Agenda for AIDS Drug Development: Report of the Conference on Promoting Drug Development Against AIDS and HIV Infection, August 31-September 1, 1987 (1987)

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Steering Committee for a Conference on Collaboration in Drug Development Against AIDS; Division of International Health; Institute of Medicine

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AN AGENDA FOR AIDS DRUG DEVELOPMENT

Introduction

The Institute of Medicine and the National Academy of Sciences issued a comprehensive report in October 1986 on the growing epidemic of acquired immune deficiency syndrome. Confronting AIDS: Directions for Public Health, Health Care, and Research contained both an assessment of the disease's likely devastation and proposals for a national response to the threat. Among the latter was a recommendation to convene researchers from industry, academia, and government for a discussion of ways to improve the development of drugs against AIDS and the virus infection that causes it.

A conference on Promoting Drug Development Against AIDS and HIV Infection was conducted in Washington, D.C. by the Institute of Medicine August 31 and September 1, 1987. A summary of the conference presentations, conclusions, and recommendations follows.

Mobilization Gets Under Way

In the year since Confronting AIDS was published there have been many activities and some advances relevant to drug development against AIDS and infection with the Human Immunodeficiency Virus (HIV). The federal government has instituted programs to speed AIDS drug discovery, development, testing, and licensure. The National Cooperative Drug Discovery Group Program for the Treatment of AIDS (NCDDG-AIDS) supports

collaboration in basic research among investigators within academia and industry through coordination at the National Institute of Allergy and Infectious Diseases (NIAID). The National Cancer Institute (NCI), applying an expertise developed in screening for anti-cancer drugs, has established an *in vitro* screening program to systematically test its existing drug repository as well as new candidates and natural products for their anti-HIV and anti-AIDS activities. When fully operational this program will have the capacity to screen tens of thousands of compounds yearly.

The AIDS Treatment Evaluation Units (ATEUs) and the recently funded AIDS Clinical Study Groups (CSGs) are organized and supported by NIAID to conduct clinical trials of safety and efficacy of potential AIDS therapies. Drugs from both public and private sources are evaluated in these programs and selected research independent of these trials is also fostered.

The Food and Drug Administration (FDA) has made evaluation of therapies for AIDS its first priority, and has made a commitment to complete agency review and judgment of such New Drug Applications in no more than six months.

Scientists from academia, together with government and industry, have focused much attention on HIV, and data on its structural and regulatory elements are being collected at a rapid pace, although much more needs to be known about its pathological behavior.

Many pharmaceutical companies have initiated or expanded research and development of AIDS drugs in the last year. An estimate made in August is that at least 70 companies worldwide have at least 80 drugs under investigation. These include antiviral agents, biological response modifiers, and drugs designed to treat opportunistic infections which accompany AIDS. Whether any of these agents will prove useful remains an open question.

Azidothymidine (AZT) is the first drug licensed specifically for the treatment of AIDS. The rapidity and thoroughness of its development, testing, and approval by the participant investigators--including the Burroughs Wellcome Company, the NIH, and the FDA--serve as goals for the future collaboration and discovery of new drugs. Clinical tests are being conducted on other antiviral therapies such as dideoxycytidine, which in initial trials has shown some neurotoxic side effects; ribavirin, which showed some promise in industry-sponsored trials and is being tested further; and AL-721.

Unfortunately, these steps toward development of drugs against AIDS are not entirely visible to the public at large, and particularly to the potential recipients of such therapies. Further, mistrust and incomplete information has led desperate people with AIDS or HIV infection to seek medication from expanding underground sources of potentially toxic agents.

Prospects for Further Development

Antiviral approaches to AIDS drugs will generally exploit events in the HIV life cycle peculiar to the virus and not shared by its host. For HIV, these events include viral attachment to the cell, entry into the cell and uncoating of the viral RNA, reverse transcription of viral RNA into double-stranded DNA, and integration of the DNA into the host genome as a provirus. Later steps of viral production, also theoretically vulnerable to specific attack, are transcription of DNA into viral RNA, splicing of the RNA, its transport into the cytoplasm, and its translation to protein, as well as the assembly of new virus particles. The virus encodes a number of proteins that act on the processes from transcription to translation providing a number of potential targets.

At least three steps might be especially fruitful targets for antiviral therapy in light of present knowledge. One is the attachment of HIV by its glycoprotein gp120 to the CD4 cell surface antigen of T lymphocytes--a key event in the virus replication cycle and in its pathogenesis. Because the relevant protein structures are largely known, inhibitors can be imagined and designed. Another step is reverse transcription of RNA into DNA, catalyzed by reverse transcriptase, the hallmark of retroviral infection. This event, not shared by the host, is the site of action of AZT and many other drugs under development. A third attractive target, at least theoretically, is the group of regulatory proteins, the products of the tat-3 and art/trs genes, first

discovered in HIV, which control the production of viral RNA and proteins. The knowledge base in molecular biology for construction of more new approaches is broad, although much remains to be learned. For instance, except for the integrated viral genome, there is no known marker to identify cells which may be latently infected. No biochemical markers, surface antigens, or enzymes have been detected in the absence of viral replication. Actually it is an open question whether latent infections occur.

Potential therapy for HIV infected persons should also be directed at less well understood aspects of infection. Some disease symptoms may be related to the patient's overall depletion of T-cells that bear CD4 antigens. The number of T lymphocytes may be decreased both by direct infection and by syncytia formation; budding virus particles and the viral glycoprotein gp120 appear to fuse cells that later die. HIV-infected macrophage-monocytes may be indirectly responsible for nervous system damage by infiltrating the nervous system, permitting infection of neurons or glial cells, and by releasing proteolytic or chemotactic factors. However, the detailed mechanisms of immunopathogenesis and neuropathogenesis remain obscure. Design of effective treatment for these disease manifestations has a high priority.

Biological response modifiers and other stimulators of the immune response also are undergoing clinical trial in AIDS patients, often in combination with antiviral drugs. These agents could be administered both

to bolster the weakened immune system and to stimulate repopulation of components of the hematopoietic system which may have been adversely affected by certain antiviral drugs, for instance AZT. Another group of compounds administered to AIDS patients includes treatments for opportunistic infections, in particular for Pneumocystis carinii pneumonia. The safety and efficacy of any drug should be evaluated in trials in the context of other medications a patient is likely to receive.

It should be noted that different sorts of drugs, aimed at different disease manifestations may be indicated over the course of HIV infection. Early intervention may focus on halting HIV replication to stem virus spread to uninfected cells, this therapy may be continued through disease progression. Agents which are effective in both lymphocytes and macrophage/monocytes would also be useful soon after infection in part to slow nervous system deterioration. Repopulation of the hematopoietic system and treatment for opportunistic infections will be needed as the infection progresses to AIDS.

Considerations in Clinical Trials

The search for drugs or biologics to treat persons infected with HIV or to prevent establishment of infection in exposed individuals is a matter of the highest priority. This does not mean, however, that the clinical trials of such materials can fail to observe the established rules to protect maximally the subjects participating in them. In AIDS

there are still large areas of serious ignorance about the virus and its pathogenic behavior. This creates risks not encountered in other infections for which better animal models are available and about which much more information is at hand to select dosage, end-points, and probable toxicity of medications.

The public needs to be aware of the hazards and limitations on clinical trials. Phase I studies, the first exposure to humans, are safety tests, but they involve toxicity as a measure of dosage limits. When larger trials are deemed possible, they must be strictly controlled to obtain the most objective answers. This almost invariably means randomization and placebo controls. Attempts to short-cut the most objective routes risk persistence of ignorance and costly delays in obtaining effective therapy.

There are now many drugs being readied for trial, and likely there will be more than can be given adequate test in humans as rapidly as one would like. Presently, the determination of how infected subjects shall be staged and followed in clinical drug trials is not certain. Priorities will have to be set and no doubt readjusted as more understanding of the encounter of virus and host solidifies conceptual strategies.

Immediate Causes for Concern

Government

Federal programs have been designed to mobilize academic and industrial as well as government participants rapidly. Unfortunately, communication of the structure and goals of these programs to academia, industry, and the general public is not yet adequate. Better communication also would enable scientists entering AIDS research to have input into the design or revision of programs. Further communication needs are described below.

The conduct and support of fundamental biomedical research have been the chief elements of NIH's success. However, those experienced in drug development predict that screening of existing compounds rather than design or discovery of new drugs for AIDS will prove more successful, at least in the immediate future. What this means is that routine, large-scale, systematic evaluation of existing drugs or compounds should be instituted. A program is underway at NCI for this purpose. It requires design of automated tests for anti-viral activity of compounds, which is measured by cell growth rather than death in the presence of HIV. Although much effort is required for the design of these systems, it is different from that of undirected research. Because advances achieved by fundamental research may not be quickly translated into therapy, in the near term screening may prove more profitable.

Industry

In industry, the success of AZT has provided a competitive financial incentive to new drug development. Antiviral research has not proved broadly profitable in the past and focus was placed on the development of antibacterial agents and on drugs to treat disease symptoms rather than causes. Antiviral research will require not only new scientists but new facilities for cell and virus isolation. It was estimated that fewer than five pharmaceutical companies have containment facilities suitable for work with live HIV.

The Nation

The fundamental problem is that a national approach designed and accepted by all relevant sectors has not been enunciated. AIDS must come to be considered as the single most urgent challenge to public health today. It is evident that the present and potential magnitude of the AIDS epidemic and its resulting mortality demand immediate and extraordinary measures. Although biomedical research has enjoyed substantial public support, future trust and investment in research may be contingent on its response to the devastation of AIDS.

The lack of full mobilization of national resources against AIDS brings attention to some specific and urgent needs that must be met, including:
(a) entrance and support of new investigators into AIDS research, (b) recruitment of experts whose fields are germane to AIDS, especially

immunology and protein crystallography, (c) expansion of research and clinical facilities to accommodate growing AIDS activities, and (d) systematic access to patients throughout the disease process.

Principal Requirements

Communication

It has been noted repeatedly that this emergency requires not only that substantial clinical and experimental progress be made, but that these efforts are made known to the public, including those persons affected.

The popular press has recognized AIDS as a major public concern. Unfortunately, communication of the research and development efforts has not been as successful as reports of the devastation of the disease. An opportunity and responsibility exist to accurately inform the public on the nature, direction, and success of research. Public education and discussion of the new federal programs are essential to the public trust and continued enrollment of subjects for trials of drugs or vaccines against AIDS.

Subjects entering clinical trials often have been exposed to much information about AIDS, some of which is inaccurate. They deserve information on the rationale of the treatment strategy, both to make

informed consent and to understand the necessity of following trial protocols. This will necessitate description in lay language of the kind of information gained from placebo controlled trials, or trials of alternative forms of therapy. Trials can be rendered useless by patients' taking other drugs, or pooling their unknown medications (placebo and drug) so that "everyone gets something." Education of potential recipients of anti-AIDS therapy is necessary also for their health, because some self-administered medication is toxic either alone or in combination with other therapies. Similarly, it is not the case that some drug is better than no drug. Even drugs that seem innocuous may be dangerous when AIDS patients metabolize or respond to established therapies differently than other patients. This particular aspect of trial design also requires clear communication. For clinical trials to be meaningful, a carefully educated patient population is a necessity.

Regular news bulletins must be published and widely disseminated by the Public Health Service (PHS), or within the popular press with information from the PHS, both to describe clinical and experimental successes and failures. Because of the intense interest in AIDS, information about research reaches the public rapidly; it is the responsibility of the PHS to be certain that accurate and current information is publicly available.

Better communication also must be established among the various sectors of the research and development community. There are no existing

mechanisms for direct communication between federal policy makers, research scientists, and private companies. Some links must be established to permit optimum design of federal programs, to accelerate progress on research, and to fully involve all interested groups in common decision making and priority setting. The FDA needs to be consulted as soon as possible in the process of drug discovery and development to assist in the design of toxicity tests and human trials for safety and efficacy. The goal is to rapidly obtain the specific information needed to rule on a drug's ultimate utility.

The academic community could be more fully enlisted in AIDS research. NIH does publish regular notice of requests for proposals and applications for projects. However, questions from academics continue to be heard, for instance, concerning the independence of an investigator on any given project. Individual communication, as achieved through the NCDDG-AIDS, has proven to be the most successful means to relay information. Although such one-on-one programs are labor intensive, they are worth the cost. Investigator-initiated research is important for the advance of knowledge but there should be more stimulation of investigation in areas deemed important and encouragement of investigators to enter into AIDS-related research.

Project initiation is often the most difficult phase in a research career, and funds and reagents should be available and their availability advertised. Communication with both young and established investigators on "how to get started in AIDS research" is urgently needed.

Coordination

Government, industry, and university have different but overlapping areas of concern and interest in drug development and patient treatment. Each sector's expertise should be utilized with appropriate communication to foresee gaps and to avoid being duplicative or redundant. Such division of labor requires definition of goals; communication of intentions, activities, and results; and monitoring of progress for the most rapid advances to be made. It is evident from discussion at the conference that establishment of a group comprised of key individuals from each sector should be considered to assure optimal and timely communication, interaction, and collaboration leading to the common goal of conquering AIDS. Such a group should contain scientists and decision makers of stature who are informed about AIDS and understand the problems unique to each sector.

Specific Areas of Need

Basic Biomedical Research

Personnel

The most visible progress in research has been in molecular biology and viral structure. Previously unrecognized genes and new types of regulatory functions have been discovered in HIV. Despite this progress, new investigators in other fields need to be brought into AIDS research.

It is imperative to recruit scientists who may have a more direct impact on drug development, including biochemists, pharmacologists, medicinal chemists, and immunologists. HIV, as a virus with a long latency, infecting different cell types, and having several distinct pathologies, presents a challenge to the creativity of drug designers.

One means to attract expertise from areas outside retrovirology is the traditional establishment of individual postdoctoral fellowships to a particular area, in this case AIDS research. For instance, a beginning scientist, with fellowship support, could enter an established biochemistry lab for a project devoted to HIV protease mechanisms of action and inhibition. High quality research could be conducted, with the only "targeted" feature being the organism of interest. This is a proven mechanism both to train young investigators and to permit them to develop their own niche. Advertisement of such opportunities will contribute to their success.

It is important to attract senior investigators to broaden the perspective of research. It would be useful to streamline the application and award of grants for AIDS research. It is imperative to maintain the high standard guaranteed by the peer review process, but mechanisms to simplify the forms and accelerate their review should be explored.

Facilities

Expanded physical facilities are needed for the desired influx of investigators into the field, and expansion of facilities requires funds for building. Research should not be limited to screening for biochemical activity of a compound, for instance, its specific ability to act on a DNA sequence or gene product, but must include work on cells harboring HIV and live HIV itself. Thus **containment facilities suitable for work with live HIV are desperately needed.**

Animal Models

Better animal models are needed. The best models will simulate the pathogenic mechanisms of disease production as seen in humans. Of necessity, virus replication, disease production, and host response ought to be similar to that observed in man. Simian immunodeficiency virus infection in macaques is presently the best model, but other models exist and need to be studied intensively. The availability of animals, particularly primates, needs to be broadened. At this time, chimpanzees are the only hosts for HIV other than humans. Exploration of ways to increase availability of appropriate animals must begin. Retrovirologists experienced with viruses infecting other animals need to be brought into AIDS research to contribute to the design of additional good animal models for AIDS and to decisions of which experiments to conduct on the limited number of chimpanzees available for this work.

Reagent Repository

Plans are underway to establish a national repository for AIDS-related reagents. It is hoped that many HIV isolates, including some prototypes, plasmids and viruses harboring HIV sequences, cell lines expressing HIV, and hybridomas producing anti-HIV antibodies will be deposited voluntarily. A more radical proposal, but one consistent with scientific practice is that all materials which are reproducible, such as molecular or cell clones, when described in the scientific literature must be deposited in the central repository. Alternatively, all reagents resulting from federally sponsored research might be obligatorily deposited. Naturally, these proposals would provoke much comment, and possibly dissent from the research community, including both scientists competing for their careers and commercial enterprises competing for profits. But this disease requires as rapid a response as we can produce so that optimal scientific collaboration is in the public interest. Therefore, making new information and reagents broadly available should have high priority.

Also, a project is planned to produce and purify large quantities of HIV enzymes and structural proteins. These plans need to be pursued with more urgency, making large quantities of each protein available. The availability of large quantities of HIV proteins would permit their structural analysis by x-ray crystallography. Their conformations can be used to design specific inhibitors of binding or enzymatic activity, so-called rational drug design. Key targets are reverse transcriptase,

including both its polymerase and ribonuclease-H function, protease, integrase, and the envelope glycoproteins. The regulatory proteins, tat and art/trs, which control the production of viral RNA and proteins, may prove to be most important in our ultimate ability to understand and control this infection. Inhibition of those proteins responsible for the overproduction of viral components may be a unique means by which alteration of replication and a change in virus-host interaction could be effected.

Untargeted Research

There is a consensus that benefits to basic virology and immunology will accrue from AIDS research. It also must be realized that undirected, untargeted research in areas such as molecular virology, genetics, and cell biology, will contribute fundamental knowledge. For instance, independently developed monoclonal antibodies which systematically identify cells bearing CD4 surface antigen and the epitopes to which HIV gp120 binds, have been tools that have taught us a great deal about HIV infection. These antibodies were not a result of "AIDS research." Continued contributions are anticipated as long as fundamental research is supported. There is no question that funds for AIDS research should be additional allocations and not transfers from areas of less differentiated search.

Screening for Active Compounds

Investigators familiar with drug innovation and development share the opinion that for the next few years most promising new drugs will come from screening available compounds for anti-retroviral activity rather than from rational drug design. Such systematic screening will require the automated systems underway at NCI and planned elsewhere. A screening program necessitates contributions from all sectors. Procedures exist to permit retention of patent rights by the submitter of a potential anti-HIV compound. Such protection is essential for commercial partners. Any system to decide on priorities for screening should take into account the opinions of all relevant sectors: government, industry, and academia.

Simultaneously, basic research, as specified above, must proceed to lead ultimately to new chemotherapeutic approaches.

Clinical Research

Physicians entering research are frequently attracted by laboratory rather than clinical research. Time spent conducting clinical trials is not regarded as conducive to promotion. Furthermore, the number of clinical investigators competent to design and conduct trials is small, and may be limiting in the very near future to the process of drug evaluation.

More physicians must be recruited and trained to be clinical investigators in AIDS. Excellent fellowship programs need to be supported so that appropriate training will be fostered. More investigators will be attracted to a career of clinical research if funding is possible. It is also important that academic institutions recognize the creativity involved in conducting clinical trials.

NIH has established two national programs for evaluation of AIDS therapies, the ATEUs and the more geographically widespread CSG. These clinical investigation units are designed to develop essential clinical data. Many excellent investigators who competed successfully for this grant support are linked to these programs but there is the erroneous perception that physicians engaged in these trials may not be available to conduct trials outside these programs, for instance, in collaboration with a pharmaceutical company sponsor. Collaboration of federally-funded units with industry has been possible for vaccine development (e.g., pneumococcal and pertussis vaccines) and the AIDS units can function in this capacity as well. Collaborative protocols have been developed and will continue to be essential.

One problem perceived by a number of investigators is the function of the ATEUs. NIAID perceived a need for coordination of AIDS trials, and in particular coordination of protocols, data gathering, and analysis. It was also felt that enrollment of patients by investigators in designated units with appropriate funding, staff, and facilities would be the most

efficient means to conduct experimental therapies. The ATEUs were awarded by a peer reviewed competitive process. The responsibility for trials may rest with NIAID as the sponsor of the Investigational New Drug (IND) application or, in principle, with industry.

Many pharmaceutical houses have not been satisfied with the existing ATEU plan. They feel that through their traditional role and accumulated experience, they have the demonstrated expertise in the conduct of clinical trials which itself would be the most effective accelerator in evaluating a new drug. There is merit in utilizing established expertise but there is a simultaneous need for comparative assessment of potential drugs so that priorities can be accurately established and evaluation of several agents concurrently developed by different firms and investigators can be handled.

The final resolution, agreed to by all sectors, is that the ATEUs and the AIDS CSG operations must evolve to meet changing needs and be flexible. NIAID welcomed industry's willingness to collaborate in designing the most efficient partnership for the evaluation of drugs. Cosponsorship of the IND is a possibility. NIAID has made it clear that the ATEU and CSG systems are not intended to replace industry sponsored clinical trials.

The FDA is another potential contributor to the design of clinical trials. Their requests for specific forms of data before a trial is begun

should facilitate their evaluation of a drug's safety and efficacy. The FDA has made a strong commitment to accelerate the review of AIDS drugs, however this investment of manpower and funds will slow the evaluation of other drugs unless additional resources are available.

As research and treatment expand, facilities need to expand to care for and to study patients enrolled in clinical trials. The outpatient facilities of most institutions cannot provide space and personnel to function as "study sites." Protocols require more personnel, longer times in clinic by the patients, and therefore crowding occurs. This is part of the larger issue of needed expansion of health care facilities for AIDS patients, including long term care, hospice care, and facilities for the demented patient. (These needs will be the subjects of future IOM studies.)

Special attention needs to be given to trials for pediatric therapy of HIV infection. Children have traditionally received experimental therapy after adults. Pharmacology may differ in infants and children so that Phase I trials must be done separately in children and in adults. Currently AZT is licensed only for use in adults (over 13 years of age). New therapeutic agents should be considered for testing in children promptly without requesting demonstrated efficacy in adults. It is important to recognize that very young children, newborn infants, and even pregnant women will have to be considered as part of carefully designed therapeutic trials based on stepwise acquisition of knowledge. HIV

infection appears to be fatal, therefore, prevention of infection of infants is a paramount goal even as drug and immunostimulators are tested.

One approach to help increase available personnel and facilities is to create community-based centers or networks for clinical investigation. This requires increased funding and personnel because care providers' first priority is medical support and therapy for patients with life-threatening illness. Community-based centers could serve multiple purposes. Treatments could be well evaluated in a post-marketing period in local facilities with additional resources. As patients receiving approved treatments increase in number this may be a critical need.

Conclusions

Substantial progress in fundamental research relevant to treatment of HIV infection and AIDS has been made by academic, industry, and government laboratories. Programs designed to promote drug testing and evaluation are in place. Plans are being made in all relevant sectors for further investment and expansion of activities in drug design, screening, animal models, and patient evaluation.

Communication among sectors and with the public is deficient. Frustration emanates from incomplete and inaccurate information. Direct communication, clarification, and open discussions must be planned to disseminate data. Persons with a fatal illness and their care providers are profoundly interested in effective therapy and must be informed about the need for carefully conducted studies so that optimal therapy can be achieved.

The IOM intends to establish a continuing forum to consider the development of drugs and vaccines against AIDS. This group will convene high-level participants from academia, industry, and government, so that direct communication can be achieved about the means to promote the easiest possible availability of therapy and prophylaxis for AIDS and HIV infection, and that specific steps can be identified for drug and vaccine development.

Summary of Recommendations

-- Systematic screening of compounds in the libraries of the world's pharmaceutical companies offers the best short term prospect and should be vigorously pursued.

-- Investigation should be stimulated and new scientists should be recruited in immunology, biochemistry, and pharmacology.

-- A national repository for AIDS-related reagents should be established.

-- Better animal models are needed and more animals should be made available.

-- Funds for AIDS research should be additional allocations and not subtracted from other areas of research.

-- Facilities should be expanded for both clinical research and for laboratory research, particularly with live HIV.

-- Physicians should be recruited to conduct clinical trials.

-- Community-based centers for clinical investigations should be considered.

-- Special attention should be given to trials of pediatric therapy.

-- ATEU's and AIDS CSG's must evolve to meet changing needs.

-- Coordination of plans and continuing communication should be established among academia, government, and industry to avoid lapses or duplication of efforts.

-- **The general public and HIV infected persons must be informed by the clinical and research communities about the progress of treatments for AIDS.**

-- **Potential recipients of treatment should be informed about the logic and design of clinical trials.**

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CONFERENCE ON PROMOTING DRUG DEVELOPMENT AGAINST AIDS AND HIV INFECTION

August 31 - September 1, 1987

AGENDA

Monday, August 31

9:00 - 10:45 I. The State of the Science in AIDS Drug Development

The Status of Preclinical Drug Development
- William Haseltine, Dana-Farber Cancer Center

Drugs in Clinical Evaluation
- Paul Volberding, University of California and San Francisco General Hospital

Drug Development Challenges Posed by the AIDS Epidemic
- David Baltimore, Whitehead Institute, Massachusetts Institute of Technology

10:45 - 11:00 Coffee Break

11:00 - 12:00 Federal Activities in Drug Development and Testing
- Anthony Fauci, National Institute of Allergy and Infectious Diseases

Industrial Activities in Drug Development
- David Barry, Burroughs-Wellcome Company

12:00 - 1:00 Break

1:00 - 3:15 II. Optimizing Basic Research and Preclinical Drug Development
Chair: Wolfgang Joklik, Duke University

Panelists
Bruce Chabner, National Cancer Institute
George Galasso, National Institutes of Health
David Martin, Genentech
John McGowan, National Institute of Allergy and Infectious Diseases
Robert Shope, Yale University
Cox Terhorst, Dana-Farber Cancer Center

3:15 - 3:30 Coffee Break

3:30 - 5:00 **III. Use of the Patent System to Foster Drug Development**
Chair: Lita Nelsen, Massachusetts Institute of Technology

Overview
- Lita Nelsen

Panelists
Carolyn Asbury, Robert Wood Johnson Foundation
Philip Chen, National Institutes of Health
Fred Fox, University of California - Los Angeles
Charles Leighton, Merck Sharp & Dohme

Tuesday, September 1

8:30 - 10:30 **IV. Issues in Clinical Evaluation of Drugs**
Chair: Catherine Wilfert, Duke University

Design and Utility of Clinical Trials
- Jerry Friedland, Montefiore Medical Center
- Thomas Fleming, University of Washington

Panelists
Patrick Gage, Hoffmann-La Roche
Martin Hirsch, Massachusetts General Hospital
Maureen Myers, National Institute of Allergy and Infectious Diseases
Edward Tabor, Food and Drug Administration

10:30 - 10:45 Coffee Break

10:45 - 12:30 **V. Regulation and Access to Drugs**
Chair: June Osborn, University of Michigan

Overview
- Frank Young, Food and Drug Administration

Panelists
Barry Gingell, Gay Men's Health Crisis
Craig Kessler, George Washington University
Mathilde Krim, American Foundation for AIDS Research
Edmund Pellegrino, Georgetown University

12:30 - 1:30 Break

1:30 - 4:00 VI. Optimal Use of National Resources

1:30 - 2:45 Optimizing the National Effort
Chair: Harry Meyer, American Cyanamid

Panelists
Terry Beirn, Senate Committee on Labor and Human Resources
John Burns, Roche Institute of Molecular Biology
Daniel Hoth, National Institute of Allergy and Infectious Diseases
Martin Rosenberg, Smith, Kline, and Beckman

2:45 - 3:00 Coffee Break

3:00 - 4:00 Is There a Need for a National Strategy?
Chair: Sheldon Wolff, Tufts University

Panelists
David Baltimore, Massachusetts Institute of Technology
Paul Rogers, Hogan and Hartson
Edward Scolnick, Merck Sharp & Dohme
Samuel Thier, Institute of Medicine

4:00 Adjourn