to convert HIV infection into a chronic, manageable illness, a shift in emphasis that will also require a concomitant shift in research loci. Currently, NIH supports a relatively small amount of research (less than 0.2 percent of AIDS research and training funds) on the chronic aspects of HIV infection: research addressing the care needs of HIV-infected persons amounted to only $730,150 in fiscal year 1989, and funds for training of professionals in this area totaled $119,504 (NCNR, 1989).

The purpose of nursing research is to effect both short-and long-term improvements in nursing practice, in addition to restoring patient health and speeding recovery from illness (Larson, 1989). Nursing research addresses a wide range of topics including relief of distressing symptoms resulting from the disease process, development of interventions to alleviate physical symptoms that are secondary to or incompletely relieved by medical intervention, identification of optimal ways to administer medical treatment, achievement of increased compliance with therapeutic regimens, management of therapeutic side effects, prolongation of distress-free intervals, and improvement of quality of life. The neglect and inadequate funding of nursing research have resulted in an underdeveloped knowledge base that must be improved if adequate care is to be provided to the thousands of HIV-infected persons who will be flooding the health care system by the mid-1990s. A report of the NCNR Priority Expert Panel on HIV Infection (1990) identified significant gaps in knowledge about the care of HIV-infected persons:

- care needs across the spectrum of HIV infection;
- development and testing of nursing interventions to alleviate or control symptoms associated with AIDS or its treatment:

—skin breakdown
—nausea, vomiting, inadequate nutrition, loss of appetite, and diarrhea
—psychological, neurological, physiological, and behavioral effects associated with organic brain changes, treatment, or being chronically ill

—dementias and depression associated with AIDS in various health care settings
—fatigue, weakness, pain, and sleep disturbances
—dyspnea and respiratory complications;

- the use of resuscitation and life support in AIDS care—patient outcomes and preferences;
- the special care needs of elderly persons with AIDS, who often have substantial comorbidity and therefore present a difficult treatment and care challenge;
- determination and evaluation of strategies to increase the compliance of HIV-infected persons with various treatment regimens;
- therapeutic effects and cost-effectiveness of nursing interventions in different settings

—comparison of patient outcomes and costs for dedicated hospital AIDS units compared with nursing care on general medical wards
—factors affecting the incidence of cross-infection and nosocomial infections among AIDS patients in institutional settings
—reorganization of hospice care to accommodate the AIDS patient's unique combination of aggressive drug therapies for opportunistic infections and palliative care and symptom control; and

- nursing interventions to enhance or maintain the functioning of people with AIDS through their own self-care or by the development of effective strategies to assist and support informal caregivers (family, friends, volunteers).

In addition to studying the physiological and psychological aspects of nursing care and its delivery, nurses can also play an important role in evaluating the effectiveness of preventive interventions. Because health education and counseling are often the responsibility of nurses, and because nurses often occupy a central position within a multidisciplinary research team, they are uniquely placed to study the effectiveness of behavioral interventions. Such studies could include testing of models of risk identification and risk reduction in primary care settings. Currently, however, this type of nursing research is not being conducted, a situation that is unlikely to change without NIH support.

Recommendation 3.11: Support should be substantially increased for nursing research on the care of people with HIV-related illness.

PRECLINICAL DRUG DISCOVERY AND DEVELOPMENT

In the past 10 years NIH's drug development program has played a pivotal role in developing therapeutic agents for HIV infection. Now, like all of NIH's AIDS research programs, it faces a new era. The early years of the program saw little pharmaceutical industry involvement; consequently, many drug discovery efforts (e.g., the mass screening program for anti-HIV compounds) were supported almost exclusively by NIH. Since the success of AZT, however, pharmaceutical companies have been more willing to expand their internally funded development programs for agents targeting HIV and its related opportunistic infections. A range of new drugs including antivirals, cytokines, immunomodulators, and anti-infectives are now under development by pharmaceutical companies (Pharmaceutical Manufacturers Association, 1990). Given present research needs and the willingness of the pharmaceutical industry to develop certain types of therapeutics, the committee believes this to be an appropriate time to assess NIH's role in preclinical drug development.

Preclinical drug development is part of a continuum of research that runs from basic science knowledge to clinical trials.[3] Drug discovery and development efforts are applied to and focus on a specific outcome: creation of a new therapeutic. The process is subject to controls and regulation by the FDA, which requires the completion of critical path components,[4] conducted under good laboratory practice (GLP)[5] conditions, for all agents for which a sponsor of a human trial submits an IND application. To fulfill these requirements, a drug sponsor must be able to synthesize the drug for preclinical or clinical studies, assess its quality (purity) and detect it in biological fluids, and prepare the compound in pharmaceutical dosage forms suitable for administration to animals or humans.

At present, NIH supports preclinical drug development for anti-HIV agents within NCI, NIAID, and NIGMS. Funding for preclinical drug development in these three institutes totaled approximately $98 million for fiscal year 1990.

National Cancer Institute

NCI supports two major initiatives for preclinical discovery and development of anti-HIV drugs: a high-capacity screen to assess compounds for activity against the HIV virus and a program for the preclinical and early clinical development of drugs with anti-HIV activity. (Clinical drug development efforts are discussed in the next section on clinical trials.) NCI's fiscal year 1990 budget for the development of therapeutic agents was approximately $40 million.

The institute's rapid, high-capacity drug screen for anti-HIV activity is a unique resource. The assay procedure identifies agents active against HIV by detecting drug-induced suppression of viral cytopathic effects in T4 lymphocytes (Weislow et al., 1989). The screen has a capacity of approximately 900 tests per week; since its implementation in 1987, more than 27,000 screening tests have been performed. To date, more than 7,000 unique chemical structures have been tested, and about 70, or 1 percent, have been identified as having anti-HIV activity.

Compounds for testing may be submitted to NCI from virtually any source, providing relevant structural and biological information accompany the submission. When a compound is submitted, the Acquisitions/Input Committee (composed predominantly of senior staff from the Division of Cancer Treatment [DCT]) reviews the current acquisitions inventory to decide whether to accept the compound for screening. If the compound is accepted, it is rated for priority and enters the screening program. All compounds progress through the NCI program in the same general manner. If a compound is shown to have in vitro anti-HIV activity, the Decision Network Committee (DNC) decides whether to proceed with further preclinical and clinical development. (The 20-member DNC includes senior NCI staff and representatives from NIAID.) If the DNC decides the compound should be considered for preliminary pharmacological and toxicological studies, it is followed by an operating committee, also composed of senior DCT staff, that monitors the preclinical testing. This system allows NCI to bring three or four promising anti-HIV drugs

[3] As used in this discussion, drug discovery and development encompass the acquisition and testing of materials, chemical synthesis and bulk drug production, toxicology and pharmacology studies, and formulation and production of a drug for use in a clinical trial.

[4] For anti-HIV drugs, critical path components include pharmacokinetics and toxicology studies, as well as synthesis and formulation of the compound. Agents for opportunistic infections require these four steps and animal-model efficacy studies.

[5] GLP guidelines are specified by the FDA and usually require special resources. For example, a laboratory operating under GLP conditions has a designated balance for weighing a specific compound and designated notebooks for recording all measurements made on the balance. In addition, these studies often require specialized containment facilities and specially trained staff; as a result they are often quite expensive.

per year from preclinical to early clinical development. At the time of this report, twelve compounds identified through the screen were in the preliminary development stage and one was in late-stage development; however, no compound identified by the screen had as yet reached the clinical trial stage.

National Institute of Allergy and Infectious Diseases

NIAID supports preclinical drug discovery and development initiatives for HIV and opportunistic infections in three general areas: (1) targeted drug development, (2) basic and applied research, and (3) preclinical investigational new drug studies. In fiscal year 1990, NIAID's budget for the development of therapeutic agents was $44 million.

NIAID's major vehicles for targeted preclinical drug development are the National Cooperative Drug Discovery Group Program for the treatment of AIDS (NCDDG-HIV) and the National Cooperative Drug Discovery Group Program for the treatment of opportunistic infections (NCDDG-OI). Launched in fiscal years 1986 and 1990, respectively, the NCDDG programs account for more than half of NIAID's preclinical drug development budget (approximately $23 million). Both NCDDG programs are investigator-initiated efforts designed to foster collaboration among academic, private, and government laboratories on basic and applied research problems in the design and development of new therapies for the treatment of HIV and related infections. The programs use a rational approach to drug design; that is, researchers study an infectious organism's structure and mechanism of replication and use this information to design therapies that target vulnerable features of the organism. If a promising compound is discovered by one of these groups, it can then be developed either by the private-sector participant or by NIH itself.

NIAID also supports about $20 million in investigator-initiated research related to drug discovery and development. Discovery grants are awarded to study the structure of proteins and viral enzymes; development grants concentrate on developing analogs and improving the formulation of therapies. As the third major part of its preclinical program, the institute maintains contracts to perform scale-up synthesis, assess drug purity, and develop dosage forms. In addition, it recently issued RFPs to expand its basic drug development capabilities for pharmacokinetic, bioavailability, and toxicology studies.

NCI and NIAID thus take different approaches and use their resources differently in the preclinical development of agents. NCI offers its resources in a programmatic manner; rather than a sponsor being able to utilize discrete NCI components, an agent enters NCI's *system* . In contrast, NIAID provides access to individual preclinical drug development resources, such as formulation, scale-up, and animal-model studies. NCI has a contract-based, large-scale mass screening program as opposed to the variety of biochemical and cell-based screens that can be made available to NIAID by NCDDG investigators. Moreover, under the terms of a 1989 interagency agreement between NCI and NIAID,[6] NIAID has sole responsibility for the acquisition and development of drugs for opportunistic infections and supports basic and applied drug development research on opportunistic infections throughout its divisions.

[6] The interagency agreement was signed March 7, 1989, by the directors of NCI and NIAID and the director of NIH. It is the third in a series of such agreements that outline the responsibilities and rights of the two institutes concerning AIDS-related research.

National Institute of General Medical Sciences

NIH's Targeted Antiviral Program, launched in fiscal year 1987, funds research on molecular structure determination and analysis for the purpose of developing antiviral drugs for AIDS treatment. Initially, the program was funded by the NIH OD and managed by NIGMS. It is now funded and managed by NIGMS alone.

The Targeted Antiviral Program operates under the premise that the best way to design drugs is to delineate the detailed molecular dimensions and structure of a potential receptor site and then synthesize a specific molecule to fit that site. The program sponsors research in the areas of structural biology, x-ray crystallography, theoretical chemistry, and nuclear magnetic resonance imaging to develop new leads on agents that can be used in the treatment of AIDS and new methods for drug screening. Many of these projects require highly purified HIV proteins that are not readily available commercially. To meet this need, NIGMS recently established a Protein Expression Lab to produce HIV proteins of sufficient purity and in adequate quantities for structural studies.

NIH's Role in Preclinical Drug Development

Anti-HIV Agents

At present, preclinical drug development of anti-HIV agents is supported in a number of arenas. Within the industry, both large, established pharmaceutical houses and emerging biotechnology firms have shown interest in developing anti-HIV drugs. NIH intramural researchers have made significant contributions to understanding the mechanisms of action of compounds; extramural researchers have also shown interest in developing anti-HIV therapeutics. NIAID's NCDDGs actively pursue targeted drug development using a wide range of approaches.

The different groups that have demonstrated an interest in developing anti-HIV drugs possess varying levels of resources and thus require different levels of assistance to support the critical path studies necessary for submission of an IND application. Established pharmaceutical firms require the least amount of assistance as they generally have in-house capabilities for completing FDA-required critical path studies; many of these firms also have a long record of expeditious drug development and approval. Similarly, NCDDGs, which include an industry representative as part of the consortium, also have access to preclinical development resources. NCI intramural researchers have access to such resources through that institute's comprehensive drug development program. The greatest need for assistance is among small biotechnology companies and independent drug sponsors, which may have the resources to complete some but not all of the studies required in support of an IND application. (For example, some sponsors may not have the resources or facilities to conduct the necessary drug formulation or animal-model studies.)

It is unfeasible for NIH to act as a national nonprofit pharmaceutical firm and develop all possible candidate agents. To achieve the goal of making HIV infection a manageable, curable disease, the committee believes NIH should promote a wide range of approaches and offer selective support to a variety of sponsors. In particular, NIH should use its resources to assist sponsors of promising compounds that do not possess the resources to complete all the studies required for an IND application. The committee notes that NIAID has expressed interest in providing resources in this manner and encourages this approach. However, the private sector alone will never pursue all of the areas of drug development needed to address AIDS concerns because commercial firms generally develop only those drugs on which they can expect to make a profit. Consequently, NIH

should be prepared to develop promising compounds that would not otherwise be developed by the pharmaceutical industry.

Recommendation 3.12: The optimal role for NIH's preclinical drug development program should be to facilitate drug development by all sectors-governmental, academic, and private-and to develop drugs whose development is not likely to be supported by the pharmaceutical industry.

Regimens that use combinations of drugs with different mechanisms of action (i.e., that target multiple elements of the HIV life cycle) are a promising therapeutic approach. To establish such regimens it will be necessary to develop a variety of biochemical and cell-based screens that identify compounds active against the various HIV life-cycle stages. NCI's mass screen for anti-HIV agents does not identify drugs that work by all mechanisms of action. NIAID, which also has responsibility for identifying and developing anti-HIV compounds, does not have adequate resources to develop and use screening tests; instead, it relies on NCDDG investigators to perform testing on a voluntary basis. This arrangement causes delays in screening potential compounds and limits NIAID's ability to assess promising agents quickly and fully. Such testing will be vital in the development of combination regimens and is unlikely to be supported by industry. As a complement to NCI's mass screening program, NIAID should have additional in-house resources to develop and use a broader range of screening tests for anti-HIV agents.

Recommendation 3.13: NIH should develop and support a range of screening tests for anti-HIV drugs. In addition, NIAID and its Division of AIDS should establish contract-based screening capabilities, and NIH should expand its intramural or dedicated extramural resources for mechanism-of-action studies for anti-HIV agents.

Agents for Opportunistic Infections

Within NIH, NIAID has sole responsibility for the acquisition and development of drugs for opportunistic infections (OI), and its divisions support basic and applied research in this area (Table 3.2). Research on opportunistic infections has a profile different from research on HIV for two reasons. First, although OIs are often referred to as one phenomenon, they are more precisely a collection of pathogens responsible for a host of protozoal, fungal, bacterial, and viral infections seen among AIDS patients. Second, the duration of support for basic research on the various organisms has varied widely, resulting in disparate levels of basic knowledge and varying availability of in vitro tests and animal models.

NIAID officials and researchers in the field have stated that one of the largest impediments in the development of drugs for opportunistic infections is inadequate basic knowledge about some of the organisms. For example, consider the following:

- *Pneumocystis carinii* pneumonia-there is still debate as to whether the pathogen is a protozoa or a fungus; moreover, it cannot be cultured in vitro. (Between 60 and 80 percent of persons with AIDS contract PCP with an approximate 25 percent mortality rate.)
- *Cryptosporidium*-knowledge about this organism is also limited. The pathophysiologic mechanism by which *Cryptosporidium* causes diarrheal disease is unknown, and the lack of suitable in vitro and in vivo model systems has hindered research.
- Toxoplasmosis-present therapies cannot predictably eliminate the latent form of the parasite, which means that AIDS patients must continue lifelong suppressive therapy. There is also no diagnostic test available to discriminate between active and latent infection.

- *Mycobacterium avium*-very little is known about its biochemical pathways and the enzymes critical to its functioning.

In addition to a dearth of basic knowledge on many organisms, other impediments exist. Two obstacles to the rapid development of drugs for opportunistic infections are the lack of good animal models and in vitro tests (see Table 3.2) The availability of isolates for certain organisms has also been cited by researchers as an impediment to further research. As of the fall of 1990, NIAID/DAIDS had drug evaluation contracts for agents active against *Pneumocystis carinii, Mycobacterium avium* complex, and *Candida albicans*; it has expressed interest in expanding this capacity to include *Toxoplasma gondii, Cryptococcus neoformans, Histoplasma capsulatum*, and *Cryptosporidium parvum*. The committee encourages NIAID in these efforts to develop an increased screening capacity. Another obstacle involves the peer-review process, which some NIH officials and researchers have asserted impedes the expansion of research on opportunistic infections. Proposals to study organisms that have a more immature knowledge base have often had difficulty competing with more sophisticated proposals for research on organisms that are better understood. (There appears to be a perception among some researchers that prestigious investigators avoid this type of research and that it is less 'glamorous' than working with HIV.) The committee believes that study sections reviewing applications for specific organisms should include individuals who are knowledgeable about the current state of the science for that organism. A final barrier cited by NIH officials has been the lack of a preclinical drug development capacity for OI agents. The committee notes that the NIAID advisory council recently approved proposals that would provide NIAID with the capacity to conduct pharmacokinetic, bioavailability, and toxicology studies, and it strongly endorses these efforts.

As noted earlier in this section, NIAID has expanded its OI research efforts by establishing six national cooperative drug discovery groups. NIH has contributed to the total research effort by sponsoring a workshop to identify research needs in this field. The committee commends NIH for both of these activities but is compelled to note that areas of further scientific opportunity still exist. Support by the pharmaceutical industry for basic research and animal-model studies related to opportunistic infections is unlikely. NIH should have the capacity to conduct this research and, indeed, all critical path studies required by the FDA for submission of an IND application for drugs for opportunistic infections.

Recommendation 3.14: NIH should increase its support for basic and applied research in the area of opportunistic infections. NIH should also facilitate the development of promising drugs for opportunistic infections through all the steps necessary to secure the IND application.

CLINICAL TRIALS

A major goal of the AIDS research program is the development for clinical use of treatments for HIV infection and the diseases it causes. To this end, clinical trials of therapeutic agents for AIDS and HIV infection are conducted by several institutes at NIH. These include NIAID, which has major extramural, intramural, and community-based systems; NCI, which conducts primarily intramural phase I studies; NICHD, which administers a network of extramural pediatric clinical trials centers; and the National Eye Institute (NEI), which has written several protocols and is currently running an extramural trial on ocular complications of AIDS. Table 3.3 shows funding for NIH AIDS clinical trials by institute for 1988-1991.

Once the federal government recognized the urgent nature of the AIDS epidemic, and the enormous challenge the disease presented, it began to increase substantially its support of AIDS-related research, the NIH therapeutics programs, and especially the NIAID clinical trials program. NIH was charged with developing the organization for a new, comprehensive drug evaluation program at the same time it was enrolling thousands of patients in clinical trials. Despite these formidable tasks, the short history of the NIH clinical trials program records several notable accomplishments, including

- determination of the efficacy of AZT in the treatment of children with AIDS;
- establishment of a national clinical trials network capable of testing new anti-HIV and anti-OI therapeutic agents;
- recruitment of many talented investigators into AIDS clinical research;
- extension of the use of AZT for persons with early and asymptomatic infections and a better understanding of the drug's most effective and safe dosage ranges; and
- initiation of dozens of important clinical trials that promise to provide essential scientific information about treatment with a wide array of antiviral and anti-OI drugs.

The committee strongly believes that the rapid growth of the NIH clinical trials program and its undertaking of a much larger number of trials than were originally envisioned, involving thousands of patients, necessitate a reevaluation of the NIH clinical trials system to ensure that it functions both efficiently and cost-effectively; this section thus discusses the committee's findings and its recommendations for improving the performance of AIDS clinical research. The committee concentrated on the AIDS Clinical Trials Group program of NIAID's Division of AIDS because it is NIH's largest AIDS clinical trials program and often provides the sites for clinical studies sponsored by other institutes. This section's principal topics are (1) establishing a specific mission for the ACTG; (2) improving management and interinstitute coordination; (3) evaluating current systems to address areas of inefficiency; and (4) providing the staffing and funding necessary to perform the tasks assigned to the NIAID clinical research program. (As the report neared completion, NIH officials announced their intention to institute a number of measures that are similar to recommendations offered by the committee.[7] The committee supports those plans and hopes that its recommendations will underscore the critical need for their implementation.)

Mission of the AIDS Clinical Trials Group

One of the major questions confronting NIH's AIDS clinical research program is how it defines the mission of the ACTG. Many of the NIH officials interviewed by the committee said that lack of a clear mission was the cause of many of the ACTG's current problems, in that the ACTG undertook more trials than its staff and clinical resources could handle. The absence of a

[7] NLAID announced a number of changes in its clinical trials program at the September 1990 meeting of the NIAID advisory council. They included: (1) recompetition of all adult ACTUs in fiscal year 1992, with future funding levels tied to performance measures (e.g., overall accrual, timely submission of data, accrual of underrepresented populations); (2) special funding incentives for ACTUs that accrue more patients than the numbers specified by the ACTG; (3) establishment of a small contract program for rapid pilot and phase 1 studies of new agents, innovative studies of new therapies, and quick evaluations of unproven therapies, to be conducted by non-ACTU institutions; (4) a separate grant program for supporting applied clinical research at ACTUs in virology, immunology, and pharmacology (e.g., studies of drug resistance, surrogate markers of disease progression); and (5) regionalization of pharmacology and virology laboratory services to ACTUs. NIAID expects to carry out these changes within the current ACTG budget (adjusted for inflation). The council also approved a $15 million-a-year expansion of the pediatric ACTG to include more sites and to provide outreach, perinatal, and obstetrical services.

clearly focused mission also contributed to unrealistic public expectations of the ACTG that led to severe criticism when those expectations were not satisfied. NIH must define the ACTG's mission more clearly with a focused statement of its scientific goals. Such a statement would delineate NIH's specific responsibilities and provide accountability for its AIDS clinical research program. In addition, it would clarify the division of responsibility between NIH and the pharmaceutical industry for clinical trials and between NIH and other government agencies for the provision of health care (see Chapter 1).

In terms of scientific goals, the ACTG leadership has sought to operate the trials group as a national nonprofit pharmaceutical company responsible for testing and obtaining approval for every potential AIDS drug at every trial phase. Thus, by June 1990, the ACTG network of 47 clinical centers was sponsoring nearly 90 active clinical trials and planned to start 33 more protocols before the end of 1990. This heavy workload stems in large part from strong societal and congressional pressure on NIH to provide new AIDS drugs rapidly. However, given the ACTG's currently limited resources (e.g., at the time of this report, the ACTG had only four medical officers who were responsible for advising its field investigators and managing all of the trials), the committee concludes that the ACTG cannot continue to perform high-quality work with the large number of trials now in progress and in planning stages.

Recommendation 3.15: The ACTG should focus its mission more narrowly and tailor the number of trials it conducts to that new mission, to currently available staff, and to the capacities of local AIDS clinical trial units.

In redefining the ACTG's primary mission, NIH must distinguish the tasks to which it is best suited and the tasks that are better left to the pharmaceutical industry, the other major resource for AIDS clinical trials in this country. Many of the major pharmaceutical firms have a long record of expeditious drug development and approval, and such firms will conduct many clinical trials. The committee recognizes, however, that pharmaceutical firms do not always perform trials well and that some small companies have little experience in conducting clinical research. In addition, pharmaceutical companies generally develop only those drugs on which they expect to make a profit, and the trials they conduct of those drugs are designed to provide only those data that are necessary for marketing approval. The ACTG, on the other hand, as a multicenter, publicly funded system, is uniquely qualified to conduct clinical efficacy trials that are in the interest of the public's health but that are not usually done by major drug companies. Such studies, which often collect other useful data besides those required for approval, include drugs for small patient populations with particular opportunistic infections or AIDS-related cancers, testing of drugs in combination, "head-to-head" trials of drugs from different companies, and, rarely, postapproval (phase 4) trials that might change the indication for already approved drugs. The large size and multicenter nature of the ACTG argue against an emphasis on phase 1 trials, which the committee believes are best accomplished by single ACTU sites, the NIH intramural programs, or experienced pharmaceutical companies.[8]

Recommendation 3.16: The ACTG should assume primary responsibility for trials that are important to the public health and that are unlikely to be conducted by the pharmaceutical industry. These include trials of drugs in combination, trials that compare drugs made by different companies, trials of drugs for small patient populations such as those with particular opportunistic infections or AIDS-related

[8] Among the ACTG's plans for the near future is the use of contracts for ensuring that phase 1 trials are conducted efficiently.

cancers, and, in rare instances, phase 4 or postmarketing trials that may not otherwise be conducted. However, the pharmaceutical companies should be encouraged to take responsibility for phase 4 trials of their products, especially those that expand the indications for already approved drugs.

The committee believes that the differing strengths and priorities of NIH and industry provide an opportunity to develop all needed AIDS therapies but that NIH must coordinate its efforts with the private sector to ensure a clear division of labor. Interviews with many NIH officials and representatives of the pharmaceutical industry indicate that the two groups have not yet established a consistently constructive, complementary relationship. Some of the problems with joint NIH-industry trials in the past have included conflicts over the control of protocol design, protocol revisions, IND possession, and data ownership; there has also been outright refusal by many drug companies to work with the ACTG and duplicative efforts between NIH and industry. ACTG officials note that problems involving trials conducted in collaboration with industry have multiplied as the ACTG's growing workload has forced it, primarily because of lack of staff, to increase its reliance on drug companies for trial management. The high-priority ddI trials are the most notable example of these types of problems. The drug company involved (Bristol-Myers) designed much of the protocol, held the IND, and managed the data. After this arrangement was made, new evidence on the use of low-dose AZT became available, which NIH officials believed necessitated a change in the protocol. It took them several months, however, to convince Bristol-Myers to lower the AZT dosage in the trial.

Industry representatives have several criticisms of the collaborative process used to conduct trials of some AIDS drugs. For example, they assert that NIH does not construct simple, focused trials that concentrate on regulatory approval. This point on the surface is true; obtaining drug approval, however, is not the sole purpose of NIH trials, which often include the broader goal of answers to a wide range of relevant scientific questions. Industry representatives also criticize NIH's consensus protocol development process as cumbersome, noting that companies lose control over their drug once it enters the ACTG system. Industry officials add that these characteristics of ACTG trials result in fewer opportunities for NIH to test novel antiviral drugs that are being developed by the major drug companies.

As described earlier, the ACTG has undertaken an overly ambitious mission in which it attempts to test every type of AIDS drug at every trial phase. The committee believes that many of the current problems in the NIH-industry relationship will ease as the ACTG focuses its clinical trials mission and undertakes a workload more commensurate with the capacity of its staff and ACTU sites. A reduction of the size of the ACTG's workload will lessen NIH dependence on industry for the trials management services that have created tension between the two sectors. In addition, clear redefinition of the ACTG's mandate to conduct specific types of trials not pursued generally by pharmaceutical firms should lessen duplication.

In redefining the ACTG's role, NIH should recognize that major drug companies, when motivated, are often capable of testing important antiviral agents that have a potentially large market. Industry should be actively encouraged to test such agents (and conduct postapproval studies), and such encouragement should include the recognition by NIH that drug companies will need to overlap with the ACTG in the use of the clinical investigators who are now involved in the ACTU network. Given that the supply of trial participants and qualified researchers is finite, it is essential that the two primary vehicles for conducting these trials (i.e., the pharmaceutical industry and NIH) clearly define their missions and roles and meet regularly to resolve conflicts. The committee believes that NIH-industry collaborations are appropriate and can benefit the development of anti-HIV and anti-OI drugs. The committee also believes that in collaborative

ACTG-industry ventures, the ACTG is providing a valuable service and should be appropriately compensated. In such cases the ACTG should negotiate for reimbursement from the pharmaceutical firm and should have control over these funds.

Recommendation 3.17: NIH should ensure maximum coordination of its clinical trials with the pharmaceutical industry by meeting regularly to resolve conflicts over rights to data ownership and access to patients and investigators at ACTU sites. NIH should also negotiate with pharmaceutical companies for supplemental financing of NIH-conducted trials (e.g., postmarketing studies) that clearly benefit the industry sponsor.

Efficiency Within the ACTG

The ACTG has evolved into a 47-center clinical trials network in less than four years owing to an unprecedented infusion of NIH money and staff. Yet as a large applied program that was built rapidly in a crisis environment the ACTG has had little time for long-range planning or evaluation. NIH's initial goals of erecting a trials system and enrolling patients as quickly as possible must give way to a new stage in which the ACTG evaluates its performance and reassesses its administrative procedures and clinical goals. The evaluation's primary purpose should be to identify inefficient ACTUs in order to take corrective action at unproductive sites and, if necessary, redistribute NIH resources to those trial units that are most productive. (Efficiency is a key issue because ACTUs that enroll very few patients continue to receive full funding, thus increasing the overall trial expenses on a per-patient basis.) A systematic evaluation of trial sites would also provide important information on patient capacities of individual ACTUs to allow better planning of future trials.

The NCI approach to evaluation of its cancer clinical trials groups illustrates several concepts that are relevant to an assessment of the ACTUs. According to NCI officials, the first priority of their evaluation is to identify what is expected of the individual trial units. For example, are the sites meant to enroll patients in the study, to involve underserved patients, to help design protocols, or to perform correlative research on such issues as surrogate markers? Once the mission and expectations for each group are clearly defined, NCI compares a list of actual results with what was expected from each group and assesses the group's performance, allowing for mitigating factors that may explain unmet goals. NCI officials caution that the criteria should be as quantitative as possible to avoid subjective disputes over a site's performance. The NCI evaluation is conducted at three peer-review levels: (1) the cooperative group evaluates its own performance, (2) committees from each regional group evaluate the other groups, and (3) a regional executive committee makes a final assessment of the groups' productivity. To provide close surveillance, evaluation of the cancer clinical trials groups occurs yearly in the context of a noncompeting renewal. The committee believes the ACTG has a strong need for a similar annual evaluation and notes several key principles that should govern its design and implementation. First, NIH must define specific expectations for each of the ACTUs; then a review body, preferably an independent study group consisting of investigators in both AIDS and non-AIDS research, should analyze the ACTUs based on objective criteria. Recently, the ACTG has begun to develop an evaluation program for the ACTUs. Criteria under consideration include the following:

- number of patients for whom full and accurate data are available;
- number of minority, IV drug-using, and female patients enrolled in trials (these patients often require more staff assistance);
- number of patients accrued, adjusted for the difficulty and complexity of a protocol;
- timeliness and accuracy of data submission;

- scientific contributions of the ACTG site personnel; and
- coordination by the ACTU with other service organizations (e.g., General Clinical Research Centers, HRSA demonstration projects, and NIDA treatment programs).

To these the committee would add:

- timeliness of submission of articles reporting research results (see the discussion later in this chapter).

Using these criteria, an expected level of performance and concomitant funding could be determined; superior performance could be encouraged with additional funding or higher priority in the next grant renewal competition. The evaluation process should also provide an opportunity for ACTUs to explain factors that may have adversely affected their performance.

Termination of funding of an ACTU is a complicated, sensitive issue, in part because some ACTUs, in addition to their role in clinical research, are the principal AIDS health care providers in their communities (although it should also be noted that ACTUs that enroll few patients enhance the care of few patients). The committee believes that the primary purpose of an ACTU is to conduct research rather than provide AIDS health care, a view consistent with its conviction that NIH should not have to assume responsibility for providing basic health care (see Chapter 1). NIAID, under the terms of the cooperative agreement that governs its relations with an ACTU, has the prerogative to withhold funding if clearly stated performance goals are not met. This function highlights the importance of an ACTU evaluation that will create data on which to base refunding decisions. The committee believes that the evaluation of ACTUs is an extremely important issue and supports the ACTG's efforts to link performance to funding.

Recommendation 3.18: NIH should conduct an annual, systematic evaluation of each ACTU. The results of these evaluations should be reviewed by an extramural group authorized to advise corrective action and recommend defunding of sites that do not meet expected performance standards.

The development and design of AIDS clinical trials are being closely scrutinized by AIDS advocates and the scientific community for sources of inefficiency and potential areas for improvement that might expedite the evaluation of new therapies. At present, the ACTG develops protocols by a multistep consensual process in which ACTU investigators develop a concept and send it through multiple ACTG committees and the Division of AIDS program office for revisions and approval. A common path for a prospective ACTG protocol is depicted in the schema below:

ACTU investigator —> Pathogen Study Group —> ACTG Committee —>
ACTG Executive Committee —> NIAID Division of AIDS —>
Appointment of protocol team —> Revisions (by multiple committees) —>
Local institutional review board approval

During interviews with committee staff, NIH officials noted that one advantage of consensus protocol development was the opportunity for many investigators to contribute to the process and to feel involved in producing the protocols. Yet many ACTG investigators contend that they actually have very little input into the protocols they conduct. NIAID officials acknowledge that the high degree of pluralism in the process causes numerous problems, chief among which is that the many layers of input and review make the process cumbersome and can lead to inordinate delays in opening important trials. Another problem noted by NIH officials is that many investigators often add a test or observation in which they have an individual interest, resulting in

protocols that are laden with data requirements pertaining only to a specific investigator but that all ACTUs must satisfy. This aspect of protocol development may produce trials that are unnecessarily expensive and labor intensive.

Despite these problems, however, the committee believes that interaction among the various levels of ACTG investigators and NIH is highly desirable for protocol development. Moreover, the ACTG has played an important public health role in encouraging many excellent investigators to enter AIDS clinical research by offering them opportunities for scientific contribution. Yet the committee also believes that the current ACTG protocol development mechanism is too inefficient. At some point, the ACTG must reduce the degree of pluralism now involved and rely on small groups to write the protocols, unencumbered by layers of review and revision. The committee further believes that if good faith efforts on the part of investigators and the ACTG Executive Committee fail to resolve differences of opinion, there should be a group available (on an ad hoc basis and similar in structure to the present ACTG protocol evaluation subcommittee) to review the protocol and resolve the dispute.

There has also been much recent debate on the appropriate role of the FDA in the development of protocols for NIH AIDS clinical trials. Proponents of proactive FDA involvement, such as ex-FDA Commissioner Frank Young, argue that the FDA can speed drug development by specifying, early in the process, the data that are essential for regulatory approval, which might reduce the amount of data collected and expedite approval of the drug, should it prove efficacious. The main argument for the plan is that the urgency of AIDS trials necessitates early, active dialogue with the FDA to ensure that trial results encounter no unexpected delays in the regulatory process. Although NIH is not a pharmaceutical company bent only on obtaining regulatory approval but also a biomedical research agency interested in answering a broad range of scientific questions, the committee recognizes that early and close consultation with FDA is desirable to expedite future regulatory approval of efficacious drugs; NIH investigators, however, should remain primarily responsible for selecting the scientific questions addressed in ACTG protocols.

Recommendation 3.19: NIH should simplify the ACTG protocol development process while retaining incentives for individual investigator contributions. Small groups of ACTG investigators should assume the decisive role in designing protocols, and NIH should establish a mechanism by which they can receive frequent informal comments and advice from an active, participatory FDA on the data needed for regulatory approval. If the ACTG Executive Committee rejects a protocol that has been so designed, a simple appeals process should be available to resolve the dispute.

The design of ACTG clinical trials has been a frequent source of disagreement both between patients and investigators and within the scientific community itself. The highly complicated clinical nature of AIDS and the large number of ACTG protocols call for simplicity and practicality in trial design. The major concerns noted by patient activists and NIH officials interviewed for this study were that ACTG trials often require excessive data collection and have inappropriately exclusive entry criteria that hinder accrual of participants. The committee commends the ACTG's new protocol evaluation subcommittee, which emphasizes reduced data collection, close examination of entry criteria, and standardization of protocols to make them easier to understand and execute. The ACTG's large burden of trials makes it imperative that protocols focus on a limited number of questions and that the trials do not restrict accrual of patients through unnecessary entry criteria.

Recommendation 3.20: The committee strongly endorses the work of the ACTG's protocol evaluation subcommittee and recommends that its guidelines on optimal

protocol design be made available to all ACTG investigators and used as part of NIH's evaluation of proposed protocols.

Accrual

The ongoing shift in the epidemic from gay men to minority populations, current and former users of intravenous drugs, women, and children has stimulated public debate on the feasibility and scientific appropriateness of increasing the representation of these patients in NIH clinical trials. Despite recent progress in minority recruitment, NIH-sponsored AIDS clinical trials include significantly lower numbers of many minority subpopulations with AIDS than their proportions of the infected population would warrant. For example, in New York City, blacks account for 35 percent of all AIDS cases but constitute only 9 percent of ACTG trial subjects.

One reason for the disparity may be that strict entry criteria exclude many patients, including many underrepresented groups, from trials. Restrictive entry criteria for ACTG protocols have been cited by ACTU investigators as a significant factor in slowing the accrual of trials. (An investigator from one New York City ACTU cited an example in which only 3 of 150 screened patients were eligible for an ACTG trial, largely owing to entry criteria.) The committee believes NIH must closely examine the entry criteria it currently employs. As AIDS moves more and more into the subpopulations that are currently underrepresented in NIH clinical trials, these patients increasingly will be the key to swift trial accruals. Furthermore, in a disease with a diversity of patient groups, inclusion in clinical trials of broadly heterogeneous groups of infected people will maximize the applicability of trial results. (For example, biological responses to drugs may differ in certain populations such as former and current users of intravenous drugs, women, and children.) The committee believes the NIH clinical trials have an ethical responsibility to obtain results that apply to all patient populations, although not all phases of clinical trials require representativeness. Some clinical trials, particularly phase 1 trials that focus on dosage and adverse drug effects, can be conducted on a narrow or homogeneous spectrum of the patient population and still yield useful results. In contrast, trials in phases 2 through 4, which focus on efficacy and rare reactions, favor inclusion of a broader, more diverse group of patients.

Because clinical trial participants, particularly in the earliest phases of the study of a drug, expose themselves to significant physical risks as well as potential benefits, the committee does not subscribe to the belief that right of access to a clinical trial can be equated with a patient's right to medical care. In phase 2-4 trials of AIDS drugs, however, there is a greater potential for clinical benefit. Therefore, although the primary purpose of the trials is not to provide treatment, they do serve that function.

The committee considers it essential that NIH improve its recruitment of minority populations, women, children, and intravenous drug users as participants in clinical trials. There are steps that NIH could and already is planning to take to improve recruitment and retention of underrepresented populations, such as providing obstetrical, perinatal, and ancillary services for women in trials. But some of the difficulties encountered by NIH-supported trials in their efforts to enhance recruitment are by-products of the much larger set of problems posed by this country's health care delivery and financing systems (see Chapter 1). The committee recognizes NIH's recent efforts to engage health professionals in outreach activities among the populations that are currently underrepresented in clinical trials (with the goal of hastening accrual) and encourages further measures, such as less stringent entry criteria, that might speed trial accrual among all infected populations. It also commends the work of the newly established Community Program for Clinical Research on AIDS for its efforts to include underrepresented populations.

Recommendation 3.21: The committee believes NIH should increase participation of presently underrepresented populations (i.e., minorities, current and former users of intravenous drugs, women, and children) in AIDS drug trials. To achieve this goal, NIH should (1) examine entry criteria for clinical trials and, where appropriate, make them less stringent, and (2) improve outreach and the provision of ancillary services to underrepresented populations.

Coordination

NIH has conducted pediatric AIDS trials at three different institutes (NCI, NIAID, and NICHD), each of which has made important and different contributions to clinical research on pediatric AIDS.

- Since 1986, the NCI intramural program has performed studies on AZT, ddI, and ddC that showed a beneficial effect of nucleoside agents in children; it continues to perform phase 1 studies on single and combination antiviral therapies in children with AIDS and HIV infection that will lay the groundwork for multicenter phase 2/3 efficacy trials.
- In 1987, NICHD created an extramural clinical trials network to evaluate the efficacy of intravenous immunoglobulin (IVIG) in reducing the incidence of bacterial infections, thereby bringing experimental therapy to patients in 27 clinical centers and urban hospitals who had no other access to it. Although there has been much controversy over the scientific value of this trial, it has served to focus attention on the question of IVIG efficacy, which was a legitimate scientific concern, as well as on pediatric and maternal AIDS, which had received very little attention from NIAID.
- Currently, NIAID has 15 pediatric ACTUs within the ACTG that have assumed responsibility for conducting phase 1 studies and phase 2/3 pediatric trials. The ACTUs provide a large cadre of experienced investigators and scientific resources. In addition, the pediatric core committee of the ACTG has taken a leading role in articulating a scientific agenda for pediatric clinical research.

The committee believes that the use of three separate institutes for a common purpose has brought a wide variety of expertise and resources to bear on pediatric AIDS research, and it commends the efforts of each. But the pediatric trials are also a prime example of NIH's need for an oversight mechanism capable of resolving interinstitute disputes and implementing necessary corrective changes. Most noticeably, NIAID and NICHD have each maintained clinical trials systems (that together total 43 sites) for nearly three years without significant collaboration (many of their sites overlap in the same urban location); they continue to operate their networks through separate management and funding mechanisms. In late 1989, the associate director for AIDS research at NIH directed the NICHD trial system to merge with the ACTG, thus creating a single coordinated network for testing drugs in children. Interviews with NICHD and NIAID officials in mid-1990, however, indicated that the two systems had not yet achieved a functional union. Thus far, the ACTG has incorporated NICHD investigators on its pediatric core committee, but the central management and financing of the two systems remain distinct. (NICHD continues to administer its own contract and use a different data center.) The committee believes that an operational merger of the NICHD and NIAID systems is highly unlikely as long as the institutes operate them independently and there is no authoritative mechanism in place to resolve conflicts and produce a functional unity.

The committee is concerned that interinstitute conflict may have hindered NIH's ability to design efficient clinical trials involving children and pregnant women and to enroll as many

individuals as possible in them. NICHD and NIAID can each make valuable contributions in a multidisciplinary approach to clinical research on maternal and pediatric AIDS. For example, the NICHD system enlists many pediatricians and obstetricians who are sensitive to the needs of mothers and children living with HIV infection; in addition, the NICHD trial sites have access to many patients who are not now available to the pediatric ACTUs. The committee believes NIH can best capitalize on its pediatric trial resources by ensuring that all ACTG trials are accessible to patients at NICHD sites. The committee recognizes that NICHD and NIAID face financial constraints in merging their systems but believes that the importance of pediatric AIDS research justifies the costs.

Recommendation 3.22: NIH should complete the merger of the NICHD and NIAID pediatric trials systems to unify their management and funding and ensure maximal use of the two institutes' resources. The merger should include sufficient funding to allow enrollment of NICHD's large pool of patients.

Besides the extramural ACTG program at NIAID, several other NIH institutes or institute components conduct AIDS clinical trials that test therapeutic agents for HIV disease. Indeed, the intramural programs at NCI and NIAID possess resources that have allowed them to achieve important advances in the development of new AIDS therapies. For example, the NCI pediatric branch has made a major commitment to perform AIDS trials without any increase in staffing or space and has played an integral role in the evaluation of drugs for the treatment of children with AIDS and HIV infection. The committee commends NCI's commitment and believes NIH should provide the NCI pediatric branch with increased resources to ensure that its AIDS efforts do not compromise the work of the institute's Pediatric Oncology Branch. NCI's adult clinical trials program has as its primary mission the transfer of preclinical lab findings into phase 1 studies that can assign priorities to new agents for larger efficacy trials. NCI scientists assert that the close proximity of their lab and clinic allows them literally to bring agents across the hall from the lab for testing in humans. The connection between lab and clinical trials promotes rapid in vivo testing of in vitro results, an important factor in NCI's considerable success in conducting studies on anti-HIV drugs.

In addition, numerous NIH officials noted that the NCI and NIAID intramural programs benefit greatly from the relative autonomy of their operations. The intramural scientists work at a single site with a small nucleus of experienced people. They write their own protocols, negotiate directly with drug sponsors to obtain therapeutic agents, and conduct informal talks with the FDA about IND and trial design issues. NIH intramural officials say that, because of their autonomy and the fact that intramural trials are predominantly small phase 1 trials, the testing process—from the origin of a trial concept to initial accrual of participants—occurs in two to four months. The intramural programs also provide comprehensive care for patients participating in the trial, including all health care costs, psychological support, and transportation expenses. These services, as well as onsite intensive education of staff and patients about how to follow complicated protocols, ensure a high rate of compliance for intramural studies.

Recommendation 3.23: NIH should continue to provide strong financial support for AIDS research efforts of the intramural clinical trials programs.

In fiscal year 1990, NCI received $35.4 million for its intramural AIDS clinical trials (both the pediatric and adult programs). This amount was approximately 22 percent of NIH's total 1990 AIDS clinical trials funding of $164.5 million. The committee believes that the NCI intramural program has provided many important results related to the clinical evaluation of AIDS drugs, most notably its phase 1 studies of AZT, ddI, and ddC. The committee notes that the productivity of

the NCI program reflects the effective coordination of NCI's preclinical and phase I resources and NCI's efforts to ensure larger-scale testing of its drugs in the ACTG or by the pharmaceutical industry.

Some NIH officials have expressed concern that NIH does not have a single track for bringing a drug through all stages of clinical testing. The committee recognizes that the many clinical trial resources at NIH and in the private sector offer the strengths of diversity and differing expertise. Nevertheless, NIH needs to assign responsibility more clearly for each step in the clinical evaluation of a new AIDS drug, taking into account the varying strengths of each trial resource. For example, several NIH officials interviewed for this study noted that the NIAID intramural program was underused for conducting phase 1 trials on novel anti-HIV drugs. These officials added that the ACTG did not routinely send new drugs for testing to the intramural program despite the ACTG's high number of prospective protocols and the available resources of NIAID's intramural program.

Recommendation 3.24: NIH should establish a mechanism for better coordination of extramural and intramural clinical trials and consider shifting more responsibility for phase I studies to the intramural program.

Information Dissemination

The extreme sense of urgency surrounding the results of AIDS clinical trials has placed great pressure on the agency to obtain and release usable trial data quickly. In turn, the mode of release of AIDS trial results, which is more rapid than for any other trials NIH has ever conducted, has generated much controversy in the past year, with the debate centering around the timing, forum, and clinical applicability of the released results. The committee believes NIH should ensure publication of all results of its clinical trials, whether the trial has a positive, negative, or indeterminate conclusion. In addition, all basic data generated in the trials should be made available because the publication process is the primary means for expanding a widely available knowledge base. Yet the results of many ACTG trials, results that include considerable data that NIH has publicly offered as ACTG accomplishments, remain unpublished. Only 4 of 27 ACTG accomplishments announced by NIAID in May 1990 had been published in a scientific journal; missing from public access were several sets of results that had a direct impact on clinical regimens being followed by many patients.

Customarily, NIH-sponsored investigators take several months to synthesize their data, write a complete report, and send it to a scientific journal for peer review and, ultimately, publication. In the field of AIDS, however, NIH officials, practicing physicians, and the patient community agree that ACTG trial results often are too important to delay their release for the six to nine months often required for standard journal publication. The committee strongly endorses the use of expeditious peer review and publication as the best method of information dissemination; it recognizes, however, that alternative, faster means may be needed for certain clinically relevant results, although the process must be managed with concern for all affected parties. For example, in the case of ACTG trials 016 and 019, which documented benefits from the early use of AZT, NIH held a press conference to announce a summary of the trial results but made no recommendations on changes for clinical practice. Using a press conference to release data without accompanying clinical recommendations left many community physicians and patients extremely uncertain about the practical significance of the results. The committee recognizes that the high profile of ACTG trials may continue to require the use of press releases, but it strongly criticizes the use of communication through the media as a primary means of dispersing information and

believes that such dissemination of trial results does a disservice to patients and practicing physicians.

The committee recognizes the substantial controversy that surrounds the question of early publication of trial results. On one hand is the understandable desire of ill persons to find rapid answers and guidance from clinical trials; on the other is the desire of researchers to ensure that their conclusions are accurate and reliable. A balance must be struck between the risks of rapid release (i.e., findings that later prove to be incorrect, incomplete, or harmful to patients) and its potential benefit. The committee believes it important to release trial results as quickly as possible; however, it also believes that released data and conclusions that are not carefully and thoughtfully considered benefit neither patients nor scientists, and do not contribute to the knowledge base. Therefore, the committee recommends that NIH establish a mechanism to ensure an element of expedited peer review before the dissemination of trial results.

Recommendation 3.25: The ACTG should institute a comprehensive policy requiring submission of trial data to a peer-reviewed journal within a specified time after completion of the trial or a major protocol change, and timely submission of results should be linked to ACTU evaluations. In addition, NIH should develop a mechanism for public reporting of data with clinical urgency soon after trial completion and prior to journal publication.

Some concerns have been raised that the early release of trial results might lessen the imperative felt by investigators to publish full scientific papers in peer-reviewed publications. An interim publication in no way lessens NIH's responsibility and that of its investigators to publish their data in full.

Recommendation 3.26: The ACTG should establish a working relationship with scientific journals to ensure rapid interim and full publication of high-priority trial results.

RESEARCH RESOURCES

As a public good for which federal support is especially suited, research resources are investments in the infrastructure of biomedical science that help researchers do their work economically and quickly. Their importance increases as the epidemic becomes endemic and the AIDS research program settles into a long-term effort. NIH supports a number of research resources programs through the AIDS budget, including (1) training grants; (2) animal models, such as the regional primate centers and the national chimpanzee and macaque monkey breeding and research programs; and (3) grants for building or upgrading facilities and equipment for AIDS research.

Training

The total number of full-time research training positions supported by NIH has been fairly constant since the late 1970s-between 11,000 and 12,000 a year-whereas the NIH research budget has increased from $3.6 billion to $7.6 billion. In terms of constant dollars, stipends have fallen. The proportion of the NIH budget going to training has declined accordingly, from 5.1 percent in 1980 to 3.8 percent in 1990. The 11,795 slots proposed for fiscal year 1990 were 308 less than the

number recommended by the NAS committee on national needs for biomedical and behavioral research personnel.

Became research training is a long-term investment, it is not surprising that the NIH AIDS program has invested relatively little in training to this point. For fiscal year 1990, NIH allocated about $7.3 million (a little less than 1 percent of the AIDS budget) for 305 AIDS research training slots (2.6 percent of all NIH training slots). The administration is asking for the same number of slots in fiscal year 1991, with no increases in stipend levels or tuition.

Recommendation 3.27: Support should be increased for pre-and postdoctoral training—to a level (about 3 percent of the budget) comparable to other training programs within NIH-in a wide range of AIDS-related disciplines: for example, molecular biology, virology, cell biology, immunology, epidemiology, behavioral sciences, infectious diseases, and clinical medicine. Increases should also be made in the number of predoctoral slots supported by NIGMS and the postdoctoral training grants supported by NIAID.

Animal Models

The lack of a single good animal model of HIV infection and disease progression is still a major impediment to research on AIDS pathogenesis, treatment, and prevention. NIH is currently underwriting development of several promising models including HIV in transgenic and severely immunodeficient mice, SIV in macaque monkeys, and HIV in chimpanzees. For example, as discussed earlier, the recent demonstration of experimental vaccination and protection from infection in the SIV-macaque model holds considerable promise for the development of an effective vaccine against HIV. An expanded effort to exploit the SIV model, however, requires better understanding of the immune system of rhesus monkeys and a larger supply of them for future vaccine research. NIH should also support the development of other animal models.

Recommendation 3.28 NIH should develop a plan that addresses animal resource needs for future research, especially vaccine research. For example, the rhesus monkey population available for research should be increased to the level required to support the expanded program of studies on SIV. This should include not only an expanded breeding program but also a larger program of research on the biology of rhesus monkeys and the construction of additional biocontainment facilities.

Facilities and Equipment

AIDS research requires special facilities and equipment to ensure safe handling of HIV and HIV-infected specimens and to permit state-of-the-art research techniques. NIH has carried out some upgrading of research facilities and equipment through regular research grant mechanisms (e.g., center core grants, cooperative agreements), and in 1989 it funded a one-time competition for 50 facility improvement grants. Historically, NIH has played a major role in underwriting the construction of biomedical research facilities and instrumentation. During the years of the Health Research Facilities Act (1956-1968), the agency supported the construction of about 19 million square feet of health-related laboratory research space, 60 percent of all such space constructed in those expansion years. Some institutes (NCI, NHLBI, and NEI) also had small construction programs during the 1970s, but little construction was underwritten in the 1980s (only about $7 million a year). Many observers consider the overall current condition of biomedical research

facilities deplorable, with the majority of facilities in need of renovation, upgrading, and expansion. Yet in an era of tight funds, there has been no consensus on the appropriate federal role in restoring or expanding the physical infrastructure of biomedical research. Congress appropriated $28.9 million for AIDS facilities improvement and associated equipment in 1988 and 1989, enough for 50 small project grants, but it turned clown an NIH request for $150 million in matching funds for construction in fiscal year 1988. No additional funds for facilities or equipment have been budgeted in 1990, and none have been requested for 1991. (Chapter 4 discusses intramural construction needs, for which NIH is requesting $88.6 million, including $16.5 million for AIDS-related construction projects.)

Recommendation 3.29: The associate director of NIH for AIDS research should plan and oversee the implementation of a program for developing an adequate physical infrastructure for AIDS research. The actual administration of the program could be delegated to the National Center for Research Resources or to other NIH operational units.

COMMUNICATION OF RESEARCH RESULTS

An earlier part of this chapter discussed the issues surrounding the release of research results from clinical trials. However, the communication of research results applies to other areas besides clinical trials and encompasses several modes of information dissemination. This section examines NIH's efforts in this area.

From the beginning of the AIDS epidemic, there has been an urgent need for swift communication of research activities and results among scientists, physicians, and other care providers; such information has also been sought by patients and the general public. In 1983 NIAID began a series of regional workshops to provide information on AIDS epidemiology, research, and patient management and on the ethical, legal, and psychosocial issues faced by health care workers who provide care to AIDS patients. In 1983 NIH also began publishing the *AIDS Memorandum*, a monthly report on AIDS research results that emphasized studies that would not otherwise be published (e.g., studies with negative results), as well as preliminary results of research that would appear later in peer-reviewed journals. In addition, since 1986 the OAR has compiled an in-house quarterly progress report on NIH intra-and extramural AIDS research.

In the past several years, NIH has developed a more extensive public information program than had been in place previously. NIAID has taken the lead in information dissemination to patients, providers, and the general public about available drugs, clinical trials, and effective therapies. For example, it has continued the regional meetings and recently increased efforts to reach more minority health care workers with AIDS information. NIAID has also sponsored workshops and speakers at national meetings of minority health professions organizations. Other NIAID activities include the dissemination of a number of brochures about its treatment research program, contributions to the support of the *AIDS/HIV Experimental Treatment Directory* published by the American Foundation for AIDS Research, and arrangements for entering AIDS clinical trials into PDQ, NCI's on-line information base for physicians on treatments and clinical trials. In 1989 NIAID introduced the AIDS Clinical Trials Information Service in cooperation with CDC and the FDA. This service, which can be accessed by a toll-free telephone number or through the National Library of Medicine's (NLM) on-line information service, provides information in English and Spanish about NIH-sponsored clinical trials and experimental therapies for AIDS and AIDS-related diseases, and about drug company-sponsored trials known to the FDA. NIAID's Office of Communications also distributes *Backgrounders* and other materials with current information on

AIDS research results. Also in 1989 NIAID's Division of AIDS began a bimonthly publication, *AIDS Research Exchange*, to 'provide timely information on major developments, issues, and events related to AIDS research sponsored or conducted by the NIAID." NIAID has announced the results of some clinical trials as "clinical alerts' mailed to every physician in the' country (a mechanism that has been criticized as medicine by press release). In March 1990 NIAID held the first of a planned series of "state-of-the-art" consensus conferences to develop practice guidelines for the use of new therapies; the first conference resulted in recommendations for the use of AZT in treating patients with early HIV disease.

Other NIH components besides NIAID are also involved in disseminating information on AIDS research. For example, NHLBI carries on information and education efforts because of its role in ensuring a safe blood supply for the nation. The institute established the National Blood Resource Education Program in 1987 to promote the adequacy and safety of the blood supply and its appropriate use, and has sponsored several consensus conferences on related issues.

The NLM supports several AIDS-related information efforts. The Health Omnibus Program Extension of 1988 authorized NLM to create a "data bank on the results of research with respect to AIDS." The library has also published a printed bibliography of AIDS citations since 1983. In 1988, the NLM added AIDSLINE, a bibliographic data base on AIDS basic research, epidemiology, diagnosis, treatment, control, prevention, and policy and administration, to MEDLARS, the NLM's family of on-line data bases. AIDSLINE contains more than 23,000 references to the published literature on AIDS dating from 1980 and is adding about 700 new citations a month. In late 1989, the NLM added two more data bases, AIDSDRUGS and AIDSTRIALS, which provide information on clinical trials of AIDS drugs and vaccines, including general patient inclusion and exclusion criteria. These data bases contain the same information available through NIAID's toll-free telephone service.

The committee commends NIH's support of an extensive AIDS communications program for scientists, clinicians, patients, and the general public. Nevertheless, continuing research advances with implications for prevention, diagnosis, and treatment raise new and urgent questions about early dissemination that NIH must address. (A discussion of this issue was presented in the earlier section on clinical trials.) The committee encourages NIH to continue its present efforts and, in addition, to solicit input from the public and scientific community and periodically review its programs.

TABLE 3.1 Funding for HIV-related Epidemiological Research (in thousands of dollars), National Institutes of Health, Fiscal Year 1990

Institute	Amount
National Institute of Allergy and Infectious Diseases	71,500
National Heart, Lung, and Blood Institute	18,290
National Cancer Institute	16,663
National Institute of Child Health and Human Development	15,017
Fogarty International Center	2,938
National Institute of Dental Research	550
National Institute of Arthritis and Musculoskeletal and Skin Diseases	320
National Institute on Aging	274
National Center for Nursing Research	241
Total	125,793

SOURCE: Office of the Assistant Secretary for Health, Budget Office, U.S. Department of Health and Human Services.

TABLE 3.2 Status of National Institute of Allergy and Infectious Diseases (NIAID) Research on Opportunistic Infections

	In Vitro Tests			Basic Research FY89			Clinical Research FY89				
Organism	Culture	Screen	Animal Models	Division	No. of Grants	No. of Contracts	Treatment Available	No. of ACTG Trials	No. of Other Trials	NCDDG-OI Grants FY90	Other Involved Institutes
Pneumocystis carinii	No	In dev.	Yes	DAIDS	9	4	Yes	12	10	Yes	NHLBI, NIGMS
				DMID	1	0					
				DAIT	1	0					
Toxoplasma	Yes	Yes	Yes	DIADS	3	0	Yes	1	2	Yes	NEI, NICHD
				DMID	9	0					
Cryptosporidium	No	No	In dev.	DAIDS	1	0	No	1	2	Yes	NIDDK
Isospora	No	No	No	DAIDS	0	0	Yes	0	0	No	NIDDK
Microsporidium	No	No	No	DAIDS	0	0	No	0	0	No	
Candida	Yes	Yes	Yes	DAIDS	4	3	Yes	0	3	Yes	NCI, NIDR, NHLBI
				DMID	15	0					
Cryptococcus	Yes	Yes	Yes	DAIDS	4	0	Yes	3	3	Yes	
				DMID	5	0					
Histoplasma	Yes	Yes	Yes	DAIDS	1	0	Yes	1	0	No	NEI
				DMID	5	0					
Coccidiodes	Yes	Yes	Yes	DAIDS	0	0	Yes	0	0	No	
				DMID	3	0					
Mycobacterium avium	Yes	Yes	Yes	DAIDS	4	3	Yes	0	3	Yes	
				DMID	4	0					
Mycobacterium tuberculosis	Yes	Yes	Yes	DAIDS	0	0	Yes	0	1	No	NIA
				DMID	3	3					
Salmonella	Yes	Yes	Yes	DAIDS	0	0	Yes	0	0	No	NIDDK, NIEHS, NIGMS
				DMID	9	0					
Treponema pallidium	No	No	Yes	DAIDS	0	0	Yes	0	0	No	
				DMID	9	0					
Cytomegalovirus	Yes	Yes	Yes	DAIDS	5	0	Yes	8	6	Yes	NCI, NEI, NIGMS, NHLBI, NICHD
				DMID	16	6					
Herpes simplex	Yes	Yes	Yes	DAIDS	0	1	Yes	1	0	No	NCI
				DMID	31	1					
Herpes zoster	Yes	No	No	DAIDS	0	0	Yes	0	1	No	
				DMID	8	7					

NOTE: Abbreviations: ACTG, AIDS Clinical Trials Group; DAIDS, Division of Acquired Immunodeficiency Syndrome; DMID, Division of Microbiology and Infectious Diseases; DAIT, Division of Allergy, Immunology, and Transplantation; FY, fiscal year; NCDDG-OI, National Cooperative Drug Discovery Groups program for opportunistic infections; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NEI, National Eye Institute; NICHD, National Institute of Child Health and Human Development; NIDDK, National Institute of Diabetes and Digestive Kidney Diseases; NCI, National Cancer Institute; NIDR, National Institute of Dental Research.

SOURCE: National Institute of Allergy and Infectious Diseases, National Institutes of Health.

TABLE 3.3 NIH Clinical Trials Spending (in thousands of dollars and as percentage) by Institute

Institute	1988 Dollars	Percent	1989 Dollars	Percent	1990 Dollars	Percent	1991 Dollars[a]	Percent
NCI	14,778	17	23,487	20	35,373	22	37,809	21
NIDR	0	0	209	0	221	0	234	0
NIAID	64,864	76	84,609	74	118,354	72	133,230	72
NICHD	2,683	3	2,739	2	6,000	4	7,900	4
NEI	3,372	4	4,006	3	4,524	3	4,799	3
NIDDK	198	0	0	0	0	0	0	0
NCNR	247	0	0	0	0	0	0	0
Total	85,895	100	115,050	100	164,472	100	183,972	100

NOTE: Abbreviations: NCI, National Cancer Institute; NIDR, National Institute of Dental Research; NIAID, National Institute of Allergy and Infectious Diseases; NICHD, National Institute of Child Health and Human Development; NEI, National Eye Institute; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NCNR, National Center for Nursing Research.
[a] Estimated.
SOURCE: Division of Financial Management, National Institutes of Health.

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4

Supporting the NIH AIDS Research Program

The success of the NIH AIDS research program depends not only on identifying the most important scientific questions and promising research opportunities and having an effective structure for managing the research effort, but also on adequate levels of high-quality resources to support the research effort. These resources include funds for the research itself, in the form of grants, contracts, and intramural projects, and for research training programs and facilities and equipment grants. They also include NIH's review apparatus for research grant and contract applications and proposals. Finally, NIH's own staff and facilities are important resources, because it takes people in offices and laboratories to plan AIDS research activities, conduct intramural research, award extramural grants and contracts, evaluate results, and determine new areas of research opportunities and needs.

AIDS research funding has expanded greatly, especially during 1986-1990, and it is slated to increase another 8.7 percent in fiscal year 1991. Some observers point to this expansion as adequate and call for maintenance, if not actual reduction, of AIDS funding levels. Yet the epidemic is still growing and spreading, and it threatens to persist for years to come. Important research advances have been and will continue to be made. Nevertheless, some research areas are underdeveloped, and scientific progress in others calls for an expansion of effort. This situation calls for a careful assessment of the adequacy of AIDS research funding. Among areas of particular concern for NIH are the inadequate facilities and staffing limits that have created an imbalance between the size of programs and the size of the staff to plan, implement, coordinate, and evaluate them. These limits have been eased, but it will take careful planning to bring staffing in line with program requirements. This chapter reviews the status of research funding, grant review resources, and NIH staffing and facilities; assesses their adequacy; and makes recommendations for strengthening NIH support of the AIDS research effort.

FUNDING AIDS RESEARCH

The committee does not believe that increased funding alone is a panacea for all of the problems noted in the NIH research effort. For this reason, the recommendations for increasing the effectiveness of management of the AIDS research program were presented first, in Chapter 2, and issues concerning appropriate balance and coordination among research areas were addressed in Chapter 3, before funding levels were considered. Funding is an input measure of research effort that is only indirectly related to the variables of most interest, which are research output and the quality and significance of that output. NIH's primary mechanism for assuring research quality, the

peer-review system for ranking research applications, is discussed in a later section of this chapter. If not a sufficient condition for high-quality research results, however, adequate funding surely is a necessary one, especially in a completely new area of research that lacks an existing body of researchers, ongoing studies, appropriate facilities and equipment, and training programs. This section reviews the history of AIDS research funding at NIH, in total and by institute, mechanism, and category of research; it also assesses its adequacy, its impact on non-AIDS research funding and progress, and the appropriateness of its allocation among categories of research, types of research support, and research mechanisms.

History of AIDS Funding

NIH and Its Institutes

The AIDS epidemic was first recognized in early 1981, a time of severe fiscal stringency in the federal budget that constrained the initial federal response (Office of Technology Assessment, 1985; Lee and Arno, 1986; Panem, 1988) and continues to affect federal action. The NIH budget for fiscal year 1981 was $3.57 billion, just 4.2 percent higher than the previous year's, and it increased only 2 percent—to $3.64 billion—in fiscal year 1982. After inflation, NIH's research purchasing power, using the biomedical research and development price index, actually declined by 5.6 percent in 1981 and by 6.1 percent in 1982, regaining its 1980 level only in 1984 (NIH, 1989a: Table 7). Yet despite the constraints on funding, some researchers in NIH's intramural programs and extramural projects and centers found AIDS to be an urgent medical problem, as well as an interesting scientific puzzle, and they began to study it.

The syndrome was first recognized and described by NIH grantees in mid-1981, and the first AIDS patient was admitted to the NIH clinical center in September 1981. Before the end of that year, NCI viral epidemiologists began studies; NCI held a national conference on Kaposi's sarcoma and AIDS-related opportunistic infections; general clinical research centers supported by the National Center for Research Resources became involved in AIDS studies; and NIAID supplemented grants to its extramural sexually transmitted disease centers and other researchers to study AIDS. In the first several years, support for AIDS research had to be reprogrammed from other areas of research. Congress first appropriated additional funding for AIDS research at NIH in a supplemental appropriations bill in July 1983, which provided about $9 million of the $21.7 million that NIH spent on AIDS in fiscal year 1983. The recent substantial growth in AIDS funding started in 1986 when Congress began "earmarking" AIDS funding in the regular appropriations to the institutes (Figure 4.1). As a result, AIDS funding began to increase more quickly than funding for non-AIDS activities (Table 4.1)—between 81 and 111 percent per year in fiscal years 1986 through 1988, and about 25 percent per year in fiscal years 1989 and 1990. In part because of the AIDS funding, NIH's budget went from $3.6 billion in 1981 to $7.6 billion in 1990, an increase of 112 percent. After inflation, the increase was 51 percent (using the gross national product deflator), or 28.8 percent (using the biomedical research and development price index). AIDS funding accounted for 18.5 percent of the overall NIH increase ($741 million of the $4 billion).

AIDS activities have grown steadily as a proportion of NIH spending, from less than 0.1 percent in fiscal year 1982 to 9.8 percent in fiscal year 1990 (Figure 4.2 and Table 4.2).[1] Most of

[1] Although the fiscal year 1991 appropriation for AIDS represented an increase of 8.7 percent, the appropriation for non-AIDS research was also larger. Consequently, the AIDS share of the NIH budget dropped slightly, to 9.7 percent.

the NIH AIDS funding (53.1 percent in fiscal year 1990) goes to NIAID; much of the rest goes to four other institutes: NCI (20.3 percent), National Center for Research Resources (NCRR; 6 percent), NHLBI (5.7 percent), and NICHD (3.6 percent). The remaining 11.3 percent is spread among the remaining NIH units (Table 4.3).

Because it receives more than half the AIDS funding at NIH, nearly half (47.3 percent in fiscal year 1990) of NIAID's overall budget is devoted to AIDS. AIDS funding amounts to 9.1 percent of NCI's budget, 6.1 percent of NICHD's, and less than 4 percent of most other units. It is a larger set of activities for the Fogarty International Center and the units providing intramural and extramural research support (NCRR, Buildings and Facilities, and the OD; Table 4.4). Because of AIDS funding, NIAID went from being the sixth largest institute in 1981 (23 percent the size of NCI, the largest institute at that time) to the third largest institute in 1990 (51 percent the size of NCI, still the largest NIH component).

Research Support Mechanisms

Early in the NIH response to the AIDS epidemic, intramural research accounted for a large proportion of the agency's AIDS effort (47 percent in 1982, 31 percent in 1983, 27 percent in 1984, and 25 percent in 1985; Table 4.5). In comparison, intramural research accounted for only about 12 percent of NIH's non-AIDS budget during that time. The use of contracts was prominent in the early years, reaching 53 percent and 43 percent of the AIDS budget in the 1986-1987 fiscal years when the large extramural programs, such as the AIDS clinical trials units, were being launched. In those years contracts accounted for about 6 percent of the non-AIDS budget (Table 4.6).

The AIDS effort has relied less on grants, especially on research project grants, than has non-AIDS research. The proportion of AIDS funding going to research project grants (RPG) reached a low of 19 percent in 1986, during a time when the proportion of non-AIDS funding for such grants was increasing steadily (from 50 percent in 1982 to 56 percent in 1986). This trend in AIDS funding was reversed in 1987 when the large contracts for ACTUs were converted to cooperative agreements, which are classified as RPGs. In 1990 RPGs account for only 39 percent of the AIDS budget (compared with 59.5 percent of the non-AIDS budget; Tables 4.5 and 4.6[2]). In addition, compared with non-AIDS programs, relatively more of the AIDS RPG dollars go to RFA-initiated cooperative agreements with ACTUs, national cooperative groups for drug and vaccine development, and other large programs in which NIH staff play a role in decision making. About 60 percent of RPGs have been individual investigator-initiated R01s (Table 4.7), but the bulk of RPG *funding* goes to cooperative agreements (U01s) and research project grants (P01s), most of which are solicited by NIH through RFAs. This is because most of the non-R01 grants are very large. U01s for AIDS clinical trials units and national cooperative drug and vaccine discovery groups, for example, are in the range of $0.5 to $1 million. As Table 4.7 shows, however, the proportion of research grants solicited by RFAs has decreased.

NIH's standard planning mode has been, first, to let the public, through Congress, indicate broad priorities among health problems by appropriating a certain amount for each categorical entity of NIH (institutes, centers, and divisions), and, second, to allow NIH and the scientific community to identify the research efforts that are needed to address priority problems. These

[2] These figures refer to overall AIDS expenditures, including extramural research, intramural research, and program support activities. In 1990 RPGs accounted for 51 percent of the AIDS budget for extramural grants and contracts, compared with 71 percent of the non-AIDS extramural budget.

efforts rely on grants, especially individual investigator-initiated grants, as the mechanism of support, and on the peer-review system, in which research applications are rated for scientific merit by disciplinary study sections of experts. Through these processes NIH supports a high proportion of basic research initiated by individual investigators as well as more directed efforts to apply the results of basic research in clinical practice and public health prevention and control programs. Thus, in fiscal year 1990, more than 60 percent of NIH's non-AIDS budget supported basic research (Figure 4.3), and 59.5 percent of the non-AIDS budget supported investigator-initiated grants (research project grants) rather than research centers, contracts, intramural research, or other research mechanisms (Table 4.6). Some of the larger institutes with a more explicit disease focus, such as NCI and NHLBI, have substantial applied efforts (e.g., drug screening and development, clinical trials) and prevention and control programs (antismoking, cholesterol and blood pressure control), but they still devote half of their resources to basic research.

NIH's emphasis on basic research and its traditional posture of waiting for high-quality research proposals turned out to be too slow in the case of AIDS. As public and congressional pressure mounted in the mid-1980s to expand AIDS research, NIH pursued several routes: it quickly expanded its intramural efforts and, extramurally, expedited grant review, used RFAs and RFPs to stimulate research in specific areas, funded some applications with relatively lower peer-review scores, and used directive mechanisms (e.g., cooperative agreements, contracts) to support specific approaches. It is for these reasons that less of the NIH AIDS budget than the non-AIDS budget goes to research project grants. The share of AIDS research funds for basic research is also comparatively lower, although the exact figure is unknown. The large-scale programs initiated through RFAs and supported by cooperative agreements—AIDS clinical trials units, the national cooperative drug and vaccine development groups, and so forth—re classified as research project grants; on the other hand, some fundamental research in immunology and virology of relevance to AIDS research is funded through the non-AIDS budget. Although the share of the AIDS budget going to research and development contracts has been greatly reduced (down from 53 percent in 1986), it still accounts for more than 26 percent of the AIDS budget in 1990 (compared with 5.5 percent of the non-AIDS budget[3]). Reliance in the AIDS program on intramural research is also higher—16.5 percent of AIDS funding compared with 10.8 percent of non-AIDS funding—although this figure includes a substantial clinical treatment program mandated by Congress.

Categories of Research

NIH has used several sets of research categories for tracking AIDS funding over the course of the epidemic. Currently, NIH uses the so-called Mason categories, which are also used by the PHS to track AIDS activities in all its agencies (see Table 4.8 for a breakdown of NIH spending in fiscal years 1989-1991). Yet none of the sets of functional categories used to report the content of the PHS AIDS program have been especially suited to a scientific characterization of NIH's program. It is not possible to determine how much of the AIDS budget goes to such basic science areas as immunology, virology, molecular biology, and microbiology, or to categories of biomedical research, such as epidemiology and natural history, etiology, pathogenesis, therapeutics, and vaccine development. From 1984 to 1989, NIH used the Charlottesville functional categories, which came closest to those used by the PHS; the agency used projected rather than actual data for 1989 and 1990, however (Table 4.9). The committee was unable to obtain a parallel breakdown of non-AIDS categories for comparison.

[3] Looking just at the extramural part of the budget, 35 percent of the AIDS extramural budget went for contracts, compared with 7 percent of the non-AIDS extramural budget.

Figure 4.4a, based on data in Table 4.9, shows that research on pathogenesis and clinical manifestations and therapeutic studies (preclinical drug and vaccine development and clinical trials research) have dominated AIDS funding at NIH. Figure 4.4b, which presents the same data but as a percentage of total funding, reveals that budget allocations among the broad categories of research have been relatively stable since 1988, with about 40 percent of the effort devoted to the development of therapies ($305.8 million in fiscal year 1990), a third to epidemiology and pathogenesis ($254 million), 10 percent to vaccine development and testing ($83.9 million), and about 3 percent to public health-oriented activities, especially public information, blood supply protection, and HIV test development ($21.1 million). Breakdowns of the therapeutics category into preclinical and clinical phases or into anti-HIV and other AIDS drugs are not available. The approximately 33 percent for pathogenesis and clinical manifestations breaks down into about 13 percent epidemiology (natural history and surveillance) and 20 percent pathogenesis.

By way of comparison, NCI obligations for preclinical and clinical treatment research accounted for 33.5 percent of NCI's budget in fiscal year 1990 ($548 million of $1.6 billion; NCI, 1990:16). Epidemiology accounted for 5.7 percent ($93.2 million) and cancer prevention and control for 4.9 percent ($80.2 million; NCI, 1990:19).

Adequacy

A major part of the committee's charge was to consider the adequacy of the AIDS research effort at NIH. As noted earlier, the AIDS program has become the third largest NIH research program, after cancer and heart disease, involving nearly 1,200 staff (out of NIH's total employment of 14,000 FTEs in fiscal year 1991) and nearly 10 percent of the total NIH budget. Indeed, federal spending on HIV/AIDS research is approaching that for cancer and heart disease and exceeds spending for other diseases that cause more deaths—cerebrovascular disease and chronic obstructive pulmonary disease, for example (Winkenwerder et al., 1989). HIV is not a chronic disease, however; it is a fatal *infectious* disease that will continue to spread unless steps are taken to prevent transmission. The effectiveness of prevention efforts depends in turn on behavioral and biomedical knowledge about how the virus spreads and causes disease. Moreover, because deaths from AIDS primarily affect young persons, the ratio of research spending to burden of illness looks more equal when years of potential life lost before age 65 are used as a comparison measure. In 1987 the YPLL for AIDS was 432,000, compared with 1.8 million for cancer, 1.5 million for heart disease, 246,000 for stroke, and 131,000 for bronchitis and emphysema (CDC, 1990:10). Unlike the rates for chronic diseases, however, the YPLL for HIV/AIDS will increase steeply, as the number of deaths per year continues to grow, to between 1.2 and 1.4 million in 1991 and between 1.5 and 2.1 million in 1993 (Buehler, 1990). The PHS estimates that, by 1991, HIV/AIDS could rank third in YPLL from disease (PHS, 1990b).

The committee reviewed carefully the size and composition of the budget for AIDS-related research, aware of a general perception that the problem is receding and that the current level of effort is adequate. The committee finds, however, that the epidemic of HIV infection and AIDS is a severe global public health emergency that is growing and spreading, increasing still further the burden of illness and death and placing severe stresses on the nation's health care system. Containing this disease must be a high national priority. More effective interventions are urgently needed.

The NIH AIDS program must respond in a balanced way to gaps in needed knowledge, emerging scientific opportunities, changes in the epidemic (for example, as the virus moves into new populations or responds to improved treatments), and other, unforeseen contingencies. The

question of program balance is thus an evolving one that should be addressed through the planning and priority-setting process recommended in Chapter 2. At this time, for instance, promising scientific developments in vaccine research urge additional research, which will require substantially more resources than the $79 million devoted to it last year (fiscal year 1990).

The committee reviewed the adequacy of investment in fiscal year 1990[4] in each program area discussed in Chapter 3, taking into account (1) the state of current knowledge, (2) scientific opportunities in each area, and (3) the overall balance desired in a comprehensive long-term research program. As noted above, recent advances in vaccine research should be exploited, which not only calls for increased support of research grants but also of such research resources as reagents, research animals, and animal and laboratory facilities and equipment. The committee also concluded that a balanced long-range program should invest more in undirected individual investigator-initiated research, given the lack of fundamental knowledge about HIV, its transmission and pathogenesis, and clinical manifestations in and immune response of the host. A number of unfunded scientific opportunities exist. Although about 37 percent of the research grant applications are rated as outstanding or excellent by scientific peer-review groups,[5] funding will be available for only about 25 percent of the nearly 1,000 AIDS grant applications expected to be approved for fiscal year 1991. Progress in treating and preventing HIV infection and AIDS would probably be accelerated if these highly rated projects were funded and all awarded grants—new, renewal, and continuing—were funded fully.

Other areas of AIDS-related research are relatively underdeveloped and should be expanded. The committee believes that behavioral research, nursing research, development and testing of therapies for AIDS-related opportunistic infections and cancers, and research training are examples of fields that have received relatively little support and deserve a much greater investment by NIH as part of a long-range effort to reduce HIV infection and deal with its consequences. The committee has recommended that about 3 percent of the AIDS budget go to the support of research training, triple the current level. Small, beginning programs such as behavioral research and nursing research on patient care will require large percentage increases for several years to reach an adequate level of effort. NIH has placed increased emphasis on OI drug development and testing in the last two years, and further increases are needed. Also of importance is a balanced emphasis on training and facilities as well as on research project funding (IOM/NAS, 1990). Training was addressed in Chapter 3; greater attention should also be paid to maintaining the other aspects of the research program—facilities and equipment—that make good research possible.

There are also possibilities of greater efficiency in some of the large-scale programs that have been running for at least several years, which could result either in greater effort for the same budget or in freeing up dollars for other, higher-priority programs. The committee has recommended, for example, that epidemiology studies be evaluated to ensure that each is worthwhile, given potential alternative uses of the funds at this time. The committee is also aware that NIH expects to improve the performance of the ACTG within its current budget, in part by

[4] 1990 is used as the base because it is the last year for which there are figures on actual program obligations, by funding mechanism, by institute and program, and by functional area. The fiscal year 1991 budget was under consideration during the time of the study. The administration had asked for $800.2 million for AIDS research, an increase of 8.1 percent (2.1 percent after inflation using the biomedical research and development price index). On October 20, 1990, after the last committee meeting, Congress appropriated an overall increase of $700 million for NIH as a whole, compared with the $354 million requested by the administration. At the time this report went to press in late December 1990, NIH planned to use about $4 million of the additional increase for AIDS, for a total AIDS budget of $804.6 million in fiscal year 1991, an increase of 8.7 percent (2.7 percent after inflation).

[5] Applications with scores between 100 and 150 are considered "outstanding"; those between 150 and 200 are considered "excellent" (see NIH, 1989b).

redefining its mission to focus on studies that are not likely to be undertaken by the private sector but also by increasing efficiencies in protocol development, laboratory services, and patient accrual and retention.

In the opinion of the committee, increased management efforts and program activity in a number of areas would not be adequately accommodated within the present level of effort ($740.5 million in 1990 dollars).[6] The committee estimated that the net effect of its recommendations could increase costs on the order of magnitude of 25 percent over the current level of effort. This figure is admittedly a very rough estimate; it would be less if there were significant savings in existing activities and more if there were major breakthroughs that needed to be exploited. The committee believes that an increase of this magnitude could be productively absorbed at once in most areas, although some underdeveloped areas may take several years to build up. The detailed phasing in of any increases that occur should be an integral part of the long-range planning effort recommended in Chapter 2.

Many people believe that the budget for NIH as a whole is inadequate and that there is an immediate crisis in funding a sufficient number of competing grants this fiscal year and next to maintain the nation's biomedical research momentum (NAS/IOM, 1990). The committee is acutely aware that many other areas of biomedical research could justify larger budgets in an absolute sense. Advances in containing and controlling HIV infection and AIDS rest on the overall strength of the institutes of NIH. Taking resources from its other components to expand the AIDS research program would impede progress in biomedical research and the AIDS program itself, which is an integral part of NIH and dependent on a wide range of its activities.

Recommendation 4.1: Implementing the long-term AIDS research program recommended by this committee will require a larger budget to ensure that the most promising basic science opportunities are supported, that underdeveloped areas of research are expanded, and that research resources are adequate to support the planned level of research effort. These opportunities and needs could justify an immediate increase of as much as 25 percent in NIH's budget for AIDS research; the exact timing of the increase should be an integral part of the long-range plan recommended by the committee. It is essential that any such budget increases be new funds and that they not be derived at the expense of ongoing NIH programs.

Impact on Non-AIDS Research

It is impossible to know what NIH's research budget would be today if AIDS had never happened. Although it is very clear that NIH appropriations for AIDS grew much more quickly than non-AIDS research, it does not necessarily follow that non-AIDS research funding suffered because of the increases in AIDS monies. In comparison with funding for the research programs of other non-defense agencies, NIH has clone comparatively well, achieving real growth most years except in 1982 and 1986 (Figure 4.5). A definite benefit for the slower-growing non-AIDS programs is that AIDS funds have supported some immunology, molecular biology, and other basic research that might otherwise not have been possible, although, as already noted, the share of the AIDS budget going to basic research is relatively small.

[6] It would take $783.5 million to sustain this level of expenditures in fiscal year 1991 after inflation (using the biomedical research and development price index).

Interviews at NIH and on Capitol Hill indicate that from at least 1985 through fiscal year 1989, the AIDS budget was considered separately from the non-AIDS budget at NIH, and there is little reason to believe that the funds appropriated to AIDS would have gone to non-AIDS activities if there had not been a separate AIDS budget. Today, however, the situation is changing. A perception at the appropriations committee level that AIDS and non-AIDS funding shares were out of balance and that AIDS research should compete with non-AIDS studies in priority setting at the institutes resulted in no formal AIDS earmark in fiscal year 1990 for the first time since 1984. Although the institutes are expected to maintain the detailed budgets submitted in the congressional justification, including those for AIDS, lack of an earmark means that "the precise amount expended is determined by the institutes based on the quality of applications submitted and competing research priorities," according to the House appropriations committee in its report (U.S. Congress, 1989:22-23). "This process relies on the judgment of the peer review system and scientific advisory boards which are the backbone of NIH's quality control system. Use of this process could result in a somewhat higher or lower final figure for AIDS."

During fiscal year 1990 NIH basically allocated funding according to the amounts in its original budget submission but used the flexibility of not being restricted to a certain budget amount for AIDS to include closely related basic research in immunology and microbiology in the AIDS program (U.S. Congress, 1990a:61, 1156). The House appropriations committee report on the 1991 appropriations bill stated the committee's preference of continuing to suggest an approximate target figure for AIDS activities in the report stage rather than setting a precise amount in statutory language (U.S. Congress, 1990c:25).[7]

The committee believes that the basic knowledge base for understanding and controlling AIDS is inadequate and has already recommended an expansion of basic research as part of a balanced long-term AIDS research program. In the past, NIH has defined AIDS research narrowly to encourage well-established researchers to shift emphasis from ongoing research in other areas. This goal has been met, and the artificial distinction between AIDS research and AIDS-related basic research has outlived its usefulness.

Recommendation 4.2 NIH should adopt NIAID's recent redefinition of AIDS research (to include closely related basic research in immunology, virology, molecular biology, cellular biology, and other related areas) for use throughout its institutes.

Spillover Effects of AIDS Research on Non-AIDS Efforts

AIDS research has depended heavily on earlier national investments in studies in such fields as retrovirology, cellular immunology, clinical trials, and infectious disease epidemiology. Indeed, without this earlier research, the progress already experienced in identifying and characterizing the causal agent of AIDS and in developing several efficacious therapies would have been impossible. For example, the 'War on Cancer' in the 1970s supported a greatly expanded research program on the virology and immunology of retroviruses. When it was suspected that AIDS was a retrovirus, the investigators and facilities involved in work on retroviruses were quickly mobilized to work on HIV, which allowed scientists in only a short time to learn a great deal about the virus and how it causes disease. In addition, the techniques developed to screen for anticancer drugs were used for anti-HIV drugs, which is how zidovudine, or AZT, was originally identified.

[7] Subsequently, the December 1990 conference report on NIH funding for fiscal year 1991 did not contain specific earmarks for AIDS.

Conversely, the intense scientific work on HIV and the disease it muses has contributed important new information to the basic and clinical research knowledge bases. Investigation of the molecular biology of HIV will soon make it the best understood of all retroviruses, and that knowledge can add understanding to work on viruses in general and on other retroviruses in particular. The discovery that CD4 is the receptor for HIV has contributed to research progress on the interaction of viruses with their specific receptors. A major effort is under way to understand the molecular controls that determine the level and timing of viral replication. These studies will provide important insights into the control of latency and of replication of other viruses, as well as better understanding of the control of normal cellular genes. In addition, as a result of AIDS research, the CD4 molecule has been cloned and sequenced and its crystal structure is under analysis, which will add to knowledge about the role of CD4 in the function of the immune system.

In general, AIDS studies are making important contributions to resolving basic problems in immunology. Not surprisingly, a survey of scientists and clinicians by the congressional Office of Technology Assessment (OTA) found that most of those interviewed believed that federally funded research on HIV/AIDS had already contributed substantially to the basic science fields of virology, immunology, microbiology, and molecular biology. Specialists in a number of clinical medicine areas, especially the disciplines of infectious disease, oncology, neurology, hematology, and pulmonary medicine, reported substantial contributions of HIV/AIDS research to their areas as well. Experts in drug and vaccine development, diagnostics, epidemiology, and behavioral sciences also cited substantial benefits from AIDS/HIV research (OTA, 1990:7-12).

GRANTS POLICY AND ADMINISTRATION

One of NIH's key resources is a large-scale process for identifying high-quality research ideas and productive investigators worthy of funding support. NIH's grant review system maintains a pipeline of research proposals deemed to have high scientific merit by other scientists. At the beginning of the epidemic, AIDS, as a new disease, did not have a community of dedicated researchers or such a pipeline. Consequently, NIH resorted to ad hoc arrangements to expedite the review and award of AIDS research proposals before developing a permanent set of review groups and procedures.

Problems in Responding to the AIDS Epidemic

Under NIH's grant review process, an investigator proposes a well-designed research project that addresses an important scientific question. Review and, if the application is successful, approval occur in two stages. A scientific peer-review group or study section conducts an initial review of the application and decides whether to approve and recommend it for funding; the group then scores it on a scale from 100 (outstanding) to 500 (acceptable; NIH, 1989b:11). The application then goes to the appropriate institute or institutes for review and approval for funding by the institute's national advisory council. Most institutes fund a few applications with scores below the cutoff point (the lowest score normally funded) to address areas of "high program relevance.' If an institute determines more research is needed in an area, it can use a variety of devices to stimulate investigator interest and applications, ranging from workshops to program announcements (stating the institute's interest in receiving applications on a particular topic) to RFAs that state the number of grants and level of funding the institute will devote to that set of applications. If an institute has a strong programmatic interest in a particular area of study or type of research, it can offer program project or center grants to support larger-scale research efforts,

or it can use a cooperative agreement. In these latter cases, and in the case of most RFAs, institutes rather than Division of Research Grants (DRG) groups review the applications.

Funding extramural research usually takes nine months from receipt of a grant application to award, but the process can take longer if, as with AIDS in the early years of the epidemic, the research area is new and investigators must be encouraged to apply. In those first years NIH was criticized for neglecting extramural research on AIDS, for taking too long to review research proposals, and for funding low-quality applications (OTA, 1985:41). For example, NCI, after cosponsoring with CDC a national conference on Kaposi's sarcoma and opportunistic infections in September 1981, began to develop an RFA for studies of AIDS. It was nearly a year before the RFA was issued in August 1982. At that time, however, NIH took various steps to expedite the review and award process. A large ad hoc review committee was formed, and mail ballots were used to make the first awards beginning in March 1983 (Stoolmiller, 1990). NIH also expedited extramural research by supplementing ongoing grants for research on sexually transmitted diseases (through NIAID) and Kaposi's sarcoma (through NCI). Subsequently, AIDS research grant applications were reviewed by the DRG in the usual manner—by regular chartered study sections or by ad hoc review study sections—although arrangements were often made to add ad hoc members with AIDS expertise to regular study sections (Maurer, 1990).

As noted earlier, NIH in those years was criticized for funding studies with relatively poor peer-review scores (see Table 4.10; OTA, 1985:42), a problem that has continued to be a concern of the scientific community. These concerns have not been mitigated by the fact that institute review groups of AIDS experts rather than disciplinary DRG study sections review many AIDS grant applications. Concerns remain because some of the studies are large, complicated projects, often solicited by the institute with an RFA, and funded through cooperative agreements, which involve institute staff in the direction of a project.

By 1986 NIAID's AIDS grant application review workload had become so large that the institute chartered a 51-member AIDS research review committee. Its work was carried out by four subcommittees: (1) basic research I (immunology); (2) basic research II (virology); (3) clinical applications, prevention, and treatment; and (4) epidemiology and technology transfer (NIH, 1990b:38). Meanwhile, DRG continued to review individual investigator-initiated grant applications.

By 1987 AIDS applications in the areas of virology and immunology were overloading the DRG study sections to which they were assigned. In response NIH established a special review committee, Special Study Section A, to handle AIDS virology and immunology applications. This arrangement, which was first used for the January 1987 round of grant reviews (Maurer, 1990), remained in place until the initiation of the expedited review of all AIDS research grant applications that began with the February/March 1988 receipt deadline. Until then, other nonvirology, nonimmunology AIDS applications were reviewed by regular chartered study sections.

The Current System

Division of Research Grants Capacity

Because of concerns about the workload and speed of AIDS grant review, in 1988 Congress began to appropriate funds designated for staff positions (FTEs) for grant review work; it also mandated an expedited review process in which reviews and awards were to be made within six (rather than nine) months of receipt of the grant application. By this time, the number and quality of unsolicited applications had begun to improve. At NIAID, for example, from fiscal year 1987

to fiscal year 1988, the number of solicited applications (e.g., stimulated by an RFA) dropped from 250 to 130, and the number of unsolicited applications increased from 150 to more than 400. As a result, the ratio of solicited to unsolicited grant awards dropped from more than 2 to 0.5, and most of the solicited awards were for the large NIAID AIDS programs—for example, the national cooperative drug discovery groups, the AIDS research centers, Programs of Excellence for Basic Research in AIDS, and AIDS clinical trial units. The priority scores of unsolicited grants improved, whereas the number of solicited grant awards with priority scores greater than 175 fell sharply (NIH, 1989a).

With the advent of the six-month expedited award policy, DRG designated separate dates for the receipt of AIDS proposals, and AIDS grant review sections proliferated, from three in 1988 (immunology, virology, epidemiology/behavior) to five in 1989 (sections for preclinical drug discovery/development and clinical research were added). In 1990, seven sections were formally chartered (the epidemiology and behavior section was split in two and neuroscience was pulled out of the clinical section). By the January 1990 review round, the study sections were averaging about 50 applications (from 40 to 70), compared with the 75 or 80 handled by the regular virology and immunology sections during each round (Meier, 1990). DRG's successful management of this process indicates that it has the capacity to handle an increased number of basic science and other individual investigator-initiated grants as recommended by this committee.

Quality of AIDS Research Applications

As noted earlier, the average priority scores and priority score distributions for AIDS and non-AIDS grants began to converge by fiscal year 1988. In fiscal year 1989, priority scores at the 50th percentile for AIDS and non-AIDS grant applications and awards were comparable for both individual investigator-initiated grants (R01s) and for all research project grants (including R01s; Table 4.11); this was true for each institute (Figure 4.6). The distribution of priority scores for AIDS and non-AIDS grant applications—as measured by the mean priority score in each decile, for example (Table 4.12)—is also similar.

Success of AIDS Research Applications

Until recently AIDS grants have had higher award rates (the percentage of approved applications that are funded) than non-AIDS grants. The award rate for all AIDS research project grants was 34 percent in fiscal year 1989, compared with 27 percent for non-AIDS grants (Table 4.13); by fiscal year 1991 both will be about 25 percent.

Conclusion

NIH was not well prepared at first to speed the review and award of grants to meet the urgency of the epidemic of HIV infection and AIDS. Review and award procedures were expedited but on an ad hoc basis, and the strain on already busy DRG and institute staff was heavy. Initially, NIH relied on contracts and then on RFA-solicited cooperative agreements and program project grants rather than on traditional investigator-initiated grants to launch studies quickly and attract productive researchers. High-quality proposals were scarce, and some awards went to applications with relatively poor peer-review ratings.

Over the past four years, AIDS research project grant applications and awards have increased in number and improved in quality, as measured by peer-review scores. The distribution of priority scores for AIDS applications has become quite similar to that for non-AIDS applications; the average scores of funded applications are also similar. The share of the AIDS budget allocated to research project grants has increased, from a low of 19 percent in 1986 to about 40 percent currently. This share is still smaller than in other NIH-supported research areas, however, where research project grants constitute nearly 60 percent of the budget. The proportion of research project grant awards solicited by RFAs has decreased relative to the number of individual investigator-initiated grants. The committee recognizes the need for solicited research and directive mechanisms in building a fast response to a public health emergency but believes that greater reliance on grants, especially individual investigator-initiated grants, is warranted in a long-range research program on AIDS.

Recommendation 4.3: NIH should continue to increase its use of research grants, especially traditional individual investigator-initiated and related grant mechanisms, to carry out the expanded research effort recommended by the committee, in particular, the increased effort in basic research.

At NIH, RFAs and RFPs are usually initiated "from the bottom up," that is, by program staff who identify gaps in research and propose grant solicitations to address those gaps. After approval at the institute and council levels, proposed RFAs and RFPs receive an administrative review in the Office of the NIH Director and are circulated to the other institutes for comment to minimize duplication of effort. The committee believes that central review of RFAs and RFPs should be coordinated with the research planning effort recommended in Chapter 2 to identify and remedy gaps in AIDS research.

Recommendation 4.4: The NIH associate director for AIDS research and the AIDS Program Advisory Committee should review all RFAs and RFPs for AIDS research to ensure coordination and avoid duplication. They should also have the authority to recommend RFAs and RFPs in the case of gaps in the NIH AIDS research program that are not being addressed by individual institutes.

ADMINISTRATIVE SUPPORT

The effectiveness and success of the NIH AIDS research program depend in part on the adequacy of the administrative support the program receives in the form of staffing and facilities, a statement that applies to both the extramural and intramural programs. Like the funding of research projects, more personnel and facilities may not be sufficient to guarantee high-quality, productive research or swift scientific progress, but a minimum of such resources is necessary for NIH to carry out its mission. At NIH, these resources are provided through centralized processes somewhat separate from those for planning and funding research projects, which makes it a challenge to ensure that resources are matched with program needs, especially in a program that has grown as quickly as AIDS research.

Staffing

It takes people to award grants and contracts, evaluate the results, and determine new areas of research. It also takes people to staff the intramural research laboratories of the institutes and the research units of the NIH clinical center. Much concern has been expressed about the

adequacy of the number of FTE staff at NIH for both AIDS and non-AIDS research. AIDS FTEs increased from 27 in fiscal year 1982 to 763 in fiscal year 1989 (Tables 4.14a and 4.14b). The administration proposed 887 AIDS FTEs in the fiscal year 1990 budget, but a year later, after allowing the Department of Health and Human Services and NIH to set staffing levels (within the overall NIH budget), the Office of Management and Budget raised the ceiling for 1990 to 1,072. The administration proposed 1,183 AIDS FTEs in its budget request for fiscal year 1991. Non-AIDS FTEs increased from 12,662 in 1982 to a high of 13,493 in 1984, but fell by 1,188 to 12,305 in 1986. The non-AIDS FTE level reached 12,712 two years later (fiscal year 1988) and was originally slated to decline to 12,327 in fiscal year 1990. The administration later revised the 1990 level upward to 12,707 and is proposing a total of 12,950 non-AIDS FTEs in its budget request for fiscal year 1991.

In 1985, OTA's study of the PHS response to AIDS found that the administration had consistently suggested decreases in personnel ceilings for NIH institutes conducting AIDS research, even as AIDS funding increased. The OTA report concluded that personnel ceilings had been a "special problem" affecting AIDS and non-AIDS research (OTA, 1985:6). In late 1986, an NIH advisory group reported to Congress that there was a "clear-cut need for additional FTEs, both scientific and administrative, at the NIH," rather than redeployment of existing FTEs from other NIH programs. The advisory group concluded that "the allocation of new monies for AIDS research will not achieve the desired goal without a parallel and proportionate increase in scientific and administrative FTEs" (Ad Hoc Consultants, 1986:29). In 1988, the Presidential Commission on the Human Immunodeficiency Virus Epidemic concluded that OMB was inappropriately trying to micromanage AIDS research at the NIH institute level through staffing ceilings and other regulations. The commission said these practices "prevent the deployment of a sufficient number of researchers to deal with pressing problems," force an incremental loss of personnel from other NIH research areas, and deny NIH the management flexibility called for in a scientific research effort (Presidential Commission, 1988:41-43). In 1988, the IOM committee to study the NIH intramural program criticized OMB-imposed FTE ceilings for inhibiting effective management: "The overall effect of FTE ceilings that grow more slowly than budgets is that managers who are best placed to make decisions about how to allocate money to fulfill congressional mandates are prevented from making the most productive decisions" (IOM/NAS, 1988:67).

The NIH AIDS effort has experienced two types of personnel problems that have hampered efforts to recruit and retain staff and thus hindered program managers from making the most effective use of public resources. One type is the traditional set of staffing problems faced by all organizations: having enough money to hire people, being able to find and hire people with the needed skills, motivating people to do their best for the program, and retaining the people who are hired by providing adequate working conditions and a competitive salary structure. These problems also include having an appropriate organizational structure, competent leadership, and a balance between the amount of work to be done and the staff to do it. NIH, however, has also faced a second set of problems caused by external limits on the number of people it can employ. These two types of problems are discussed below.

Traditional Personnel Problems

NIH and its AIDS research program have been constrained by government-wide personnel policies and procedures that have made it difficult for the agency to recruit and retain senior scientists, especially physicians, and some types of support personnel—for example, nurses, allied health workers, and secretaries (IOM/NAS, 1988:3-4; PHS, 1990a:61-62). NIH has not been able to offer competitive salaries for M.D. or Ph.D. senior-level scientists and science administrators or

for mid-level physicians, and there have been significant pay problems with regard to research support personnel (IOM/NAS, 1988:64-65). In addition, personnel hiring procedures make timely appointments quite difficult: in fiscal year 1988, it took an average of 8.5 months to process senior-level appointments at NIH (IOM/NAS, 1988:65). Historically, good scientists have been willing to forego higher pay to enjoy the distinctive research environment at NIH, which they find conducive to scientific productivity and creativity. Others want to participate in an extramural program they believe makes a difference in addressing a major health problem. Increasingly, however, widening pay differentials, cumbersome personnel procedures, and other "barriers to a productive work environment" (IOM/NAS, 1988:68-72), such as inadequate space and equipment (discussed below), threaten NIH's ability to recruit and retain high-quality staff.

These problems have been especially severe for the AIDS program because of its fast growth, long work hours, and intense pressures associated with implementing AIDS research programs with inadequate numbers of staff. For example, congressionally mandated plans to double the AIDS outpatient and inpatient capacity of the NIH clinical center were slowed by problems in recruiting nurses and other support staff. The Division of AIDS at NIAID has experienced major problems in filling high-level positions and recruiting physicians as medical officers in its treatment research program. Staff turnover rates have been high at DAIDS—about 33 percent a year. Thus, NIH has had problems filling positions, and keeping them filled, even when they are made available. The AIDS FTE ceiling for fiscal year 1988 was 544, but NIH finished the year with 537; the ceiling for fiscal year 1989 was 780 positions, of which 763 were filled. Current plans call for an increase of 309 AIDS FTEs in fiscal year 1990, bringing the total to 1,072, and another 111 in fiscal year 1991, for a total of 1,183 slots. Both increases will pose additional challenges for the NIH personnel office.

Several steps have been taken to address personnel problems at NIH generally and for the AIDS program in particular.

- Legislation passed in July 1986 permits NIH to offer more competitive salaries for nurses and (since September 1988) for 10 allied health personnel categories, a policy that has reduced position vacancies and turnover rates. Thus, the number of nurses at the NIH clinical center increased by 25 percent, vacancy rates decreased from 10 percent in early 1987 to 7 percent in January 1990, and the turnover rate fell from 25 percent in 1986 to 13 percent in 1989 (U.S. Congress, 1990a:93).
- A pay raise in January 1990 and one scheduled for January 1991 will reduce much of the pay differential for Ph.D. scientists and some of the differential for physician researchers. According to NIH, its physicians in the Senior Executive Service are paid an average of 49 percent less than their peers in U.S. medical schools; NIH Ph.D. scientists average 19 percent less in pay than comparable scientists in research-intensive universities (U.S. Congress, 1990c:698).[8]
- Physical working conditions will improve considerably if current construction and renovation plans are carried out (see the discussion later in this chapter).
- In June 1988 NIH and the Office of Personnel Management (OPM) agreed that OPM would process and certify eligible candidates within 21 days; the Health Omnibus Programs

[8] For example, in 1988 a physician at the highest level of the Senior Executive Service (SES) received $77,500 plus a physician's comparability allowance (PCA) of up to $20,000 plus possible performance bonuses, subject to a total-salary statutory limit of $99,500; the average pay for NIH M.D.s in the SES in 1988 was about $89,000 (IOM/NAS, 1988:84, 100) and $94,400 in 1989 (U.S. Congress, 1989:87). As of January 1991, SES pay levels will increase between 22.2 percent (level 1) and 29.5 percent (level 6; Balz, 1990:A1). If the PCA is reauthorized, a physician scientist at the highest SES level could make up to $128,300 (base pay of $108,300 plus PCA of up to $20,000), as well as any performance bonuses, although a statutory salary cap of $120,000 is likely (U.S. Congress, 1990c:697). Only one NIH employee is at the highest SES level, level 6; most are at level 4 (for which the base pay will increase to $100,500 in January 1991; U.S. Congress, 1990a:64).

Extension Act of 1988 (P.L. 100-607) subsequently granted authority to NIH to request expedited approval of requests for AIDS personnel and administrative support or space. Such requests are deemed to be approved if not denied by the director of OPM or administrator of the General Services Administration within 21 days.

Constraints of Federal Personnel Ceilings

In addition to the more traditional types of staffing issues discussed above, NIH has also faced a second set of problems caused by external limits on the number of people who can be employed. The limits set on the number of FTE positions an agency may support are a peculiarly governmental problem that is not directly related to sufficient funds for the positions or the ability to recruit and retain qualified staff. OMB sets overall FTE ceilings for each federal department and independent agency. The Department of Health and Human Services (DHHS) then allocates positions under its ceiling to the Public Health Service, which in turn subdivides its allocation among the various PHS agencies, including NIH. The NIH positions are allocated among its institutes and other organizational components by the NIH director, based on the recommendations of the Resource Allocation Group (RAG). The RAG is composed of senior staff in the Office of the Director and several institute directors.

The FTE ceilings have caused significant personnel problems for the AIDS research effort in several ways.

- Although Congress controls appropriations and specifies them in some detail for each NIH component, OMB controls the allocation of FTEs. Until recently at least, OMB was unwilling to raise the NIH FTE ceiling to keep pace with the needs of the AIDS research program.
- Cuts in its overall FTE ceiling since the early 1980s have left DHHS with little latitude to provide NIH with extra positions. Total FTE employment at DHHS has declined steadily, from 138,480 in fiscal year 1982 to 115,045 in fiscal year 1989. Although the majority of the cuts were in the Social Security Administration, every major component, including the PHS, lost FTEs. FIE employment in the PHS fell from 42,904 FTEs in 1982 to less than 40,000 in 1989.
- NIH, together with CDC and ADAMHA, has maintained and even increased its FTE employment during the 1980s. Because the FTEs for AIDS research have come from the overall ceiling authorized for NIH, however, increasing AIDS FTEs has reduced the number of personnel available for non-AIDS research. In the early years, when the NIH AIDS effort was mostly intramural, most AIDS FTEs were shifted from other work. In 1986, for example, just 9 of the 235 AIDS FTEs were additions rather than transfers (U.S. Congress, 1988a:351). Since 1986, most but not all increases in AIDS FTEs have been additions. Nevertheless, as the number of FTEs related to AIDS increased from 0 in fiscal year 1981 to 780 in fiscal year 1989, the net number of non-AIDS FTEs declined by 165—from 12,637 to 12,472 (Table 4.15). (The decreases in non-AIDS staffing occurred while NIH's non-AIDS budget grew in constant dollars.)

These personnel constraints have acted to redirect intramural staff from non-AIDS to AIDS research and to hold down the number of staff available to plan, implement, and monitor the extramural AIDS research programs. Initially, NIH institutes responded to the AIDS epidemic with their most flexible resource, the intramural program; FTE ceilings subsequently hampered needed adjustments to compensate for the shifts of intramural staff to AIDS work. This situation can be seen most clearly at NCI. In 1989, half of the 188 FTEs allocated to AIDS research had come from NCI's non-AIDS FTE allocation. That year the institute received 42 additional AIDS FTEs over its 1988 level, but instead of using them to free up staff to return to non-AIDS work, they were assigned to expanded AIDS activities—primarily the large-scale drug screening and development

program initiated in 1988 (NIH, 1989b). Not surprisingly, the institutes are using much of the new flexibility allowed them in fiscal year 1990 to set personnel levels for "a restoration of the previous losses" (U.S. Congress, 1990a:63).

The constraints on FTE levels and problems in filling available positions were also acute on the extramural side, where funding growth has outstripped the available staffs ability to administer it. This problem has been most apparent at NIAID's Division of AIDS, which administers 60 percent of the extramural AIDS research dollars at NIH. DAIDS was established in January 1986 to develop and manage a large extramural AIDS research program, but it has been chronically understaffed and has had difficulty planning, implementing, and monitoring its many fast-growing activities. Most of its activities are supported by such mechanisms as cooperative agreements and contracts that involve more staff effort to develop, fund, monitor, and evaluate than is normally required to administer a portfolio of traditional individual investigator-initiated grants. For example, DAIDS took over the MACS and launched the multicenter ACTG and NCDDG programs. Funding for these efforts totaled $52.3 million in fiscal year 1986 and was administered by only a 4-person staff. In 1987, with a staff of 13, DAIDS expanded the ACTG greatly, added more NCDDGs, developed the NCVDG program, and put out a number of animal-model and other contracts totaling $129.6 million; in 1988 it launched additional programs, studies, clinical trials, and associated contracts for total expenditures of $203.2 million with 42 FTEs. To accomplish the work, 80-hour work weeks were typical—as was staff burnout and turnover of 33 percent a year.

In response to a congressional hearing on AIDS research needs, NIAID estimated it would need 116 more FTEs through fiscal year 1989, 63 for extramural research management and support (DAIDS), 40 for expedited review and award of AIDS research grants and contracts, and 13 for intramural research. Its projections also included a need for additional FTEs in fiscal years 1990 and 1991 (U.S. Congress, 1988a:329).[9] Internally, NIAID was arguing that it was not receiving enough additional FTEs to manage its AIDS research activities, especially the ACTG program and the vaccine research and testing effort. Although it received an increase of 74 FTEs (for a total of 232) in fiscal year 1989, the institute estimated that it was 83 FTEs short of meeting its needs (NIH, 1989a). NIAID was given a further 31 FTEs (for a total of 263) in fiscal year 1990, but expanded activities as well as new responsibilities imposed by the Health Omnibus Extension Act of 1988 led NLAID to estimate that it was still 89 FTEs short at the beginning of the 1990 fiscal year (NIH, 1990a).

Faced with a health emergency, the small staff of DAIDS worked long hours to develop and issue RFAs and RFPs, usher them through the review and award process, help successful applicants set up and begin work on their projects, and coordinate the activities of multiple sites. The heavy workload took a heavy toll on staff members, however, at the same time causing delays and other implementation problems for the research projects.

OMB and DHHS recently gave the NIH director increased authority to determine NIH staffing ceilings, which will allow the agency to bring its staffing levels into line with program requirements. As a result of more realistic FTE planning, NIH increased substantially NIAID's allocation for fiscal year 1990 in January 1990, from 263 to 306 (3 more slots than were requested

[9] Overall, NIH estimated it would need 955 FTEs in fiscal year 1989 (it was actually allocated 780), 1,143 in 1990 (the original allocation of 887 was increased to 1,072 in January 1990), and 1,311 in 1991 (the administration proposed 1,183 in the 1991 budget request for NIH; U.S. Congress, 1988a:326).

by the institute in its initial budget request for the 1990 fiscal year). The DAIDS ceiling increased from 95 to 115. The overall 1990 FTE ceiling for NIH, originally 38 FTEs smaller than in 1989, increased 527 FTEs; an additional increase of 354 positions has been requested for fiscal year 1991. A majority (292 of 527) of the additional FTEs in fiscal year 1990 are for AIDS research; a third (111 of 354) of the additional FTEs proposed for fiscal year 1991 would be for AIDS. These increases must be achieved, however, within NIH's overall budget total because NIH is not slated to receive additional funds for personnel and must pay for staffing increases out of program funds. Determining appropriate staffing levels for all NIH programs will require careful analysis of program needs and difficult choices. It will also require closer integration of program planning, budgeting, and personnel planning in the future.

In conclusion, OMB's imposition of arbitrary personnel ceilings for NIH as a whole has constrained the AIDS research program because the number of scientists and science administrators could not increase as quickly as the scientific opportunities for intramural AIDS studies or the number of extramural AIDS grants and contracts that had to be reviewed, awarded, and managed. This constraint in turn hampered NIH's ability to conduct AIDS research and adequately plan, administer, and evaluate its extramural AIDS programs.

Recommendation 4.5: The committee strongly opposes arbitrary restrictions on NIH staffing levels that are established without regard to program requirements because they hamper effective, efficient management. Personnel ceilings should be abandoned permanently, and future staffing decisions should be part of the strengthened program planning and budgeting processes as recommended in Chapter 2 and coordinated by the Office of the NIH Director. Adjustments in staffing levels should be made carefully over several years to achieve appropriate balances between AIDS and non-AIDS programs, between the elimination of past deficits and the needs of new initiatives, and between the budgets for extramural grants and contracts and for staff to administer those grants and contracts.

The committee also supports broader efforts to maintain the excellence of the NIH staff by addressing personnel problems relating to compensation and to inflexible or cumbersome policies and procedures of government personnel systems. It endorses as well special efforts to resolve problems specific to the AIDS program, such as recruitment and retention of medical officers in the NIH AIDS treatment research (clinical trials) program.

Facilities

Over the years, NIH more than once has delayed construction of new facilities and maintenance and structural improvements in old buildings in the face of constrained budgets (U.S. Congress, 1990c:7). The resulting problems with inadequate space and deteriorated and obsolete facilities have hindered the agency's research efforts and added to problems in recruiting and retaining high-quality staff. Indeed, the IOM committee studying the NIH intramural program found that space was inadequate for a number of institutes, that facilities had deteriorated in recent years, and that scheduled improvements had been delayed (e.g., renovations of the six oldest laboratory buildings that were scheduled for completion in 1991 are now projected to take until 1997; IOM/NAS, 1988:69). Facilities problems have become quite serious in terms of obsolete laboratory space, deteriorated heating and cooling systems, substandard research animal facilities, and unsafe patient and research areas, as well as sheer lack of space for AIDS and other growing research areas.

These NIH-wide space limitations and inadequacies have affected the AIDS research program disproportionately because it is a new, fast-growing set of activities. Also, because of the general delays in renovating, modernizing, and expanding laboratory facilities on campus and in constructing a consolidated office building for 2,700 extramural program administrators and support staff now located outside NIH's main Bethesda campus, much of the AIDS space is scattered in off-campus sites. These dispersed locations hamper communication and collaboration between AIDS basic and clinical researchers and between AIDS and non-AIDS researchers involved in related studies; they also impede coordination among administrators of extramural AIDS and AIDS-related research programs in the different institutes, centers, and divisions.

To address these problems, NIH is preparing a comprehensive facilities plan for Congress and has made facilities modernization and improvement a high priority in its 1991 budget request. According to acting NIH director William Raub, NIH requires a building program that could cost up to $1 billion over the next 10 years (U.S. Congress, 1990a:51). The agency's 1991 budget request includes $88.6 million for buildings and facilities, including $16.5 million for AIDS facilities.[10]

The need for more—and more appropriate—facilities specifically for AIDS work was acutely apparent in early 1988 when NIH director James Wyngaarden and NIH AIDS coordinator Anthony Fauci testified before several congressional committees (U.S. Congress, 1988a:259, 1988c:331). Their concerns were echoed in the June 1988 report of the Presidential Commission on the HIV Epidemic. The commission noted that plans for AIDS office and lab space were seriously delayed, and recommended that intramural construction and instrumentation needs be assessed and made a high priority in future budget requests. They also called for expedited approval of the proposed consolidated office building (Presidential Commission, 1988:40-41, 44). In 1989, NIH outlined its AIDS facilities problems, noting that rapid scientific developments might require adjustments in these priorities:

> The most critical concerns at the NIH are the provision of high-level biocontainment facilities to enhance safety in the workplace; the consolidation of currently dispersed laboratories to improve communications and efficiency among the many scientists involved in the program; the alleviation in scientific areas of overcrowding; the creation of a modern, consolidated facility for the primates so essential in vaccine and drug development; and the accommodation of increasing numbers of inpatients requiring intensive care. (U.S. Congress, 1990b:1285)

In the past several years, Congress has appropriated funds for AIDS research and office space that have greatly reduced the backlog of needs. Congress appropriated $19.2 million for AIDS buildings and facilities in fiscal year 1988 to build a three-story addition to the clinical center for lab facilities and offices, to lease and renovate space for AIDS labs and animal facilities off campus (the Twinbrook II facility), and to construct a new biocontainment facility for producing HIV at NCI's Frederick Cancer Research Facility (U.S. Congress, 1988b:63). Part of the appropriation was used to lease 16,000 square feet of off-campus office space for extramural program administration; in addition, the General Services Administration was asked to find 25,000 square feet (U.S. Congress, 1988a:270). Outpatient examining rooms and a new 26-bed unit in the NIH clinical

[10] The remainder is for initial funding ($19.2 million) of a $150 million program to modernize the utility infrastructure of the Bethesda campus (boilers, chillers, steam lines, etc.), continued renovation of the clinical center (which eventually could take between $400 million and $800 million to complete), rehabilitation of the older laboratory buildings, and renovation of animal facilities, as well as routine repairs (PHS, 1989:234). In addition, initial construction of a new Child Health and Neurosciences Building and planning and design of a consolidated office building will be supported by carryover funds.

center were assigned to AIDS research (although at first it was only possible to staff 14 of the beds; U.S. Congress, 1988a:268).

Congress appropriated $4.9 million in 1989 and $14.9 million in 1990 for AIDS facilities at NIH. In its budget request for fiscal year 1991, NIH reported that the addition to the clinical center was under construction, as were a new building at the Frederick Cancer Research Facility and renovations of NIAID lab space in the Twinbrook II facility. NIH's 1991 request of $16.5 million would allow completion of the renovations of lab space in Twinbrook II, construction of a new primate facility, and renovation and expansion of NCI AIDS labs at the Frederick facility (PHS, 1989:244,246). If the 1991 request is approved, appropriations since 1988 for AIDS buildings and facilities will total $55.3 million.

As a result of the major effort begun in 1988 to accommodate the space needs of the NIH AIDS research program, space occupied by NIH AIDS activities has doubled between July 1988 and March 1990, from 109,000 to 226,000 square feet, although it is still short of the 309,000 square feet planned. Additional funding will be needed, however, to complete planned renovations, expansions, and new construction of AIDS space at NIH (for example, an on-campus retrovirus lab and full renovation and expansion of one of the buildings at the Frederick facility). NIH's original request for AIDS facilities at NIH was $85.5 million, which was reduced at the PHS and DHHS levels to the $16.5 million included in the President's budget request (see the 1991 AIDS budget chronology in U.S. Congress, 1990a:170).[11]

Conclusion

As with personnel compensation and problems with the personnel system, NIH-wide space limitations and inadequacies have affected the AIDS research program disproportionately because it is a new and fast-growing set of activities. Similarly, efforts to address the overall problem—in this case by providing adequate amounts and types of modern, safe space and equipment for NIH as a whole—would go far toward solving the problems of inadequate facilities for AIDS research and research administration at NIH. In the meantime, Congress has appropriated funds specifically for AIDS research and office space that have greatly reduced the backlog of needs in the last several years. The next step is to consolidate AIDS activities on campus to promote joint research efforts, the exchange of research information, and program coordination.

Recommendation 4.6: As part of its long-range building and facilities program, NIH should consolidate AIDS research and research administration on the NIH campus. This consolidation will facilitate communication between the intramural and extramural programs and coordination of the multiple institutes, centers, and divisions involved in AIDS research activities. The committee endorses NIH's effort to take a systematic, sustained approach to upgrading and maintaining the campus infrastructure, which will benefit the AIDS program as well as non-AIDS research.

[11] The final 1991 budget, enacted in October 1990, included $9.5 million for AIDS buildings and facilities.

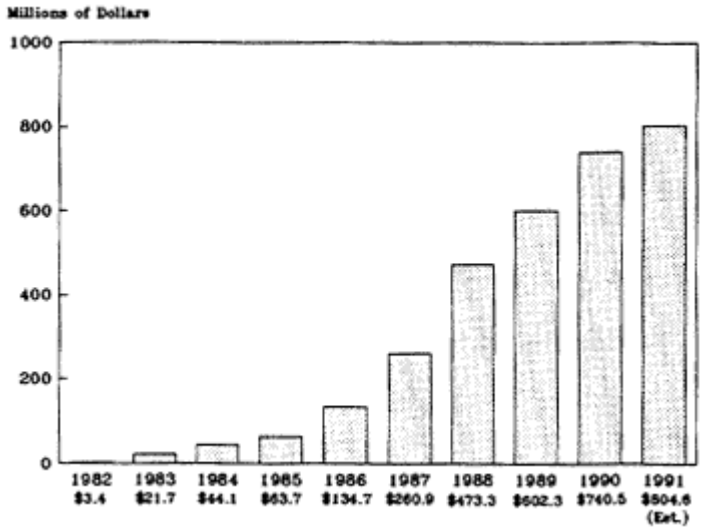

Figure 4.1
National Institutes of Health AIDS expenditures, fiscal years 1982-1991.
Source: Institute of Medicine's National Institutes of Health AIDS program data base, which is based on published and unpublished data from NIH's Division of Financial Management and Division of Research Grants and from the National AIDS Program Office.

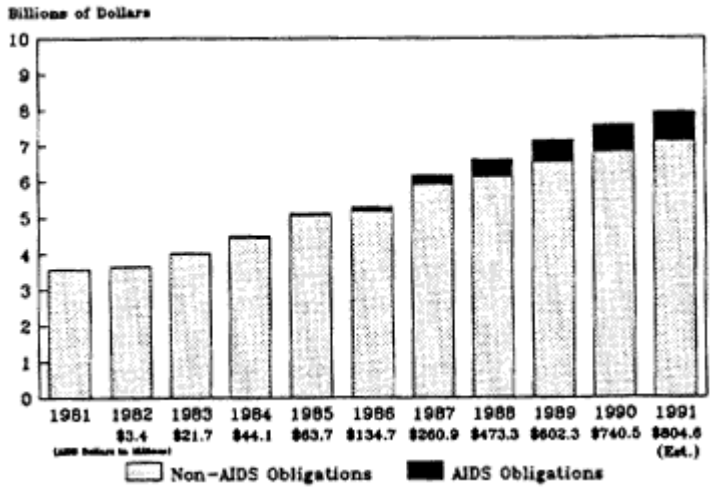

Figure 4.2
National Institutes of Health funding: non-AIDS obligations and AIDS obligations (in current dollars). Source: Institute of Medicine's National Institutes of Health AIDS program data base, which is based on published and unpublished data from NIH's Division of Financial Management and Division of Research Grants and from the National AIDS Program Office.

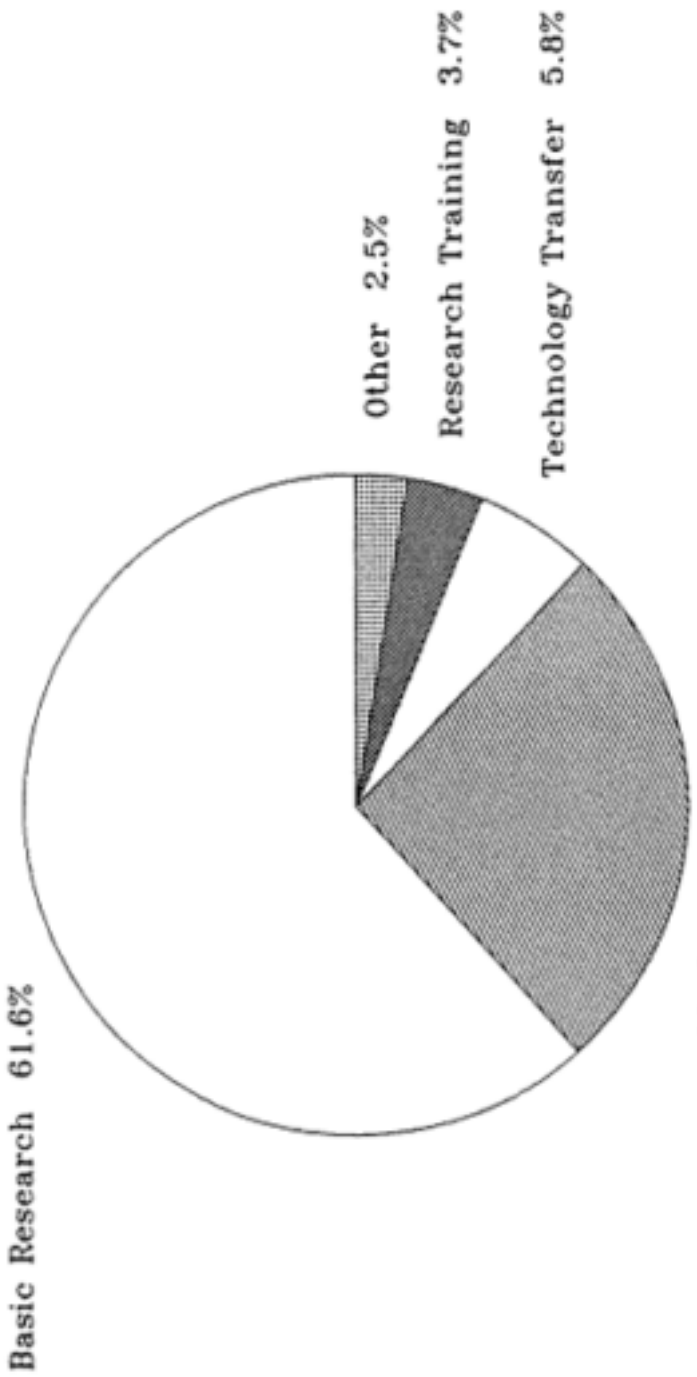

Figure 4.3
National Institutes of Health budget by type of activity, fiscal year 1990. Other activities include funds for other development activities, the National Library of Medicine, and buildings and facilities. Source: U.S. Congress, 1989:170.

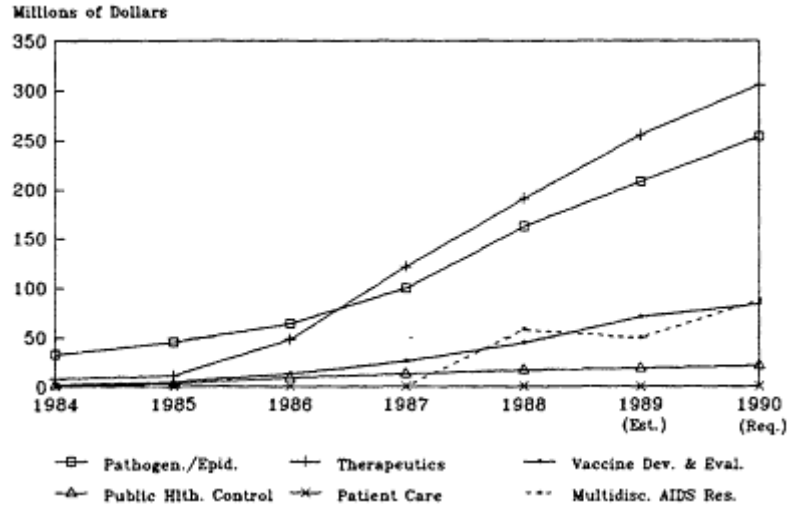

Figure 4.4a
AIDS funding by functional category, fiscal years 1984-1990.
Source: Division of Financial Management, National Institutes of Health.

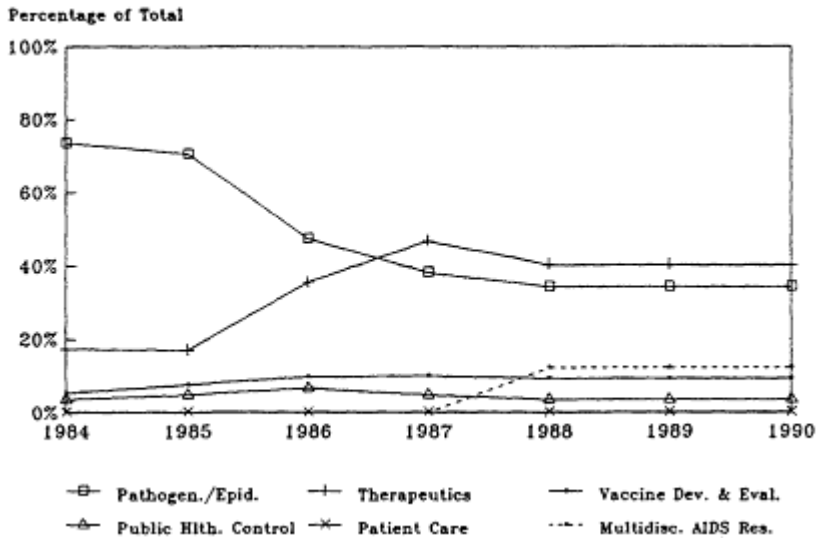

Figure 4.4b
AIDS funding by functional category as a percent of fiscal year totals, 1984-1990.
Source: Division of Financial Management, National Institutes of Health.

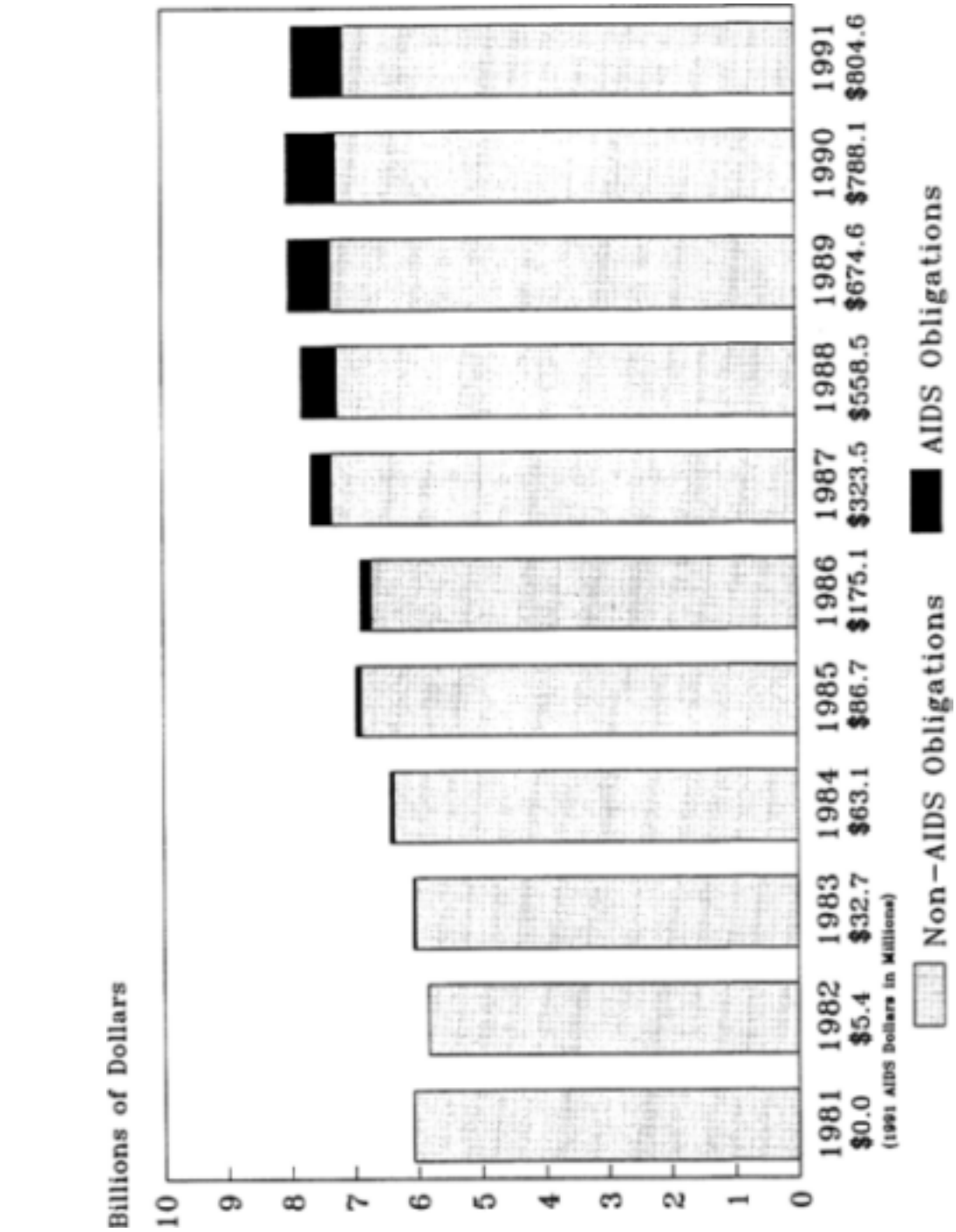

Figure 4.5
National Institutes of Health funding: non-AIDS and AIDS obligations (in 1991 dollars). The numbers were deflated using the biomedical research and development price index.
Source: Institute of Medicine's National Institutes of Health AIDS program data base, which is based on published and unpublished data from NIH's Division of Financial Management and Division of Research Grants and from the National AIDS Program Office.

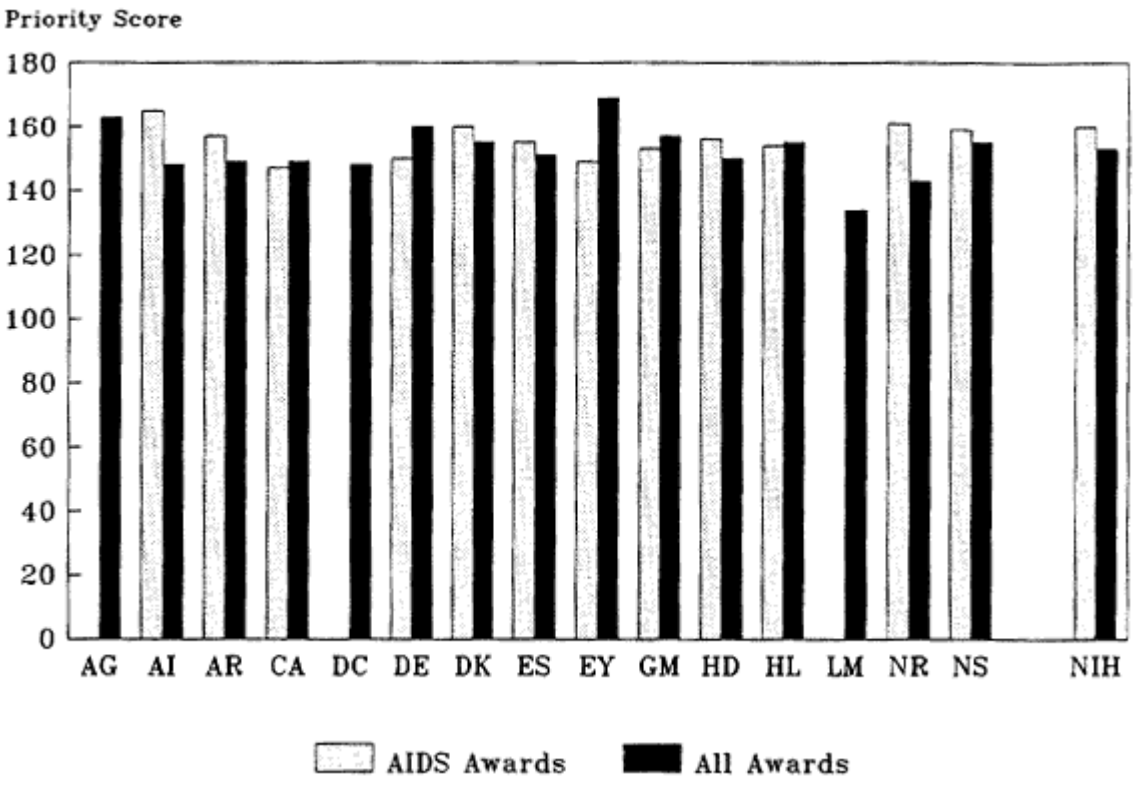

Figure 4.6
Priority score at the 50th percentile for National Institutes of Health AIDS R01 and all R01 awards.
Abbreviations: AG, National Institute on Aging; AI, National Institute of Allergy and Infectious Diseases; AR, National Institute of Arthritis and Musculoskeletal and Skin Diseases; CA, National Cancer Institute; De, National Institute on Deafness and Other Communication Disorders; DE, National Institute of Dental Research; DK, National Institute of Diabetes and Digestive and Kidney Diseases; ES, National Institute of Environmental Health Sciences; EY, National Eye Institute; GM, National Institute of General Medical Sciences; HD, National Institute of Child Health and Human Development; HL, National Heart, Lung, and Blood Institute; LM, National Library of Medicine; NR, National Center for Nursing Research; NS, National Institute of Neurological Disorders and Stroke.
Source: Division of Research Grants, National Institutes of Health.

TABLE 4.1 Growth of AIDS, Non-AIDS, and Total National Institutes of Health (NIH) Funding (in thousands of dollars), Fiscal Years 1982-1990

Year	NIH AIDS Obligations	Percent Increase	NIH Non-AIDS Obligations	Percent Increase	Total NIH Obligations	Percent Increase
1981	0	n.a.	3,572,506	n.a.	3,572,506	n.a.
1982	3,355	n.a.	3,640,106	1.9	3,643,461	2.0
1983	21,668	*545.8*	3,991,467	9.7	4,013,135	10.1
1984	44,121	103.6	4,449,432	11.5	4,493,553	12.0
1985	63,737	44.5	5,057,820	13.7	5,121,557	14.0
1986	134,667	111.3	5,163,310	2.1	5,297,977	3.4
1987	260,907	93.7	5,914,131	14.5	6,175,038	16.6
1988	473,285	81.4	6,137,145	3.8	6,610,430	7.1
1989	602,294	27.3	6,542,470	6.6	7,144,764	8.1
1990	740,509	22.9	6,840,975	4.6	7,581,484	6.1
1991[a]	804,567	8.7	7,472,172	9.2	8,276,739	9.2

n. a. Not applicable.
[a] Appropriated.
SOURCE: Institute of Medicine's NIH AIDS program data base, which is based on published and unpublished data from NIH's Divisions of Financial Management and Research Grants and from the National AIDS Program Office.

TABLE 4.2 Growth of AIDS Funding (in thousands of dollars), at the National Institutes of Health (NIH), Fiscal Years 1981-1990

Year	NIH AIDS Obligations	Total NIH Obligations	AIDS as Percentage of Total NIH Obligations
1981	0	3,572,506	0.0
1982	3,355	3,643,461	0.1
1983	21,668	4,013,135	0.5
1984	44,121	4,493,553	1.0
1985	63,737	5,121,557	1.2
1986	134,667	5,197,977	2.6
1987	260,907	6,175,038	4.2
1988	473,285	6,610,430	7.2
1989	602,294	7,144,764	8.4
1990	740,509	7,581,484	9.8
1991[a]	804,567	8,276,739	9.7

[a] Estimated.
SOURCE: Institute of Medicine's NIH AIDS program data base, which is based on published and unpublished data from NIH's Divisions of Financial Management and Research Grants and from the National AIDS Program Office.

TABLE 4.3 Percentage of National Institutes of Health AIDS Funding by Institute, Center, and Division, Fiscal Years 1990–1991

Unit	1990 Percent	1991 Percent[a]
National Cancer Institute	20.3	20.0
National Heart, Lung, and Blood Institute	5.7	5.4
National Institute of Dental Research	0.6	0.8
National Institute of Diabetes and Digestive and Kidney Diseases	0.7	0.7
National Institute of Neurological Disorders and Stroke	2.2	2.1
National Institute of Allergy and Infectious Diseases	53.1	53.8
National Institute of General Medical Sciences	2.0	1.9
National Institute of Child Health and Human Development	3.6	3.9
National Eye Institute	0.7	0.7
National Institute of Environmental Health Sciences	0.6	0.6
National Institute on Aging	0.1	0.1
National Institute of Arthritis and Musculoskeletal and Skin Diseases	0.2	0.2
National Institute on Deafness and Other Communication Disorders	–	0.1
National Center for Research Resources	6.0	5.9
National Center for Nursing Research	0.1	0.4
Fogarty International Center	0.7	0.7
National Library of Medicine	0.1	0.1
Office of the Director	1.6	1.6
Buildings and Facilities Program	1.7	1.2
Total	100.0	100.0

[a]Estimated.
SOURCE: Division of Financial Management, National Institutes of Health.

TABLE 4.4 AIDS Funding as a Percentage of Total Funding by Institute, Center, and Division, Fiscal Years 1990–1991

Unit	1990 Percent	1991 Percent[a]
National Cancer Institute	9.1	9.4
National Heart, Lung, and Blood Institute	3.9	3.9
National Institute of Dental Research	3.4	4.4
National Institute of Diabetes and Digestive and Kidney Diseases	0.9	1.0
National Institute of Neurological Disorders and Stroke	3.3	3.0
National Institute of Allergy and Infectious Diseases	47.3	47.7
National Institute of General Medical Sciences	2.1	2.1
National Institute of Child Health and Human Development	6.1	6.5
National Eye Institute	2.3	2.2
National Institute of Environmental Health Sciences	1.9	1.9
National Institute on Aging	0.4	0.3
National Institute of Arthritis and Musculoskeletal and Skin Diseases	0.7	0.8
National Institute on Deafness and Other Communication Disorders	–	0.5
National Center for Research Resources	12.6	14.2
National Center for Nursing Research	2.9	7.2
Fogarty International Center	31.6	30.5
National Library of Medicine	0.6	0.6
Office of the Director	11.0	13.4
Buildings and Facilities Program	19.2	5.6
Total	100.0	100.0

[a]Estimated.
SOURCE: Division of Financial Management, National Institutes of Health.

TABLE 4.5 National Institutes of Health (NIH) AIDS Funding (percentage) by Mechanism, Fiscal Years 1982-1991

Mechanism	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991[a]
Research grants										
Projects	20.1	41.5	32.6	28.0	18.8	30.9	40.5	38.3	39.0	39.3
Centers	19.0	5.8	3.8	5.3	4.7	4.1	8.3	8.7	7.9	7.7
Other	0.2	0.1	0.4	1.4	1.3	0.9	2.8	2.5	1.8	1.7
Total	39.4	47.4	36.8	34.7	24.8	35.9	51.7	49.5	48.7	48.7
Research training	-[b]	-	<0.1	0.2	<0.1	0.1	0.7	1.1	1.0	1.2
Research and development contracts	13.4	21.5	34.9	39.1	53.4	42.9	29.4	27.7	26.7	26.5
Intramural research	47.2	31.1	27.2	25.1	20.1	16.9	14.0	15.5	16.5	16.9
Research management and support	-	-	1.0	0.9	1.5	2.4	2.8	3.6	3.5	3.8
All other[c]	-	-	-	-	0.1	1.8	1.4	1.8	3.5	2.9
Total NIH	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
AIDS funding (millions of dollars)	$3.4	$21.7	$44.1	$63.7	$134.7	$260.9	$430.6	$602.3	$740.5	$804.6

[a] Estimated.
[b] No funds allocated.
[c] Allocations for the National Library of Medicine, Office of the NIH Director, Buildings and Facilities program, and extramural construction grants.
SOURCE: U.S. Congress (1989:136-137) for 1982-1988; Division of Financial Management, NIH, for 1989-1991.

TABLE 4.6 National Institutes of Health (NIH) Non-AIDS Funding (percentage) by Mechanism, Fiscal Years 1982-1991

Mechanism	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991[a]
Research grants										
Projects	50.3	52.3	53.4	54.4	56.0	57.2	57.7	58.3	59.5	56.0
Centers	9.6	9.3	9.6	9.3	9.0	8.7	8.5	8.3	8.1	8.7
Other	*5.7*	*5.5*	*5.5*	6.1	5.9	5.9	5.8	5.5	4.7	5.1
Total	65.6	67.0	68.4	69.8	70.9	71.8	72.0	72.1	72.3	69.8
Research training	4.1	4.1	3.7	4.3	4.1	3.9	3.8	3.7	3.7	4.0
Research and development contracts	8.8	7.9	7.4	6.9	5.4	6.3	6.0	5.6	5.5	5.4
Intramural research	12.4	12.3	11.9	11.0	10.5	10.5	10.6	10.6	10.8	10.6
Research management and support	5.1	5.0	4.8	4.3	4.0	3.9	4.2	4.3	4.0	4.6
All other[a]	3.9	3.6	3.8	3.6	5.0	3.6	3.3	3.7	3.6	5.7
Total NIH	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Non-AIDS funding (billions of dollars)	$3.6	$4.0	4.4	$5.1	$5.2	$5.9	$6.1	$6.5	$6.8	$7.5

[a] Estimated.
SOURCE: U.S. Congress (1989:134-135) for 1982-1988; Division of Financial Management, NIH for 1989-1991.

TABLE 4.7 Number of AIDS Research Project Grants (RPG) by Type and Proportion Solicited by Requests for Applications (RFA), Fiscal Years 1986-1988

		R01s					Solicited by RFA	
Fiscal Year	Total RPGs	Number	Percent	P01s	U01s	Other RPGs	Number	Percent
1986	182	111	61	17	42	12	57	31
1987	292	182	62	24	62	24	142	78
1988	501	307	61	45	101	48	90	29

NOTE: Abbreviations: R01, traditional (individual investigator-initiated) research grant; P01, program project grant; U01, cooperative agreement.
SOURCE: Division of Research Grants, National Institutes of Health.

TABLE 4.8 National Institutes of Health AIDS Funding (in thousands of dollars) by Mason Functional Categories

Category	Fiscal Year 1989 Budget Authority	Fiscal Year 1990 Appropriation	Fiscal Year 1991 President's Request
Basic science research			
Biomedical research			
HIV and HIV genome	62,120	66,320	71,887
Immunology	37,954	44,911	48,075
Blood/blood products	11,063	12,154	8,879
Diagnostic methods/reagents development	7,869	10,853	11,956
Animal models and related studies	29,683	36,308	39,264
Subtotal	148,689	170,546	180,061
Neuroscience and neuropsychiatric research	16,645	20,324	21,669
Behavioral research			
Mechanisms of behavior and behavior change	3,863	4,188	4,530
Prevention of high-risk behaviors	1,315	611	642
Subtotal	5,178	4,799	5,172
Therapeutic agents			
Development	131,421	163,712	176,082
Clinical trials	103,840	139,966	150,306
Subtotal	235,261	303,678	326,388
Vaccines			
Development	49,238	64,301	70,499
Clinical trials	10,581	14,332	15,631
Subtotal	59,819	78,633	86,130
Research enhancement			
Training	6,473	8,253	9,445
Construction (extramural)	4,940	– [a]	–
Subtotal	11,413	8,253	9,445
Total, basic science research	477,005	586,233	628,865

TABLE 4.8 continues

Category	Fiscal Year 1989 Budget Authority	Fiscal Year 1990 Appropriation	Fiscal Year 1991 President's Request
Risk assessment and prevention			
Surveillance–diseases associated with HIV	7,206	8,263	8,981
Population-based research			
Transmission			
Sexual	33,201	37,353	43,290
Intravenous drug abusers	8,583	10,683	11,460
Hemophilia populations	4,692	4,676	4,856
Blood recipient/donor studies	9,420	9,400	8,839
Perinatal infection	18,480	23,341	25,254
Occupationally related	83	83	100
Other/miscellaneous	13,560	16,245	17,284
Subtotal	88,019	101,781	111,083
Natural history and cofactors	12,717	16,154	16,951
Subtotal	100,736	117,935	128,034
Information and educational/preventive services			
High-risk or infected persons			
Health education/risk education	2,057	1,797	1,826
Counseling, testing, partner notification	275	344	369
Perinatal AIDS prevention projects	447	560	601
Subtotal	2,779	2,701	2,796
School and college-aged youth–national efforts	533	668	716
General public and special programs			
National–treatment trials and therapy, information services	7,017	10,014	10,846
Regional, state, and local	9	540	820
Subtotal	7,026	10,554	11,666
Health care workers and providers			
Education and training centers	999	1,249	1,342
Other types of training	1,110	1,164	1,264
Subtotal	2,109	2,413	2,606
Subtotal	12,447	16,336	17,784
Total, risk assessment and prevention	120,389	142,534	154,799
PHS-wide activities– construction (PHS facilities)	4,900	14,765	16,500
Grand total	602,294	743,532	800,164

[a]No funds allocated.

SOURCE: National AIDS Program Office, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services.

TABLE 4.9 National Institutes of Health AIDS Funding (thousands of dollars), by Charlottesville Functional Categories, Fiscal Years 1984–1990

Category	1984	1985	1986	1987	1988[a]	1989[b]	1990[b]
Pathogenesis and clinical manifestations							
Epidemiological studies	16,202	20,468	27,848	38,964	59,869	87,896	98,598
Virology	1,500	2,500	2,983	8,843	25,651	21,399	33,305
Surveillance	40	600	1,979	620	1,387	1,736	3,267
Etiologic agent and co-factors	5,521	9,224	12,412	22,465	30,490	45,734	53,223
Immunologic studies	6,534	9,683	15,215	20,038	28,539	29,283	40,376
Simian AIDS	2,589	2,351	3,541	8,057	11,627	17,564	19,248
Psychosocial factors	38	124	39	692	4,976	4,739	5,968
Subtotal	32,424	44,950	64,017	99,679	162,539	208,351	253,985
Therapeutics							
Studies of therapeutic intervention	7,680	10,332	38,437	105,922	174,350	232,630	278,234
Drug purchase and distribution	–[c]	500	9,564	16,132	16,284	22,755	27,519
Subtotal	7,680	10,832	48,001	122,054	190,634	255,385	305,753
Vaccine development and evaluation	2,379	4,839	13,300	26,174	44,333	70,926	83,886
Public health control measures							
Information/education	573	643	1,682	5,253	7,215	5,386	8,717
Prevention of transfusion-related AIDS	22	536	622	1,733	3,196	4,033	4,000
Development and evaluation of blood tests	1,015	1,879	6,866	5,782	6,548	9,684	8,419
Subtotal	1,610	3,058	9,170	12,768	16,959	19,103	21,136
Patient care and health care needs							
Treatment demonstration project	–	–	95	90	295	–	50
Bioethics and safety	28	58	84	142	86	337	348
Subtotal	28	58	179	232	381	337	398
Multidisciplinary AIDS research	–	–	–	–	58,439	49,697	87,512
Total, National Institutes of Health	44,121	63,737	134,667	260,907	473,285	603,799	752,670

[a]Includes $23,935 of no-year extramural construction funds in the National Center for Research Resources and $18,780 in Building and Facilities construction appropriated in fiscal year 1988 that will be obligated in fiscal year 1989.
[b]Estimated.
[c]No funds budgeted or allocated.

SOURCE: Division of Financial Management, National Institutes of Health.

TABLE 4.10 Comparison of AIDS and Non-AIDS Priority Scores for Research Grants, Fiscal Years 1982-1985, National Institutes of Health

	AIDS Research Grants								
	1982	1983			1984			1985	
Priority Score Range[a]	NCI	NCI	NHLBI	NIAID	NCI	NHLBI	NIAID	NCI	NIAID
100-180	13	8	0	12	8	4	20	17	8
181-200	4	5	1	2	1	0	4	0	0
201-250	6	7	0	2	6	3	4	0	1
251-300	1	10	1	1	0	0	0	1	0
300+	0	0	0	0	1	0	0	0	0
Total AIDS grants	24	30	2	17	16	7	28	18	9
Payline[b] for non-AIDS grants	183	181	195	166	184	201	167	172	159

NOTE: Abbreviations: NCI, National Cancer Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases
[a] All research grants are reviewed for scientific merit and receive a score ranging from 100 (best) to 500 (worst).
[b] The payline is the score dividing funded and unfunded grants.
SOURCE: Division of Financial Management, National Institutes of Health, May 16, 1986.

TABLE 4.11 Priority Score[a] at 50th Percentile for Applications and Awards, AIDS and Non-AIDS R01s and All Research Project Grants, Fiscal Year 1989

	AIDS	Non-AIDS
R01s[b]		
Applications	242	235
Awards	160	153
Research project grants[c]		
Applications	240	231
Awards	161	153

[a] 100 is best score, 500 is worst.
[b] Traditional individual investigator-initiated grants.
[c] Includes R01, R22, R23, R29, R35, R37, R43, R44, P01, P42, U01, and National Institute of General Medical Sciences P41 (no National Library of Medicine or National Center for Research Resources grants).
SOURCE: Division of Research Grants, National Institutes of Health.

TABLE 4.12 Comparison of Peer Review Scores of AIDS Grant Applications with Scores of All Other Grant Applications Reviewed in Division of Research Grants Study Sections, Council Year 1989[a]

	Mean Priority Score	Mean Priority Score, by Deciles				
		First Decile	Second Decile	Third Decile	Fourth Decile	Fifth Decile
AIDS applications						
All	254	135	155	176	199	225
Type 1[b]	259	135	155	176	199	225
Type 2[c]	199	135	154	175	200	224
All other applications						
All	240	133	153	170	191	212
Type 1[b]	251	133	153	170	191	213
Type 2[c]	210	133	153	170	190	212

[a] Council year 1989 includes applications received for consideration at national advisory council meetings held in January, May, and October 1989.
[b] Type 1 applications are applications for funding of new research projects.
[c] Type 2 applications are applications for continued funding of research projects for which previous grants are running out or expiring. (Also included are type 9 applications, which are also competing renewal applications that are changing institutes.)
SOURCE: Division of Research Grants, National Institutes of Health.

TABLE 4.13 AIDS and Non-AIDS Individual Investigator-Initiated Grants (R01s) and All Research Project Grants (RPG), Fiscal Year 1989

Grant Type	Reviewed	Approved	Awarded	Success Rate[a] (percentage)	Award Rate[b] (percentage)	Recommendation Rate[c] (percentage)
AIDS R01s	700	638	205	29.0	31.8	91.1
Non-AIDS R01s	15,191	14,714	3,971	27.0	26.0	96.6
AIDS RPGs (includes R01s)	886	790	273	30.5	34.2	89.2
Non-AIDS RPGs (includes R01s)	19,521	18,317	5,383	29.4	27.5	93.5

[a] Number awarded divided by number reviewed.
[b] Number awarded divided by number approved.
[c] Number approved divided by number reviewed.
SOURCE: Division of Research Grants, National Institutes of Health.

TABLE 4.14a Cumulative Summary of AIDS Staffing (in full-time equivalents [FTE]) by Unit, National Institutes of Health

Unit	1982	1983	1984	1985	1986	1987	1988	1989	1990[a]	1991[b]
Institute, center, or division										
National Cancer Institute	20	31	72	85	98	129	146	188	281	300
National Heart, Lung, and Blood Institute	–[c]	–	–	1	1	5	9	18	23	35
National Institute of Dental Research	–	–	1	2	4	8	10	16	18	19
National Institute of Diabetes and Kidney Diseases	–	–	–	–	–	5	5	10	10	10
National Institute of Neurological Disorders and Stroke	1	2	10	11	16	21	23	40	40	40
National Institute of Allergy and Infectious Diseases	–	12	45	46	57	119	158	229	306	343
National Institute of General Medical Sciences	–	–	–	–	–	–	–	2	2	2
National Institute of Child Health and Human Development	–	–	–	–	–	10	12	21	22	25
National Eye Institute	–	–	–	–	1	1	1	4	5	7
National Institute of Environmental Health Sciences	–	–	–	–	–	2	6	7	7	8
National Institute on Aging	–	–	–	–	–	1	2	3	5	5
National Institute of Arthritis and Musculoskeletal and Skin Diseases[d]	–	–	–	–	–	–	–	2	3	4
National Institute on Deafness and Other Communication Disorders[e]	–	–	–	–	–	–	1	–	–	–
National Center for Research Resources	–	–	–	–	–	3	5	7	7	7
National Center for Nursing Research[f]	–	–	–	–	–	–	–	2	2	4
Fogarty International Center	–	–	–	–	–	–	2	3	3	3
Subtotal	21	45	128	144	177	304	379	552	735	813
National Library of Medicine	–	–	–	–	–	–	–	2	7	8
Office of the Director	–	–	–	–	–	2	7	16	35	37
Clinical center	6	14	40	47	58	90	131	–	–	–
Division of Research Grants	–	–	–	–	–	3	10	193	295	325
Office of Research Services	–	–	–	–	–	–	10	–	–	–
Total	27	59	168	191	235	399	537	763	1,072	1,183

[a]Estimated.
[b]Requested.
[c]No FTEs allotted.
[d]The National Institute of Arthritis and Musculoskeletal and Skin Diseases was established in 1986.
[e]The National Institute on Deafness and Other Communication Disorders was established in 1988.
[f]The National Center for Nursing Research was established in 1986.

SOURCE: Division of Financial Management, National Institutes of Health, January 28, 1989.

TABLE 4.14b Cumulative Summary of AIDS Staffing (in full-time equivalents [FTE]) by Administrative Area, National Institutes of Health

Administrative Area	1982	1983	1984	1985	1986	1987	1988	1989	1990[a]	1991[b]
Intramural	21	45	118	129	145	224	275	378	498	555
Research management and support	-[c]		10	15	28	80	104	174	237	258
Office of the Director and Central Services	6	14	40	47	58	95	158	211	337	370
Total	27	59	168	191	235	399	537	763	1,072	1,183

[a] Estimated.
[b] Requested.
[c] No FTEs allotted.
SOURCE: Division of Financial Management, National Institutes of Health, January 28, 1989.

TABLE 4.15 Staffing Levels (in full-time equivalents [FTE]) for the National Institutes of Health AIDS and Non-AIDS Programs, 1981-1991

	FTEs		
Fiscal Year	Total	AIDS	Non-AIDS
1981	12,637	0	12,376
1982	12,689	27	12,662
1983	13,414	59	13,355
1984	13,661	168	13,493
1985	13,100	191	12,909
1986	12,540	235	12,305
1987	12,720	399	12,321
1988	13,249	537	12,712
1989	13,204	763	12,441
1990[a]	13,214	887	12,327
1990[b]	13,779	1,072	12,707
1991[a]	14,133	1,183	13,031

[a] President's budget request.
[b] Revised budget (January 1990).
SOURCE: Division of Financial Management, National Institutes of Health, January 29, 1989.

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Appendix A

Study Issues

- Adequacy of NIH's response to the emerging epidemic of HIV infection (see Chapter 1: "NIH's Response to the Emerging Epidemic").
- Appropriateness of the scope and content of NIH's AIDS research program, and the relationship between AIDS and non-AIDS research, especially the impact of the support of AIDS research on non-AIDS research and the impact of the science from AIDS research on the science of non-AIDS research (see Chapter 4: "Adequacy [of Funding]," "Impact of Non-AIDS Research," and "Spillover Effects of AIDS Research on Non-AIDS Efforts").
- Adequacy of NIH's organizational structure and processes for planning, implementing, monitoring, and evaluating the AIDS research program (see Chapter 2).
- Use, structure, and composition of advisory groups in the NIH AIDS research program (see Chapter 2: "Strengthening External Advisory Processes").
- Balance between directed and investigator-initiated research, appropriate dollar allocations among the various research categories (e.g., therapeutics, vaccine development, pathogenesis), and mechanisms for funding research in those categories (e.g., traditional research grants, other types of research grants, cooperative agreements, research contracts, intramural research, and research centers) (see Chapter 4: "Grants Policy and Administration"; and Chapter 3).
- Role of public opinion in influencing the direction of AIDS research (see Chapter 2: "Strengthening External Advisory Processes").
- Adequacy of the level of funding of AIDS research at NIH and needed space, personnel, and other research resources (see Chapter 3, which discusses adequacy of funding in each area, including "Research Resources"; and Chapter 4: "Adequacy [of Funding]," "Administrative Support [NIH Staffing, Facilities]").
- Type and degree of coordination between NIH research and the activities of other agencies within and without the Public Health Service (within PHS and with WHO, see Chapter 3: "Behavioral Research" and "Epidemiology"; within the pharmaceutical industry, see Chapter 3: "Preclinical Drug Discovery and Development" and "Clinical Trials").

- Adequacy of NIH's efforts in communicating AIDS research activities, such as its drug and vaccine development and testing processes, to the scientific community and the public (see Chapter 3: "Communication of Research Results").

Appendix B

Persons Who Were Interviewed by Committee or Staff or Who Provided Written Materials

Ronald Abeles, National Institute on Aging, NIH[1]

Donald Abrams, Assistant Director, AIDS Activities, San Francisco General Hospital

Donna Adderly, Office of the Director, NIH

Reid Adler, Office of Technology Transfer, NIH

Duane Alexander, National Institute of Child Health and Human Development, NIH

James Allen, National AIDS Program Office, Department of Health and Human Services

John Bader, National Cancer Institute, NIH

Barbara Baird, Clinical Center, NIH

Wendy Baldwin, National Institute of Child Health and Human Development, NIH

James Balsley, National Institute of Allergy and Infectious Diseases, NIH

Steven J. Berkowitz, National Institute of Allergy and Infectious Diseases, NIH

Bernard Bihari, Community Research Initiative[2]

William Blattner, National Cancer Institute, NIH

William Borkowsky, New York University Medical Center

Bernard Branson, Physicians Association for AIDS Care[3]

Sandra Bridges, National Institute of Allergy and Infectious Diseases, NIH

Samuel Broder, National Cancer Institute, NIH

James W. Buehler, Centers for Disease Control

Virginia Cain, National Institute of Child Health and Human Development, NIH

Marvin Cassman, National Institute of General Medical Sciences, NIH

Bruce Chabner, National Cancer Institute, NIH

Eileen Chusid, Mt. Sinai Medical Center

Edward Connor, Children's Hospital of New Jersey

Ellen Cooper, Food and Drug Administration

Lawrence Corey, University of Washington School of Medicine

Deborah Cotton, Harvard School of Public Health

Charles L. Coulter, National Center for Research Resources, NIH

George Counts, National Institute of Allergy and Infectious Diseases, NIH

[1] The affiliation provided for each individual is at time of interview or receipt of material.
[2] Submitted written testimony to committee.
[3] Testified before committee, December 4-5, 1989.

James Cradock, National Institute of Allergy and Infectious Diseases, NIH
James W. Curran, Centers for Disease Control
William N. Darrow, Centers for Disease Control
Martin Delaney, Project Inform[3]
Lawrence Deyton, National Institute of Allergy and Infectious Diseases, NIH
Patrice Edwards, Albert Einstein College of Medicine
Susan Ellenberg, National Institute of Allergy and Infectious Diseases, NIH
John Fahey, University of California at Los Angeles Medical Center
Anthony Fauci, National Institute of Allergy and Infectious Diseases, NIH
Judith Feinberg, National Institute of Allergy and Infectious Diseases, NIH
Patricia Fleming, Congressional Office of Representative Ted Weiss
Lorraine Fishback, Office of the Assistant Secretary for Health, Department of Health and Human Services
Michael Friedman, National Cancer Institute, NIH
George J. Galasso, Office of the Director, NIH
William Gartland, National Institute of Allergy and Infectious Diseases, NIH
Jacob A. Gayle, Centers for Disease Control
Ronald Geller, National Heart, Lung, and Blood Institute, NIH
Clarence Gibbs, National Institute of Neurological Diseases and Stroke, NIH
James J. Goedert, National Cancer Institute, NIH
Michael Goldrich, National Institute of Allergy and Infectious Diseases, NIH
William H. Goldwater, Office of the Director, NIH
Edward Gomperts, Children's Hospital of Los Angeles
Rosalind Gray, Office of the Director, NIH
Edward Gubish, National Institute of Allergy and Infectious Diseases, NIH
Kurt Habel, Office of the Director, NIH
Maya Hadar, National Institute of Allergy and Infectious Diseases, NIH
Margaret Hamburg, National Institute of Allergy and Infectious Diseases, NIH
John Hartinger, National Cancer Institute, NIH
Peter Hartsock, Alcohol, Drug, and Mental Health Administration
Suzanne Haynes, National Cancer Institute, NIH
Janet Heinrich, National Center for Nursing Research, NIH
Aria Sue Hinshaw, National Center for Nursing Research, NIH
Martin Hirsch, Harvard Medical School
Patricia Hoban, Office of the Assistant Secretary for Health
June Homer, Health Resources and Services Administration
Marc Horowitz, Office of AIDS Research, NIH
Daniel Hoth, National Institute of Allergy and Infectious Diseases, NIH
Peter Barton Hutt, Law firm of Covington and Burling
John C. James, Division of Research Grants, NIH
Stephanie James, National Institute of Allergy and Infectious Diseases, NIH
John Jarman, Office of the Director, NIH
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Stan Katzman, Office of AIDS Research, NIH
Jack Killen, National Institute of Allergy and Infectious Diseases, NIH
Jane Kinsel, National Institute of Allergy and Infectious Diseases, NIH
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Wayne Koff, National Institute of Allergy and Infectious Diseases, NIH
Lloyd J. Kolbe, Centers for Disease Control
Richard M. Krause, Fogarty International Center, NIH
Michon Kretschmaier, Office of the Assistant Secretary for Health, Department of Health and Human Services
Clifford Lane, National Institute of Allergy and Infectious Diseases, NIH
Elaine Larson, American Nurses' Association[3]
Catherine Laughlin, National Institute of Allergy and Infectious Diseases, NIH
Barbara Laughon, National Institute of Allergy and Infectious Diseases, NIH
Missy LeClaire, National Association of People With AIDS[3]
Claude Lenfant, National Heart, Lung, and Blood Institute, NIH
Norman Letvin, New England Primate Center
Carl Leventhal, National Institute of Neurological Diseases and Stroke, NIH
Wendy Liffers, National Institute of Allergy and Infectious Diseases, NIH
Charles Litterst, National Institute of Allergy and Infectious Diseases, NIH
Iris Long, AIDS Treatment Registry[3]
Claire Macklan, Agency for Health Care Policy and Research
John D. Mahoney, Office of the Director, NIH
Barbara Masters, Congressional Office of Senator Alan Cranston
Henry Masur, Clinical Center, NIH
Samuel Matheny, Health Resources and Services Administration
Bruce Maurer, Division of Research Grants, NIH
John McGowan, National Institute of Allergy and Infectious Diseases, NIH
Jean McGuire, AIDS Action Council[3]
Merle McPherson, Health Resources and Services Administration
Gerald Medoff, Washington University School of Medicine
Gilbert Meier, Division of Research Grants, NIH
Mike Meridian, National Association of People With AIDS[3]
Thomas Merigan, Stanford University School of Medicine
Abbey S. Meyers, National Organization for Rare Disorders[3]
Michael Miller, Office of AIDS Research, NIH
Richard Miller, Office of the Director, NIH
John Mills, San Francisco General Hospital
Greg Milman, National Institute of Allergy and Infectious Diseases, NIH
Janet Mitchell, National Minority AIDS Council[3]
Horoaki Mitsuya, National Cancer Institute, NIH
John La Montagne, National Institute of Allergy and Infectious Diseases, NIH
W. Meade Morgan, Centers for Disease Control
Richard Mowery, National Eye Institute, NIH
Jay Moskowitz, Office of the Director, NIH
Maureen Myers, National Institute of Allergy and Infectious Diseases, NIH

Marti Nash, San Francisco General Hospital
Antonia Novello, National Institute of Child Health and Human Development, NIH
Joyce O'Shaughnessy, National Cancer Institute, NIH
John Petricciani, Pharmaceutical Manufacturers Association
Carla Pettinelli, National Institute of Allergy and Infectious Diseases, NIH
Pharmaceutical company representatives (spoke on condition of anonymity)
Philip Pizzo, National Cancer Institute, NIH
William Powderly, Washington University School of Medicine
Patricia Randall, National Institute of Allergy and Infectious Diseases, NIH
Matilda Riley, National Institute on Aging, NIH
Dennis Rodriguez, Office of AIDS Research, NIH
Karyn Ross, National Institute on Aging, NIH
Henry Sacks, Mount Sinai School of Medicine
Polly Sager, National Institute of Allergy and Infectious Diseases, NIH
Robert T. Schooley, Massachusetts General Hospital
Lewis Schrager, National Institute of Allergy and Infectious Diseases, NIH
Neil Schram, AIDS Task Force, American Association of Physicians for Human Rights[3]
Daniela Seminara, Alcohol, Drug, and Mental Health Administration
Valerie Setlow, National AIDS Program Office, Department of Health and Human Services
Hilary Sigmund, National Center for Nursing Research, NIH
Elaine Sloand, National Heart, Lung, and Blood Institute, NIH
Steve Smith, Human Rights Campaign Fund[3]
Ruy Soeiro, Albert Einstein College of Medicine
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Allen C. Stoolmiller, National Institute of Allergy and Infectious Diseases, NIH
Judith Swan, Office of AIDS Research, NIH
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Melanie Thompson, Atlanta AIDS Research Consortium
Cherry Tsutsumida, Health Resources and Services Administration
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Diane S. Wax, National Institute of Allergy and Infectious Diseases, NIH
Tim Westmoreland, House Subcommittee on Health and Environment Staff
Judith Whalen, National Cancer Institute, NIH
Jack Whitescarver, Office of AIDS Research, NIH
Richard Whitley, University of Alabama
Anne Willoughby, National Institute of Child Health and Human Development, NIH

Ronald Wilson, Centers for Disease Control
Robert Wittes, Bristol-Myers Squibb, Inc.
Joyce Woodford, National Institute of Allergy and Infectious Diseases, NIH
Robert Yarchoan, National Cancer Institute, NIH
Frank Young, Former Food and Drug Administration Commissioner

Appendix C

National Institutes of Health Aids Program Advisory Committee

Martin S. Hirsch (chair), Professor of Medicine, Harvard Medical School, Boston, Massachusetts

Baruj Benacerraf, Fabyan Professor of Comparative Pathology and Chairman, Department of Pathology, Harvard Medical School, Boston, Massachusetts

Dani Paul Bolognesi, James B. Duke Professor, Department of Surgery, Surgical Virology Laboratory, Duke University Medical Center, Durham, North Carolina

Purnell W. Choppin, President, Howard Hughes Medical Institute, Bethesda, Maryland

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Robert J. Levine, Professor, Department of Internal Medicine, School of Medicine, Yale University, New Haven, Connecticut

Thomas E. Malone, Vice President, Division of Biomedical Research, Association of American Medical Colleges, Washington, D.C.

Wendy K. Mariner, Professor of Law and Public Health, Boston University School of Public Health, Boston, Massachusetts

William Raub, Acting Director, National Institutes of Health, Bethesda, Maryland

Gary R. Smith, Professor, School of Law, Emory University, Atlanta, Georgia

Jose Szapocznik, Research Professor, Department of Psychiatry, University of Miami

Diane W. Wara, Professor of Pediatrics, School of Medicine, University of California, San Francisco

Constance B. Wofsy, Co-director, AIDS Activities Division, and Assistant Chief, Infectious Diseases, San Francisco General Hospital

Anthony S. Fauci (executive secretary), Director, Office of AIDS Research, and Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Appendix D

Abbreviations and Acronyms

ACTG	AIDS Clinical Trials Group
ACTU	AIDS clinical trials unit
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
AIDS	acquired immune deficiency syndrome
APAC	AIDS Program Advisory Committee
AVEU	AIDS vaccine evaluation unit
CDC	Centers for Disease Control
DAIDS	Division of AIDS
DCT	Division of Cancer Treatment
DNC	Decision Network Committee
DRG	Division of Research Grants
FCRF	Frederick Cancer Research Facility
FDA	Food and Drug Administration
FIC	Fogarty International Center
FTE	full-time equivalents
GLP	good laboratory practice
HATS	Heterosexual HIV Transmission Study
HCFA	Health Care Financing Administration
HIV	human immunodeficiency virus
HRSA	Health Resources and Services Administration
ICD	institutes, centers, and divisions
IHS	Indian Health Service
IND	investigational new drug
IOM	Institute of Medicine
IV	intravenous
IVIG	intravenous immunoglobulin
MACS	Multicenter AIDS Cohort Study
NAEC	NIH AIDS Executive Committee
NAPO	National AIDS Program Office
NAS	National Academy of Sciences
NCDDG-HIV	National Cooperative Drug Discovery Group Program for the treatment of HIV/AIDS
NCDDG-OI	National Cooperative Drug Discovery Group Program for the treatment of opportunistic infections
NCI	National Cancer Institute

NCNR	National Center for Nursing Research
NCRR	National Center for Research Resources
NCVDG	National Cooperative Vaccine Discovery Groups
NEI	National Eye Institute
NHLBI	National Heart, Lung and Blood Institute
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDR	National Institute of Dental Research
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NLM	National Library of Medicine
OAR	Office of AIDS Research
OASH	Office of the Assistant Secretary for Health
OD	Office of the Director
OI	opportunistic infection
OMB	Office of Management and Budget
OPM	Office of Personnel Management
OTA	Office of Technology Assessment
PA	program announcement
PCA	physicians comparability allowance
PCP	*Pneumocystis carinii* pneumonia
PEBRA	Programs of Excellence in Basic Research on AIDS
PHS	Public Health Service
RAG	Resource Allocation Group
RCMI	Research Centers at Minority Institutions
RFA	request for application
RFP	request for proposal
RPG	research project grant
SES	Senior Executive Service
SFMHS	San Francisco Men's Health Study
SIV	simian immunodeficiency virus
SMSA	standard metropolitan statistical area
STD	sexually transmitted disease
U.S. DHEW	United States Department of Health, Education and Welfare
U.S. DHHS	United States Department of Health and Human Services
USAID	United States Agency for International Development
VRDB	Vaccine Research and Development Branch
WHO	World Health Organization
WITS	Women and Infants Transmission Study
YPLL	years of potential life lost