

Elswood...Here's what I told
you I'd send you.

- Kamikaze #1



National Institutes of Health
Bethesda, Maryland 20892
Building : 31
Room : 7A03
(301) 496- 2263

MAY 12 1987

Enclosed you will find the final, printed version of the report you developed last summer, "Future Directions for AIDS Research." I apologize for the lengthy delay in transmitting the completed document to you. Regrettably, we experienced delays in obtaining the necessary clearances, however, I am pleased to inform you that the report has been sent to Congress.

Once again, I want to extend my appreciation for the time and effort you devoted to complete this difficult undertaking.

Sincerely yours,

Anthony S. Fauci, M.D.
NIH AIDS Coordinator

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
Building : Shannon
Room : 228
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May 12, 1987

NOTE TO: Ad Hoc Consultants to the NIH AIDS Executive Committee

In addition to the enclosed copies of the final report, I have included a copy of the companion transmittal document that accompanied the report when sent to Congress. NIH was directed to develop this document to reflect the Department of Health and Human Service's position with respect to the recommendations as a prerequisite to obtaining official clearance.

Dennis Rodrigues
Executive Secretary
NIH AIDS Executive Committee

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

FUTURE DIRECTIONS FOR AIDS RESEARCH

A handwritten signature in dark ink, appearing to read "James B. Wyngaarden", is written over a horizontal line.

James B. Wyngaarden, M.D.
Director, NIH

April 1987

FUTURE DIRECTIONS FOR AIDS RESEARCH

INTRODUCTION

Congress' report on the fiscal year 1986 appropriation for the Department of Health and Human Services (House Conference Report No. 99-402) stated:

"The conferees believe that it is essential to marshal the scientific resources available both within and outside the Government to address this serious public health problem. Thus, the conferees urge the Director, NIH, to convene a working group of NIH institutes involved in AIDS research, and expert representatives of the extramural research/scientific community to examine in depth, and on a periodic basis, AIDS research issues and requirements. The conferees would welcome a report from such a group on unmet needs in AIDS research; a suggested plan for the future direction that AIDS research should take; and the efforts that need to be undertaken to stimulate additional interest and participation in this effort by the extramural community and relevant industries."

In response to this request, the Director of the National Institutes of Health (NIH) assembled the extramural Ad Hoc Consultants to the NIH AIDS Executive Committee to prepare the following report. The views expressed in this document are those of the Ad Hoc Consultants to the NIH AIDS Executive Committee and do not represent the position or judgment of the NIH, the Department, or the Administration on those research and policy issues discussed in the report.

The Department of Health and Human Services has reviewed this report and developed the following response.

Response to the Report by the Department of Health and Human Services

The Department agrees with the report's overall conclusion that while advances made in AIDS research thus far are impressive, the resolution of the AIDS crisis is still a distant and elusive goal. The report suggests that expansion of resources to support additional investigation is necessary. Since the time that the report was developed, however, the Administration has increased significantly its commitment to the Federal AIDS research effort, as reflected in the President's FY 1988 budget request to Congress for \$343 million to support this effort at the NIH.

Specific responses to the recommendations contained in the report are listed below.

RECOMMENDATION 1. "The allocation of new monies for AIDS-related research is obviously of the utmost importance and is currently proceeding at an accelerating pace. It is important to fully recognize that the AIDS epidemic represents an entirely unprecedented and unpredictable health challenge. To meet this challenge requires new funds dedicated to AIDS-related research."

- The funding levels established in the FY 1988 President's Budget represent a significant increase in the Federal Government's commitment to combat AIDS. The President's FY 1988 budget will provide NIH with approximately \$91 million over the FY 1987 level bringing the NIH total to approximately \$343 million in FY 1988.

RECOMMENDATION 2. "In parallel with the allocation of new monies is the clear cut need for additional full-time staff (FTEs), both scientific and administrative, at NIH."

- In FY 1987 the Administration added over 150 positions to meet the need for outstanding new requests for AIDS positions, bringing the total to 387. Also, the President's FY 1988 Budget will add three additional positions.

RECOMMENDATION 3. "The ad hoc consultants recognize the need for a strong, centralized intramural committee to coordinate all NIH AIDS activity, with the objectives of determining the goals for AIDS-related research, preventing intrajurisdictional gaps in the research program, and avoiding redundancy."

- The Department questions the need to alter the structure of the principal coordinating body for AIDS research at NIH, the NIH AIDS Executive Committee. This Committee, which combines scientific expertise with institute authority, has been effective in coordinating NIH AIDS research. Intramural scientists do participate in Committee deliberations on an ad hoc basis when topics related to their expertise are scheduled for discussion. There is no need for an additional committee which would simply duplicate existing efforts.

RECOMMENDATION 4. "The ad hoc consultants recommend the creation of an ad hoc extramural group of scientific consultants, appointed by the Director of NIH, to review AIDS-related research activities and to assist in the formulation of research priorities."

- The Department supports the thrust of this recommendation. The National Institutes of Health is currently in the process of establishing a formally chartered AIDS Program Advisory Committee to be chaired by the Director, NIH.

RECOMMENDATION 5. "The ad hoc consultants strongly recommend that NIH create special study sections for AIDS-related research. The consultants further recommend that the study sections should have increased discretion in allocating funds for capital expenditures when such funds are deemed essential for the expeditious achievement of critical scientific objectives."

- The Department has not yet concluded its review of this recommendation. Problems associated with the review, referral, and processing of AIDS research proposals are currently being studied at the National Institutes of Health. We believe it appropriate for study

sections to review and recommend approval/disapproval of requests for capital expenditures within current guidelines; however, the allocation of funds is not an appropriate function for an initial peer review body.

RECOMMENDATION 6. "The consultants support the creative utilization of the contract mechanism to facilitate research in AIDS-related areas. The consultants, therefore, recommend that NIH create initiatives that will encourage additional experienced and talented investigators to redirect their efforts toward the solution of the AIDS problem."

- While the Department agrees that the use of the contract mechanism has been very effective in rapidly filling critical gaps in AIDS research, the point may now have been reached where increased resources (if they were made available) should be channeled into basic science via investigator-initiated projects.

RECOMMENDATION 7. "The consultants strongly support the development of the AIDS Treatment Evaluation Units (ATEUs) and urge the maximum utilization of the ATEUs for the acquisition of data regarding the effects of therapeutic agents on each of the major sub-groups of patients with HIV infections. The consultants also strongly recommend that extramural scientists, from both academia and industry, with expertise in the management of AIDS patients and in new, targeted approaches to the development of antiviral drugs, be included as ad hoc members of the AIDS Drug Selection Committee."

- The Department supports this recommendation calling for continued support in the development of the ATEUs. It is noted that NIH is already pursuing a course that will allow extramural scientists to participate in the work of the NIH AIDS Drug Selection Committee. Representatives from the academic community have been named as ad hoc consultants to the Clinical Drug Development Committee. Representatives from industry participate in the Committee activities by invitation to provide essential proprietary information regarding candidate agents under consideration for clinical evaluation in the ATEUs. In addition, representatives from industry are actively involved in the development of protocols for candidate agents undergoing clinical evaluation in the ATEUs. The AIDS Preclinical Drug Development Committee will use extramural scientists on an ad hoc basis as needed for specific issues.

RECOMMENDATION 8. "The NIH Scientific Vaccine Committee is now providing close coordination of all intramural work on vaccine development. When and if one or more vaccines appear suitable for testing in humans, it will be of critical importance to include academic scientists as well as representatives of industry as ad hoc members of the NIH Scientific Vaccine Committee which will be responsible for determining which candidate vaccines are to be evaluated in field trials."

- While the Department agrees in principle that extramural representation is necessary in the area of vaccine development, the NIH AIDS Scientific Vaccine Committee is not the appropriate mechanism for this collaboration. This Committee is a small working group made up of NIH intramural scientists currently conducting basic research in this area. Its purpose is to provide a forum for communication and to improve coordination of intramural initiatives in vaccine development. Rather than invite ad hoc consultants to participate in a small internal working group, it would seem more appropriate to hold periodic open scientific meetings and conferences to address global issues in the field of vaccine development and invite the participation of the extramural scientific community.

RECOMMENDATION 9. "The consultants recognize the predictable shortfall of chimpanzees and endorse the establishment, by PHS, of a committee which is responsible for the allocation of chimpanzees for AIDS-related research. The consultants strongly recommend augmenting the chimpanzee allocation committee by the addition of experienced extramural scientists, from both the academic sphere and industry, including individuals expert in animal retrovirology as well as vaccine development."

- The Department feels that the recommendations for establishment of a PHS committee on allocation of chimpanzees for AIDS-related research should be carefully evaluated in light of the just organized National Advisory Committee on the Chimpanzee Breeding and Research Plan. One of the major tasks of this Committee will relate to research allocation of chimpanzees to be produced. Extramural scientists will serve as members of that Committee. Another concern is that responsibility in this area falls under the aegis of the Public Health Service AIDS Task Force. Currently, the membership of all committees reporting to the Task Force is comprised solely of PHS staff. Therefore, implementation of this recommendation at the NIH level would be a departure from the precedent, would need to be evaluated in the context of its effect on the PHS-wide coordination efforts, and would necessitate PHS comment and approval.

RECOMMENDATION 10. "An essential complement to the basic NIH-supported virological, immunological, and molecular genetic research is the expanded support of broad-based epidemiological studies of the HIV infection in high- and low-risk populations. Additional broad-based studies of high- and low-risk populations in the United States and other nations are critical to a full understanding of the natural history and pathogenesis of HIV infection."

- The Department supports this recommendation. Emphasis on high- and low-risk groups and on the inclusion of other nations where the pattern of transmission, male/female ratios, and other essential epidemiological data vary calls attention to the extreme importance of such research. The recent isolation of vastly different viruses from AIDS patients in Africa underscores the importance of these efforts. In FY 1987 and FY 1988, investigator-initiated epidemiologic studies will be supported to expand our current epidemiology research portfolio in an effort to elucidate molecular pathogenesis associated with this disease.

Future Directions for AIDS Research

**Report to Congress From the Ad Hoc
Consultants to the National Institutes of
Health AIDS Executive Committee**

November 1986

Preface

Congress' report on the fiscal year 1986 appropriation for the Department of Health and Human Services (House Conference Report No. 99-402) stated:

The conferees believe that it is essential to marshal the scientific resources available both within and outside of Government to address this serious public health problem. Thus, the conferees urge the Director, NIH to convene a working group of NIH institutes involved in AIDS research, and expert representatives of the extramural research/scientific community to examine in depth, and on a periodic basis, AIDS research issues and requirements. The conferees would welcome a report from such a group on unmet needs in AIDS research; a suggested plan for the future direction that AIDS research should take; and the efforts that need to be undertaken to stimulate additional interest and participation in this effort by the extramural community and relevant industries.

In response to this request, the Director of the National Institutes of Health (NIH) assembled the Extramural Ad Hoc Consultants to the NIH AIDS Executive Committee (a list appears on the following page), all of whom are leaders in their respective fields and represent a broad cross section of expertise

in AIDS research. The following report was prepared by these consultants.

In order to facilitate the process of reviewing NIH AIDS research activities and developing this report, the 19 consultants were divided into three working groups of six members each, with one member serving as overall chairman. Each work group examined a major component of the overall NIH AIDS research effort, as follows:

- The Pathogenesis/Natural History Work Group, which met on August 12, 1986;
- The Vaccine and Prevention Work Group, which met on August 14, 1986; and
- The Treatment: Opportunistic Infection/Antiviral/Immune Reconstitution, Modulation Work Group, which met on September 23, 1986.

Each group met initially for a full day, followed by extensive telephone conversations and written exchanges to accommodate the numerous comments, corrections, additions, and deletions. After the initial draft report was developed, all the consultants met on October 14, 1986, to review the completed working draft and develop the final recommendations to be included in the report.

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Introduction

Over the 5 years since the initial descriptions of the Acquired Immunodeficiency Syndrome (AIDS) epidemic, the etiological retrovirus Human Immunodeficiency Virus (HIV)* has been isolated, its genes identified, and many of the gene products have been characterized. However, no curative antiviral therapy or effective vaccination is available. At the present time, between 1 and 2 million individuals in the United States have been exposed to HIV and, thus, are at risk for developing AIDS. By 1991, almost 300,000 individuals in the United States will have been diagnosed with AIDS, resulting in almost 180,000 deaths. This will make AIDS one of the most common causes of death in the United States, possibly second only to cardiovascular diseases. During the year 1991, it is estimated that almost 75,000 individuals will be newly diagnosed with AIDS.

In addition to the human suffering of individuals with AIDS and the difficulties presented to friends and family, the health care needs of individuals who are symptomatic with HIV infection are extraordinary, resulting in billions of dollars of increased health care costs. In this context, the expenditures made by the Public Health Service to understand the natural history of HIV infection and develop strategies to prevent or attenuate

the sequelae have been entirely appropriate. Scientists working at the National Institutes of Health (NIH) have been in the forefront with the discovery of the etiological agent of AIDS, the characterization of the genome, and descriptions of immunopathological effects. They have set up major seroepidemiological studies which will help elucidate the natural history of AIDS among higher and lower risk group members. They are actively engaged in the process of testing antiviral agents both *in vitro* and *in vivo*, and in developing vaccine strategies for the prevention of infection.

The Ad Hoc Consultants to the NIH AIDS Executive Committee do not think that any of the programs currently under way at the NIH are inappropriate. They do, however, identify several areas of concern which should be addressed to help improve the Federal response to the most serious health crisis of this century in the United States.

The consultants are concerned with the "robbing Peter to pay Paul" syndrome. Although Federal outlays for AIDS-related research have been accelerating, the Executive Branch has not allocated the full resources that have been suggested by Congressional health-related subcommittees. Whereas more money does not guarantee earlier resolution of the problem, it is one of the few means available to generate innovative research that may result in rapid advances. In an effort to fund AIDS-related research, the Office of Management and Budget has required specific NIH institutes to reallocate funds, thus shortchanging other types of research. Some of the research that is not considered "AIDS-related" may, in fact, provide important basic information in areas

*HIV is the generic name recently endorsed for the retrovirus responsible for AIDS by a majority of members of the International Committee on Taxonomy of Viruses. The lymphadenopathy associated virus (LAV), human T lymphotropic virus III (HTLV-III), and AIDS-associated retrovirus (ARV) are other names commonly used for this virus in the literature.

of immunology, virology, and molecular biochemistry that will be critical to the resolution of the AIDS epidemic. In this regard, the rapid progress in AIDS research to date has resulted, in large part, from funding of basic research on the retroviral etiology of cancer over the past two decades.

In addition, the consultants are concerned that other areas of vital health-related research are being truncated in an effort to save funds for AIDS research. This may result in lack of progress in resolving other major health issues facing the American public. The consultants think that the funds dedicated to coping with the AIDS epidemic represent a necessary addition to the budget to deal with an entirely new health problem and that it is not appropriate to think that the budgetary allocations can be made in a "business as usual" fashion.

The consultants recognize a clear and present need to utilize the contract mechanism to encourage research in areas critical to the development of effective vaccines against, and treatment for, HIV infection. The contract mechanism is essential for the support of clinical trials and for vaccine development and is also important in directing research to fill gaps in our knowledge of the pathophysiology and immunopathogenesis of AIDS. The contract mechanism is one of the very few funding avenues which does not infringe upon non-AIDS research areas.

The consultants think that, in parallel with creative utilization of the contract mechanism, it is most important to encourage new investigator-initiated projects, since the optimal approaches to immunization against, and treatment of, AIDS are far from certain. The consultants strongly agree that investigators who are funded in related areas and have considerable skills which might contribute to the resolution of this epidemic, e.g., retrovirologists working with other animal species, should be vigorously encouraged to move into AIDS research. The commitments by the NIH for financial support for such talented and established investigators need to be longstanding so that investigators who are

changing research directions in midstream will feel reasonably secure in doing so.

The ad hoc consultants recognize a need for a strong, centralized intramural committee to coordinate all NIH AIDS activity, with the objectives of determining the goals for AIDS-related research, preventing interjurisdictional gaps in the research program, and avoiding unnecessary redundancy. The authority of the NIH AIDS Executive Committee should be strengthened in order to more effectively serve this purpose. The NIH AIDS Executive Committee may be hampered by its current structure, i.e., one executive committee seat for each involved institute. **The consultants think that ongoing review and input from a carefully chosen ad hoc extramural group of scientific consultants would be helpful to the NIH AIDS mission.** The proposed ad hoc scientific consultants to the Director of the NIH would provide a review of ongoing work and proposed initiatives two to three times a year for a defined time period. The consultants would provide both a stronger linkage with the extramural scientific community and some degree of institutional memory as the AIDS research program necessarily increases in breadth and depth.

The consultants also agreed that it would be advantageous to create special study sections to evaluate all extramural AIDS-related research proposals. Several consultants are concerned that, under the current review process, AIDS-related research proposals may receive less than appropriate priority scores for a number of reasons. This proposal is consistent with the current initiative by the NIH to form separate AIDS study sections. It is also congruent with the plan of the National Institute of Allergy and Infectious Diseases (NIAID) to establish a separate AIDS subcommittee of the NIAID National Advisory Council to provide final review and recommend approval of AIDS-related grants.

The consultants strongly recommend that steps be taken to decrease the elapsed time between approval and funding of AIDS-related research. A delay of several months between approval and funding is not reason-

able in dealing with research related to a rapidly accelerating epidemic.

The consultants are concerned about the potential shortfall of a readily depleted resource, chimpanzees. At the present time, over 40 chimpanzees have been inoculated with HIV. Although chimpanzees do not develop the human pattern of persistent, progressive immunodeficiency within a relatively short time interval, they are the one known animal species in which the virus has been shown to replicate over a period of months or years. The consultants think that, at the current time, the use of chimpanzees should be largely limited to challenge studies to evaluate the neutralizing and possible protective effects of candidate vaccines. The consultants strongly agree that **experienced extramural scientists should be added to the Public Health Service committee responsible for the allocation of chimpanzees for biomedical research.** Other primate models, e.g., STLV-III infection in the Rhesus macaque, should prove helpful in delineating the early events in viral pathogenesis and **should be utilized whenever possible** for these purposes.

There is a need to focus more on the clinical biology of HIV infection in addition to the well-characterized molecular immunology and excellent broad-based epidemiological studies that are now under way. For example, which cells become infected first and at what sites in the body, e.g., on mucosal surfaces versus intravascularly, when an individual is exposed

to HIV? What are the stereotypic sequences of early infection with HIV, and to what extent can pharmacological interventions succeed in modifying disease outcomes at these specific times? The committee is concerned that although superb research has been carried out in circumscribed areas, the understanding of how the retrovirus causes disease in humans is not sufficiently complete to support the development of optimal intervention strategies.

The consultants are concerned that industry and the NIH are not working as closely together as possible. **The consultants recommend that the NIH scientists, members of the academic research centers, and representatives of the private bioscientific community work together more closely** in order to more rapidly elucidate appropriate strategies in dealing with the AIDS epidemic.

None of these concerns suggest that the present efforts are in any way inappropriate. The successes in recent months have been extraordinary and are indicative of the high caliber of intellectual, humane, and technical achievement at the NIH. Since the AIDS epidemic is accelerating at a time when the numbers of individuals with clinical disease are already causing a major burden on the health care system, we think that the additional measures suggested in this report should be implemented as rapidly as possible, in order to maximize their effectiveness in coping with this serious emergency.

Pathogenesis/Natural History

CURRENT RESEARCH

The ramifications of the AIDS epidemic continue to grow as our understanding of the natural history of HIV infection increases. Although neither curative antiviral therapy nor an effective vaccine are available, enormous progress has been made in identifying the etiological virus and understanding its natural history. A great deal of the leadership and intellectual impetus for the progress has been due to scientific accomplishments at the National Institutes of Health (NIH).

Scientists at the National Cancer Institute (NCI) have delineated the pathogenic role of HIV in AIDS and have enhanced the basic molecular understanding of how the virus functions. Investigators at the National Institute of Allergy and Infectious Diseases (NIAID) have helped to describe the immunopathogenesis of HIV infection and, in collaboration with scientists from the NCI, have clinically evaluated new compounds which show promise in altering the devastating sequelae of prolonged HIV infection. A transfusion study at the National Heart, Lung, and Blood Institute (NHLBI) is providing data on the natural history of HIV in individuals who have been parenterally (by injection) exposed. Intramural and extramural scientists at other NIH institutes have enhanced the basic understanding of the epidemiology of HIV infection and mechanisms of viral pathogenesis. A sophisticated collaborative effort by the NCI and the NIAID has resulted in a multicenter study that is presently evaluating the natural history of HIV infection in a 5,000 member cohort (a defined group) of high-risk homosexual males (the Multicenter AIDS Cohort Study (MACS)).

Other high-risk cohort studies under way include U.S. hemophiliacs, Danish homosexuals,

and intravenous drug users in the New York/New Jersey and Miami areas. Cohorts of homosexual males are being followed in New York City and Ithaca, New York, to contrast the natural history of infection in high- and low-prevalence areas. Studies undertaken by the NCI in Trinidad among homosexual males may elucidate genetic cofactors related to the development of AIDS after HIV infection, as well as the interactions between HTLV-I and HIV in co-infected individuals.

Studies of transfused individuals funded by the NHLBI have added new insights regarding the natural history of HIV infection. Whereas 91 percent of individuals transfused with blood containing the virus developed HIV-related antibodies, less than 10 percent of them have developed AIDS, thus far. However, 12 of 14 children with hematological malignancies developed AIDS within months after receiving HIV-contaminated blood. Investigations are also under way to assess the safety of different blood products. The low rates of development of AIDS among the majority of HIV-exposed hemophiliacs may suggest that they have not been infected long enough to develop clinical disease, or that their antibodies represent a response to transfusion of inactivated HIV components. Whether specific blood products purified from already infected individuals can play a therapeutic role, i.e., by transfusion of neutralizing antibodies, remains to be seen.

Molecular genetic studies of HIV have led to important insights regarding viral pathogenesis. This HIV retrovirus has four unique genes with novel regulatory roles. These functions vary from initiating replication to maximizing rates of replication. Isolates have been identified that can replicate but are

noncytopathic (do not kill cells), suggesting other causes for cell destruction. These basic studies enhance our understanding of viral pathogenesis and natural history of clinical disease and should assist in the assessment of the efficacy of different antiviral interventions.

In vitro studies at the NIAID have shown that a variety of antigenic stimuli, ranging from other viruses to protein antigens, may change latent HIV infection to productive infection. This results in rapid viral replication and new cell lysis (destruction). These observations suggest, but do not prove, that the natural history of HIV infection may be altered by minimizing new antigenic exposures. Multiple cell lines besides T helper lymphocytes (white blood cells that help prevent new infections and tumors) may become infected with HIV; these include Epstein-Barr Virus-infected B lymphocytes, monocyte/macrophages, certain macrophage-derived cells of the central nervous system, and colorectal cancer cells. This list is by no means complete, as discoveries of target cells continue to be made. The presence of the CD4 molecule on the cell surface is a characteristic of all cells thus far known to be susceptible to infection by HIV; the total repertoire of cells that express the CD4 molecule is, however, uncertain.

BASIC QUESTIONS

The consultants believe that the projects initiated by the specific NIH institutes to date have been appropriate and have enhanced basic understanding of pathogenesis and natural history of HIV infection. However, many basic questions still remain unanswered. Some may be further elucidated as some of the larger cohort studies continue, but other questions will need further intensive investigation supported by the allocation of appropriate resources. Highly sophisticated studies involving the molecular genetics of HIV and its effects on specific immune cells have been undertaken; more general studies of biological mechanisms of pathogenesis have, however, not been as fully developed. Although excellent epidemiological investigations are currently under way, further longitudinal studies

will be necessary to assess the spread of infection into the general population. Integration of the epidemiology of HIV infection in high- and low-risk groups with studies of the molecular pathogenesis of viral infection of target cells is necessary in order to answer more fundamental questions, such as:

- Is the natural history of HIV infection altered by presentation of the virus via different routes of administration?
- Where are the sites of primary multiplication of the virus, and how is it subsequently disseminated?
- Is the virus transmitted equally efficiently via the same body secretions at all times in all hosts?
- Do different strains of the virus that have been reported to have different tissue tropism (affinity for a specific part of the body) have different patterns of dissemination?
- Are there alterations in host response prior to exposure to the retrovirus that affect the way in which the viral infection develops?
- Do repeated exposures to HIV accelerate the development of AIDS?
- Do antecedent or concurrent infections with herpes viruses facilitate the transmission or enhance the virulence of HIV?
- What are the salient components of tissue injury?
- Are the same viral gene products deleterious to all host tissues or does the viral/host cell interaction vary among different cell types?
- Do autoimmune phenomena play any role in disease pathogenesis? Do viral antigen/antibody complexes play an important pathogenetic role?
- What are the roles of humoral and cell-mediated immunity in the expression of viral infection and host protection?

ANIMAL MODELS

The consultants strongly agree that enhanced utilization of animal models would be essential to answer certain critical basic questions regarding the biology and pathogenesis of HIV infection. In addition to the questions mentioned above, the animal models could more clearly define the virulence of specific HIV strains, as well as the importance of specific biological and inanimate cofactors. They would also provide an enhanced capability to predict responses to therapeutic interventions and a system for the testing of candidate vaccines.

At the present time, many chimpanzees have been infected with HIV. The information that will be obtained from these ongoing experiments may be useful in understanding the effects of chronic HIV infection. However, none of the chimpanzees thus far have developed persistent immunological abnormalities, lymphadenopathy, opportunistic infections, or characteristic neoplasms. Therefore, it is important that other animal models be developed and utilized rapidly in order to answer some of the important questions that remain. The simian AIDS in macaque (Rhesus monkey) species caused by STLV-III may provide useful information regarding questions of pathogenesis. Inoculation of these monkeys with STLV-III (intravenously, per rectum, per vagina, and by mouth) may answer important questions regarding the transmission of retroviral infections.

In addition, other retrovirus infections should be investigated aggressively in other species. The study of new retroviruses in primates may not replicate the natural situation for these animals but may give new insights into pathogenesis for human AIDS. Likewise, experimentation utilizing human retroviruses in primate species will be important in order to develop other models of retroviral infection resulting in immunodeficiency in related species.

The rate of development of more sophisticated relevant models of retroviral infections will be enhanced by encouraging researchers with experience in these areas to redirect their

efforts into studies of the pathogenesis of HIV infections. It is, therefore, important for the NIH to have the flexibility to issue awards that will provide relatively long-term support to talented individuals, currently funded in other areas of research, who are being recruited to work on problems directly related to AIDS. The research experience with other animal retroviruses extends back several decades; therefore, recruitment of experienced retrovirologists to study the analogies between their animal models and the unique problems presented by HIV is especially important.

BARRIERS TO RESEARCH

The consultants recognize that a major barrier to more extensive studies in animal (especially primate) models of HIV infections is the limited number of institutions which are currently equipped for such investigations. The consultants, therefore, urge that the NIH be given sufficient flexibility with designated funds to provide capital expenditures for the upgrading of essential animal facilities for the prevention of biohazards and for the acquisition of major equipment which may be critical to the necessary studies in animal models of retroviral infections.

A second major bottleneck in AIDS research, one which is rapidly increasing in magnitude, results from the lack of a suitable mechanism for the free distribution of various strains of HIV and related retroviruses, HIV-related DNA clones, enzymes, and structural proteins to appropriate laboratories. The consultants strongly suggest that the NIH assume the major responsibility for the distribution of the relevant retroviruses and their gene products to scientists in this field. Because the supply of certain such biological products will necessarily be limited, the consultants think that decisions relating to the distribution of such products should be determined by an NIH committee which includes knowledgeable representatives of the extramural scientific community.

FURTHER STUDIES NEEDED

Further studies of the natural history of HIV infection in humans are much needed. Early events after initial infection with HIV are not well understood. Further immunological studies of the viral/host interaction have been undertaken; however, early immune functional changes have not been fully elucidated. Studies in subjects at the time of viral exposure in regard to the localization of the virus in specific tissues will be extremely important for therapeutics and vaccine development, as well as for understanding public health implications of HIV infection. Knowledge of the sequence of infection of lymphocytes, monocytes, and other cell types will be extremely important. The sequence of events following exposure at mucosal surfaces (vagina, rectum, mouth) needs explanation. Which cells become infected and how the virus spreads remain unknown. Studies in the macaque in which macrophages infected with STLV-III are sequentially observed, utilizing gene probes or other tracking techniques, will be important. Careful studies utilizing viral probes of individuals newly exposed to the virus could help answer some of these questions. Sequential studies of the extent of viral infection in specific cell types before and after new antigenic exposures will be helpful in determining the rapidity of the cycle of latent infection, reactivation, cell lysis, and propagation of infection.

Large-scale studies of high-risk populations are presently under way. However, the consultants think that large-scale studies of lower risk individuals, such as female sexual partners of intravenous drug users, in areas where the prevalence of AIDS has been increasing would be important in order to assess the rapidity of the incursion of the virus into the general population. Long-term prospective studies of teenage populations, in cities where the prevalence of HIV is already appreciable, e.g., New York, will require careful evaluation to assess the movement of HIV into the general population. Repeated cross-sectional studies of the prevalence of seropositivity in sentinel population groups will be essential to assess the extent and rapidity of the spread of HIV infection.

In order to better elucidate the early events that occur at the time of exposure to the retrovirus, more frequent sampling of participants than the 6-month intervals that are standard in the Multicenter AIDS Cohort Studies (MACS) would be desirable. Studies focused on the differences, if any, in pathogenetic features between females and males are also desirable. In addition to in-depth studies of higher risk heterosexual populations, cross-sectional population studies would also be desirable in order to get a better sense of the true prevalence of HIV infection among different subgroups in the United States. These denominator data are extremely important given the wide range in estimates of the numbers in the two highest risk groups for the development of HIV infection and AIDS—homosexual/bisexual males and intravenous drug users.

Studies should examine the relationship of other sexually transmitted diseases and infections to susceptibility of HIV infection and specific disease outcomes. Data from African studies suggest that mucosal lesions from other sexually transmitted diseases may potentiate heterosexual spread of the AIDS virus. The greater prevalence of HIV infection among the heterosexual population in Africa and different epidemiological features, as well as the presence of STLV-III and HTLV-IV retroviruses, make Africa an extremely important site for further virological and epidemiological studies. Other geographical areas, e.g., the Caribbean, where HIV infection has distinctive clinical and epidemiological features, warrant further studies.

Studies regarding pathogenesis should try to utilize newer technologies when available. Large-scale cohort studies, such as the MACS study, and the NIH-funded AIDS Treatment Evaluation Centers should evaluate newer means of detecting the virus, including the detection of antigen and recombinant antibody profiles. Techniques are urgently needed to be able to grow the virus more rapidly and to detect smaller quantities of the virus or its antigens. Utilization of DNA or RNA probes and antigen detection assays may help clarify where the virus resides in infected individuals

at specific times in the course of infection. These newer technologies may also help to better characterize the extent of viral infection at a given time and may prove to be less expensive than viral culture technology. Therefore, the NIH should fund pilot studies to investigate the utility and accuracy of specific new assay techniques.

Newer technologies should be applied to studies of animal models of HIV infection as well. The ability to generate recombinant and mutant retroviral strains, to isolate specific gene products, and to study them separately and in combination will enhance the ability to understand the pathogenesis of HIV infection. Utilization of related retroviral strains, such as HTLV-IV, may facilitate contrasts and comparisons that will allow for a more sophisticated understanding of the role of the specific retroviral genes.

More work in the understanding of the pathogenesis of the neurological sequelae of HIV infection is needed. The pathways of infection of specific infected cell types, e.g., mononuclear versus endothelial cells, and soluble mediators need clarification. The routes of entry of the virus into the central nervous system (CNS) in individuals who develop neurological disease remain unknown. The time at which the virus gets into the CNS in relation to initial HIV infection, needs further clarification. There is insufficient understanding of which cell types are most important to the development of the dementia or other neurological manifestations of AIDS. Routes of viral entry into the CNS need clarification. The mechanisms of nerve tissue damage are unclear, as is the relationship of the histopathology to clinical syndromes. Serial studies of animals infected with the retrovirus may allow a better understanding of the natural history of HIV neurological disease.

Further studies in the natural history and pathogenesis of AIDS in pregnant women and their offspring are also needed. The extent of organ involvement in the embryopathy needs clarification. Much of the current knowledge is based on following infants after they have been diagnosed with pediatric AIDS.

However, studies that would prospectively follow infants who were born to seropositive mothers should shed further light on the natural history of infection. Current data are derived from a small number of women of lower socioeconomic status, whose prior nutrition and other relevant variables may differ from the general population; therefore, the study of other cohorts of women at risk and their offspring are needed. Animal and human studies focusing on the differences in the immune dysregulation seen in neonates and infants as compared to adults would also assist in understanding the immunopathogenesis of AIDS. Studies to delineate whether pregnancy is an independently exacerbating factor in HIV-infected women will be of importance as well.

Although major work has been under way toward understanding the cellular immunopathogenesis of HIV infection, questions remain. The mechanism(s) by which the virus destroys cells is not known. Additional cell lines that may be infected by the virus should be sought. Structure and function relations of the viral genome need further clarification to answer questions regarding whether different HIV strains with antigenic variants produce different clinical patterns.

The rapid development of enhanced scientific understanding that has come with the major research efforts associated with the AIDS epidemic also underscores the fact that much fundamental knowledge of basic immunological mechanisms remains to be developed. For example, the role of specific lymphokines in the immune response is not totally understood. Experimental studies on the role of lymphokines in the pathogenesis or prevention of HIV-related sequelae are lacking. Further studies of fundamental monocyte/macrophage biology are essential to answer whether these cells could become a lifelong reservoir of HIV infection. Further studies of viral-cell interactions are urgently needed to define other cell lines that may naturally be infected by HIV.

The incidence of several forms of cancer are increased in AIDS, and the factors contributing to these forms of cancer involve

immunodeficiency and, possibly, special exposure to carcinogenic factors. The high incidence of Kaposi's sarcoma in homosexually active men with HIV infection contrasts with that observed in hemophiliacs and others who have contracted the HIV infection through blood products. Epidemiological, immunological, and virological studies to exploit this difference should facilitate the search for factors contributing to the occurrence of Kaposi's sarcoma. The incidence of B cell lymphomas are also increased in AIDS. It is not clear whether this relates to direct effects of HIV infection or to the secondary T helper/inducer cell deficiency (or both). Investigations of the immunopathogenesis of B cell lymphomas in AIDS should help to shed light on B lymphomas occurring in other situations. Further studies of the etiology and pathogenesis of neoplasia in AIDS are urgently needed. Increased incidences of the more common neoplastic diseases have not yet been seen in association with the persistent cellular immune deficiency of long-standing HIV infection. This is important conceptually in relation to "immune surveillance." Further observations of patients with HIV infection should provide opportunities for studies of resistance factors to neoplasia in individuals with severely depressed T cell immunity. As a means of further understanding the pathogenesis of AIDS-associated opportunistic infections and opportunistic tumors, investigations of neoplasms which may occur in subjects with HIV infection are warranted.

It is, therefore, the sense of the consultants that more funding for basic immunological investigation will be extremely important to proceed in parallel with intensive research regarding HIV. Information that has not yet been discovered in related areas may have a major impact on how the AIDS epidemic is finally resolved. This underscores the necessity to augment Federal funding for NIH AIDS-related programs rather than to deploy funds from existing programs. It would be penny-wise and pound-foolish to reduce basic investigation in areas, important in themselves, that could eventually provide leads which are critical to the solution of the AIDS problem. There can be no guarantees that current lines of investigation will provide all

the information necessary to resolve the epidemic.

Current knowledge of the natural history and pathogenesis of AIDS, albeit far from perfect, emphasizes the potential impact of preventive measures. A study is currently under way to assess the efficacy of condom usage and preventive education among high-risk homosexual males. The consultants feel that additional studies are needed in lower risk (heterosexual) populations where modes of transmission clearly differ. The promotion of preventive behaviors and the clarification of the role, if any, of putative cofactors are worthwhile goals.

SUMMARY

In summary, the working group feels that, at the present time, specific areas that merit enhanced resources include:

- Understanding of basic immunological mechanisms;
- Development of appropriate animal and retroviral models of HIV infection;
- Careful studies of the early pathogenetic events associated with HIV infection;
- Clarification of the sequence of events by which infection is established;
- Definitive studies of the neurological aspects of HIV infection;
- More studies of perinatal pathogenesis of HIV infection;
- Continuation and extension of studies of the natural history of HIV infection and the immunopathogenesis of AIDS; and
- Generation of better epidemiological data for estimating the prevalence of HIV infection in high- and low-risk groups in various areas of the United States and other geographic locations where there are distinctive patterns of HIV infection.

Vaccine Development/Prevention

OVERVIEW

Major areas of research at the National Institutes of Health (NIH) relating to prevention of further spread of the AIDS epidemic have included the discovery of HIV as the etiological agent of AIDS, the demonstration of the mode of transmission of the virus in high-risk communities, the development of ways of growing virus and measuring immune responses, and initial studies directed toward developing an effective retroviral vaccine. Laboratories at the NIH were among the first to demonstrate that antibody to the envelope glycoprotein (gp120) inhibits replication of HIV *in vitro*. It is not certain, however, whether or not the antibody-mediated inhibition will constitute a protective immune response in man. More specifically, it is not known whether or not preexisting neutralizing antibody, such as that which might occur in response to prophylactic immunization, would protect humans against infection by the virus. Also, since it is not known where the virus initially attaches to susceptible cells, e.g., on mucosal surfaces, in lymphatics, or in the central nervous system, the types of antibodies (IgA, IgG) that might provide protection are uncertain. Thus, further intensive studies are under way to determine the clinical significance of neutralizing antibody against the envelope glycoprotein. This provides an example of how a lack of understanding of the basic biology of HIV virus infection impairs the development of effective strategies to prevent the acquisition of HIV infection. In this regard, the consultants emphasize the need to continue intensive studies of the natural history and pathogenesis of HIV infection in order to aid in the development, as well as to enhance subse-

quent determinations of the efficacy, of specific vaccines and vaccine strategies.

Ongoing studies of the natural history of the disease are designed to determine whether a protective immune response to HIV exposure exists in man. The simian AIDS (STLV-III) model is being investigated as a possible paradigm for vaccine efficacy. Further studies are under way analyzing the molecular biology of HIV to determine which proteins are most important in the host immune response to infection. Reagents and analytic procedures are being developed to measure the host immune response as well as to characterize the specific proteins of the virus. Antigenic preparations currently being developed as vaccine candidates include all known types of vaccines, and NIH scientists are also studying methods of potentiating or maximizing protective immune responses, including the use of immunoadjuvants.

NIAID APPROACHES

The Laboratory of Viral Diseases at the National Institute of Allergy and Infectious Diseases (NIAID) has focused its attention on two approaches to the development of an AIDS vaccine. The first approach is using vaccinia recombinants as viral vectors for expression of glycoprotein antigens of HIV. The genes for expression of the gp120 antigen have been cloned into vaccinia, and antibody to the vaccinia recombinant has been detected in immunized squirrel monkeys. Recombinant vaccinia viruses have also been used to express gp120 and other viral antigens in tissue culture. The expressed antigens may be suitable as inactivated vaccines.

Concern was expressed by several of the consultants in regard to the problems that would be faced by the use of a recombinant vaccinia vaccine. Present vaccinia strains cannot be used in immunocompromised hosts, and their administration to infants and children raises considerable anxiety regarding complications seen in earlier years when routine smallpox vaccination was the policy. A great deal of research will be needed on alternative vectors if this approach is to be used. Nevertheless, the consultants recognize the importance of doing basic research with a live virus vector in order to gain a better understanding of the formation of antibodies to gp120 in this way, and the vaccinia model can serve that purpose. Studies of the efficacy of such a vaccine in animal species will be important; however, the consultants felt that it might be appropriate to consider alternative virus vectors, such as adenovirus or herpes virus, as a means of generating an appropriate immune response.

The Laboratory of Molecular Microbiology at the NIAID has focused its attention on studies of the regulation of viral replication, gene expression, and genomic heterogeneity of HIV. This laboratory is also constructing viral mutants with potential as vaccines. The consultants feel that this work is extremely important in terms of understanding pathogenetic mechanisms of this retrovirus; however, concern was expressed as to the suitability of utilizing live mutant virus vaccines derived from a virus that can be potentially oncogenic and whose immunosuppressive properties have not been fully characterized. Nevertheless, such candidates might eventually prove to be useful as sources of virus for inactivated whole virus vaccines or as suitable live attenuated virus vaccines.

The Laboratory of Infectious Diseases is concentrating on the standardization of viral inocula for experimental studies in animals, particularly the chimpanzee. The consultants felt that this work is extremely important but cautioned against overreliance on the chimpanzee as the definitive model for HIV infection. Other simian species may respond to challenge with other retroviruses and provide useful information regarding the efficacy of specific candidate vaccines.

The Laboratory of Immunoregulation has analyzed the immune response to HIV infection, with the expectation that protective immune responses can be identified. The work of this laboratory in defining the analytical methodology to detect and analyze humoral and cellular immune responses is extremely important.

An Intramural Vaccine Development Unit has been established by the NIAID to support the general vaccine development effort of the institute. It is initiating collaborative studies with the private sector and should be encouraged to pursue this approach. Major efforts currently under way include the development and characterization of monoclonal antibodies against HIV and the development of methodologies for the purification and biochemical characterization of viral proteins, some of which are potential components of a subunit vaccine for AIDS. Again, the consultants expressed caution about the use of subunit vaccines against HIV until the structure-function relationships of the viral proteins and the pathogenesis of the disease are more thoroughly understood.

The NIAID extramural program is primarily developing new information through the contracts mechanism. Initiatives are under way on development and evaluation of vaccines in animal models and in man. This unit has designed a step-wise sequential approach to developing and evaluating candidate vaccines through Phase IV evaluations in humans. This step-wise system should prove useful for assessing the progress of vaccine candidates. At the present time, it is being used appropriately for program planning and budget recommendations. The consultants fully approve of this type of thoughtful planning for vaccine development.

NCI CONTRIBUTIONS

Investigators at the National Cancer Institute (NCI) have been instrumental in the identification of HIV as the etiological agent of AIDS. They are in the process of conducting independent and collaborative efforts to characterize immune responses after exposure

to HIV. They believe that the most promising approach to vaccine development will be through utilization of the gp120 envelope glycoprotein. Methodological problems appear to include, however, the fact that the gp120 glycoprotein is fragile and relatively unstable after purification; the purification process itself may also be difficult. Technical improvements in growing HIV now enable NCI investigators to grow up to 250 liters of virus culture fluid each week, thus facilitating purification studies and molecular and immunological characterizations.

Intramural studies at the NCI include assessing the efficacy of gp120 and gp160 glycoprotein vaccines containing specific adjuvants as well as trying to determine the structural configuration of specific epitopes of the glycoproteins which elicit protective immunological responses in animal hosts. They are actively evaluating ISCOM technology, in which micelle-like particles are generated which permit presentation of large concentrations of the gp120 glycoprotein in a special configuration designed to maximize the immune response. Studies on immunoadjuvants, such as Freund's adjuvant, indicate that the antibody response to gp120 can be significantly increased through their selective utilization.

As noted earlier, despite the fact that high titers of antibody against the gp120 glycoprotein may neutralize the virus *in vitro*, it is by no means certain that these antibodies will prove to be effective either by inhibiting viral attachment and/or replication or by any of the other pathways by which antibody can inhibit the infectious process. Immunity to HIV infection may be more related to cell-mediated immune function, such as T or NK cell cytotoxicity, or to those functions that involve antibody, such as antibody-mediated cytotoxicity. Therefore, the consultants urge the continuation of basic investigations to determine how HIV attachment and replication may be inhibited.

A further problem of utilizing gp120 as a vaccine antigen is the fact that the virus envelope gene may vary up to 20 percent in its amino acid sequence. Therefore, even if

one specific strain generates cross-reacting antibodies, a monovalent vaccine may not be effective. Thus, future research will have to assess the ability of different viral strains to induce the production of antibodies against a number of other strains; it may also be necessary to assess the efficacy of polyvalent vaccines. In addition, since the molecular evolution of HIV is not fully clarified at the present time, further studies of antigenic variation of the surface glycoproteins will be necessary in order to assess the type of vaccine required for populations that are geographically dispersed, as well as for utilizing the vaccine over long periods of time.

ADDITIONAL AREAS FOR RESEARCH

Currently, only a small number of extramural NIH-supported projects dealing with AIDS are directed toward vaccine development. The consultants feel that this number is insufficient, and further efforts must be undertaken in order to generate a greater response from the research community toward AIDS vaccine-related projects. Approaches toward vaccine development that have not been adequately explored include studies of antibody response to whole virus vaccines, specific viral peptides (as opposed to envelope glycoproteins), and anti-idiotypic vaccines. It is not known which epitopes of the virus may prove to be relevant to the development of protective immune responses. Clearly, further basic molecular investigations are needed to determine the structural components of HIV that will be most effective in the generation of desired specificity for protective antibodies.

In addition to basic research regarding immunology, approaches that may utilize aspects of the immune response, other than the simple production of neutralizing antibodies, may be important in preventing infection. Attention particularly should be directed specifically to ways in which infection of monocyte-macrophages and that of other specific cells by HIV may be prevented. The degree to which vaccines are able to prevent CNS infection may prove to be particularly important.

Investigations of different technical means of preparation of relevant antigens and adjuvants must be vigorously pursued, including use of recombinant DNA technology. Exhaustive work regarding different antigens, doses, and routes of administration in different animal systems will be necessary to identify an immunogen that may promote the optimal response against HIV.

The molecular relationships of STLV-III, HTLV-IV, and HIV need further clarification. Present data indicate that these viruses are related but have many dissimilarities. If humans can be infected with STLV-III (or HTLV-IV), and this is followed by the production of antibodies reacting with HIV virus but without the development of clinical disease or occult immunodeficiency, then comparative studies of the different genomes and immunological responses will be useful. This area of research could lead to identification of suitable live attenuated vaccines. On a cautionary note, it is still not certain that individuals cannot be infected with both STLV-III and HIV viruses; thus, attempts to develop infection with the different types of retroviruses in animal hosts would be useful to elucidate this question. The data from cell cultures indicate that if one virus is infecting a cell line, the other closely related retrovirus cannot cause a productive infection; however, one must be cautious in extrapolating *in vitro* data in the *in vivo* situation.

The use of a wide range of animal models for the study of newly identified retroviruses will clearly enhance knowledge of HIV infection in humans. These studies should be undertaken, however, in full recognition of the fact that the vagaries of response to retroviral infection may be such that a thoroughly safe and effective retroviral vaccine for humans may not be possible.

RESEARCH AT OTHER INSTITUTES

The National Heart, Lung, and Blood Institute (NHLBI) is supporting research investigating transfusion-related AIDS. Several of those efforts are directed toward the development

of appropriate second and third generation tests, including antigen screening and the utilization of more specific, monoclonal antibody-based viral detection systems. The institute is also funding projects that are evaluating various means of inactivation of HIV indifferent blood products. The use of some of these techniques may be helpful in development of vaccines that are immunogenic but not infectious. NHLBI scientists are also interested in assessing whether hyperimmune sera can be developed for use as postexposure prophylaxis, with resultant prevention of spread of virus so that clinical disease is prevented or delayed in individuals who have been recently infected with HIV. Other studies are directed toward hemophiliacs and their spouses to try to assess whether the low rates of development of clinical disease in this cohort of individuals (who have had a high degree of exposure to HIV) reflects a protective effect of HIV antibody in the factor VIII preparation, a protective immune response to viral antigens in the preparation (but not live virus), or simply more recent exposure to the virus. The consultants feel that increasing funds for immunization-related research would be appropriate.

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has been working with several animal models of HIV infection in order to elucidate the nature of CNS infection with this retrovirus. They are attempting to understand how the virus gets into the CNS and which cells will need to be protected by future vaccinations in order to prevent neurological disease in exposed individuals. In addition, the NINCDS is actively working with simian AIDS and inactivated vaccines for these agents in order to determine their possible relation to the pathogenesis and prevention of HIV infection and AIDS in humans.

PITFALLS OF SPECIES-SPECIFIC RETROVIRUSES

Concern was expressed regarding the reliance on chimpanzees in view of the scarcity of these resources. As indicated, animal models are important for the development of AIDS-

related vaccines; it was noted, however, that many retroviruses behave in different fashions in different species and may be quite species-specific in their pathogenicity. Therefore, the consultants caution against reliance on one specific vaccine model. This is especially important in view of the need to analyze multiple types of responses to related retroviruses in different species, as well as to study HIV in the most appropriate models, all of which is necessary in order to determine future vaccine strategies in humans.

A recurrent theme in the course of the deliberations was the fact that basic immunological mechanisms in response to retroviral infections in animals, as well as humans, are not fully understood. A great deal more basic research on the immune system and how it responds to viral infection is needed before one can be reasonably certain that a vaccine against HIV will be effective and will not result in some undesired reaction. It is possible that the generation of IgA antibodies on mucosal surfaces will not correlate with the generation of serum IgM and IgG antibodies in different hosts; this may have a great deal of bearing on the pathogenesis of disease. Isolations of HIV from the saliva of individuals infected with the virus have been rare, particularly when IgA antibodies have been detected. It may be that future immunization programs should focus on the development of adequate mucosal antibodies so that target cells in superficial locations cannot be infected with the virus. On the other hand, the experiences with blood recipients and intravenous drug users demonstrate that parenteral transmission does occur, thus the generation of serum antibodies may be important as well. These considerations again underscored the need for more basic investigations of the immunological responses to various retroviral infections in multiple species, as well as the specific immunological responses to infection with HIV in humans.

EDUCATION AND INTERVENTION

Outreach education activities have been conducted under NIAID auspices since the beginning of the AIDS epidemic. Educational

programs for physicians, other health care professionals, and the public by individuals knowledgeable about AIDS have proved valuable for conveying accurate and reliable information on all aspects of AIDS. With the spread of AIDS in the heterosexual population, there is need for interventions to reach the newer populations increasingly at risk for acquiring AIDS. This is particularly urgent in urban centers where AIDS is already present. Programs for heterosexual men and women to help them protect themselves from acquiring (or spreading) HIV infection are urgently needed. This is important also for protection of the infants and children to be born in the next 5 years. It appears likely that a vaccine or a fully effective antiviral treatment will be some years away. Conducting preventive programs in the context of already ongoing immunological, virological, and epidemiological studies will provide essential resources for the education programs as well as for accurate determination of the effectiveness of various modes of intervention. Exploration by NIH scientists of innovative modes of disease prevention programs may be necessary.

SUMMARY

The gravity of the current situation, i.e., the rapid increase in the numbers of individuals with AIDS and those at risk for future infection, necessitates the commitment of large amounts of new funds in order to facilitate the rapid expansion of knowledge regarding the pathogenesis of HIV infection, the immune response to the HIV virus, and strategies for prevention of HIV infection via vaccination. In addition, the consultants feel that novel approaches to collaboration with the private sector in vaccine development are appropriate in view of the gravity of the problem. The consultants also recognize the need for discussions on liability assessment with regard to vaccine use, a difficult topic that will take considerable time to resolve.

In summary, the consultants feel that specific areas that merit research emphasis at the present time are:

- Developing animal models suitable for elucidating the pathogenesis of HIV and evaluating candidate vaccines;
- Characterizing fully the function of each viral protein in the infectious process;
- Developing recombinant DNA methods for production of each viral protein and selected peptides;
- Improving available methods and evaluating the role of humoral and cell-mediated immune functions in man and selected animal models;
- Studies of immune responses and immunity during investigations on the pathogenesis of human HIV infection;
- Evaluating various vaccine candidates and approaches in suitable animal models, including surface glycoprotein vaccines, whole virus vaccines, peptide vaccines, recombinant viral vector vaccines, anti-idiotypic vaccines, and suitable live attenuated vaccines;
- Evaluating the effectiveness of hyper-immune antisera for prevention of infection with HIV or other retroviruses in animal models;
- Evaluating suitable antivirals as chemoprophylactic agents; and
- Evaluating the effectiveness of outreach programs in preventing exposure to HIV.

Treatment/Antivirals

RECENT DEVELOPMENTS

Although the mortality figures for individuals diagnosed with AIDS continue to be appallingly high, recent therapeutic developments now offer more promise for those infected with HIV. These major developments result from the enhanced understanding of the genetic makeup and replication mechanisms of HIV that has occurred over the past 2 years, due in great part to scientists supported by the National Institutes of Health (NIH).

However, many questions remain regarding the clinical indications and ultimate efficacy of newer antiviral compounds, such as Azidothymidine (AZT). Much fundamental knowledge regarding viral immunopathogenesis needs to be acquired; new, potentially safer and more effective antiviral compounds need to be investigated; and other approaches to the reconstitution of the immune systems of infected individuals and the effective management of debilitating, often life-threatening, opportunistic infections are needed.

In order to meet these challenges, the Public Health Service (PHS) has established the PHS AIDS Executive Task Force, which includes a Committee on Vaccines and Therapeutics, chaired by Dr. George Galasso. This group, in turn, interfaces closely with the NIH AIDS Executive Committee, chaired by Dr. Anthony Fauci. The NIH AIDS Executive Committee is to be commended for the close cooperation that it has fostered among institutes, particularly the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID), as well as with extramural investigators.

Federal outlays for therapeutically oriented AIDS programs at the NIH have increased

markedly over the past 2 fiscal years, commensurate with the development of clinical protocols based on the emerging understanding of the biology of HIV infection. Total outlays in FY85 were \$5 million, and this figure increased to \$47 million by FY86. It is expected that this figure will continue to increase as more potentially effective therapeutic approaches are developed.

In response to a solicitation from the NIH, many university medical centers applied in early 1986 for contracts as AIDS Treatment Evaluation Units (ATEUs). The 14 centers which received contracts are: Memorial Sloan-Kettering Cancer Center, Johns Hopkins University, University of Washington, University of Rochester Medical Center, University of Miami School of Medicine, University of California at Los Angeles, Harvard University, University of Pittsburgh, University of Southern California, University of Texas System Cancer Center - M.D. Anderson Hospital and Tumor Institute, Stanford University School of Medicine, University of California at San Francisco, University of California at San Diego, and New York University. Several additional ATEU contracts are pending.

ROLE OF THE ATEUs AND THE AZT STUDY

The development of the ATEUs provides exciting new opportunities for enhanced cooperation between intramural investigators and clinician-scientists at medical centers across the country. The Clinical Center at the NIH and the ATEUs should work in close cooperation, synergistically enhancing each others' strengths. Intramural scientists should utilize the unique strengths of the NIH

to carry out studies which complement those undertaken at the ATEU institutions, in order to maximize the information derived from the ATEUs. These NIH evaluation and support functions must be developed to their fullest capacity.

Extramural as well as intramural scientists should be encouraged to undertake Phase I studies of potential new therapeutic agents, thereby more rapidly laying the groundwork for more extensive clinical trials. Once the potential roles for newer therapeutic agents emerge, along with pharmacokinetically appropriate means to deliver them, the ATEUs should rapidly test emerging new hypotheses on sufficiently large cohorts to lead quickly to definitive answers.

Funding of the ATEUs should also allow sufficient flexibility to meet the multiple demands posed by this multifaceted epidemic. Some studies will require large numbers of individuals that may be recruited at one or a few sites, and others will need careful coordination between multiple facilities because of the uncommon nature of the specific problems, e.g., AIDS-related lymphomas. The investigators at each of these centers possess great expertise, but specific talents and interests may vary greatly. Therefore, maximal flexibility in the utilization of funds would facilitate the most rapid development of treatment approaches by specific investigators which, if successful, can then be incorporated in the protocols of the full group of ATEUs.

The consultants think that these ATEUs will be the most efficient means to develop collaborative efforts to evaluate effective regimens for the management of specific HIV-related syndromes. The centers chosen have also demonstrated great strengths in basic science aspects of AIDS research. Thus, it is hoped that the centers will also enhance the understanding of key questions regarding viral immunopathogenesis and the natural history of HIV infection. There should be no intention to utilize these ATEUs as drug distribution centers once therapeutic agents have been judged to be clinically useful.

Recently, important studies have shown for the first time that an antiviral drug can improve the outcome of HIV infection in infected patients. Twelve centers participated in an industry-sponsored clinical trial of AZT (double-blind, placebo-controlled) in patients with moderately severe disease related to HIV.

Over a 4-month period, 282 patients (AIDS recovered from PCP and late AIDS-Related Complex (ARC)) were entered into a placebo-controlled study which was scheduled to last 6 months. Half of the patients were assigned to receive AZT at a dose of 250 mg every 4 hours (1.5 g daily), and half were to receive placebo. Many patients on AZT required a reduction in dosage or interruption of treatment, primarily because of anemia. The groups were comparable at entry for a variety of variables including age, sex, race, weight, mean Karnofsky score, and severity of illness.

As of September 18, 1986, 17 deaths had occurred: 16 patients receiving placebo and one patient receiving AZT. In general, the deaths were attributed to opportunistic infections, e.g., toxoplasmosis, PCP, cytomegalovirus (CMV), cryptococcosis, and mycobacteriosis. Because of the marked imbalance in mortality, primarily in AIDS patients, an independent Data and Safety Monitoring Board (DSMB) reviewed the data on September 18, 1986, and recommended that the study be terminated. Patients had received between 3.5 to 7 months of therapy (median of 4.5 months) at the time the placebo group was discontinued.

A preliminary review of the results prepared for the DSMB indicates that 47 of 145 patients receiving AZT experienced greater than 25 percent reduction in hemoglobin, compared with 13 of 137 patients receiving placebo. Blood transfusions were required for approximately 25 percent of the patients receiving AZT and for very few of those on placebo. In general, decreases in hemoglobin and neutrophils occurred during the second month of therapy and appeared to be reversible if the dose was decreased or the drug discontinued. However, cumulative toxicity manifesting as progressive suppression of the

bone marrow may theoretically occur with continued administration of AZT, and only a few patients have received the drug for more than 6 months.

CRITICAL QUESTIONS REMAIN

As exciting as these results may be, they do not answer many of the critical questions regarding the treatment of AIDS. Although the mortality of post-Pneumocystis patients with AIDS is decreased by AZT after 4 months followup, it is not known whether this result will be sustained over longer periods of time. Whether or not patients with other opportunistic infections, Kaposi's sarcoma and other AIDS-associated malignancies, or other forms of HIV infection (including constitutional symptoms, generalized lymphadenopathy, neurological syndromes, or asymptomatic persons) will benefit from treatment with AZT is also unknown. Future research will be necessary to establish appropriate dosing schedules that result in clinical improvement but minimize side effects. Although AZT is now the only drug known to be helpful, it is not known whether its activity can be maximized and toxicities minimized if it were to be used with a second antiviral agent, an immunomodulator, or another type of biological response modifier. Another important question is which new antiviral agents, if any, may result in even better clinical outcomes.

FUTURE ROLE OF THE ATEUs

The ad hoc consultants conclude that the ATEU program is well managed and addresses the issues raised by the new information concerning AZT appropriately. Protocols are now in place to address the benefits and risks in the following populations: (1) asymptomatic HIV carriers; (2) persistent generalized lymphadenopathy; (3) HIV neurological disease; (4) Kaposi's sarcoma; (5) AIDS-Related Complex (ARC); (6) advanced AIDS in adults; and (7) pediatric AIDS and ARC.

How rapidly these protocols have been put together since the preliminary AZT findings were discovered in September 1986 is impres-

sive and is a tribute to the coordination between the NIH and participating institutions. Other studies, e.g., combining AZT with alpha-interferon or acyclovir, further trials of ribavirin, phosphonoformate, and HPA-23, are also planned.

The enhancement of funding flexibility should enable ATEUs to most efficiently perform their primary function: the careful evaluation of newer agents for the management of AIDS and HIV-associated illness, utilizing appropriate study designs which allow major questions of immunopathogenesis to be addressed while therapeutic interventions take place. A network should be developed so that a chasm does not develop between the rigorous protocols and clinical monitoring of the ATEUs and the patterns of drug utilization in the general practice community. The development of satellite centers which are geographically distinct from, but cooperate with, specific ATEUs may allow for continued systematic observation of the long-term effects of compounds that are initially shown to be effective and then released for general use by the Food and Drug Administration.

Given the seriousness of the AIDS epidemic and the importance of the knowledge created by the ATEUs, the Federal Government should assist the process of translating research into clinical practice by reinforcing efforts to educate the public and medical practitioners regarding utilization of newer therapeutic agents for AIDS and related disorders. The NIH can facilitate the efforts of all basic scientists and clinical investigators by expeditiously informing them of the status of drug development, screening programs, and clinical trials. This should enhance cooperation and reduce redundancy. Occasionally, a compound that is not active for one indication may be useful for another, or testing conditions may vary the degree to which a drug appears to be effective. With full knowledge as to how specific drugs were studied and the conclusions in regard to optimal clinical utilization of each therapeutic agent, extramural clinicians and investigators will be able to function more effectively, and a useful dialogue will be promoted.

AIDS DRUG SELECTION COMMITTEE

In order to assess the roles of newer agents, the NIH has established an AIDS Drug Selection Committee, consisting of members from the NCI and the NIAID. This group has assessed more than 500 potential therapeutic compounds at the present time, using rigorous criteria that analyze the *in vitro* activity, the ability to obtain adequate amounts for subsequent research, the toxicology and pharmacokinetics, as well as the chemical stability and bioavailability of candidate agents. At the present time, the AIDS Drug Selection Committee feels that high priority compounds to be evaluated in clinical trials include AZT, alpha-interferon, Dideoxycytidine, Foscarnet, HPA-23, and Ribavirin. Screening of newer agents has been done intramurally, but the Southern Research Institute has recently been awarded a contract to expand these endeavors. However, many extramural investigators do not know which substances have undergone specific analyses or why specific compounds were excluded from further investigation.

The consultants strongly suggest that knowledgeable extramural scientists, including, but not limited to, experienced investigators involved in ATEUs, be added to the AIDS Drug Selection Committee, which could be greatly strengthened by such participation. Since the ATEU centers will evaluate the candidate drugs, representatives of the ATEUs, as well as other knowledgeable extramural scientists, should be closely involved in the decisions regarding which drugs require testing. The NIH has already begun to restructure the AIDS Drug Selection Committee to make it more representative of both extramural and intramural investigators.

NEW THERAPEUTIC APPROACHES

Most current antiviral strategies are based on the premise that the reverse transcriptase, which is essential for viral replication and is unique for retroviruses, presents an excellent target for antiviral drugs. However, other unique HIV genes presumably encode gene products not found in mammalian cells. The

functional significance of two open reading frame genes—SOR and 3'ORF—are still unknown, so that more basic investigation is needed in order to better understand the HIV genome (and its products) and to develop drugs that may inhibit other retroviral functions, in addition to reverse transcription. The TAT and ART (TRS) genes are involved in viral replication and posttranscriptional events. Thus, drugs directed against their gene products may be able to attenuate damaging effects of viral proteins in cells that are infected with the virus, rather than simply preventing viral replication. Newer techniques, such as the development of synthetic oligonucleotides and chemical alterations of nucleic acids, may create substrates that result in the termination of viral replication when bound by TAT or TRS gene products. Other experimental approaches include the development of monoclonal antibodies against specific sites of viral attachment and the use of intraspecies genetic hybrids.

While applauding the recent success with AZT, the consultants are concerned that most of the work directed toward an effective antiviral agent has been based on the empiric approach, i.e., the screening of drugs known to be effective against enzymes such as reverse transcriptase essential for viral replication. Meanwhile, relatively little effort has been directed toward a targeted, or structural, approach toward antiviral drug development. This targeted approach, often referred to as the rational approach, is based on high resolution x ray crystallographic structural determinations of HIV and its gene products, i.e., reverse transcriptase, integrase, protease, and regulatory proteins, both separately and in combination, followed by an attempt to "build" an antagonist, based on the precise molecular configuration of the target protein. This approach would take advantage of the precise selection of unique viral proteins as antiviral targets. With the current availability of excellent facilities for x ray crystallography in several major research centers, the consultants suggest that a major effort be directed toward the targeted, structure-based development of antiviral agents. The consultants fully

recognize that targeted or rational drug design is a long-range project, and, despite theoretical appeal, there is no guarantee that this effort will be productive. On the other hand, the standard empiric approach to development of antiviral agents has been a singularly inefficient effort over the past two decades.

Each of the potentially promising new therapeutic agents will have to be measured against the recent experience with AZT. Two important criteria for wide acceptance of a given drug are oral bioavailability, since the drugs may need to be administered chronically to suppress reactivation of latent virus, and the ability to achieve significant levels in the CNS. Other congeners of purines and pyrimidines are being evaluated for their retroviral activity by the drug evaluation unit at the NIH. Dideoxycytidine looks especially promising and is undergoing further study. Combinations of compounds which act by different mechanisms are receiving increased attention. When Acyclovir, interferons, or phosphonoformate are added to AZT, synergistic effects are noted in decreasing viral activity *in vitro*. The indications for combined therapy, as well as the possibility of the emergence of resistant retroviral strains after chronic AZT therapy, demand further study.

Further research regarding immunomodulators and other biological response modifiers is also needed. Alpha-interferon has resulted in tumor regression and diminished reverse transcriptase activity in some, but not all, subjects recently studied at the NIH. At the present time, the role of immunomodulators per se appears limited; their utilization in combination with antiviral agents offers much promise but will require further intensive study. Other approaches, such as the use of transfused lymphocytes and bone marrow transplantation in individuals receiving antiviral therapy, can only be performed on a limited number of individuals but offer new insights into the potential immune reconstitution of HIV-infected individuals. While the treatment of HIV infection is of paramount importance, treatment of life-threatening

opportunistic infections, as well as associated neoplasms, also demands intensive research.

Therapeutic advances against specific opportunistic infections are proceeding slowly and merit continued attention. Dapsone, DFMO, Fansidar, and Trimetrexate, which are all dihydrofolate reductase inhibitors, are being studied for their activity against *P. carinii* infections. Trimetrexate has the added virtue of activity against toxoplasmosis and is being studied for this indication. DHPG, an Acyclovir analog, has been found to be useful against cytomegalovirus (CMV) infections of the retina, the gastrointestinal tract, and the lung. The limitations of DHPG for other disseminated infections and the tendency for subjects to relapse once the drug is discontinued underscore the need for further research for antivirals against CMV, as well as Epstein-Barr Virus (EBV). A drug discovery program to develop anti-CMV compounds has recently been initiated by the NIH.

BROADER FOCUS NEEDED ON AIDS-RELATED PROBLEMS

The ATEU program is also planning new protocols directed at improving patient survival from a number of infections and cancers associated with AIDS, including: CMV infection; pneumocystis pneumonia; toxoplasma encephalitis; mycobacterium avium-intracellulare infection; cryptosporidium enteritis; cryptococcal meningitis; Kaposi's sarcoma; and B cell lymphoma.

The ad hoc consultants feel that more attention should be focused by institutes in addition to the NCI, the NIAID, and the NHLBI on certain AIDS-related problems. The eye is involved in the majority of patients with AIDS. CMV retinitis is a major problem despite advances made through treatment with DHPG. There is a need to develop less toxic oral agents for treatment of CMV retinitis. The National Eye Institute (NEI) should initiate programs on AIDS-associated eye disease without compromising the present programs on ophthalmological diseases.

By the same token, AIDS in infants and children poses unique problems in clinical presentation and challenges in regard to drug delivery. Development of therapeutic protocols for pediatric AIDS will require close collaboration between intramural National Institute of Child Health and Human Development (NICHD) scientists and extramural clinical investigators. The neurological manifestations of AIDS are currently a major focus of clinical investigation. The development of protocols to determine the effectiveness of therapeutic agents on HIV infection of the CNS will likewise demand close collaboration between the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) investigators and extramural neuroscientists.

Four NIH grants have recently been awarded to investigators to develop new drugs for treatment of AIDS under the Drug Discovery Program; it is expected that additional grants will soon be awarded under this program. New applicants will be able to indicate whether they have broad expertise or whether they prefer to specialize in the development of antiretroviral, immunological, or other biological modifying agents. Other extramural initiatives will encourage the definition of the receptors in the surfaces of cells infected with HIV, the targeting of drugs for infected cells, and the targeting of drugs with particular efficacy for treating HIV infection of the CNS. For example, lipophilic drugs could, in theory, better penetrate macrophages and then be more readily carried into the CNS.

NIH initiatives have also included the awarding of contracts for the study of the effects of antiviral drugs in retroviral animal models, particularly Simian Acquired Immuno-deficiency Syndrome (SAIDS). These animal model systems may give valuable insights regarding dose regimens, toxicity, and organ distribution of individual drugs and combinations.

While the consultants applaud these initiatives, they think that the effort to develop effective antiviral agents should be intensified by: (1) strongly supporting the targeted approach to drug development; (2)

developing more widespread cooperative programs between governmental, academic, and industrial bioscientists; and (3) stimulating a free exchange of scientific information among all involved investigators. The informed estimate that no effective vaccine against HIV will be available for at least 5 years further emphasizes the urgency for a more intensive, far-ranging, Federally supported antiviral drug development program.

SUMMARY

In summary, the consultants conclude that specific areas that require intensified effort include:

- Close coordination between the NIH Drug Selection Committee and the ATEUs, utilizing the available expertise from better intramural and extramural sources to develop novel, antiviral strategies;
- Close integration of intramural and extramural clinical trials to maximize the acquisition and interpretation of information in regard to new treatment regimens;
- Development and implementation of new clinical protocols to evaluate AZT and other antivirals in a wide variety of HIV-associated conditions;
- Development of effective mechanisms to inform the medical and general public concerning the status of drug development and clinical trials;
- Expansion of drug discovery programs and animal model studies to identify and evaluate new antiviral agents that act by a variety of mechanisms to inhibit HIV replication; and
- Expansion of efforts to develop and evaluate new treatments for opportunistic infections and neoplasms, in pediatric as well as adult AIDS patients.

Recommendations

The ad hoc consultants enthusiastically applaud the remarkably swift and effective response of the National Institutes of Health scientific and administrative staff to the AIDS crisis over the past 4 years. There is no historical precedent for so well-organized and rational a response, on such a large scale, to a health crisis of similar magnitude. The ad hoc consultants support each of the initiatives which have been undertaken by the NIH to date and feel that none of the current research efforts should be phased out.

The ad hoc consultants believe that, at the present time, the extraordinary magnitude of the AIDS crisis demands novel approaches on the part of the NIH. Certain thoughtful new initiatives have already been carried out, and others will be appropriate in order to deal most effectively with the accelerating AIDS epidemic. Pursuant to those ends, the ad hoc consultants offer the following recommendations:

- The allocation of new monies for AIDS-related research is obviously of the utmost importance and is currently proceeding at an accelerating pace. It is important to fully recognize that the AIDS epidemic represents an entirely unprecedented and unpredictable health challenge. To meet this challenge requires **new funds dedicated to AIDS-related research**. The challenge cannot adequately be met by a "business as usual" approach. The reallocation to AIDS research of funds originally designated for other projects critical to the NIH scientific mission is both inappropriate and counterproductive.
- In parallel with the allocation of new monies is the clear-cut need for **additional**

full-time staff (FTEs), both scientific and administrative, at the NIH. The essential administrative and scientific staff cannot be acquired simply by redeploying human resources currently committed to other segments of the NIH mission. The number of new staff should be clearly related to the needs of new initiatives engendered by the AIDS program. The rapid acquisition of complex data by the 14 AIDS Treatment Evaluation Units (ATEUs), for example, demands expeditious, accurate, and thoughtful assessment and coordination by a skilled administrative and scientific staff who are totally dedicated to this project. The administrative and clerical staffing requirements will increase significantly as additional therapeutic agents undergo field trial and as potential immunizing agents move into the field testing phase. Both administrative and professional staffing must be enhanced to ensure meaningful collaborative efforts which reinforce the strengths of the cooperating centers while minimizing duplication of effort. Additional professional staff will also be essential to coordinate the recommended studies at the interface between clinical epidemiology and the basic mechanisms of viral pathogenesis in the human host. 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.

- The ad hoc consultants recognize the need for a **strong, centralized intramural committee to coordinate all NIH AIDS activity**, with the objectives of determining the goals for AIDS-related research, preventing intrajurisdictional gaps in the

research program, and avoiding redundancy. The consultants believe that the NIH AIDS Executive Committee has functioned well to date but will be hampered, in the long run, by its current structure, with one executive committee seat for each involved institute. A committee more representative of the AIDS-related research strengths of the NIH will be more appropriate in the immediate future. Members of the extramural group of ad hoc scientific consultants (discussed below) should interact closely with the strengthened executive committee.

- The ad hoc consultants recommend the creation of an **ad hoc extramural group of scientific consultants**, appointed by the Director of the NIH, to review AIDS-related research activities and to assist in the formulation of research priorities. The ad hoc scientific consultants should have the mandate to examine all facets of the NIH AIDS program as it functions within the institutes, as well as between the NIH, other governmental institutions, and the extramural research community. In addition, the ad hoc scientific consultants should be given the option of participating, singly or severally, in the meetings of the NIH AIDS Executive Committee, at the discretion of the Director of the NIH. Productive interaction will be facilitated if the minutes of the NIH AIDS Executive Committee are distributed to the proposed ad hoc scientific consultants and if presentations are made to these consultants on a periodic basis by members of the reconstituted NIH AIDS Executive Committee. The ad hoc scientific consultants should facilitate interactions between the intramural and extramural research communities and support appropriate allocations for needed research projects. The ad hoc scientific consultants should report no less than twice yearly to the Director of the NIH and to Congress on a periodic basis, as requested by House Conference Report No. 99-402.
- The ad hoc consultants strongly recommend that the NIH create **special study sections for AIDS-related research**.

The study sections should be made up of scientists who are sufficiently knowledgeable about research in AIDS and related areas (including dynamic epidemiology, relevant areas of viral biology and immunology, and the rational approach to the development of antiviral drugs) to be responsive to both the progress and the scientific gaps which relate to resolution of the AIDS epidemic. This is an area in which the ad hoc consultants feel that the magnitude and urgency of the AIDS epidemic dictate a modification of the time-honored routines of the DRG. The consultants feel that the study sections should have enhanced flexibility to develop new methods for the expeditious review of proposals. The goal should be to expedite the awarding of grants so that meritorious, essential research can be initiated as rapidly as is consistent with the maintenance of high scientific quality. The consultants further recommend that the study sections should have increased discretion in allocating funds for capital expenditures, e.g., to upgrade biological containment facilities, to improve the capacity to grow the HIV virus, and to obtain appropriate equipment for AIDS research when such funds are deemed essential for the expeditious achievement of critical scientific objectives.

- The consultants support the **creative utilization of the contract mechanism** to facilitate research in AIDS-related areas. The contract mechanism is essential for the support of clinical trials and for vaccine development. This mechanism is also important as a means of filling critical gaps in knowledge of the pathogenesis of AIDS. The contract mechanism is one of the few funding approaches that does not directly infringe upon non-AIDS research areas. The consultants strongly agree with the NIH leadership that, in parallel with the contract mechanism, it is critically important to encourage new investigator-initiated projects, since the optimal approaches to immunization against, and treatment of, AIDS are far from certain. New funding mechanisms

should be utilized which will maximize long-term commitments to resolving the difficult basic research problems posed by AIDS. The consultants, therefore, recommend that **the NIH create initiatives that will encourage additional experienced and talented investigators to redirect their efforts toward the solution of the AIDS problem.** The commitments to such established investigators must be of sufficiently long duration to ensure the possibility of success in the study of the unique and unusually complex HIV.

- The consultants strongly support the development of the AIDS ATEUs and urge the **maximum utilization of the ATEUs** for the acquisition of data regarding the effects of therapeutic agents on each of the major subgroups of patients with HIV infections. The consultants encourage ATEU development of satellite relationships with outlying communities, so treatment evaluation is viewed as a truly National collaborative effort. The consultants strongly urge that the clinical investigators in the ATEUs, as well as those responsible for the MACS program, broaden the basic protocols to carry out parallel investigations of the early events in the pathogenesis of HIV infections in selected segments of the study populations. The consultants also strongly recommend that **extramural scientists, from both academia and industry, with expertise in the management of AIDS patients and in new, targeted approaches to the development of antiviral drugs, be included as ad hoc members of the AIDS Drug Selection Committee** which determines the candidate drugs for field trials. Preclinical and clinical sections of the AIDS Drug Selection Committee may function independently but need to meet periodically to integrate the thrust of drug development and evaluation.
- The NIH Scientific Vaccine Committee is now providing close coordination of all intramural work on vaccine development. When and if one or more vaccines appear suitable for testing in humans, it will be of critical importance to include academic scientists as well as representatives of industry as ad hoc members of the NIH Scientific Vaccine Committee which will be responsible for determining which candidate vaccines are to be evaluated in field trials. Although it appears that no candidate vaccine will be ready for testing in humans within the next 2 or 3 years, the consultants recommend that the NIH consider the **addition of extramural ad hoc representatives to the Scientific Vaccine Committee** in the near future, so that broad-based scientific input can be optimally utilized at all phases of vaccine development, in a manner parallel to the proposed modus operandi of the AIDS Drug Selection Committee.
- The consultants recognize the predictable shortfall of a relatively depleted resource—chimpanzees, the only animal species in which HIV has been shown to replicate over a period of months or years. The consultants endorse the establishment, by the PHS, of a committee which is responsible for the allocation of chimpanzees for AIDS-related research. The consultants strongly recommend **augmenting the chimpanzee allocation committee by the addition of experienced extramural scientists**, from both the academic sphere and industry, including individuals expert in animal retrovirology as well as vaccine development.
- An essential complement to the basic NIH-supported virological, immunological, and molecular genetic research is the **expanded support of broad-based epidemiological studies of the HIV infection in high- and low-risk populations.** The data derived from such studies will be critical to answering fundamental questions regarding the basic biological events by which HIV initiates infection and disease in man. Additional broad-based studies of high- and low-risk populations in the United States and other nations are critical to a full understanding of the natural history and pathogenesis of HIV infection, including the interaction of environmental and nutritional factors, as well as intercurrent infections, on the clinical expression and outcome of HIV infection.