PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

RESEARCH HEARINGS
Community-based Clinical Trials; HIV Co-factors; Women and HIV; Behavioral Research

The Hearing was held at
the Metropolitan Life Building Auditorium
New York, New York

Saturday, February 20, 1988

COMMISSIONERS PRESENT:

ADMIRAL JAMES D. WATKINS, CHAIRMAN
COLLEEN CONWAY-WELCH, Ph.D.
JOHN J. CREEDON
THERESA L. CRENSHAW, M.D.
BURTON JAMES LEE, III, M.D.
FRANK LILLY, Ph.D.
BENY J. PRIMM, M.D.
PENNY PULLEN
CORY SerVAAS, M.D.
WILLIAM WALSH, M.D.

POLLY L. GAULT, EXECUTIVE DIRECTOR

COMMISSIONER NOT PRESENT:

RICHARD M. DEVOS
KRISTINE M. GEBBIE, R.N., M.N.
JOHN CARDINAL O'CONNOR

Research Hearings
February 20, 1988

I - N - D - E - X

P R O C E E D I N G S

February 20, 1988 [9:00 a.m.]

MS. GAULT: Good morning. Ladies and gentlemen, members of the President's Commission, my name is Polly Gault. I serve as the designated Federal official, and in that capacity it is my privilege to declare this meeting.

Chairman Watkins?

Opening Remarks

CHAIRMAN WATKINS: Good morning. Today the Commission begins its third and final day of hearings on subjects related to research and drug development. In the past two days we have heard a great deal from representatives of large entitles attempting to handle the research and drug production problems related to AIDS, the NIH, the FDA and the private sector pharmaceutical companies.

We also heard very moving testimony from persons with AIDS frustrated with those systems, testimony that will remain with us as we continue our work. Today we turn our attention to individuals. We will hear about a research group born out of the frustration of persons with AIDS who needed access to drugs and others who formed underground networks to distribute drugs.

The fact that PWAs and their advocates found it necessary to go outside the established system is a symptom of the problems these hearing are intended to address. We will also hear testimony about the special problems of HIV positive women and on the subject of co-factors.

This afternoon we will change our focus to behavioral research, to see if we have the tools that we need to construct effective prevention programs to stop this epidemic.

I would like to thank this opportunity thank Commissioner John Creedon and his excellent professional staff for their tireless efforts on our behalf in making these hearings efficient and possible.

I would also like to thank Dr. Frank Lilly for his guidance through these hearings on such difficult and complex issues, and for bringing so many of his colleagues in the science and PWA communities before the Commission to give us testimony.

I will now turn the chair over to Dr. Frank Lilly.

DR. LILLY: Thank you, Admiral Watkins. I think that without further ado we will continue into the planned program this morning. Our first session will have people presenting testimony to us about an organization formed for community-based drug trials. Dr. Joseph Sonnabend and Thomas Hannan are going to be our speakers. I think that Dr. Sonnabend will be our first speaker?

MR. HANNAN: No, in fact it will be myself, Thomas Hannan.

DR. LILLY: Mr. Hannan, I'm sorry.

Community-based Clinical Trials

MR. HANNAN: Good morning and thank you for the opportunity to allow us to present some information about the Community Research Initiative. My name is Thomas Hannan, and I am a person with AIDS. I am acting as the Administrative Director of the Community Research Initiative. On my right is Dr. Joseph Sonnabend, who is serving presently as Medical Director.

The woman who is seated between us is Suzanne Phillips, a fourth year medical student who has been volunteering her time to support the CRI and assist Dr. Sonnabend in his research. On my left is Carol Levine, formally of the Hastings Institute and currently with the Citizens Commission on AIDS. She is a member of our Institutional Review Board.

Before your questions I would like to briefly describe what the CRI is and what projects we are currently doing or are about to begin. Dr. Sonnabend and Ms. Levine would like to make brief remarks also before taking your questions.

The Community Research Initiative or CRI, is sponsored by the PWA Coalition. It has an impressive institutional review board or IRB and scientific advisory committee, and is registered and approved by the New York State Department of Health to sponsor well designed meaningful clinical trials of promising AIDS and ARC treatments in a community setting, conducted by qualified physicians in cooperation with informed volunteer subjects recruited from their practice.

Through the CRI a larger pool of interested patients may participate in trials and the statistical power of the results of the studies will increase, leading to faster progress in research. Although there is precedence for community sponsored research, the most exciting aspect of this project is that it originates from the AIDS community, empowering ourselves to participate in the research that may save our lives and

dramatically expand the number of patients who have access to experimental drugs.

This is a project conceived by and carried out by the AIDS community. We are taking the initiative to seek promising interventions against this disease in a responsible manner. The Community Research Initiative will utilize the largely untapped resource represented by the patients of private physicians providing health care to the gay community and other communities in order to seek interventions that can prevent the development of full blown AIDS in those at risk.

It will conduct controlled trials of promising interventions in a large group of human volunteer subjects and design protocols from the perspective of the patient. The CRI will also expand the number of experimental protocols under study, including alternative treatments and areas of research which might otherwise be neglected and are being neglected because no financial incentive exists for pharmaceutical companies.

Other activities of the CRI will be to provide an opportunity for both community physicians and their patients to contribute to vitally important research efforts, to monitor the results of private physicians' treatment of persons with AIDS or ARC using available drugs and natural substances such as lipids, to help to define directions of research and to serve the community with the latest data, and when appropriate to facilitate the formulation of guidelines for the day-to-day management of PWAs.

In general, the CRI will take the initiative to pursue any research and conduct any other activity which may contribute to the effort to learn about and eradicate AIDS.

The CRI represents a unique phenomenon. It is historic in two respects. It is the first time in history that people with a disease took the initiative to organize research to find a solution to the disease. When we embarked on our pentamidine trial it represented the first large scale trial in America to use community physicians to collect data to be used toward FDA approval.

In the packets which I believe the staff is going to distribute to the Commission, you will find the list of individuals comprising the various components of the CRI. Our Board of Governors which meets weekly, includes Dr. Mathilde Krim; Virginia Apuzzo, Deputy Commissioner of Consumers Affairs for the State of New York; Dr. Bihari and Sonnabend as well as Michael Callen, a person with AIDS.

As you will read in our packet, our Scientific Advisory Committee which generates and reviews ideas for research and from which principal investigators are drawn for our studies includes some of the leading scientists involved in AIDS; Dr. Donald Armstrong, Chief of Infectious Diseases at Memorial Sloan-Kettering; Dr. Donna Mildvan of Beth Israel Medical Center; and Drs. Michael Lange and Donald Kotler of St. Luke's-Roosevelt, among others.

Our Institutional Review Board (required by law whenever research is conducted on human subjects), and about which you will hear more from Carol Levine, includes seven doctors, two professors of law, religious leaders as well as people with AIDS. I can confidently say that no other IRB considering protocols about AIDS is as committed to protecting the interests of subjects and to guaranteeing the equitable entry to trials as our IRB is.

Included in your information packet is a list of 80 physicians who have private practices in New York City which include people with AIDS and ARC. These names represent the participating physicians who will submit patients for our clinical trials and who will cooperate in executing the protocols and providing the data for collection and analysis.

The CRI has only been in existence since May of 1987, but we already have five major clinical trials approved by our IRB and underway. We also have other important projects in progress.

The CRI appears to be increasingly attractive to pharmaceutical companies for carrying out the trials of their drugs. Our belief that we can do it quicker, more economically and better, seems to be shared by pharmaceutical companies.

Lyphomed, one of the manufacturers of pentamidine is funding a 200 person trial at the CRI which is already in progress with Dr. Sonnabend as principal investigator. This was the first trial to be approved by our institutional Review Board.

The 200 people with AIDS in the study are receiving either 100 or 150 milligrams of aerosolized pentamidine weekly as prophylaxis against pneumocystis carinii pneumonia or PCP, the number one killer of people with AIDS. The subjects will receive the drug for one year at no cost. The cost of the entire trial will be just under $400,000.00, which includes $43,000.00 contributed by the pharmaceutical company toward general operating expenses of the CRI.

Now that this trial is on its feet, we have been approached by both pharmaceuticals who manufacture pentamidine,

Lyphomed and Pfeizer Corporation, with offers to pay for a 500 person clinical trial for people with ARC who are at risk for PCP.

Ortho Pharmaceuticals is paying the CRI to study its drug, erythropoietin in a small trial. The study, which is underway, involves patients who are anemic either associated with the use of AZT or as a direct symptom of AIDS. The subjects will be drawn from the practices of Drs. Barbara Starrett and Nathaniel Pier and Dr. Starrett will serve as principal investigator.

A third trial approved by our IRB is Dr. Donald Kotler's protocol to test the efficacy of a therapy for cryptosporidiosis, a devastating disease, which involves the ingestion of cows' milk containing large amounts of antibodies as a result of infecting the cow with cryptosporidium. Seven patients from the practices of community physicians will be studied. Bristol Myers is paying for all the costs of this trial.

Our fourth trial is currently enrolling subjects. It is a comprehensive study of AL-721 about which I will tell you more in a moment. A parallel study of intravenous administration of lipid which is being done nowhere else, will be considered at our IRB meeting this Thursday.

A fifth trial which will cost approximately $.75 million has already been approved by our IRB and is about to begin. DuPont has chosen the CRI to conduct its first trial of Ampligen in people with full blown AIDS and will pay for the study. The protocol which was submitted to our IRB by Dupont originally excluded women and IV drug users. A clear example of our IRB's concern for equitable entry to trials is its stand to approve the trial only on the condition that the study be expanded in the number of participants to include women and IV drug users.

In spite of the increased costs to the company, Dupont agreed to the conditions. This promising drug will require three one-half hour infusions each week for the 50 participants.

An extremely important project for which the CRI is ideally suited is our informal monitoring project or Lange Project, so named for Dr. Lange who helped to formulate it. Critical information about the hundreds of patients perhaps thousands who may or may not be improving on substances which they are currently using, like AL-721, Dextran sulfate, WOB enzyme, or DHEA is falling through the cracks.

I am personally using these substances as well as others and am very anxious to know whether these substances are helping me.

Our current Antabuse monitoring project will be expanded to include other substances using a generic data collection form for computer inputting. Dr. Bihari has drafted the design for the antabuse monitoring which should establish whether clinical improvement and increase in T4 count occurs when patients take antabuse, a prescription drug for control of alcoholism.

The name Community Research Initiative should say it all. This the AIDS community, all people affected by AIDS taking the initiative to contribute to research responsibly. This community is not prepared to roll over and die.

This community watched and waited as Dr. Robert Gallo published in the New England Journal of Medicine in November of 1985, a report on in vitro findings that AL-721 appeared to be a promising candidate for further research especially in light of its nontoxic nature and ability to inhibit the AIDS virus. This community watched and waited as two years passed with absolutely no follow-up to Dr. Gallo's recommendations.

Years passed, people died, and zero research was conducted by the government. At the same time a tiny company with a very inappropriate name of Ethigen formerly Praxis, claimed a patent on AL-721 and kept all other manufacturers from supplying it but refused to make it available without medical claims, as they could under FDA regulations, while simultaneously pursuing drug approval.

In the meantime, people with AIDS were traveling in wheel chairs to Israel to get AL-721, just as they were traveling to Mexico to get Ribavirin, as I did. This community stopped waiting for the government or the so-called patent holder to move. This community moved. We organized an effort to make AL-721 available by whatever means possible.

Brave people with AIDS like James Perez, a very close friend covered with lesions, used his last ounce of energy on this earth to produce the egg yoke extract by a labor intensive and dangerous acetone extraction process. With people with AIDS assuming the risk of Ethigen suing for patent infringement, manufacturers were found to provide the substance.

Thousands of people are now taking AL-721 because this community took the initiative and still we do not know the degree to which or even whether AL-721 works. The CRI has embarked upon a study of AL-721 involving dozens of blood parameters to quantify its antiviral and immune-modulating effects, if any, at

various dosages. The study, by the way, is being paid for by money raised directly from community -- people taking action against AIDS.

I cite the example of AL-721 to illustrate two critical points: one, that people with AIDS should not and will not wait until the cumbersome, time consuming process of FDA approval is complete, especially with non-toxic substances which may help but can't hurt; and two, that meaningful research cannot be delayed on any substance which may prove to be effective alone or in combination with other drugs to work against AIDS.

On the one hand we have a research establishment which is slow and often misguided, ignoring potentially important interventions. At the same time we have an FDA which stands as an obstacle to people with AIDS getting as yet unapproved AIDS drugs.

The CRI provides an answer to the two part problem I have been describing. Large numbers of people with AIDS and ARC will be receiving drugs which they could not otherwise access while they are contributing to data about those drugs by participating in controlled studies.

We hope that New York City's CRI will serve as the prototype for many CRI's in other cities with large populations of PWA's. We are anxious to export the concept of community-based research to other cities and have prepared how to packets to facilitate other communities in starting up their own CRI's.

Dr. Krim has convinced AmFAR to fund a program to support CRI's and provide seed money to create CRI's in other cities. This program is called CARE - Community AIDS Research Endowment.

Finally, I cannot stress too strongly that the research conducted by the Community Research Initiative is just as legitimate as anything done at the National Institute of Health or anywhere else. Our data is just as meaningful and our methods at least as correct.

For instance, the protocol for our 200 person trial of aerosolized pentamidine was submitted in advance to the FDA for their approval of the study design. Our data will be analyzed with the data from the San Francisco General Hospital Study with Dr. Bruce Montgomery as principal investigator. Our combined results will contribute to a faster approval of pentamidine in this form and establish the effective dose.

Professor Peter Duesberg, who will be speaking before the Commission a little later today, made a very amusing slip of the tongue recently. After a public forum sponsored by the PWA

Coalition, he approached a person from ACT UP who was wearing a button which read "Silence Equals Death," but he mistakenly read it aloud with is charming accent, "Science Equals Death."

We cannot allow science to equal death. We must insist that research proceeds expeditiously and properly, exhausting every lead.

We have a responsibility to do it right. We have a responsibility to those we have allowed to die, like my lover who died in my arms this month, and we have a responsibility to those that still have a chance to live. I guarantee that the CRI will accept the responsibility of doing its part in finding a solution if one is possible to find. And I guarantee as well that people with AIDS will hold us all accountable to provide the very best that we are capable of, because that is precisely what it is going to require.

Thank you for hearing my testimony. I would now like to introduce Dr. Sonnabend who has a few remarks.

DR. SONNABEND: I am grateful to have this opportunity to tell you something about the Community Research Initiative and how it particularly can contribute to the development of effective treatments against AIDS.

Of the many emergencies that comprise the AIDS crisis, the need to develop effective treatments is maybe the most pressing and it is in this area that the CRI can make a significant and special contribution. The need to rapidly develop effective treatments means that we have to test many different treatments and combinations of treatments simultaneously. This is going to require access to a large population of patients with AIDS and AIDS-related conditions as well as, of course, an appropriate administrative structure that will enable the trials to be conducted in a proper fashion, the data to be gathered efficiently and the analysis done well.

Tom Hannan has just described something of the structure that we have in place in order to conduct trials in this fashion. The Community Research Initiative can tap into the practices of physicians who are providing care to individuals with AIDS in the community and this is how the CRI really started. It started with the idea that physicians here in New York City with large practices who see people with AIDS could provide a great resource for doing treatment research.

We realized very early that the group of patients in these practices are largely white gay men. Our Institutional Review Board at its second meeting -- this is almost a year ago -- addressed this issue of equitable entrance into treatment trials for all people with AIDS. I think this illustrates

already a responsiveness and responsibility that is an advantage -- I think peculiar to a community-based research endeavor in contrast to research that is conducted in medical centers.

One only has to look at the demographics of the large multi-center AZT trial to see this contrast. There were virtually no women, no black men who were enrolled at any of the study treatment centers.

As a community-based organization sponsored by people with AIDS, the CRI is particularly sensitive to their needs. The importance given to the issue of equitable entrance is not the only example of this sensitivity. The issue of pneumocystis pneumonia prophylaxis and the use of placebos in critically ill individuals are two further examples.

As Tom Hannan said, pneumocystis pneumonia is the most frequently occurring opportunistic infection that is seen in AIDS. This infection is almost definitely preventable although the kind of data that is needed in order to prove efficacy has yet to be obtained. It is of course, of great importance to obtain this kind of proof of efficacy.

It is also important that people with AIDS are not denied access to an intervention that will most probably prevent pneumocystis pneumonia even while trials establishing efficacy are underway. The CRI is meeting both these needs; the need to do a controlled trial and the need to provide patients with access in other trials to a means of preventing pneumocystis pneumonia.

As Tom Hannan mentioned, we have a formal 200 person trial that has been underway since the beginning of the year. This is a formal study of the effect of aerosolized pentamidine in preventing pneumocystis pneumonia. As Tom Hannan mentioned, the data obtained from this study which will last for a year will be combined with the data obtained from a similar study that is underway at the San Francisco General Hospital in providing evidence regarding efficacy and longer term safety of this particular intervention.

Now at the same time as conducting a systematic study on PCP prevention, the CRI when it considers other trials in AIDS patients has required that PCP prophylaxis is not denied to trial participants. Of course, this means that the occurrence of PCP in a particular trial can no longer be used as an end point. When one is testing a particular drug for efficacy, you can no longer look at the occurrence of PCP in a placebo group as an end point in such a trial. This simply means that the studies are going to be much more difficult to design but certainly not impossible to design.

I should also point out that the move towards pneumocystis pneumonia prevention has originated largely in the community of people with AIDS. I believe it is largely in response to pressure from this community. It is because of this pressure that the use of a life saving intervention is now being offered to more individuals.

In addition, the CRI has shown that the wider availability of such an intervention off protocol is not incompatible with the systematic gathering of data that is required to obtain proof of efficacy. These can be going on simultaneously. In other words, while we are doing the formal studies we should not be denying other individuals an intervention that in all likelihood will prevent them getting what may be a fatal infection.

On the issue of placebo controlled trials, the CRI is also responsive to the community of people with AIDS in resisting the use of placebos in trials where the life expectancy of the individual may be shorter than the duration of the trial. Of course, there are places for placebo controlled trials but critical illness with a short life expectancy is not one of them.

There are other ways to conduct controlled trials that do not require the use of a placebo. For example, the CRI is about to begin a blinded trial comparing two doses of active lipids analogous to AL-721 and Tom Hannan did say something about this particular trial.

There is a further advantage that community-based trials offer in comparison with those conducted in medical centers. This relates to the fact that people with AIDS who are trial participants at medical centers are frequently taking numbers of interventions on their own initiative. This is much to the dismay of the investigators who are aware that individuals in their trials are taking substances and are even resorting to drug testing trying to determine whether or not these individuals are taking other interventions.

People of course do not admit to this because to do so would exclude them from entrance into the trial. The CRI trials are more likely to acknowledge this reality, the reality that people are indeed taking other substances and to design the trial around this reality. I believe it is possible to do. There are, of course some instances in a specific trial, where the use of a particular substance would make it impossible to interpret the results. Overall, I believe that it is possible to design the trial around the fact that people are taking additional interventions as long as one knows what these are and designs the study around this.

The conduct of trials outside medical centers is a novel approach but it is certainly not unprecedented. Together with Dr. Krim I founded the AIDS Medical Foundation some years ago. One of our tasks was to conduct the kind of community-based research that the CRI is now undertaking. Our experience in establishing an Institutional Review Board and approving and sponsoring trials in a community setting indicates that such trials can indeed be successfully conducted.

In fact, many of the CRI IRB members were also members of the AIDS Medical Foundation IRB and thus have experience in reviewing community-based trials.

I would like to end on a personal note. I am a microbiologist and until 1978 most of my professional life was spent in a research laboratory with some clinical experience limited to infectious diseases in a hospital setting.

It is from this background that in 1978 I started to see patients in a private practice in Greenwich Village in New York City. Many of these patients were gay men who at that time already manifested a variety of hematologic abnormalities which in retrospect were the first and earliest manifestations of AIDS.

Thus, I have had the opportunity to observe this epidemic from its onset. My views about AIDS have been shaped by this practical experience of seeing many, many patients with AIDS from the onset of the epidemic, and also my research background as a microbiologist.

The view that I have about AIDS is that the causes of this disease remain unknown. I do not believe that HIV is the cause of AIDS. In my view, and of course this is not the CRIs view it is my personal view, but I will mention it now because I believe that the premature acceptance that HIV-1, and now HIV-2, cause AIDS has resulted in a commitment of almost all treatment resources towards the development of anti-retroviral treatments. While of course such work on anti-retrovirals has to go on, it should not go on to the exclusion of other approaches. I believe that the CRI is less likely to be constrained by the limitations that have been seen in previous treatment research.

For all the above reasons, I believe that the CRI and hopefully other organizations similar to the CRI which will come into being in other cities in the United States, that the CRI represents a very significant hope for the future in bringing larger numbers of individuals into a diversity of treatment trials and it deserves all the help and support that it can receive.

[The prepared statement of Dr. Sonnabend is included in the Appendix.]

MR. HANNAN: Would the Commission indulge us for a very brief remark by Carol Levine and then we would be receptive to answer your questions?

DR. LILLY: Ms. Levine is not a scheduled witness but we can do that. However, I would like to point out that some of our most useful sessions are the question and answer sessions, and we would like to reserve as much time as possible for that.

MR. HANNAN: Of course, I appreciate that. I am grateful.

DR. LILLY: I would appreciate it if you would make it brief so that we could move to the questions.

MR. HANNAN: Certainly.

MS. LEVINE: Yes, I will be very brief. My name is Carol Levine. I am Executive Director of the Citizens Commission on AIDS. I will be testifying before you at another time in another city on another subject. I am here as a volunteer. I am a member of the Institutional Review Board of the Community Research Initiative.

You all, I am sure, know that the IRB system is in place about 20 or 25 years and is required by Federal regulation and state law. This IRB operates under all of those regulations much as other IRBs do. It looks at risk benefit ratio, it looks at the informed consent process, and it looks at the selection of subjects. You've heard about that.

Why this IRB is different, you have heard one reason, and its particular concern with equitable access to trials which we have discussed at great length. It is also different, I think, because of the presence on the Board of physicians who treat people with AIDS and people with AIDS. That has made a difference in the evaluation of the protocols and in some cases, changing the requirements and reducing the number of tests, being sensitive to the burdens of the research even though it is considered a benefit and it is a benefit to be in a research protocol.

It also involves additional blood tests and other interventions. We have been very sensitive to that and the people with AIDS have made that very, very clear to us. For me, why do I do this and each of you have heard personal reasons, I really have a firm belief that the desire and demand to have access to clinical research must be channeled in a very productive way. This is a resource that we must use productively not only in the hope that it will benefit those individuals who are in the trials, but that it will lead to generalizable research for others.

I have a second belief that is extremely important, that local community-based efforts should be supported in research and education on all levels. This immense problem cannot be solved unless we really deal with communities where they are.

Finally, a very firm belief based on what I have heard for seven or eight years that there is no single answer, that there will be a number of research findings that taken together will make it possible to treat this disease. This kind of initiative does help that. It should not been seen in any way as a substitute for Federal, State and large scale interventions and initiatives.

It can provide additional important information. Thank you.

DR. LILLY: Thank you. I would like to start the questioning with Dr. Lee. I would hope that during the questioning that we could come to some perhaps slightly more concrete idea of in what way the Commission can make recommendations to the Administration that will be of use to you and organizations like you.

DR. LEE: Thank you, Dr. Lilly. I have three sets of comments, and I would like the panel to keep them in mind and then come back to me with your responses.

First of all, your inclusion of active drug addicts in your research studies, I believe is a bad mistake. For whatever percentage of drug addicts you have in your trial, you will have that percentage of completely flawed material available to you. Anyone who has ever worked with drug addicts knows, especially IV drug addicts, that they are unpredictable at almost the 100 percent level.

If you have good medical people on your Advisory Board and you do, I am sure they will dissuade you from including those people in your trials or collecting data in an unsegregated manner.

Number two, your community-based research initiatives are being strongly pumped by NIAID, by Dr. Hoth. We heard a great deal from him last night about that. He was, as you know, transferred out of cancer work into the AIDS effort. He is one of the best people in this country, he is strongly on your side, and I would hope in the next six months I would hear more cooperation from your end instead of this constant bashing.

A last comment, you brought up this business of Ethigen. We heard a very similar thing yesterday from HEM

Research. The dragging of the feet when one has a drug on tap for personal reasons, or private reasons, or economic reasons is something that certainly this Commission wants to address. If there is more detailed material available on this type of activity we would like to know about it.

One additional thing. The companies that are supporting you seem to be getting these drugs approved in some way and giving them to you. We have been told that the companies are not having any hold up here at the FDA level. Is that true or not true?

MR. HANNAN: In the context of the controlled trial there is no hold up. My reference to people with AIDS trying to access other substances was with regard to products like dextran sulfate which may not be in a controlled study at this time but people with AIDS may want to access them.

If I may respond to your remarks and maybe Dr. Sonnabend is much more qualified that I, would also like to respond. I am deeply distressed by your remarks that our trials would in some way compromised because we include IV drug users.

I am not a scientist and I don't know the details of how well science is properly conducted. It is not my job at the CRI to do that. We have a search currently for an administrative director to replace me who is more qualified with FDA regulations, et cetera. I am a person with AIDS who took the initiative to get this started and other people on this panel are probably much more qualified to respond to your remarks in terms of the science.

If Dr. Bihari, who is on our institutional Review Board and Board of Directors were here to respond, he is the Director of Addictive Services at Down State Medical Center and has on many occasions, said that there are populations of IV drug users and former IV drug users who could in fact be the most very responsible participants in trials.

People in methadone centers, et cetera, who are anxious. People with this disease have their lives on the line and they are going to cooperate. There are IV drug users who are participating in our trials currently and who are coming every other week as they are supposed to for the pentamidine trial. Without breathing this pentamidine they are in tremendous risk of getting pneumocystis pneumonia. We have IV drug users who are now former IV drug users because they are taking seriously concerns for their lives. They are taking responsibility for their lives, perhaps in some cases for the first time.

Secondly, with regard to your feeling that you have been listening to remarks about the CRI positively which seem to

be strongly pumped by the NIH, I am very grateful for their positive remarks with regard to the CRI's activity. In fact, we have met with Dr. Killen on many occasions and he has been very enthusiastic about a cooperative effort.

If I seemed to be constantly bashing the system it is because heretofore things have been going slowly. I have tremendous optimism that the NIH especially insofar as it will cooperate with the Community Research Initiative, will be making great progress.

When you refer to Dr. Hoth coming over from the NCI where he has some experience with a community-based research in cancer research and Dr. Killen, I am quite enthusiastic and confident that we are going make progress hence forth.

My remarks referring to what trouble we are in today are because things have been so sluggish.

DR. LEE: My life has been spent doing drug studies in cancer patients. There is not a cancer study anywhere that will include active drug addicts, because their participation is too unreliable, and therefore, the data is too unreliable.

What we do is, we will treat these patients "off protocol," with the drugs or radiation, but we do not include them in our statistical data. Now, we are in a very difficult situation. So much needs to be learned about HIV in immune-compromised, drug addicted individuals. And while I am sympathetic to your wanting to include them, any complicated protocol in which active addicts are included will be difficult to evaluate, at best, especially a small study like yours.

MS. LEVINE: The IRB chose to put the conditions in this way: the ability to comply with the protocol is a valid criterion; but that we would not consider simply being an IV drug user automatically exclusionary. It would be up to the investigator to determine on an individual basis whether a person who five years ago was an IV drug user and is no longer, that person might be perfectly able to comply.

In fact, the importance is the population of the future will include many people in this category. It is important to know how these drugs act in that group. I would also like to say as a fourth year medical student doing my clinical rotations at Brooklyn Hospital, that I am approached many times by patients who are not necessarily themselves IV drug users, but who are diagnosed as having contracted -- who believe they have contracted AIDS through sexual contact with people who had AIDS.

Many of these are married women with children. They cannot afford to tap into the network in Manhattan which can be

very expensive. They beg me with tears in their eyes after they have asked me for what arrangements they should make for their funeral and the disposition of their children, do I not know of some sort of research protocol that they might not be able to get into. The desperation and determination, I have seen many lives turned around by this disease, Dr. Lee.

Many people re-evaluate choices that they had made in the past that they now view as mistakes and want very much to live.

DR. LEE: Emotionalism is not a substitute for evaluating these drugs properly.

MR. HANNAN: Dr. Lee, our institutional Review Board has some very qualified people, extremely qualified, and serious consideration entered into the decision to include IV drug users in the particular trials. I am confident of their decision.

DR. LILLY: I would like to go on to another question.

MR. CREEDON: I would like to comment on it, because I for one, felt good about the fact that the CRI was including IV drug users and I would think that there would be some way of having a statistical method, even though you are including them you can report results both with them in and out. I would think there would be a way of approaching it, and I would certainly urge that you do it if you can figure out a way of doing it without compromising the study.

DR. LILLY: I would also say that in fact since there may be possibly differences between the responses of IV drug users and gay males for example, that it would be a very good idea to do one's best to collect data on that population.

MR. CREEDON: Absolutely.

DR. LILLY: Dr. SerVaas?

DR. SERVAAS: I am impressed with what you are doing, because I think anyone of us at the table who had AIDS would probably be doing the same thing. I really believe that. I think that we can help you because I understand Dr. Lee, where he is coming from. We have tested a number of former drug addicts who are now completely turned around, completely responsible people who are AIDS, HIV positive.

If you send to the Commission where we reach you, if you are nationwide, we could help you get these very responsible rehabilitated former drug addicts who now want to live as you have pointed out, want to do everything right and have a great deal of interest and are not going back to drugs.

I believe we could help supply these HIV positive individuals who were former drug addicts from around the country if you will give your address and information to the Commission. I got the impression that you are nationwide; is this right? You have now locations in other cities?

DR. SONNABEND: We are attempting this.

MR. HANNAN: We are attempting to create Community Research Initiatives in other cities, as I mentioned. Right now the Community Research Initiative in New York City is the only one with trials underway, and we hope to serve as the prototype for other centers and are trying to facilitate other groups in other cities getting started.

I would like to continue with the IV drug users just very briefly, because I don't want to dismiss Dr. Lee's concern for the compromising of the science in trials. I don't believe that the CRI would ever allow science to be compromised just for the social responsibility of including IV drug users.

I believe it is possible with a creative approach. I am quite certain that we should stratify the information that we are collecting about IV drug users, because as Dr. Lilly indicated, there may be physiological differences in the way this treatment progresses in different groups including women and IV drug users.

It is essential -- this is the only way that people in these groups can be treated. Treatment for AIDS today is with as yet unapproved substances and that means controlled trials.

DR. SONNABEND: Just one further point about drug addicts and their participation in our trials. The future of this disease the way it is moving, is largely as Carol Levine said, into this population. When that happens I believe the support for AIDS research is going to decline. So we have a very important moment now when we have the ability to reach out and make connections with this population, that we should utilize the time very efficiently in linking to the drug addicted community and bringing them into trials now before the mood and climate shifts.

DR. SERVAAS: Are you doing things with people who are HIV positive before they get ARC? Do you have any protocols?

DR. SONNABEND: We don't currently have a protocol for that.

MR. HANNAN: None of the five protocols that we have in place currently are specifically to look at agents working in HIV

positive. Our informal monitoring project which I described, does of course include all people in various stages of this disease, and will be looking at large numbers of people who are doing various interventions including HIV seropositive who are otherwise asymptomatic to see whether those people over the long term do not become symptomatic by using these agents.

It certainly is our intention to be doing protocols in the future which would include those people. It is central to our concern.

DR. LILLY: Mr. Creedon?

MR. CREEDON: I think one of the great strengths of our country really is the whole concept of competition. I think what you are doing is introducing an element of competition into the realm of ideas on how to deal with the AIDS problem. I certainly commend you for what you are doing and I say right on.

I think it is very frustrating to hear about this AL-721. I think we ought to find out about why it was identified by Dr. Gallo two years ago and nothing was done about it. There has to be some kind of an explanation for that.

The other thing, I would urge you and I'm sure the Chairman will, to let us know how you think we can help. I would suggest that you might consider applying to the insurance industry for some help too.

MR. HANNAN: Very good suggestion. We thought of it, thank you.

DR. LILLY: Dr. Walsh?

DR. WALSH: I, too, have been very encouraged to hear what you all are trying to do this morning. I am doubly encouraged by the attitude that we heard yesterday, particularly from the FDA because if you were not here yesterday, Mr. Hannan, I think that you should be alerted to the fact that Frank Young really said his door personally is open to do everything that he can to expedite the clinical trials.

I think that when we hear things like this we ought to quick take advantage of them before they have a chance to change their mind. I really feel that you should contact them right away and tell them what you are doing.

I am sure, as I think as Dr. Lee suggested to you on your IV drug users, that in the interest of your own research and in the interest of your own patients and colleagues that if you find somebody violating protocol you will put them in a different column. You may not drop them out but you will put them in a

different column, just like Dr. Lee does as Sloan-Kettering so that you would have some collateral information.

I think any good scientist does that. Dr. Sonnabend is going to do that. I am sure he's not going to let your protocol be disturbed.

I have one question and then I am going to as you to help us. The question that I have is I was not clear -- I think you said -- I know in your paper that you are doing placebo trials on people without AIDS that are not in danger of death. But are you doing some of these drug trials at all on just seropositives that are not people with AIDS to see whether anything is happening to change the course of the disease? I think I heard that you are, but I wasn't sure.

MR. HANNAN: No. In fact, we don't have a formal protocol approved by IRB yet. We have only been existence since late 1987. It is our greatest anticipation of course.

DR. WALSH: The other thing that encouraged me so much is that you are getting financial assistance from the pharmaceutical companies. Now again, this is something that I would urge you continue to do. If we are getting into bashing from a different framework it is much better to go to them for financial support for your studies because they are very anxious to have them done, than to worry about what the ultimate cost might be later. You can bash about that later but don't antagonize them.

Go to them for help because you are helping them and they will help you. The request that I have from you is can you give us either today or in writing, some concrete suggestion of what we could do to help expedite more community-based trials. We do have concern, and I think some of us expressed it yesterday, that with all the good intention in the world NIH can restrict what drugs are to be tried.

You have to remember that these men come -- and Dr. Sonnabend will appreciate this especially -- from a scientific trained way of approaching things. They get on a hot drug and that's the one. The think here we have an answer and we are going to push this one all the way until we find something better.

There has to be a way for us to get them to perhaps be more relaxed somewhat with their funding or with their ability to put out study funds, to support more clinically community-based trials in the way in which you have organized them rather than just the university-based trials at these so-called ATEUs that they have.

The pharmaceutical companies are having trouble with the ATEUs and they testified to this. They feel, I am sure your method of clinical trial is much closer to what pharmaceutical companies normally do in clinical trial. I think they would be sympathetic to this. Perhaps we as a Commission as well as them could help you expand this concept.

We are very conscious that your concern with people who are dying now -- this is a different disease than say the longer range illnesses that we see, cancers and heart diseases, where you can take a little more time with research.

You have too many people dying too quickly. I think that everyone is interested in finding an answer but without violating serious scientific protocol, and I don't think you want to do that. I know you don't want to do it, because you are going to jeopardize yourselves if you misapply the use of drugs or combinations of drugs as you know you can set back treatment rather than advance it.

Your purpose is to advance and help the PWAs and not to set them back. Let us know as specifically as you can, what we can do to get more support and more interest and more consideration directed to community-based trials, modeled after your experience.

MR. HANNAN: Dr. Walsh, thank you very much for your suggestions. We intend to provide to the Commission in writing, details of the specifics and how you could help us and what our needs are. Specifically right now, I can tell you that you could reinforce your unique position of power in the report that you come up with. You could reinforce what already is apparently happening; that there is support for this kind of idea.

As Dr. Lee already indicated, the NIH appears to already realized the potential of systems such as this, as alternatives and systems which can cooperate with the NIH. Dr. Hoth has already gone on record indicating that he would like to support the CRI financially and use its resources as a tool for the NIH work.

You can help us a great deal by encouraging that in your report.

DR. WALSH: We want to turn those words into action.

DR. LILLY: A very quick question. Have you received any government support whatsoever?

MR. HANNAN: We haven't formally requested. We have had meetings with Dr. Killen and he has made indications that it

would be possible in the future, but I am not going to bash the NIH for not giving us money.

DR. WALSH: Keep in mind incidentally, that although the FDA is normally not a granting agency, Dr. Young did indicate yesterday that they have given four modest support grants for some kind of trials. I frankly don't recall what they were. This was very unusual.

But apparently they have a small pot of money and you are not talking about a great deal of money when it comes to the granting cycles. It might pay to see number one, what he can do and number two, what he could influence.

MR. HANNAN: Thank you for the suggestion. That is the reason that I am being replaced as Administrative Director.

DR. LILLY: I would like to go to Dr. Crenshaw because we are running very late. I'm very sorry.

DR. CRENSHAW: In relation to the inclusion of IV drug abusers issue, in drug research not related to AIDS that I have done in California, one of the things that we routinely do is drug screens because you never know who is clandestinely taking drugs. I don't know if you are already including this in your protocols or not, but that is helpful in monitoring these issues so that you are not surprised.

I am also very pleased to see the interest in antabuse, which I think raises questions that can rapidly and cost-effectively answered relatively quickly.

The thing that I would like to ask you and both to help us with reflect upon -- although I know you've given it a lot of thought -- as leaders and representatives for the PWAs, you hold in your hands enormous power relating to the manner of spread of the disease because we all agree the major motive spread we are concerned about is sexual transmission.

What exactly do you advise in relation to sexual behavior to prevent the spread, and how do you advise someone in spite of the advice that you give continues to be sexually active or not warn their partners or not use protection. I know it is a struggle for all of us.

What are you doing; what is the current approach?

DR. SONNABEND: As a research endeavor it hasn't been our role to -- you are asking if the CRI has a role in terms of giving specific advice to people. We have not assumed that role, but I think the advice that the CRI might be seen to be giving is that of the People with AIDS Coalition. That is that there is a

concept of safer sex, of the use of condoms and this is promoted.

Information about safer sex and access to condoms and information about their use is, in fact, actively promoted.

DR. CRENSHAW: I guess the comment that I would then make is that you have a unique opportunity and even though it may not be perceived as traditional in research from my bias, behavior research and the issues of preventing transmission of this disease will help you in the long run so much in the people you are trying to protect.

The challenges that this AIDS epidemic poses, if you can break tradition a little and see what it is that you can do in the role of prevention since you have the opportunity in the patients that you are working with. I think it would be very valuable.

DR. LILLY: Dr. Primm.

DR. PRIMM: I would just like to commend the panel on their stand about including intravenous drug users in the studies that you do. I find that they are awfully responsible and particularly when they are infected with the virus or, indeed, when they have full-blown disease. And I want to let you know that you can call on me and get some responsible intravenous drug users who are in treatment from my program at any time you want.

It's good to see you, Suzanne.

DR. LILLY: Admiral Watkins?

CHAIRMAN WATKINS: Well, I, too, am enthusiastic about what you are doing. I think you are at the heart of perhaps a concept in the nation that needs to be critically looked at, not only for the near-term, but the long term as well. I believe that when we have a rapidly moving emerging crisis of this type that it is very important to mobilize the community-based initiatives in the country and pull them together as you have done.

I think you have done it in a very responsible way. I think you are a tremendous adjunct to what can and should be done at the national level as well, and what I am thinking of, I am wondering if, Mr. Hannan, you could give us a little better picture on how the Commission might ensure that there is some potential to have a linkage, some kind of a linkage with the NIH in perhaps a little more -- maintaining the independence on the one hand, but technical link, because you are so treatment-oriented with scientific data being supplied, which is very necessary in this crisis, and we have seen the importance of

sensitivity to immediate treatment to people with AIDS. At the same time we want to get scientific data, it seems to me you are providing a nice sense of balance between the two different approaches to clinical trials, and so I commend you for it.

I wonder if there might be a separate initiative, for example, for direct NIH grant programs to this community-based concept of research. Is there something there that can be done to enhance not only the value of CRI, but perhaps CRI tentacles that would be elsewhere in the country, and begin to move in that direction to test your approach to clinical trials.

At any rate, it would be useful if you could give us a little better idea of how there might be a coupling there for the near term and for the longer haul as we begin to look at some downstream concepts that might be a lesson learned out of this infectious disease that we need to leave for the nation.

So would you be willing to do that and give us some feel for whether or not there are some things that we can do right now perhaps to enhance what you are doing, and to get a better coupling, between NIH and you and, at the same time, give us an idea of how this might be looked at for the longer haul?

MR. HANNAN: Admiral Watkins, it is incumbent upon us to make specifics to the NIH, which we have informed them that we will do. They have substances which they have not yet moved on, which they have in the high priority classification, such as dextran sulfate. We are in a unique position with this simple substance, which is taken orally, to monitor and do a serious trial very quickly.

In fact, the PWA health group, about which you have heard before, which makes lipids and other substances available, is making dextran sulfate available so that the time is right now, before too many people are doing it and we don't have data on it, to get a controlled study in place.

Now we could approach the NIH for that particular project or hosts of other projects. As I mentioned, the informal monitoring project of hundreds, perhaps thousands, of people doing various substances is something that is not being done anywhere else, and direct funding by the NIH for that project would be money well spent and, in fact, it's been discussed with Dr. Killen.

DR. SONNABEND: Maybe, Admiral Watkins, there was something else you may be suggesting, which is how can we link, in terms of sharing data or having some kind of dialogue. Because, as you suggested, we represent an alternative or a rather different way of going about this business of treatment trials, and there would be some value if in fact there was some

kind of dialogue in a formal fashion that could be set up between what we are doing and what future CRIs are doing, and the research that the NIH itself is sponsoring. And it would be a mechanism for a dialogue, the exchange of information, to our mutual benefit.

CHAIRMAN WATKINS: Thank you very much.

DR. LILLY: Thank you, gentlemen and ladies, for your participation this morning.

"Underground Drugs" and Information Networks

DR. LILLY: Our next panel will present four individuals who will expand upon some information that we received yesterday as well. It would appear that in their search for treatment for their disease, PWAs have felt that they needed to resort to information-gathering on their own, and the development even of systems of finding drug treatments not through the regular channels.

We will now have a panel consisting of four individuals who are going to explore this area for us. The first speaker this morning is Mr. Martin Delaney, who comes to us from San Francisco, where he has been in charge for some time of the group called Project Inform.

Mr. Delaney.

MR. DELANEY: Thank you, Dr. Lilly.

I would like to begin by thanking the Commission for inviting us to speak here today. I don't know, but some of you may be aware of the fact that I was one of this Commission's harshest critics when it was first formed. I had some strong comments to make in the media, and I must say that since that time I have had to eat my words, and I have been quite impressed by the fairness and objectivity with which you have proceeded.

I was particularly impressed with your initial report because it simply did not live up to some of the nightmares that I had had about where this Commission was going. So I am glad that we are in a cooperative mode at this stage.

Now, unfortunately, in my testimony today I am going to have to say some things that I feel are critical, and I hope I can do it in as constructive a manner as possible. I don't want to feel that I am up here to bash the federal authorities.

On the other hand, I sat here for hours yesterday listening to testimony that I felt was vastly removed from the reality that we have experienced in the community.

I would also like to begin just by following up on the last presentation. I know we heard about NIH's interest in supporting community research. This Commission should know that San Francisco has had a community-research initiative in operation since 1985, perhaps a more conservative group than the one we talked about here, but as recently as last week that commission, that consortium, was denied funding by the NIH.

DR. LILLY: What is the name of that group?

MR. DELANEY: Pardon?

DR. LILLY: What is the name of that group?

MR. DELANEY: That's the County Committee Consortium operating out of San Francisco General.

Based on the testimony that we heard yesterday, it is probably evident to the commission right now that the AIDS community exists in a very different universe than the one that federal officials presented.

They claimed before us yesterday that there are no statutory obstacles preventing access to helpful drugs; that no one has ever been denied access. We in turn have experienced a system in which we are denied access to dozens of drugs which have shown promise in early trials.

They claimed that drugs may be made available on the basis of many possible criteria, including in vitro data, animal studies, Phase 1 data, even the structure of a drug. We have experienced a system which has denied treatment IND for drugs which have met all of those criteria.

They see a system which is bending over backwards to make drugs available to people in need. We have experienced a system which has delivered a single drug.

They see a wealth of new treatment INDs coming just around the corner. We have heard that same promise virtually every month for the last year and have not seen the results of it.

They describe a utopian vision of efficiently-run agencies which are squarely on top of the problems we face together. We instead yesterday saw round after round of slick presentations created by public relations specialists and, in

fact, they were the same presentations we have heard for the last two years.

I have to ask, does the Commission seriously believe everything it has heard from the Federal agencies over the last two days. I desperately hope not. It has in effect been asking the fox how things are going in the chicken house.

[Applause.]

MR. DELANEY: And in contrast to Dr. Young's point yesterday, I do not say this to raise funds for my organization.

MR. CREEDON: We are also asking the chicken.

MR. DELANEY: Yes, and I do appreciate that, as I said. I think it's wonderful that you are hearing both sides of this.

FDA yesterday attempted to have you believe that the problems exist primarily as a perception gap between the AIDS community and what in fact has been done for it, that we simply aren't well informed. That is simply not the case.

The member of the AIDS community who testified before you yesterday and the people who spoke here today and will follow me this morning in fact are among the 10 or 15 most knowledgeable people in the country on what has been done and how the system actually works.

These people have spent together many dozens of many years attempting to make the system on our behalf. We have followed their procedures, we have tested their systems, we have filled out their paper work, we have repeatedly listened to their same presentations over and over again, and in all honesty, I must say we conclude that they are not telling you the whole truth, at least not as it impacts upon us.

The facts are these:

To date, only AZT has been made available in general under the federal process. A few days ago Trimetrexate was released for a few hundred patients with PCP. Other than that, all other drugs have been turned away by the regulatory process, and most have been ignored in the testing process. The rest of what you have heard is mere talk.

Manufacturers across the country fear using the treatment IND process because of the manner in which it has been managed by FDA. We have heard this repeatedly from pharmaceutical companies who tell us they won't in a cold day in hell attempt to use the treatment IND process. Their attorneys, everyone else, is telling them that to use that process is an

invitation to trouble, both with FDA and, as you recognized yesterday, with legal issues as well.

Therefore, in our experience in the community, this lack of access to treatment has created the vast underground of smuggling, manufacturing and distribution of unapproved drugs. I don't pretend to you that this is all a wonderful or glorious thing. As they pointed out in the last presentation, we don't know whether much of this is helping or hurting, yet it goes on largely because people feel that it works. And I must say that people are very quick to dismiss products that they find that are harmful or worthless.

For years we have seen what appeared to be clinical improvements brought about by the use of products that FDA will not recognize and NIH will not test. I don't think we are crazy because our lives depend upon making the right choices.

Today great numbers of HIV infected people who have experimented with both the approved solution, AZT, and these unapproved solutions have in fact gone on to choose the unapproved solutions.

You have probably heard over your various hearings that many people believe that those facing death should be permitted access to any treatment which is shown to be safe, whether or not that treatment has been proven effective. Many find this argument particularly compelling where no proven treatments are available.

Many others believe that life-threatened people and their physicians should be permitted to decide what risks they undertake; whether that risk be to their health or merely to their wallets.

Currently the power of making that choice rests solely in the hands of federal bureaucrats far removed from the agonies of fatal illness.

Project Inform as a group concurs with this view that people ought to be given that right, particularly people who face life-threatening illnesses, that it ought to be up to them and their physician to decide what choices they can make.

However, we realize in a practical sense that it would require enormous changes in the American system of medicine to make that a reality and, therefore, I am here today to suggest some other things that fall perhaps short of that, but which I feel would be possible to achieve within the current structure.

We feel basically that the treatment IND regulation as described by FDA was a major step in the right direction, at

least in intention. However, we find that process has to date been crippled before its final passage. Now you know by way of background that the regulations have only produced one drug, and to date not a single HIV-infected person has had access to any drug under those regulations.

Dr. Young contends this is because no worthy drug has yet been available. We believe, instead, that this is because of flaws in the structure of that regulation.

Treatment use process has failed because the regulation itself appears to have been deliberately emasculated before its final passage. Now this is a fairly complex subject here, and I think it is critical that the commission know the actual language of the treatment IND regulation as it was passed and the language under which it was first proposed by Dr. Young, and there are some significant gaps between what he originally proposed and what in fact he was able to move through the federal system.

In the original version he proposed that a treatment use of an experimental drug should be denied to a patient only when the evidence, taken as a whole, showed that the drug did not provide a therapeutic benefit, or when it was harmful.

In other words, he had relaxed the standard of efficacy required for releasing a drug, a concept we agreed with. This version was completely consistent with the advertised purpose of the regulation.

In the final version of the regulation, however, that was changed. In the current version of it, as printed in the Congressional Record, it says that treatment use would be denied when the scientific evidence, taken as a whole, fails to provide a reasonable basis for finding the drug effective. In other words, the drug must now again be shown to be effective. And if we insist that efficacy be proven for a drug, we are back to square one. No change has taken place.

At best, under the regulation, all that has been eliminated is some of the ludicrous paper-pushing that normally occurred even after a drug had been proven effective. We have taken perhaps a year off the treatment process or the treatment licensing process, not the many years that had been proposed.

Now you have to ask, "Why did this take place, what happened here?" because it did seem that Dr. Young had moved in the direction that we had wanted.

Our investigation tells us that this change came about in response to pressure from the Pharmaceutical Manufacturers Association, which acted to protect the interests of the largest

manufacturers, primarily against inroads by the smaller ones. Under the current system, only the largest manufacturers can afford to support the many millions of dollars it takes to license a clinical drug. Under the new system, that would have been changed and in fact Dr. Young said that was one of his intentions in making that new regulation.

That aspect of the regulation was also opposed by the most conservative members of the medical establishment, whose concern as you noted the other day for risk overweighed their concern for possible benefits.

Commissioner Young in private meetings with us including just here yesterday while sitting in the audience admitted that this was a failing of the regulation. But he pleads with us for understanding on the grounds that he got what he could within the federal system, even though it is not the ideal that he had asked for.

I think it is critical that this Commission in private ask Dr. Young and how you can help get what he actually asked, how you can help him get around the objections that he had faced.

The regulation is further damaged, we feel, because the language used to describe efficacy, once efficacy was put back into it, that language is extremely vague and subjective, yet in effect it leaves all power to release a drug solely in the hands of the Commissioner. We believe that to date that power has been wielded in a somewhat capricious manner and we can point to examples in which that has been the case.

There are currently no accountability for how Dr. Young interprets that efficacy standard and there are no printed standards which he must adhere to.

Now obviously we believe that the immediate, wider treatment use of AIDS-related therapies for drugs which are safe and have a reasonable expectation of efficacy will benefit many people in our community. We also feel it will speed the process of research and make more drugs available to the community research initiative.

As it stands now, many of the drugs which could be made available in the manner are already in use by patients, as you have heard. People are getting them from other countries, they are manufacturing them on their own. However, this method of getting them adds greatly to the cost, diminishes the effectiveness and probably raises grave questions of safety and adds nothing to the database of treatment information.

Now to rectify this, we suggest several specific changes.

Number one is simply to define or remove the efficacy requirement in the existing regulation. My preference is that we go back to the original language that Dr. Young proposed; if not, that we ask him to define in concrete, measurable terms what standard of efficacy a drug must meet in order to get a treatment IND. I don't believe that our group should be the only one to have input on this, nor do I believe that FDA should be the only one. I believe that pharmaceutical manufacturers, the National Institutes of Health and the AIDS community itself should have input on what the level of efficacy required should be.

To date, this failure or refusal to define the standard of efficacy has led to a crippling fight over the release of one AIDS drug: you have heard it referred to repeatedly in these meetings as "the Ribavirin story," in which FDA has turned down the treatment IND in direct opposition to the ATEU sponsored investigators who studied the drug. I have supplied you with a great deal of information on that situation and I would hope the commission would read it.

Recommendation number two: This commission should ask to establish a national databank for monitoring the treatment use of new drugs.

Number three: It must to establish clear endpoints for treatment use. We certainly don't want drugs out there that can't be taken off the market if they are hurting people.

Number four: We need to ask for certification of physicians for their role under treatment use, so that not everyone in the world is out there using these drugs, but rather physicians who are certified to use them and to supply data in a clear and consistent manner.

Number five: We must establish legal protection for sponsors and physicians for treatment use. We are in complete support of the commission's expressed interest yesterday in creating legislation to provide this protection.

Number six: We ask that you establish a National Clearinghouse for Treatment Use Information, so that patients and physicians be in the position to make informed consent on the use of these drugs.

Number seven: To establish a formal link between this treatment use process and the community research efforts you have heard described here this morning; they are natural partners.

Number eight, and a very important point: We must establish a mechanism under which manufacturers can be induced to make their products available under the treatment IND. Currently

it is solely up to the whim of the manufacturer to do that and that is not acceptable.

In conclusion, we want to say that FDA is on the right track with these regulations but has shot itself in the foot with the way the regulation was worded. I don't fault Frank Young for that; I think he tried to do it correctly and he was forced by forces beyond his power to change that regulation and I would ask you to give me support to correct it.

In closing, I want to make a brief statement here about the conflicting voices that you hear over so many of these issues. I know we are saying one thing, FDA, NIH may be saying another. But I want you to look at the historical record before you decide who you listen to.

Historically, in 1981 through 1984, the gay community activists urged the country to allocate necessary resources to fight this problem. Those shouts fell on deaf ears for four years while the epidemic grew out of control. Finally people are listening to us.

In 1982 gay activists warned of problems in the blood supply while the public health service ignored us. They have listened now.

For the last two years we have been urging wider trials and investigator-initiated research to deaf ears at NIH. Yesterday you heard them urge the same thing.

And finally, since 1984 we have been telling you that there are safe and effective remedies already in use, please listen to us.

DR. LILLY: We have three more speakers and very little time left now. I would hope that the other speakers can keep to a somewhat more reasonable time frame.

The next speaker will be John James, who has for some time been putting together a newsletter with respect to information about drug treatments for AIDS.

MR. JAMES: Thank you for having us here and for having such a broad range of viewpoints in these hearings. That builds confidence.

Just one change in the schedule. The name of the newsletter is "John James Newsletter." It has gotten called that but that has never been its name. I don't know where it came from. The name is "AIDS Treatment News." I think you have my statement, so I won't read it all. But I will indicate some of what is there and leave it for the record.

Anyway, this began as a volunteer effort for an AIDS organization of Documentation of AIDS Issues and Research Foundation in San Francisco and it just grew. It was not started by intent. It grew to a circulation of 3500 in one year with no advertising or promotion, just be word of mouth, indicating the need of people for the information.

People with AIDS react in different ways. The people I hear from are the people who do want to take a personal involvement in their medical care. The people who resign themselves to death or who decide that they are just going to follow their doctors and not be involved, I don't hear from them.

But from these people I do hear it is a unique viewpoint, being on the phone continuously -- that is how the newsletter is put together. I am not a physician, I am not a scientist. I am doing this as a journalist, talking to people, getting on computer databases, talking to scientists and physicians to persons with AIDS and ARC.

One of the comments -- thoughts in trying to bring this together was that oddly enough, there doesn't seem to have been a survey -- I don't know of a survey of people with AIDS or ARC or antibody positive asymptomatic people, as to what they think is a scientifically, professionally conducted survey as to what they see as going on, what they would like to see as changes in the process.

In fact one of my recommendations in this paper is that such studies be conducted. In the absence of that I took as putting together a wish list -- actually we're just one item on the wish list from Dr. Nathaniel Pier, who is a physician in New York in private practice with a caseload of about 300 people with AIDS or related conditions.

He commented that above all that anybody diagnosed said for the wish list of what he believes we should have, which I believe is as close as anything I have hear to what the AIDS community I am in touch with wants. Anybody diagnosed with HIV-related disease or immunodeficiency be given a full assessment of their situation and be allowed to choose to receive a therapeutic regimen or decline it.

Theoretically all 500,000 persons infected in New York should be allowed access to some form of therapy if they wished.

To satisfy scientific needs they could be enrolled in formal protocols. Otherwise clinicians should be allowed to use empirical regimens with patients properly monitored. This way everyone would be given the optimal chance to save their lives and nobody would be allowed to twist in the wind. Furthermore,

we could look at the results and get a sense of what works much more rapidly than under the current system.

Persons could use single drug treatments or rational combinations based on the best judgment of experienced physicians. What is happening now is that it takes several years of preliminaries on single drugs before combinations have been approved and yet most of the experts have believed for years that combinations are going to be required.

What we propose here is what is already done -- this is Dr. Pier again -- with cancer patients. Almost no one diagnosed in the United States today with cancer is denied an opportunity to participate in potentially life-saving therapy. There is in place a widely-accepted system for providing these experimental and established therapies to cancer patients. This system advances our knowledge of the treatments for this disease, but is also a humane and compassionate way of caring for patients.

To the argument that there are no AIDS treatments except AZT because no others have been proven effective, we would answer that we are currently capable of choosing safe, rational approaches to therapies. In addition, people are using these therapies anyway. Our proposal would allow them to do so under supervision so this can be done safety and the data developed can be critically evaluated and thereby be helpful to others instead of remaining anecdotal.

Okay, the next section on problems I will have to skim that and get on to recommendations, but there are a lot of details in here, there are some things in here in fact that have never been public before and I recommend that investigators for the commission take a look at the written material.

Just to briefly -- Dr. Pier worked for about two years trying to get some consideration of the drug called Lentinan, which I understand has currently been placed in the highest priority at NIH, but he worked two years completely fruitlessly on it. He was surprised by the current interest and it is my understanding from him that, talking to one of the people on the community, there wasn't any new information. It was just a hunch. In other words, the decision could have been made four years ago when the first indications in Japanese research -- this drug is used in cancer treatment in Japan -- and it was reported that it was effective in treating retroviral infection to patients, HIV and HTLV-1.

Anyway, there is a pack of correspondence which is submitted into the record with this and that can be reviewed. That is his correspondence with federal agencies and others in attempting to get some consideration and his effort was entirely fruitless until possibly today.

Some other concerns besides that one, we have heard -- this is one of the pieces of new information on AL-721, a comment of the unhappy story of repeated failures are described at length in the back issues of my newsletter which have been put in a 15-page computer generated index and they have been entered into the record also. So there is a copy of this. That you can follow historically. The old articles have not been changed except for update sections, so you can just see historically as it has been covered over the last year and a half, what's happened.

We have also heard reliable information that AL-721 was used to treat one person successfully before it was even brought to Dr. Robert Gallo's attention in the laboratory test. My understanding is that Dr. Gallo did not know that, however some of the people involved in promoting the drug believed in it because of the results in an actual case. This has never been public before. Part of the investigation by the way, there is somebody writing a book on AL-721 and I can get you in touch with him. His number is in the back issues here also.

One of the commissioners yesterday asked Dr. Frank Young of the FDA what about the possibility of medical treatment to help with the drug abuse problem. AL-721 was originally developed and is still a promising candidate as something to help relieve withdrawal symptoms and therefore help people get off of the drugs permanently. However we have not had even a little pilot test with 10 or 20 people to see if this approach merits further investigation. It has been known for years, it's been known from animal, from laboratory, from theoretical considerations only -- not even a small test on people.

Trimetrexate is another concern. That is the one that was just released in the treatment IND, which of course we are very happy to see. But there is theoretical reason to believe, and physicians who are knowledgeable are quite interested in Trimetrexate as a possible use for cryptosporidiosis also. There is no satisfactory treatment for that; that is the one that causes a severe and often fatal diarrhea in people with AIDS. It looks like this would work. It is so safe that almost nobody had to be taken off the treatment of people with AIDS for pneumocystis. However, I learned yesterday in talking with one of the company spokespeople that the manufacturer has no intent of developing it for any other opportunistic infection than pneumocystis for AIDS and I have been hearing that physicians have been unable to receive it under compassionate use for cryptosporidiosis. So in other words in the current system, it will never be tested.

The Salk polio vaccine -- this is not the new Salk vaccine that is being worked on, this is the old one from the '50s -- several physicians have used this in treatment of

persons with ARC especially and are quite enthusiastic. They don't say that it works, but it ought to be tried. Recently physicians have had a hard time purchasing the vaccine from the only company in the United States authorized to supply it. They have been getting things like, "You have to sign an affidavit that you will use this only for immunization against polio."

Now this is a drug that is regularly available. Physicians have every right to use it for use other than the approved use and I don't know how this is going to resolve itself but I have heard from two different groups of people that they have had trouble with the company buying this regime.

DR. LILLY: I am sorry to interrupt you but I am afraid we are going to run out of time and you said in your write-up you have 10 recommendations coming up. It is that we would like really most to hear.

MR. JAMES: Right. I'll skip to the recommendations.

DR. LILLY: I'll skip to the recommendations as to what we can do to help out. Much of what we are talking about we have here before.

MR. JAMES: Okay, recommendations:

1. The Commission or another body investigate the problems cited above.

2. The Commission arrange for a survey of people with AIDS or ARC as to what they see going on, what they would like to have happen.

3. The Commission ask the FDA to provide guidelines to researchers outlining what studies would be required to qualify a drug for a treatment IND. You have heard that. And it should also say when it is or is not ethical to require a placebo and when it is or is not ethical to withhold proven therapies such as pneumocystis prophylaxis. The problem is that we are concerned that some of these requirements are being placed on the studies under the table. We want the FDA to put its name on exactly what the ethics requirements are. We are concerned that studies -- a placebo is required when it shouldn't be and the pneumocystic prophylaxis and other important treatments are withheld.

4. The Commission recommend creation of a public computerized and printed registry of all human trials and should include from each one, each drug the protocols and language that can be understood by a lay person -- required for federally funded programs and encouraged for private ones -- and take steps to make access equally available to all qualified persons.

5. A system must be established for ensuring fair access to everyone in need, such as a lottery. If you look it has been almost entirely white and often gay people in the protocols so far and male very often.

6. That the commission suggest the creation of a confidential, voluntary registry of individuals affected whereby they be informed of trials for which they qualify. That would also help in the recruiting which scientists say they have a problem with, but if everybody who wishes to register is told the people that want to get into these trials.

7. The commission recommend the immediate expansion of funding for experimental trials organized and run at the community level, such as CRI.

8. Encourage the current attempts to share are disseminate reagents, materials and scientific data within the scientific community. NIH has done some programs on this that make it possible for researchers to obtain good monoclonal antibodies and such cell lines and such.

9. That the Commission recommend the development of a system such as compulsory licensing, which would prevent proprietary restrictions on data and access to drugs from impeding development of AIDS treatment.

10. We urge the Commission to recommend that individual patients and their physicians be allowed to choose safe experimental therapies under supervision even before efficacy has been confirmed if informed consent is obtained.

And the rest of it is in the record.

[The prepared statement of Mr. James is included in the Appendix.]

DR. LILLY: Thank you very much. Our next speaker is Mr. John Scafuti representing a buyers' club in Orlando, Florida, as well as Home Health Care Services, AID Orlando, the University of Central Florida Task Force on AIDS, and Orlando Gay Community Services.

MR. SCAFUTI: Dr. Lilly, Admiral Watkins and distinguished members of the Commission, thank you for allowing me this opportunity to offer proposals to defeat this epidemic.

While it is a little difficult for someone from the South to talk rapidly, I will do my best in the interest of time.

[Laughter.]

DR. LILLY: Thank you.

MR. SCAFUTI: My testimony is dedicated to the memories of three particularly motivated men who have preceded me here, Tom Jefferson, Patrick Haney and Jim Sammone. They have all expired within the last two months, highlighting the urgency of our task.

I will present two sets of recommendations for expediting delivery of unauthorized or investigational new drugs at the earliest possible time. The first set of suggestions are made within the current framework of the drug approval system. I estimate this method of proceeding to be only half as effective as the second more comprehensive set.

Under the new regulations governing IND compassionate use treatments and IND protocols, a specific example is cited on page 19467, column two, next to the last paragraph, qualifying all stages of HIV infection as "immediately life-threatened," thereby clearing the way for even the asymptomatic patients to receive the most advanced treatments as soon as possible.

With as many as two million potential clinical subjects, there should be no problems filling clinical trials, a requirement for consideration of IND compassionate use treatments.

In most of the current trials in progress clinical subjects are recruited from the most financially secure and most pharmaceutically sophisticated patients. Both the FDA and the pharmaceutical companies fail to address the implications of this reality.

These patients are much more likely to follow through with the full term of the trial but are not nearly as likely to adhere to the conditions of the trial. This results in a smaller subject population but questionable validity.

A far more fertile source of clinical subjects is in the very clinics where current care is significantly inferior, VA hospitals, prisons and free government clinics. This would offer some hope of advanced treatments to the underprivileged that doesn't now exist.

While the populations in the trials would have to be expanded to allow for a higher dropout, the trials would be far more valid due to closer adherence to the testing conditions. There will be charges of bias against the underprivileged and of using them as guinea pigs.

The truth is that their care will be significantly improved, they will enjoy a sense of contribution to society and

the financial burden for much of their care will be shifted to the private sector, the pharmaceutical companies. The test results would be far more valid due to closer adherence to the conditions of the trial. In short, the positives far outweigh the negatives, regardless of the potential criticism.

Under the new FDA regulations for IND compassionate use treatment protocols, a surprising possibility has emerged. By the time a drug has neared the end of Phase II, small controlled studies, and the four general criteria have been met allowing IND treatments to begin, there may be more liability to the physician, pharmaceutical company and the FDA for not providing the drug than that which is associated with providing it.

An interesting historical fact is that only one case has been tried where an investigational new drug was administered. The decision in all of the courts was consistently for the defendants. What this indicates is that early usage of promising new drugs for AIDS is likely to be rather non-litigious, while delaying usage, conversely, could attract significant class-action litigation.

Two major defects in the IND treatment approach could and probably will nix the whole system. While the FDA seems to be bending over backwards to provide promising drugs at the earliest possible time, the pharmaceutical companies are not compelled to provide the drugs and the third party payers, Medicare, Medicaid and private insurance, are not compelled to pay for the drugs.

Historically, the FDA has played a passive role. Even if they are now inclined to be more proactive, it will be some time before they will be capable of making that adjustment.

To make the system work, the government must put the public interests of the ravaged populations above the proprietary interests of the pharmaceutical companies. The appropriate legislation accomplishing this must be enacted.

Part of that same legislation should include a requirement that third party payers must pay for all IND treatment situations. Without this legislation, the new FDA regulations are clearly worthless with only the very wealthy having any opportunity to use expensive investigational new drugs such as Ampligen.

The next set of recommendations fall outside of the current health care and drug approval systems. Do not pursue a Manhattan Project for AIDS. The historical Manhattan Project had a narrow well-defined purpose. The scope and implications of this disease are far too broad and comprehensive to be dealt with in the same manner.

Such a project would likely be biased towards strictly HIV theory, be focused on magic bullets rather than disease control, and would not adequately address multifactorial possibilities.

Instead of the Manhattan Project, the Congress or the President should literally "Declare War on AIDS" and appoint "Joint Chiefs of Staff" under the Department of Health. This body should have the same power to fight AIDS as its military counterpart during times of war.

Represented on this committee should be the Surgeon General, the Commissioner of the FDA, the head of the NIH, the Commissioner of Insurance, a representative of the pharmaceutical industry and the head of the Department of HRS.

Balancing the traditional government and bureaucratic bias in the composition just stated, it is essential that leaders of groups hardest hit by this epidemic be well represented on this panel: homosexuals, blacks, hemophiliacs and women.

Since many of the anticipated decisions will be economic and based upon questionable statistical data, it is essential to include cost accountants and statisticians as well. At no time should the private representation be outnumbered by the government representation.

A significant effort should be made to include HIV positive individuals whenever possible. No one has a greater inherent human right to make decisions affecting survival than those who are struggling personally to survive. This would formulate strategy, implement policies and serve as a board of appeal for conflicts which would inevitably arise.

Rather than trying to squelch the AIDS drug underground, those efforts would be miserably unsuccessful, ill-advised and a huge waste of time, money and energy. We should instead devise a strategy for gaining as much information as possible from that system. We must provide physicians with incentives to track and report the polypharmaceutical treatment strategies which are being followed by their patients.

Most experts agree that ultimately a multifactorial approach consisting of combinations of anti-virals, immune enhancers and immune modulators will effect the greatest degree of disease control.

Instead of fighting what is going to occur anyway, we could gain valuable insights for controlled combinational studies based upon subjective indications which become apparent when the data is reported in huge numbers by physicians throughout the country.

To create incentives for this project, I propose the following:

--Number one, statisticians working with highly informed physicians and researchers who have an understanding of the polypharmaceutical possibilities would design computerized patient histories, regimens, baseline and maintenance lab data in the most convenient fashion possible.

--Number two, participating physicians should be given a prestigious labeling which could be recognized by the general public in advertising media, for example, NDI - "New Drug Investigator."

--Number three, provide participating physicians with the most sophisticated interactive data retrieval system to date, enabling them to know immediately as evolutionary advances in treatment possibilities are occurring. Also include a complete registry of all trials planned or in progress relative to any AIDS issue.

--Number four, the government should pay the physician for his additional efforts on a per patient basis.

The significance of creating the model described above cannot be underestimated. While there are very few reports of drug interactions with AIDS, there is no responsible tracking going on and extremely useful combinations may be going unnoticed.

By expanding the subject population to enormous proportions we can validly include a large number of variables and still produce extremely valuable subjective indications for more controlled research. This offers the opportunity of "leap frogging" current step-by-step traditional research.

Another area of concern that heretofore has gone unaddressed is the degree of infectiousness by those that are pursuing aggressive anti-viral regimes and are consistently antigen negative and consistently viral culture negative. Virtually all other retroviruses go into relative infectious remission and yet remain in the body.

We cannot let these epidemiological possibilities go unexplored. I do not suggest that behavioral changes be abandoned, quite the contrary but we must not ignore any possibilities for epidemiological control. There is no research that I am aware of that explores this issue. We are told that saliva does not transmit AIDS because viral concentrations are too low to accomplish infection. It is notable that we are not told that there is no virus in saliva. What about other areas of drug-induced low viral concentrations?

These proposals are obviously not "business as usual." Imagine the progress we could make if they are implemented. It is long past time to drop a "business as usual" approach. Several enclosures have been included which support the conclusions reached above.

Enclosure number one is a lengthy example of a child thriving by using unauthorized drugs. Enclosure number two is an example if inferior medical care which exists in VA hospitals and enclosure number three is an example of results using drugs prior to marketing approval, DHPG.

Thank you very much for your consideration.

[Applause.]

[The prepared statement of Mr. Scafuti is included in the Appendix.]

DR. LILLY: Thank you, Mr. Scafuti. I would like rapidly to go on to finish this segment with a presentation from Dr. Herb Spires who represents the organization ACT UP here in New York.

DR. SPIERS: Mr. Chairman and distinguished members of the President's Commission on AIDS. Thank you for the opportunity of presenting the testimony on behalf of ACT UP, the AIDS Coalition to Unleash Power.

In the race against time, I will read like the hare if you promise me that you will listen not like the tortoise. For us, AIDS is not only about health, it is about politics. This is a connection many of you may find difficult to accept. I first became aware of AIDS in the summer of 1981 when it was called "gay cancer."

I now realize that I made a fatal error in my understanding then. I focused on the word "cancer" and assumed that this new and mysterious disease would be dealt with in the same manner as Legionnaire's Disease, which is to say with great urgency from our medical establishments and the White House alike. It was not.

It was a politically unpopular illness and not until a few courageous voices spoke out against the lackadaisical political and medical response to the by then already epidemic proportion of the disease did the true personal, social and cultural horror begin to stir the national conscience.

This historical context is the framework by which we judge today's promises of fast-tracked drug developments and redesigned systems for clinical trials.

It is from within this tradition of neglect, even though perhaps benign neglect, that we are compelled to make sense of the fact that as of this moment a person with AIDS has, in the entire breadth of this nation, access to only one ATEU trial testing a drug other than AZT and at that, there are only 25 slots available.

This historical context prompts us to ask embarrassing and provocative questions. Is scientific methodology really the only reason that as of February 5, 1988 83, percent of all people enrolled in ATEU trials are on AZT? Are our scientific wits so dull that we cannot find effective alternatives to cruel and self-defeating double-blind placebo trials? Are women, Blacks, children, Hispanics and drug users somehow innately unqualified for drug trials for they are woefully under represented in trials currently underway?

Is the NIH really committed to a worldwide search for potential new drugs or is it too comfortably wedded to domestic products? Why must drug companies retest potentially life-saving drugs because the FDA fails to make its rules and regulations for the design of acceptable protocols clear and comprehensible?

In making answer to these and other questions the politics of drug development must be addressed. There is still a leadership vacuum in the fight against AIDS. Despite the noble intentions of political and bureaucratic functionaries, AIDS will remain a controversial issue on the national agenda until the Chief Executive of our country removes it from partisan and ideological politics by personal moral examples and by bold leadership.

We have been told that AIDS is the nation's number one health problem, yet this four letter word was not once uttered in President Reagan's State of the Union address last January.

Is this the type of example to set for his subordinates? Does this demonstrate commitment and concern? Can the President not hold publicly an AIDS baby in his arms or avail himself of a photo opportunity to shake hands with a Person with AIDS to educate the public about compassion and how this disease is really transmitted? Let's start at the top. Let's start with the role of the Chief Executive. Recommend to this President and the next to become truly involved in the fight against AIDS.

You know that the AIDS Treatment and Evaluation Program has not been a resounding success. After 18 months not a single report has been published. You have been told that it has been revamped and redesigned, that new committees have been added to expedite the testing of more and different drugs.

Nothing could please us more than to see that happen. But we have had experience with the ATEU program first hand and we know that if it is going to work it must, one, include participation from community physicians and, two, must win the confidence of the very people it seeks to recruit.

This means outreach to AIDS communities in culturally appropriate ways such as designing clinical trials commensurate with nonwhite, non-middle class values. It means alternatives to placebo trials and it means convincing people like Dr. Iris Long sitting to my immediate right that genuine efforts are being made.

ACT UP is singularly proud of Dr. Long. There is perhaps no more informed person on drug treatments currently underway in this country than she. What we have learned about the problems with the ATEU program can be of use in preventing similar errors in the new program.

Not content with simply a critic's role, Dr. Long and several other ACT UP people have undertaken a pilot project that will serve as a prototype for a national effort. We are developing our own data bank on treatments at hospitals in the greater New York area.

Physicians and PWAs need up-to-date information about drugs and drug treatments and this information is nowhere available. Certainly, the government's databases, PDQ and CLINPROT are not the answer. In addition, ACT UP will demonstrate the importance of a Central Registry of clinical trials for researchers and physicians, another idea we strongly urge this committee to take under advisement.

For many of us, perhaps for many of you as well, there is still a mystery as to how drugs are selected for clinical trials by the NIH. Successes or failures notwithstanding, it has never been satisfactorily explained why AZT and not some other drug or drugs was put on a fast track approval process by the NIH and the FDA.

Recent press reports once again testify to the inherent suspicion on the part of our great medical establishments to substances developed abroad. To ensure that domestic business considerations should never be allowed to impinge upon drug selections we urge the creation of an Ombudsagency to examine the experience of other countries in the search for new drugs to be tested.

"The real problem," says Commissioner Young, "is where do you get the ideas and where do you get the compounds from? That is the major block." Mandate imagination and creative research through such an Ombudsagency.

To de-mystify the process of drug selection and to inspire trust and confidence within the various AIDS communities we make two recommendations. First, both the FDA and the NIH must make greater efforts in providing timely and current information that is organized and systematized. The above mentioned national database is indispensable in this regard as are monthly and weekly publications and a National Hotline on drugs and treatments to which physicians and PWAs can make reference. Second, structure community physicians' and PWAs' participation in all drug review committees.

On Tuesday of this week with not a little fanfare, the FDA announced that trimetrexate had been approved under a Treatment IND. Bravo! But questions remain as to liability and treatment costs within a Treatment IND protocol and in spite of a two day conference just this week, the regulations pertaining to Treatment INDs remain murky, prompting a number of informed persons to wonder whether pharmaceutical companies would indeed submit their drugs for Treatment IND approval.

You have heard some glowing reports from the FDA Commissioner. Let's hope they come to fruition. But again we have historical reasons for being more than a little skeptical. Supposedly thousands of drugs have been examined, over 40 are "in-the-works" yet only AZT is approved.

What is the status of DHPG, the only hope for people suffering from CMV infection? Will or will not the Commissioner approve its release or must the parent company put it back into trials causing further delay of the only drug effective against CMV retinitis?

And who in the government is willing to take even a modicum of responsibility for possible abuse of The Orphan Drug Act? The government grants exclusion drug marketing rights to companies, yet it refuses to monitor possible abuses of a federally created monopoly.

In 1984, Pentamidine cost $24.95 a vial. It now costs four times that amount. Who pays for this whopping increase? Individuals, insurers and in a variety of ways, taxpayers.

While the government granted a marketing monopoly to Lyphomed for Pentamidine, the FDA's Office of Orphan Products Development says that it has no monitoring power. We all know too well the astronomical cost of AZT, another Orphan Drug Act product.

This act was intended to induce companies to develop drugs that otherwise would go undeveloped without forms of

financial assistance. A wise policy and within the tradition of Chrysler and Lockheed bailouts.

But has it become a government handout? Perhaps it is time to consider a Untied States Drug Development Corporation that would be self-financing and would treat drug patents and marketing rights as part of the public commonwealth.

Time does not permit me to focus attention on other issues with which we are concerned. For example, does the FDA's Informed Consent Regulation, 21 CFR 50, which requires informing patients of alternative therapies before signing them up for a trial mean making them conversant with drugs and treatments being used in a limited geographical area or does it mean all drugs and treatments used throughout the country?

Obviously, the answer to this question is of significant moral and legal importance. Discrimination, housing and health care, education are all part of the politics of AIDS.

The National Leadership Coalition Against AIDS, a group of business leaders, recently suggested a bill of rights for Persons with AIDS and for seropositives. Its time has certainly come and I commend their idea to you.

I wish to close with that with which I began. We the women and men of ACT UP are gadflies, the grassroots variety. That is why this Commission, the White House, Dr. Young at the FDA, Dr. Fauci at the NIH, governors, mayors, representatives, council members, senators, health commissioners, candidates and many other varieties of politicians and bureaucrats and their anointed appointees, find us buzzing about.

We are driven by the Politics of AIDS and despite attempts to shoo us aside, to ignore us, spray us with insecticide, and all other means to dispel unwanted pests, or more accurately, those perceived to be pests, we will in the tradition of political gadflies keep you honest by "ACTing UP."

[Applause.]

DR. SPIERS: Recent rhetoric would have us believe that the epidemic is over, at least here in the U.S. It is a consummation devoutly to be wished. Still, one cannot help but wonder if the very same people who were so late in coming to the battle are not prematurely calling it at an end?

For many here present this morning, the full effect of the politics of AIDS was brought home forcefully by the death in one's arms of a lover or a son or the diagnosis of Kaposi's sarcoma in oneself or in a friend.

My mistake, the mistake of those most effected by this disease, was to remain silent too long; quiet in the assumption that the health of the body politic was above the ideological issues of partisan politics.

With our mouths closed we watched the deaths mount. In high school, we were taught that the price of freedom is eternal vigilance. Sad to say, in the Age of AIDS, many of us have learned that in our democratic society the price of health is perpetual pressure and an ever ready pair of vocal cords.

In fighting for the cause of human life, no price is too high. And so, even though some contend that the epidemic is over because they believe it has not entered the white middle-class, heterosexual population, we will continue to bring pressure to bear commensurate with the goal we are seeking, an end to AIDS, an end to dying.

My testimony, then, is a kind of pressure, delivered before you in the form of verbal pleading. We ask you to examine fairly, carefully, critically all the testimony that you have heard and received. Weigh it on the scale of scientific merit and reason, but also measure it with the rule of your own personal integrity. You will be making recommendations affecting who will or will not suffer, who will or will not die.

On this issue, we cannot and will not ever be silent again. We ask that your officially sanctioned voices speak out with us. Thank you.

[Applause.]

[The prepared statement of Mr. Spires is included in the Appendix.]

DR. LILLY: Thank you, Dr. Spiers. The length of the presentations precluded us from asking questions. Those members of the Commission who have questions to ask you will submit them to you in writing and I would be appreciative if you would respond to them as rapidly as possible.

MR. DELANEY: Dr. Lilly, let me say that I resent the fact that our community members have been forced to squeeze their presentations and are limited in time here. Three PWAs yesterday were given seven minutes each to speak. Dr. Young got two and a half hours.

DR. LILLY: I am sensitive to that. I think, however, that we have understood your points of view and I will certainly do everything in my power to see that the Commission pays attention to your points of view.

HIV Infection in Women

DR. LILLY: The next panel will consist of two presentations concerning HIV infection in women, an issue that the previous panel has stressed as being of considerable importance.

Our panel on HIV infection in women is represented by two individuals, Denise Ribble, a nurse educator at the Community Health Project will be our first speaker.

MS. RIBBLE: Good morning, members of the Commission, the three of you that are still there.

In the context of women and AIDS, transmission studies have established that men can infect women sexually, that female IV drug users can get AIDS, that women can infect men sexually to a much lesser degree and that infected mothers can pass this on to their babies.

However, transmission studies do little for the woman who has been an epidemiological guinea pig. Though researchers often glean a very complete medical, social, sexual and drug history from these women, they do not provide risk reduction education. They do not provide support in dealing with transmission dynamics.

Transmission dynamics is a polite way to describe a situation when a woman in a culture that doesn't talk about sex would like to practice safer sex with a man who doesn't want to put on a condom.

Transmission studies do not provide information on what kinds of care and services infected women need. In New York City, in fact, infected mothers are enrolled in studies and once they have their babies, their babies are enrolled in follow-up medical studies and the women are not enrolled in any kind of follow-up medical or psychosocial study.

No one cares about prostitutes as infected women, however, there is considerable interest in their role as a vectors of disease, forcing those men to have sex with them, no doubt.

[Applause.]

MS. RIBBLE: The reality in my experience is that men pay 15-year old girls a premium price to have sex without a condom.

There has been a disturbing trend recently to minimize the risk to heterosexual women based on transmission to the general population and I just kind of want to review kid of what two percent or 2.6 percent transmission in the general population means. In New York City what that means is that if there are a million women who are living in New York and 2.6 percent are infected, then there are 26,000 infected women living in New York City right now.

These are not women who are at high risk because we know the transmission rates in women who are at high risk are much higher than 2.6 percent. These are women who decide that they will participate in a transmission study.

The fact is that women are at risk, okay, and the fact that they are not necessarily perceived at risk and, then, not in need of services continues to be a problem in everything from public health education to research protocols.

For women at risk or infected this perception is another obstacle in access to medical care and psychosocial support. Where is the research into prevention for risk reduction strategies for women and the resources to reach them as individuals in families and in their diverse communities?

There are 4,100 cases of CDC documented AIDS in women. There has been a statement made that these women are sicker and die faster. Eight years into the epidemic, we don't know why. Where is the research into saving women's lives?

There are no co-factor studies right now that specifically address co-factor issues in women. There is a study that is starting in New York City at Columbia University. When I called Columbia to ask to enroll some of my female clients in their study they told me that they could be enrolled through a methadone maintenance program.

However, most of my clients are not, nor have they ever been, IV drug users. There are also a few lesbians in my female clientele population and for them to go to a methadone maintenance center to participate in a transmission co-factor study is kind of ridiculous.

I was informed that the questionnaire that would address those women, the ones in my clinic, was being worked on right now and would probably be piloted three or four months from now.

Studies have shown that ethnicity is a high risk but there are no studies that discuss ethnicity and/or being female. Researchers have suggested that the disease may have a different etiology in women and they suggest further study but they do

little to actively recruit women into those studies. When asked why, they make statements like "women are a harder population to study. They are unreliable. They are not homogeneous." Yes, indeed. You are right. They are not.

[Applause.]

MS. RIBBLE: Other possible co-factors that might contribute to the disease in women include things like female hormones, other infectious agents, genetics, psychological state, ethnicity, chemical dependency, health related activities, support networks and stress. Since there are no studies we don't know the role these co-factors play and what others might be involved.

Co-factor studies should include women and while we are at it, let's not just study women for five years, let's plan for co-factor interventions and study for improving the odds of their survival.

There are no studies of the efficacy of alternative treatments for women. This is compounded by the fact that there are almost no studies of alternative treatments at all.

Current testing protocols for experimental drugs in clinical trials exclude women in a discriminatory way. For example, one of the inclusion criteria for the Ampligen study is to be a gay and bisexual man. A woman can meet all of the medical criteria but she doesn't have the biological requirements to get into the study.

Other studies which specifically exclude women are Isoprinosine, Immunthiol and Thymopentine. Many justifications are given for this but the bottom line is that the FDA will approve a drug that has never been tested in women and, in fact, they recommend that no drugs be tested on women of child bearing age unless it is a life threatening illness. I think AIDS is a life threatening illness.

[Applause.]

MS. RIBBLE: Experimental drug protocols are sometimes made available to people who are very ill. There are even fewer formal protocols available for people who are infected but not severely symptomatic or immunosuppressed.

Only one experimental AIDS treatment drug has been released for compassionate use. Most of these drugs are not released for compassionate use and one of the reasons often given is that the drug has not been tested in women.

This places women in the position of a double bind; they cannot receive experimental drugs because they are excluded from drug trials, and, they cannot receive drugs that are not released for compassionate use because the drugs have not been tested on women.

Women must have equal access to experimental drugs and this must be mandated in all protocols. When dealing with a life threatening illness, it is unacceptable to disenfranchise women.

The only other option available to women who are infected but not sick are alternative therapies. There are really no good studies of alternative therapies; so there is no way to know if they are going to be effective in women; because there is no way to know if they are going to be effective at all; because they have not been studied.

A lot of times women do not have access to alternative therapy information because their traditional practitioners do not inform them that these things are available. If you are living on welfare and you have food stamps and it costs $25.00 per month to buy vitamin C to just take 1500 milligrams a day, there is a good chance that you cannot afford $125.00 every three months to buy AL-721 and there is a real good chance that unless you live on the East Coast or the West Coast, that some drugs just won't be available to you at all.

I will to now turn the microphone over to Dr. Davis who is going to be more specific about the needs of women and especially minority women.

[Applause.]

DR. LILLY: Yes, the next speaker will be Dr. Iris Davis who is the AIDS Assessment Coordinator of the Bushwick Medical Clinic in Brooklyn and with her is Dr. Aliyah Morgan who is the Medical Director of this clinic. Dr. Davis will speak.

DR. DAVIS: Good morning to all members of the Commission and audience. We are here today, Dr. Morgan and myself, to present and highlight issues of HIV related disease including the full blown syndrome of AIDS in women especially dealing with women of color, those of African and Latino derivation.

It is a difficult topic to begin with, the issue of women with HIV disease because it is an ill-defined population not fully stratified and without question not well studied.

The difficulties exist due to lack of definition of health status of Black and Hispanic women in general in this country. However, extrapolating from prior evidence and

knowledge that we have of morbidity and mortality, the numerous indicators from cardiovascular disease to the rates of cancer within these subgroups, the statistics are supportive of a decreased health status of those communities in general as per prior federal reports.

If we continue to look at data for women with a history of intravenous drug use, we are struck by even higher morbidity and mortality rates. Due to a lack of seroprevalence data, there are marked limitations of discussion of eventual cases of women in all of the defined risk groups whether it be intravenous drug use, sexual transmission or "other," including blood transfusion.

Indeed, because present percentages are based on a subset population of the total at-risk population and an examination of other medical co-factors that have been linked to the rising number of cases of AIDS in minority communities such as tuberculosis, pelvic inflammatory disease, the increased incidence of endocarditis, et cetera, we feel that we have defined as a nation and certainly as a city the tip of an iceberg alone.

The medical model of study and research is an excellent one perhaps for a definition of vector. However, for definition of vector relations of sex and race and causative co-factors, it does not help us decide how to change behavior patterns, how to mobilize and educate communities or how to support those within the community that are ill as cited per Friedland, et al.

When speaking of studying women with HIV disease, especially Black and Hispanic, one must remember that they do not present as primary patients to academic centers and their emergency rooms. Those academic centers, however, are the ones that determine research initiatives, support them and frequently define the governmental response to health and disease in this country.

Therefore, issues of clinical care, who cares for the population at risk and who ultimately defines the access to care both quantitatively and qualitatively may have a critical impact on who survives or has a lower morbidity with HIV disease.

What is interesting to note in both Weston and Rothenburg's data is that Blacks have a decreased survival time versus whites of eight months after initial diagnosis of CDC defined AIDS versus 18 to 24 months. In Rothenburg's multi-varied analysis which I do not believe as yet has been published, even when initial diagnosis, date of diagnosis, risk group and sex are controlled, Blacks and Hispanics with AIDS still survive for shortened periods. The reasons are still unknown. They have not been looked at.

The epidemiology of HIV disease is defined by cases of CDC defined AIDS. This continues to change in New York as the proportion of AIDS cases after 1985 continues to increase in Blacks and Hispanics. Women in New York City represented 11 percent of the total cases in New York City and they represent almost half of the female cases in the nation. As of 1986 per one hundred thousand women when we look at New York City in the 25 to 44 year old age group, there is an incidence rate of 55 per hundred thousand for Blacks, 42 for Hispanic and ten for whites.

Eighty-four percent of all female cases are Black and Hispanic. Only 61-percent of those cases, however, are women who have a known history of intravenous drug use at some point in their recent medical history. Twenty-two percent are actually due to sexual transmission. What is very important to note about the mean age of the group is that it is in the early 30's, prime child bearing years.

When we begin to examine characteristics of the male partners which I do not think has been sufficiently discussed in the media or in medical journals, we note that 37 percent of males in the Black community and 23 percent of males in the Hispanic community are bisexual. Another interesting point from ARTC data which is data from an intravenous drug treatment program located here in Brooklyn, that intravenous drug using males usually tend to have non intravenous drug using partners. These are all critical issues.

When you couple the issues together of possibly increased incidence of bisexuality versus homosexuality within the minority communities, as well as the fact that intravenous drug users tend to have non-intravenous drug using partners, the overall seroprevalence within the community might be frightfully high and the cumulative indices, I think, give us some indication of this.

For example, non intravenous drug using gay and bisexual Black males have a 1.6 percent times higher incidence of eventually developing AIDS if they are HIV positive. It is eight times greater for Black women, 6.8 percent times greater for Hispanic women to go from HIV positive to AIDS versus the White population.

It is important to look at those co-factors and determine why they exist across the spectrum for both males and females but especially for women at such higher rates. It is important we feel also to look at the data within New York City as a pattern that is beginning to change not only here but is beginning to change nationwide.

There are an increasing number of cases in San Francisco, Houston, wherever I have had verbal communication with

practicing associates like myself who are community based across the nation and practice in minority and urban communities.

New York City has 30-percent of the total cases in the nation. Now 16-percent of all cases in the nation are in the municipal system of the New York City Health and Hospitals Corporation.

Therefore, it becomes extremely important to look at preconceptions based on misleading data. Statistics do not reveal the distinction between those individuals who have had intravenous drug use ten times in their life or every day, 15 times a day. They do not distinguish between those populations and therefore do not help us define patient behavior. They do not help us define patient relationships to health care status and health care access.

We have noted extensively within our own community center that our patients repeatedly expressed the fact that they thought that they were safe because they are predominantly recreational drug users, as is most drug use in this country, frequently recreational, whether it be heroin, cocaine or alcohol. It is a weekend phenomenon, sometimes a monthly phenomenon. It does not classify someone as an addict nor as an untreatable person.

These stereotypes then lead to questions. The question is how large is the true population at risk in this nation in all communities not only within the minority community but especially how many women are at true risk and at what point are we going to see the true number of cases present themselves to medical institutions.

There is another interesting subset of patients that we are following. These are "clean" drug users. These are people who have been clean for greater than three to five years but after struggling with addiction and changing major life behavior, these people find themselves stricken with a fatal illness.

They bring their partners to us. Their partners find that men that they accepted as men who had changed a pattern and are now "clean." Now, they see themselves as "punished" for having accepted a man whoever had a history of drug use. You know, there is no such thing any more in New York City as a clean drug addict. If you have ever used drugs, you are a tainted man.

So when you also look at the issues of drug therapy, it becomes critical to look at the issues of intravenous drug use not only in women in therapy, and how they respond to therapy, but the non-intravenous drug using partners and how they respond to therapy, how they look at therapy for their partners and how they do or do not support any type of adaptive behavior.

The issues of seroprevalence and latency within the disease especially for women are areas to examine for future therapeutic decisions. Therapy for women is not discussed, I do not find as a medical practitioner as a whole. The more important question it seems to me when people speak to me is, is the woman infecting the man or is she infecting the child. No one asks me about the status of the women.

[Applause.]

DR. DAVIS: Not a single research trial in this country for HIV disease has had a significant female population, not one! Whether we are discussing antiviral agents such as AZT or more recently developed drugs such as Ampligen, especially when you discuss the drug trials in Ampligen which is manufactured by duPont which without question decided not only would they not take any women, they would without question never take anyone who ever touched intravenous drug use whether they were an addict or not an addict thereby precluding all but the 37 percent, presumed 37 percent, known minority gases that are gay and bisexual males. They left out anybody who was black, Hispanic or women, period.

[Applause.]

DR. DAVIS: Access in general to clinical trials has been limited for women based on women's entrance point into the medical system, their multiple social problems such as lack of support structures, transportation to the centers, running certain trials, day care arrangements and general lack of understanding and knowledge about experimental treatment modalities so that most women from the types of communities that we serve that we had heard of from anecdotal references do not seem to have knowledge that AIDS and HIV disease may be a treatable disease especially if you present at an early point in the disease process.

So to even start discussing co-factors, I find somewhat unreal. It means defining ways of gaining large enough cohorts to look at women with HIV disease from all spectrums of the disease from asymptomatic to AIDS.

Drug testing should be done where patients are treated. Frequently for women of color, community health centers are the first line of treatment. Flexibility should be sought within medical institutions to share data and research modalities. Women in all chronic illnesses, as supported by a large number of psychosociologic data usually bear the brunt of caring for sick individuals within a family structure.

When you start talking about a woman who is HIV positive and has a sick husband and may have a sick baby and this is how she found out she was sick, that then means that she

delays her entry into the medical system even further to care for those sick individuals within her own family. We find that pattern repeated daily.

We would like to delineate further on local issues to touch upon problems that we feel are important in caring for women with HIV disease. The institution which we are affiliated with, Woodhull Hospital and Medical Center, is a typical community hospital in the municipal health hospital system of New York City. It has been caring for an increasing number of cases of HIV related disease since it opened in 1982.

The ambulatory care centers of Woodhull see over a third of a million cases annually and, in fact, the New York City Health and Hospitals community health centers see four million cases annually.

Within our community even in light of increased federal cutbacks every year since this administration began its present reign, we operate at or above capacity. Our service community is a poor one which is born out by the 1980 census tract information. Thirty-five percent of the incomes are below the poverty level. Twenty-five percent are below $5,000.00 per year. Fifty percent are below $10,000.00 per year.

All health indicators such as cirrhosis, infectious diseases, increased infant mortality are well above New York City rates. Our ambulatory AIDS treatment unit was opened in July of 1987. Referrals are from anonymous testing sites, physicians and primarily from patients. Our clinic sees approximately 700 patients in a general medical population per month but of that percentage, a mean number of 130 cases are HIV related disease.

We have an active case load of 300-plus HIV patients. Eighty percent of those cases are of color. Hispanic is almost 50 percent. Black is approximately 40 percent. Haitians are five to ten percent, and the others include whites as well.

Women comprise approximately one-third of our present HIV case load which increases every month as women tell women that there is a place where you can go where someone speaks Spanish, where someone is of color, and where a lot of the practitioners are female.

We offer testing, counseling and general medical care including drug trials to our patients. Even our statistics are not consistent with other figures as previously cited. We have difficulty with the incidence figures as cited of seroprevalence, since within our own testing which is totally voluntary and is primarily of women who present themselves saying, "Oh that dude I might have dated ten years ago, maybe he used drugs." We have a 28-percent seropositive rate in asymptomatic women.

Counseling is a dramatic process within our clinic and the need is compelling within our community. We begin with one target case and often end up counselling and treating family members whether HIV positive or not. This labor intensive process in any situation becomes acutely severe for us due to issues of homelessness within the community, unemployment -- especially as households lose their female wage earners, lack of insurance, which limits visits to the clinic and real issues of discrimination based on the fact that you have HIV disease, that you are female and that you are of color.

It often takes weeks to months for us to treat either the male or the female sexual partner or to have them come in, because of the need for wage earnings within the household. However, our patients return for a re-visit rate when they enter the system that would make any private or public institution happy.

Although we have not adequately studied the reasons why we believe this is because we provide one of the few places where they can openly discuss their disease, we provide group support, and we can discuss issues that cannot be discussed in the community at large, especially within the Black and Hispanic communities. You do not go around telling people that you have a bisexual husband, and that this is the way you found out you have HIV disease.

We attempt in these counseling sessions to empower our client, which is very important to us. We wish them to be able to discuss issues, we wish them to be able to deal and cope with their illness as well as to learn how to live with it to the best extent possible, and we try to help them to educate their own surrounding community.

Treatment of HIV disease is limited by the number of staff people and the resources of a very strained municipal system. We are able to offer AZT, for which we have not noticed significant sexual difference thus far although we have not yet correlated all our data, and in coordination with another community-based research initiative have instituted disulfiram and aerosol pentamidine in studies as well, and we hope to have more drugs available within the next three months.

Here then is where we think perhaps the Federal government can step in. First and foremost, the real importance of community health centers must be realized. We are a primary link to under-served populations.

[Applause.]

When you speak especially about populations that are high in terms of low insurance rates, that they have low income,

they're poor and they're undocumented -- you're looking at the physicians who take care of those type of populations. Further federal cutbacks will lead to a further diminution of quality of care in community health centers. As it presently stands, we do not have significant numbers of outreach workers in the community to educate the populace about a disease that is now best handled within the "medical best knowledge" with preventive behavior.

Multiple studies have documented changes in behavior among the "hard core group" of intravenous drug users who may not have stopped using drugs but they do stop sharing needles. They do learn how to use bleach. If you can change behavior in the "untreatable" group with prevailing medical presumptions, then certainly you can change people who do not even have that underlying behavior as their risk behavior and risk factor.

Further, monies are needed to support efforts within the community to educate and protect itself such as ADAPT, a group of prior intravenous drug users within the New York City community. Staffing in our institutions for support services such as social workers, technicians, community outreach workers is stretched to an unbelievable point that I find hard to describe to you here today. In our facility, we reached saturation three months ago. Now remember, we opened in July. Our numbers have increased steadily every month.

Municipal systems have not been able to adequately subsidize salaries. This limits our ability to retain and recruit staff, especially when dealing with nationwide problems such as the nursing shortage. Loss of designation as medically underserved areas, especially during the time course of this administration, hurts us for the recruitment of physicians and other health care workers. Perhaps in the solving of individual problems, for example, one real practical solution we can give is physician indebtedness to the Public Health Service. AIDS ambulatory care facilities should be given priority status. We can use all the doctors we can get.

We would also like to note that AIDS is another case in point that should really be looked at in the context of the full health care within the community. It is the last insult on a number of insult. It is not an isolated disease in an otherwise healthy community.

When women cannot have enough money to support their families, find adequate housing, feed their children and pay for medical bills, they drop out of a wage-earning system. Most of our women enter our system working; they quickly have to stop. They do that because Medicaid provides transportation, medication and other ancillary benefits.

Housing is a major and critical issue and cannot be looked at outside of the AIDS issue. It is -- especially for low-income communities when you talk about crowding, poor living conditions and no place to house sick people, especially if you have a sick woman with three children, then you see, the way the present system is structured there is nowhere to put a woman like that when she lost her apartment because she went into the hospital and she was sick for a month from PCP and she farmed her children out to her family -- this is a real incident. She lost her apartment, there's nowhere to put her. So then the Bureau of Protection for Children in New York City came and took her children away. It's either that or they must give their children away for adoption. Obviously, family structure is not considered important within the context of the overall health care of the initial patient. Housing initiatives are therefore desperately needed, especially for women with AIDS.

Equal rights and the lack thereof is also frequently set in tone by the Federal government. I think it is critical to understand the impact the Federal government can have in this area where all trials should be open to any individual who complies with the rules of the treatment regulation. It is discriminatory to do otherwise.

[Applause.]

There is a lack of coordination between major medical institutions and local community medical institutions. There is a vast amount of data that is just not being looked at, it's not compiled. When you have two doctors and two nurse practitioners, it is difficult to look at the data when you're seeing 19 to 20 cases a day. There is just not enough time, there's not an epidemiologist on service, and you don't have a computer. However, the Federal government could certainly step in by asking bodies such as NIH to compile data if it was sent voluntarily by those institutions so that large patterns of change in the disease and who it affects could easily be seen in that type of a setting.

An initiative on drug abuse and therapy is critical, without statement. What this epidemic may help us to really define is common behavior in all our communities across this entire nation that is hidden. It should be remembered in the process of teaching about HIV disease, you teach much, much more about health care and we have been able to see real change. I do not believe that the gay model in which that community was able to turn around so many things such as sexually-transmitted diseases, the decreasing incidence of gonorrhea, et cetera, and changes in actual behavioral patterns, cannot be replicated in any community within the United States.

Our government, insofar as positions in the front line aspect of coping with women with AIDS disease, in addition to all the other health problems of the population, we are astounded at the stigmatization presently occurring within the media and the presumption that a stigmatized patient who will get AIDS has to be either Black, Hispanic or a chronic intravenous drug user, this is just not qualifying, it's not correlating with the data we are collecting.

Ignorance -- we remember the War on Poverty. The three women you see right here were born at the institution of such. We cannot believe that the end of the War on Poverty is going to be the benign neglect and ignorance of a major epidemic that can change the entire face of this nation, and that this is the only answer this nation has to offer.

[Applause.]

DR. LILLY: We will now have a questioning period. Dr. Davis has given us an extraordinarily detailed presentation and we will now have a brief questioning period. Perhaps we could start with Ms. Pullen.

MS. PULLEN No questions.

DR. LILLY: Dr. Primm?

DR. PRIMM: Dr. Morgan and Dr. Davis and Ms. Ribble, I want to thank you for a very complete presentation, and I'm sure that as well as I am very proud of what you have said today, that unquestionably your father, who I served with in the Army as you know, would also be very proud, Dr. Davis.

I'm happy that you cite the study that was done at the Addiction Research and Treatment Corporation that you are involved with on an ongoing basis in your own work, where a number of men who are intravenous drug users have as sexual partners non-intravenous drug-using women who certainly are more than likely to be positive for the antibody to the virus.

I noticed something else that you didn't talk about in your presentation. In this week's Science magazine, or last week's Science magazine, I don't know whether you read that article that talked about oral contraceptives may be making women even more susceptible because of the kind of receptivity that's created in the endometrium when oral contraceptives are used. And you all might want to look at that factor as a co- factor in the seroprevalence or the incidence and prevalence of the problem -- infectivity among your patient population.

Again, let me commend you. I have no questions. Your presentation was complete and succinct and with great candor, and thank you very much for that.

DR. LILLY: Dr. Crenshaw.

DR. CRENSHAW: I also would like to thank you for your presentation, and you raised so many important points, I'm sorry to be limited to address just a few because I think this issue deserves much more time and airing.

In a disease that kills two generations at once, we tend to focus on the babies, as indeed they deserve the attention, but the women often get lost. I really am troubled that this far into the epidemic there are destructive articles such as have appeared recently, minimizing the threat to heterosexuals, to people in general. I think it kills people, I think they lower their guard, and I think we need to be more responsible. And even if we're wrong, if we're inadvertently exaggerating the threat, we'll save lives and we'll be careful.

So I completely agree with you that we need to learn the extent of the disease among women so that we can respond and address it better. I have, long before the AIDS epidemic, struggled with the problem -- and you're probably aware -- that in all drug research, long before the AIDS issues, women are considered as modified men. The studies are done primarily on men unless it's endocrine or birth control, and the special side effects that could affect women in very devastating ways aren't addressed.

I would love to have help on how to change the situation, and maybe this is one of the positive spin-offs of research in AIDS because women will have to be completed in these studies, and they need to be entered now, five years ago, not five years hence. So anything you can give me on good ideas on how to encourage all of the research to address the special problems of infected women I would be most receptive to.

MS. RIBBLE: Could I comment on that? I'd like to make two comments. I think the first comment is that one way the Federal government has of directly addressing that issue is to mandate to the FDA that no drugs will be released unless they have been tested in women, and that the recruitment of women into studies will begin immediately, that they will back- recruit into studies that don't include women at this time, and that they will really make an effort to recruit minority women.

And I also want to include not just women but the straight men, for example, who have also been excluded from those studies. You know, not every man wants to go to a study and

pretend that he's gay or bisexual to get a drug, which he may not get because he might be getting a placebo.

My second very strong recommendation is that the CRI has an initiative which is to provide treatments that have been shown in modified testing to be safe and that need to be reviewed in terms of efficacy and to not do placebo control trials on drugs already shown to be safe. Women could certainly benefit by having more CRI type drug trials and less scientific testing that demands that you will denote the effectiveness of a drug based on how many people in the placebo group die.

DR. CRENSHAW: Thank you. And I might also add that I think in the area of prevention women are being both misled as a result of much of this kind of information we described, and deluded by the lack of sophistication we have about sexual practices and the lack of understanding that artificially classifies as two separate compartments heterosexual and homosexual, and women are usually the last to know what their sexual partners are truly doing if it's something they want to keep from them. So we need greater sophistication and understanding, and we need women to become a little more alert and aware so that they don't inadvertently put themselves at risk.

DR. DAVIS: I think some statistics that can easily be looked at -- we are part of the Community Research Initiative here in New York, we have just joined it in the hopes of gaining more drugs for our patients. As a physician, I do not wish to unleash large trials of drugs that have not at least been having some type of placebo testing in small groups because I have seen what AZT can do in a negative fashion to people. It is really remarkable. We do not have the same result overall that were cited in the original study, but of course I can't give you that kind of specific information here.

But I'm just saying that if one community practitioner in the most drug-ridden, low-income area of New York City can give you this kind of information, do you have any idea of how much information is out there when you look at Harlem, North Bronx, the South Bronx, Staten Island and Long Island. And this is just New York City.

There's a National Cancer Registry. Wy can't we have national statistics on AIDS on what treatment has done for somebody at somebody's clinic. I mean, there's Medlines. We can all plug in. I'll go to the local library and plug in my data. And the NIH I do think is capable of doing that.

I do think also the Community Research Initiatives need to receive more funding in terms of the RFP process -- you know, that's a difficult process to mount. You're talking about

statisticians, et cetera. When you look at the RFP process someone who is in a community project like myself really doesn't have the capacity to necessarily get an NIH grant. I can assure you it won't be due to lack of determination.

However, the reality of the process is that if I'm seeing 19 acutely ill patients a day, counseling, treating, running a group three times a week, I need some kind of help. We cannot take anymore cuts in funds in community health centers.

DR. CRENSHAW: You're doing a remarkable job with a paucity of funding, and you are a remarkable example that shows what is possible, not what's impossible, so thank you very much.

DR. LILLY: Dr. Walsh?

DR. WALSH: Dr. Davis, I had to step out because I was talking with Mr. Delaney about what he and Mr. Hannan are interested in, in trying to clarify a way to get some of these things to help you and to clarify a strategy because we didn't have time for questioning, so I missed a little bit of the early part of your presentation.

When I came in I think I heard you say, however, or point out the much greater incidence in women of HIV positivity than has at least been reported. And I was wondering, you know this Commission is informed on a weekly basis by CDC of the incidence of disease, the distribution of the disease and where it comes from and so on. And it just seems to me that those figures, as I see them, don't represent anything like what you are talking about, and I'm sure it's not intentional on CDC's part to --

DR. DAVIS: No, actually CDC is now coming to look at our community. We called them, we told them. We have a 46 percent rate in men -- 33 percent in children.

DR. WALSH: This is what my concern is because I share what Dr. Crenshaw has said; this sort of complacence that there's not much heterosexual transmission, that women are not getting the disease, and I think that we may be living in Fairyland on that.

DR. DAVIS: I can assure you, you are.

DR. WALSH: It just isn't true.

DR. DAVIS: I don't mean to be facetious; I just am telling you the numbers rise every day.

DR. WALSH: But again, I think it also supports so strongly the position that Mr. Hannan and his colleagues took

this morning of how much more use can be made of the community-based efforts. And this Commission has to find a way to do that, or to urge it. We can't do it; we can urge it. And I just think it would be helpful to us, certainly to me, if we could get more frequent information from people like yourself telling us exactly what's happening in the real world, and maybe in a sense you share the responsibility to the extent that maybe you get impatient with them because I'm sure you send them statistical information; maybe they just don't accept it or don't use or whatever. Who knows?

But for some reason, it's not surfacing, and I think it's important that the Chairman be able to include in his recommendations to us as the Commission the fact that there seems to be something wrong with this statistical information, and ways in which we could take samples to correct it. Because again, this would benefit the efforts at treatment that you want, the efforts at getting more funding that you want or more diversified funding. And I would be very grateful.

But I did hear you correctly, then. I was astonished at what I thought I heard. And I am sure this can be replicated, as you said, not only in Bushwick but in Staten Island and in other places, which means to me it's a much greater problem than the country has been led to believe. And when we're criticizing high officials in the administration, keep in mind they're only getting the same official information, also, that we're getting.

DR. DAVIS: Well, please take my information straight to them.

DR. WALSH: So that's what you have to do. Unfortunately, they don't get it. But you know, those things -- I wish it were true. I wish that everybody who wrote a letter in some way that it would get there but it doesn't.

But I think that we can get it to them through this Commission, and I think it's very important that we find other sources of data so that we can raise questions. We have no basis to raise them unless we get that information.

And I want to thank you for waking us up.

DR. DAVIS: Thank you. Can I just respond a little bit to both of you. I think one other major problem is that -- and I'm very aware of this. I chose to be a public health physician, and I think that often physicians of my generation, especially of my racial and sexual background, have chosen this path. However, it also means that when you talk about the liaisons between public and private medicine, let's just be very real. That's that world on that side of town, and this is this side of the tracks. There is no question that the Federal government

supports private institutions and public institutions. You all can make rules -- or rather, the federal institutions can make rules about how much has to go across the tracks; I don't care if it tunnels under or if it goes over, but it does have some control over those issues.

It's real important -- community health centers can't take AZT levels, but most women in New York City receive AZT in community health centers. I can't get an AZT level; you think I an afford to pay for AZT levels? Who's going to pay for it? Burroughs Wellcome is making too much of a profit; I've already asked them. There has to be greater cooperation. It's a national epidemic; it's not only in Bushwick, you know. It's not only in Brooklyn.

Sometimes it seems to me when I go to conferences with other physicians, there's a real lack of saying if you bleed, I bleed. You know? There's a real lack of understanding that it really is one nation with many diverse populations.

DR. WALSH: Again, shouldn't Medicare and Medicaid, for example, pay for the experimental drugs? That's something the Congress has to handle; that's something that maybe we should be recommending.

DR. DAVIS: Or a protocol to establish such.

DR. LILLY: Mr. Creedon.

MR. CREEDON: I really don't have any questions but I think that the testimony has been very valuable, and as Dr. Walsh says, it proves the importance of groups like your own and Mr. Hannan's; the local groups are really going to make the difference here. The Federal government can't do it all; they can help pay for it but I think efforts of groups like yourselves are going to make the difference. Thank you.

DR. DAVIS: But there is a differential in front of you now. New York Hospital does get more than Downstate Medical Center.

MR. CREEDON: Well, we have to address that.

DR. LILLY: Dr. SerVaas.

DR. SERVAAS: Thank you for coming. I really like your suggestion about a national AIDS registry, and I'm surprised that we don't have one, like the National Tumor Registry. I wonder if you could tell us in your own observation -- I've heard conflicting advice from different sources in the country -- about women when they become pregnant. Do you observe that they are

more likely to become ill with AIDS when seropositive women become pregnant?

And then I had another question. I don't know how many women you have who are HIV antibody-positive, but would these women, in your opinion, be willing to try non-toxic preparations to see if they could go on longer and not get ARC or AIDS? In your opinion.

DR. DAVIS: Let me answer the second question first because it is actually easier for us. If I can be so asinine, the day when we called DuPont we literally had a face-down about Ampligen. The two of us stood in the hall and cried, and our patients surrounded us. Our staff continued to surround us until you had 29 crying people in the hallway.

Our people beg us for treatment. In the media, there is not sufficient knowledge, especially because I think especially in the minority communities people feel so stigmatized, it's like you're saying these are not bank clerks, which they are -- most of my women are bank clerks, they're the people who serve you at McDonald's, they're the people who have low-income jobs in society, and you're saying that they have given nothing of value in the society. And so they don't come for treatment often, and they hide all aspects of their disease. So that when I'm not able somehow to put them into that system, they just give up. It is just unreal.

There's no question -- we're using disulfiram, which as I'm sure you all know follows the principle of DTC and is a T-cell stimulator. We're using that because it's a drug that New York City Health and Hospitals Corporation already has; I don't have to write but a certain number of protocols and I can put it on the streets today, which I've done.

DR. SERVAAS: So how many women could you find who are seropositive who would likely participate in --

DR. DAVIS: All of my women participate in drug trials, if allowed. I have over 100 women now.

MS. RIBBLE: And I have another 135. And I have some who would fly in from Wisconsin if they could get Ampligen, because that's how far my phone calls come from.

DR. SERVAAS: And have you observed that women, when they become pregnant, become ill more quickly than the women who are seropositive --

DR. DAVIS: I don't think we can adequately respond. We are both internists; we tend to see a general medical population. We're picking up HIV disease from our hypertensive

lady who says, well, I know you have this program here and my husband did that 10 years ago so can you just test me? Do you understand? So we're coming from a different base of population. We get women after they've had a baby and after the baby got sick and somebody said you'd better go get HIV tested over in that clinic. So I would prefer not to give improper data.

DR. SERVAAS: Thank you.

DR. LILLY: Dr. Lee?

DR. LEE: Dr. Davis, first, I wonder, because we were given so many figures, if you could give your epidemiologic stats on your patient population to us in writing. Could you do that? I'm not asking for a document; I'm asking for what percentage of what population that you're seeing is positive for HTLV. Maybe you've got three or four subset numbers. I'd like them. And I'd like to know exactly what population you're looking at in Bushwick. Okay?

DR. DAVIS: I would love to give them to you.

DR. LEE: Number two, I cannot get a handle on really what effect the bisexual man is having on women. When I look at the patients, my gut feeling is that it would have been very large; that women have a bad exposure at a high level, but looking at statistics, I can't find that.

Now, you say you're seeing it, and I'd like to know. Do you have anything specific on that? We can't come up with that number.

DR. DAVIS: First of all, we're citing New York City incidence numbers right now. We've only been in reality for six months, Dr. Lee, so you can understand how upsetting these statistics are to us, too. If we collected this in six months, what are we going to collect in a year?

We are finding the prevalence rates of bisexuality to be much greater than that of homosexuality among both Blacks and Hispanics. I can't give you a number. I give you my word, I will go home, look it up and send it back to you.

DR. LEE: If you can find something, I would be very interested in that.

SPEAKER: Why?

DR. LEE: Why? Because this has a big effect on, or should have a big effect on women's attitudes towards sex. One of our conferences in April is going to be focused on the drug abuse problem, the family, difficulties in the inner cities that

seem to promote drug abuse, the high level of single parent households in this area; the problems that women are facing that seem to us in our research are getting worse in these communities rather than getting better. And we'll be in touch with you, Dr. Davis, to perhaps participate in that conference in some way.

Lastly, I didn't get from you -- are you really involved with the Community Research Initiative? I sensed hesitation in many ways. Now the reason I'm saying this is I can guarantee you that this is going to be a prominent part of our Interim Report. I know we're going to be strongly supporting these Community Research Initiatives. We have been told that there is a very high level of receptivity at the NIH for these efforts, and we have been told that the funding is coming very rapidly for this.

So personally, from what we're seeing, I would urge you to join forces with these people rather than try to do it all on your own. Now, am I wrong there?

DR. DAVIS: Oh, no. I just ask that you fund them sufficiently. I have no secretary, I have no epidemiologist, I do not have a computer --

DR. LEE: Well, they do.

DR. DAVIS: They do, but they have to use it for their work. There are three community health centers such as mine in New York City alone that just are devoted to a general medical clinic with an AIDS treatment unit within it. Then if you start talking about the local physicians that we hope to pull with us, somebody's got to collect that data. So they've got to be given sufficient funds to give us that kind of administrative, bureaucratic support. The community health center doesn't have it.

DR. LEE: As I understand it, these people do, though. They have volunteers, they're very well organized, they have funds. They're going to get more funds, and I would say --

DR. DAVIS: Wonderful.

DR. LEE: If I were in the community, I'd join forces with them. Mr. Hannan, would you like to comment on this?

MR. HANNAN: I met Dr. Davis two days ago when we were giving testimony at Albany, and at that time she wasn't familiar with the fact that our IRB had insisted that IV drug users and women be included in our Ampligen trial.

I am so incredibly encouraged by the fact that groups such as Dr. Davis' group are willing to join forces with us because it has to be a team effort. We need more people in our trials. Those people need to get the substances which they deserve before they have yet been approved as therapies for AIDS.

Thank you, Dr. Davis, because your testimony was brilliant and I'm so proud to be cooperating with you.

[Applause.]

DR. DAVIS: Thank you, Dr. Lee, for the support.

DR. LILLY: I would like to ask just one very brief question. One thing that you said just in passing that I think I agree with you on but I'd like just a couple of comments and I hope it won't take me terribly long.

You said that although gay men were able to get themselves together very early in the epidemic and to, in a sense, take charge of their own lives and form organizations and help themselves out to a very considerable degree of success, that minorities and women may not be able to bring that off, and I wonder if you could --

DR. DAVIS: Oh, no, I totally disagree with that. I think that people are people, okay. And I really believe that communities, even though there is this perception of the gay community as this very well-off, middle class, white institution that can take care of itself -- well, 10, 15 to 20 percent of my patients are gay white men who come from the Village because they can't afford anybody below 14th Street.

[Applause.]

I think the whole issue of sexuality that Dr. Crenshaw and Dr. Walsh raised and what is really known about sexuality, lower income and especially when you're talking about poorly educated gay men, whether they're white, Black or Hispanic, they really don't know how to integrate into a GMHC, and it's not because of GMHC. I'm going to tell you, I wish to give credence and support for what gay people have done for all people's lives in this country today.

I think, though, that you must deal with cultural issues. You know, homophobia really exists in this country. That's not an illusion. And when you talk about Black and Hispanic communities, homosexuality is really not part of our cultural norm in general; this issue has been discussed in national Black magazines like Ebony, Jet, and Essence. We really, as a culture, often do not tolerate it. When you start talking about religious aspects of our community, which is -- if

you remember, we have come all the way from King through Jackson -- the church has been a major source of political power. It has been a difficult coming together.

I do think that the communities can be mobilized. I'm just saying that you have to look at different aspects of the community to decide where to mobilize it. Some of the groups that are mobilizing I can tell you right now within our community are gay, bisexual men, the National Conference of Negro Women. We hope to try and apply and go to various sororities, fraternities, certainly. But that type of network -- just like GMHC -- didn't start yesterday; it started out with 20 volunteers and people who were dying of AIDS and were committed to giving something back before they left this earth. And I think what you will be seeing is that process replicated for women, for Blacks, for Hispanics, for whoever gets touched by a disease where they hold their child while they die.

DR. LILLY: I certainly hope you're right. I would be very happy to see it. Admiral Watkins.

CHAIRMAN WATKINS: Dr. Davis, we're going to be making recommendations here in the very next few days on our Interim Report to the President, and I think your testimony and that of Ms. Ribble has been very important to us today. I know it's been difficult for you to get the kind of support you need in many areas, and so we'd like to take your written testimony that you have and your handwritten notes there, if we can, and let us photocopy it while we have the staff to do that. So we don't want you to get out of the room.

The reporter here will eventually give us that piece of information through the transcript, but I think we could use it right away if that's acceptable to you.

DR. DAVIS: We will do our best.

CHAIRMAN WATKINS: We can do it for you.

DR. DAVIS: It was only through the kindness of the network that exists among those of us who work with AIDS that we were informed 36 hours ago that we would be testifying, so we will write it up today. We have been up for the past 24 hours. We will type it this afternoon.

CHAIRMAN WATKINS: I merely meant to have copies of your handwritten notes, if that's something that you would be willing to let our staff have to trigger our thoughts off as we prepare our Interim Report.

DR. DAVIS: Okay.

CHAIRMAN WATKINS: Another question, just one question for either one of you two. If the Federal government were to directly fund community-based drug trials, let's say through CRI, for example, and with your new affiliation, close affiliation with CRI, how could we include your organizations in that? And would that be a logical way to move with this CRI under this federal funding mechanism?

DR. DAVIS: I'm sorry. You're asking whether we wish you to directly fund the community health center, or you're asking whether to directly fund CRI? I think I've missed the question.

CHAIRMAN WATKINS: We were talking earlier about the linkage between your organization, say, and the CRI trials where women would be included and drug users would be included. I'm just asking the question would this -- how could we include your organization as part of that effort were additional funding to go to CRI to conduct trials, along the lines that both you and former witnesses have recommended this morning for women and drug users?

DR. DAVIS: I think money has to -- I mean, with CRI here in New York City, I am not frightened of the fact that minorities and women -- they've obviously got outreach efforts trying to adequately serve those communities, and we will attempt to help them organize as well as we can through the network of people that we are aware of. However, I think it has to be specified. I think the same laws that exist for discrimination on the books right now have to be applied to medical care. Medical care is not an option always in this country; it is often a privilege.

DR. LILLY: The Commission is very grateful for your participation this morning. It's been unusual; you have said many things that we had not heard before and we certainly will take them into close consideration in our further work. And thank you.

[Applause.]

HIV Infection Co-factors

DR. LILLY: There are three speakers in the next panel on Co- Factors who are going to speak to us with respect to things that are not perhaps the direct cause of the epidemic but play strong factors in its occurrence.

Our first speaker in this session is Dr. George Solomon, who is Professor of Psychiatry at UCLA. We would be very grateful if the speakers could keep their presentations relatively short and concise.

DR. SOLOMON: I think I shall start by referring to psychoneuroimmunology that began over 20 years ago, but really is burgeoning at the present time as a result of realization that the immune system is not really autonomous but is influenced by neuroendocrine mechanisms. For example, there was a conference late last year co-chaired by me and Dr. Lydia Temoshok sponsored by NIMH on the relationship of psychoneuroimmunology to AIDS research.

Psychoneuroimmunology is concerned with complex bi-directional, two way, interactions between the central nervous system, which not only mediates psychological but also biological processes, and the immune system. The immune system itself is not only responsible for resistance to infectious diseases and cancer, but also is being found to play an important bio-regulatory function. This field reinforces the view that all disease is multi-factorial and bio-psychosocial in onset and course, and the result of interrelationships among specific etiologic agents, such as bacteria, viruses, and carcinogens, and genetic, endocrine, nervous, immune, emotional and behavioral factors.

As a result of the various hypotheses and postulates of psychoneuroimmunology that began a number of years ago with a single one, that stress could express immune function and now number some 40 odd, there are hypotheses that can be derived that are more specifically applicable to AIDS, and I would like to mention these very briefly.

These questions include:

--Are stress or other psycho-social factors related to vulnerability to HIV infection? We certainly know that homophobia, for example, may make the gay lifestyle a particularly stressful one in certain circumstances, and certainly a drug abusing lifestyle is full of emotional distress.

--Is pre-existing immunosuppression a facilitating factor for infection and seroconversion? We know that some infections, such as Epstein-Barr virus infection, can be immunosuppressive, but we also know that drugs, particularly exogenous opiates, and emotional distress can be immunosuppressive.

--Can stress activate HIV from a latent to a rapidly replicating state? It is now known, of course, that HIV can exist for long periods of time in a latent, low replication state. We also know, and there is good research, that stress can activate other viruses, particularly the herpes viruses. The discoverer of the tat gene -- transcriptional activating gene --

himself referred to stress as a possible cause of activation of that gene, one of the two genes that can activate HIV.

--Are psycho-social factors related to progression of HIV disease? In seropositive asymptomatic individuals, there are varied courses of drops in helper T-cell, T4, numbers. Some people's numbers gradually decline. Others have a more rapid slope of decline. Some people's plateau out. Some declines are quite flat and then suddenly begin a rapid drop. Research currently underway by Dr. John Fahey and Dr. Margaret Kemeny, at UCLA, is hoping to see whether psycho-social variables can influence the decline or steadiness of immune function in HIV antibody positive asymptomatic individuals.

--Can psycho-social variables be correlated with specific alterations in immune function associated with HIV infection? We have current evidence in persons with AIDS that there are psycho-social correlates of a number of specific immune functions including numbers of helper T-cells, virucidal cells, cytotoxic cells, suppressor cells and natural killer cells and their activity. In general, in a very over simplified summary, one can say that better immune function is associated with better psychological status in sick individuals and worse emotional state with lower numbers of specific T-cells. Indeed, there possibly may be psycho-social correlates of elevations of sets of cells that may serve a compensatory function in the face of deficiencies of helper T-cells induced by the virus. In other words, cytotoxic T-cells or natural killer (NK) cells may be elevated in some positive way and help out when there is deficiency of other components of the immune system, which has to be thought of in a complex and interacting way.

--Is length of survival related to psycho-social factors assessed at an earlier point in time? I really wish I could go over with you some of the psycho-social variables that we found associated with long survival in persons with AIDS. It has been a great privilege to get to know some of the most remarkable people I've ever met, who are among the long survivors with AIDS. Their remarkable emotional strength and coping capacity and their long survival I don't think are just coincidentally correlated.

This correlation has very important implications, I believe, for the problem of the disease among IV drug abusers. I also happen to run a substance abuse center in a VA setting. I really think we are dealing with quite a different population often times among such individuals who almost by definition are non-copers, using very maladaptive and self-destructive means of dealing with life and their problems. I think psychosocial factors such as poor coping ability, as well as continued substance abuse, may well account in part at least for far

shorter survival of drug abusers with AIDS, on average, than gay persons with AIDS.

At any given level of deficient immune function, do psychological factors relate to presence or severity of secondary disease? Again, we have seen a number of people who, just looking at their immune function on laboratory tests, seem in very bad shape, but they are doing quite well clinically. There seem to be some psycho-social correlates of the relationship of any given level of immune function to the severity of clinical illness.

Can psychological interventions ameliorate the stress associated with AIDS and ARC and improve immune status and the clinical picture? Research again at UCLA by Doctor Sheila Namir shows that group interventions that are aimed at improving coping skills are not only supportive but having to do with active ways of dealing with the problems associated with the illness, markedly decreased emotional distress. Current studies are now underway to determine whether these decreases in distress are also associated with improved immune and clinical status.

I'd like to make basically three recommendations. The first is that any social policy that is developed for dealing with the HIV epidemic take into account the role of emotional distress that may be engendered by whatever that policy is. In view of the fact that there are so many people who are already infected and asymptomatic, how policies affect how one feels about one's self, one's place in society and what sort of support one is getting, may have a great deal to do with the actual rapidity of decline in immune function or incidence or progression of the disease itself.

Secondly, I should like to recommend that psycho-social variables along with biomedical and immune parameters be included in as much research as possible on course and treatment of HIV disease, in view of evidence which suggests that such factors may play a role in progression, and perhaps even in treatment response.

Finally, I should like to recommend that the Government's own programs, particularly within the VA, should serve as models. Current cutbacks in provision of treatment for drug abuse for addicted veterans, are absolutely appalling and in contrast, need to be expanded in conjunction with an active program for prevention of infection as well as for psycho-social support of those already infected.

I could go into detail about expanding programs to help addicted veterans, many of whom became addicted in VietNam. I wrote the first paper on drug abuse in VietNam and testified in Congress about that in 1971. The Government itself is cutting

back its own programs in these areas. For a long time, the VA was not even offering voluntary testing for asymptomatic at risk individuals. I think that is utterly appalling, along with cuts in staffing and duration and intensity of treatment for IV drug abusers.

Those, essentially, are my recommendations, again emphasizing that we should not separate psycho-social and biomedical research, but should integrate them.

Thank you.

DR. LILLY: Thank you, Dr. Solomon.

The next presenter will be Dr. Elinor Levy of the Boston University School of Medicine.

DR. LEVY: Thank you. I would first like to say that primarily I'm an immunologist, so my remarks are those of an immunologist with an interest, strong interest, in AIDS.

I have a brief statement. Each year, we learn a little bit more about the natural history of HIV infections. We now know that following infection with HIV, some individuals develop AIDS within a year, while others remain without any symptoms for at least seven years. Similarly, we know that some individuals with Kaposi's sarcoma die within months of diagnosis, while others live longer than six years.

At this point, however, we have little evidence or information to explain the differences, these variabilities, and therefore we're unable to advise the one to two million, estimated one to two million Americans infected with HIV how to maximize their longevity. Should they change their habits, their diets, their attitudes?

I personally believe that the focus on drugs alone is too narrow a focus. There is evidence that suggests, as Dr. Solomon has mentioned, that these factors, including nutritional ones, may have important influences on the progression of HIV-related diseases, and I was pleased to hear the Commission's interest in the large number of healthy seropositives. Very little at this time is being done to look at what co-factors are involved in progression to clinical symptoms and frank AIDS.

I will concentrate my remarks on nutrition as a possible cofactor in HIV-related disease. In general, malnutrition is associated with a significant impairment of immune response. The immune response is also sensitive to deficiencies and excesses of single nutrients and to the quantity and quality of fat intake. Nutrition can be shown to affect

susceptibility to a variety of infectious agents and is implicated in the development of cancer.

I have been involved in a pilot study of men with AIDS-related diseases who chose to follow a macrobiotic regimen. This regimen includes a vegetarian diet, a change to a healthy lifestyle, and a sense of hope and control. The large majority report an improvement in AIDS-related symptoms and additionally in the group with KS, we've also seen an increase in the number of lymphocytes, a significant increase over the first three years after diagnosis. Six out of 19 of these men are alive now more than three years after a diagnosis with KS.

Research into nutrition as a cofactor for the progression of HIV-related diseases is difficult for several reasons; among them, prevailing research priorities, the complexity of studies in this area, and certain methodological problems.

Research priorities have focused on finding a cure and developing a vaccine, both worthwhile but still elusive goals. Only recently has there been a shift to improve education to prevent HIV infection and an interest by ADAMHA in the role of psychosocial factors, including alcohol and drug abuse, in the progression of AIDS.

The group we have been studying is an example of the likely interrelationship between nutritional, psychosocial, and behavior choices. Studies must take into account these interrelationships in order to interpret data correctly. Additionally, there are methodological problems in accurately assessing nutritional status, especially in AIDS where absorption may be a problem.

I would recommend that the NIH foster more of an interest in nutritional and other co-factors through organizations of small workshops, such as that organized by Drs. Solomon and Temoshok having to do with psychosocial factors, to bring together the multidisciplinary talents needed to work out design and methodological issues and by encouraging research through RFPs.

I would recommend that nutritional components be added onto ongoing natural history studies, and/or that new studies focusing on psychosocial and nutritional factors be encouraged, including those with intervention designs.

Finally, I would recommend that the NIH create multidisciplinary review committees to properly review these grant applications.

In view of other testimony this morning, I would also suggest that the CRIs and other informal, community-based data-gathering organizations include information on alternative therapies, including nutritional approaches, to their database. Many, many people who are at risk are trying alternative approaches, and that shouldn't be ignored.

At this time, I cannot give an estimated cost for implementing these recommendations, but suggest it would be a modest investment compared to what would be saved in health care and social service costs if onset of debilitating symptoms can be delayed or prevented.

Although the state of our knowledge about the factors predisposing to the progression of HIV infection is not extensive, it is still likely that these co-factors play an important role. There is an urgent need for research in these areas, so that accurate information can be used as a basis for more effective treatment strategies and educating persons at risk.

Thank you.

[The prepared statement of Dr. Levy is included in the Appendix.]

DR. LILLY: Thank you, Dr. Levy. I certainly would agree that nutrition studies have often, in many senses, been the poor stepchild of the biomedical world.

Our next speaker is Dr. Peter Duesberg, who comes to us from the University of California in Berkeley, where he is Professor of Molecular Microbiology.

DR. DUESBERG: I thank the Commission.

The hypothesis that the AIDS virus is the cause of AIDS, as we heard on many occasions yesterday and today and the day before yesterday when I wasn't here, I assume, is the basis for a $1 billion research effort in this virus, which is by now probably the most expensive virus in history. It is the basis for the rather toxic AZT therapy of AIDS patients, and, in fact, that is now being extended as a prophylactic therapy for those who have no symptoms yet, and it is also the basis for the famous AIDS test, which is, to say the least, at least psychologically somewhat toxic, at least to some people who commit suicide or get their homes burned down when they are positive.

Now all of this would be highly justified, of course, if we indeed knew that the virus is the cause of AIDS, but I submit to you that I don't think this is proven and there wasn't any time to prove it. The scientific community was under

tremendous pressure to come up with the cause for AIDS, and in this rush to come up with the answer, probably many questions were left unanswered, and what I think is actually worse, many questions were never asked.

There was no time for slow answers. There were only fast answers, as we heard in the testimony yesterday from Drs. Roper and Sam Broder. We had fast tests within five or six months. We had fast vaccines. The vaccines didn't work, but we had faster AIDS yet, and in fact we just read in The New York Times last Sunday how many vaccines we have. None of them works. And there were pages and pages of discussions why they don't work, except to mention the possibility that the virus may not be the cause of AIDS, and that's why they don't work. This may be a rather simple answer, but too simple for The New York Times.

[Applause.]

Now what I would like to address today in the little time that I have are the problems that I have with the hypothesis, the questions that haven't been asked, and answers -- I don't have too many answers unfortunately, but also the questions that haven't been answered.

One of the problems that I have with the hypothesis is that the AIDS virus doesn't follow the rules that all other viruses, known to me at least, and all other retroviruses known to me, follow.

One of these rules, for example, that viruses follow, believe it or not, when they cause a disease is, they are active. They are biochemically active, metabolically active. They do something in order to get something done, exactly like you and me. When we want to get something done, we have to work for it. It's true for chemistry; it's true for physics and biochemistry, except for the famous AIDS virus.

That one isn't doing no nothing, as they say. That virus is latent and inactive. In fact, it is only detectable by the most expensive laboratories in the country, even in the fatal course of the disease. It is no more active in those who are dying from it -- or inactive, I should really say -- than in those who have no symptoms whatsoever.

Perhaps the best case in point here is the famous controversy between Drs. Gallo and Montagnier's labs where the virus came from. It has escalated into an international controversy between the United States and France, which was finally only settled by Presidents Reagan and Chiriac. The difficulty would have never happened 100 years ago when Robert Koch and Pasteur were competing, because they were dealing with microbes that were active at clinically relevant concentrations.

It would never have happened to Salk and Sabin either. They were isolating viruses when they were clinically relevant at high concentrations.

This virus is at such low concentration that it is very difficult to isolate it. That's why we had that famous controversy.

It is also relevant to point out, in view of the famous AZT therapy for this virus, AZT is an inhibitor of DNA synthesis, an analog of thymidine which when incorporated into the DNA of a growing cell or replicating virus stops DNA synthesis right there. The buck indeed stops right there. As Sam Broder put it nicely, it is aesthetically pleasing to see the sequencing of DNA when he is treating patients with that drug. He would indeed do that only if there were any DNA synthesis.

Again, not even the most expensive laboratory in the country can detect DNA synthesis. All they could come up with is, in 15 percent of AIDS patients, they find some DNA, not actively being synthesized, but that's five-year-old DNA. The latent period, as you perhaps recall, is five years for that virus to cause the disease.

So that AZT therapy does one thing for sure. It kills all growing cells. Whether it does anything else, I haven't heard any discussion about. It certainly can't hurt DNA synthesis when it is not going on, but it may be like it often is in medicine, like chicken soup, things have unpredictable benefits. But in this case, it's a designer drug. One thing it does for sure, it kills every cell in which it's incorporated.

Now another rule that viruses regularly follow when they cause diseases, they intoxicate or infect or kill more cells than you could possibly spare or afford to lose during the course of the disease. That is to say, the hepatitis virus only bothers you if it is chewing up half of your liver or a third of it. If it claims 1/1000th or 1/10,000th of it, you will never notice you were infected. The same is true for polio virus. 99 percent of all polio virus infections are latent, because the same thing is happening as in vaccination. A couple of million cells are killed in your guts. You make antibodies. You will never notice it.

But only when the virus penetrates deep into host territory, kills off or infects or intoxicates large fractions of specific organs of the host will you experience symptoms of a disease.

Paradoxically, the AIDS virus doesn't do anything like that. It actively infects never more than one in ten thousand T-cells, even during the fatal course of the disease. This is

the equivalent of losing one drop of blood every day approximately. You and I could sustain that for approximately 10,000 years without changing anything. We would look exactly as we look now.

Another rule that viruses commonly follow when they cause a disease is that shortly after exposure, after a take, you develop symptoms, or you don't. If you're lucky, you don't; if you are not lucky, if you took, then you have a disease a month or two months later. This is true for both casually and non-casually transmitted viruses. You know a month or two months later whether you have hepatitis, when you are stuck by a needle, or herpes when you have had some intimate contact or rabies when you're bitten by a dog or polio or measles or mumps when you are simply casually exposed to somebody who has that disease.

So that is to say, viruses work quickly or not at all. Again, the AIDS virus seems to be the exception to the rule. This virus is said to cause disease only after a latent period of at least five to seven years. What it does in those five to seven years, how it's making up its mind to cause a fatal disease, if it couldn't do that five to six years prior to this, is not ever explained in any of the papers I have seen.

Another cardinal rule in virus infection, in immunology, is that viruses cause disease or at least the primary symptoms of the disease before immunity, not after immunity. The host, in other words, has to be permissive to the virus to let it happen. If you are not permissive -- that is to say, if you have antibodies, if you are vaccinated -- the virus has no show or has not a good chance to cause a disease. In fact, typically it doesn't.

This is exactly why vaccination works so well. Ever since Jenner discovered the principle of vaccination 200 years ago, antibodies were seen as evidence for a successful rejection of the prior infection and as protection for the future. That's why we were all vaccinated against polio, against measles, against mumps, against herpes or hepatitis, whatever is available in the form of vaccines.

Now the HIV establishment has reeducated 250 million Americans to know otherwise. Now we are all educated to know if you make antibody to this virus, this is a prognosis for death. It's bad news. You're going to die five years from now. You can start committing suicide or do other things.

So the AIDS test is measuring nothing but antibody to the virus, which until a few years ago was something you should be pleased about, you were to be congratulated for because your immune system was intact. You could make antibody to the virus.

The AIDS test not only measures antibody to the virus. It also tells us that the antibody works really well, so well that it is extremely difficult to isolate the virus. I already alluded to the difficulties in isolating the virus. That's a typical example.

Unlike all other viruses, the AIDS virus is not killing cells. It is a retrovirus. The hallmark -- wait a minute; I have a couple of slides. I began to forget my slides.

[Slide.]

This is the first statement I made. I will just leave it there for a second. That the viruses have to be active when they cause a disease.

Now I have to find the right button. Wait a minute. This one would be it.

[Slide.]

Okay. This is the next one, that they have to infect a large number of cells when they cause a disease. Again, the AIDS virus doesn't do that. And I'll be catching up in a second.

The third one was that the viruses usually act fast or never. The AIDS virus needs five to seven years.

And this is the immunity statement that typically once you have antiviral immunity, you are protected. That is not to say that nothing is ever perfect on this planet. You can lose it, and the virus can come back. But typically that works. With AIDS, the rule is, the disease follows only after antiviral immunity, at least it is said to.

[Slide.]

And here, I am at this point. The AIDS virus is a retrovirus, and the retroviruses, unlike all other viruses, do not kill cells. They need living cells in order to replicate, to survive.

This is why retroviruses were the most plausible viral carcinogens or models for viral cancer in Nixon's war on cancer. And a number of us owe our careers to the cancer-virus program, studying retroviruses as possible human carcinogens. One of them is, for example, the famous Dr. Frank Lilly, who is in this room, and the other is Dr. Peter Duesberg. All of us were retrovirus hunters, because we were all convinced that retroviruses are very likely carcinogens, because unlike all other viruses, they do not kill cells when they infect the host. In fact, they often

accelerate growth. That's why they were considered possible tumor viruses. Other viruses always kill.

Now the HIV establishment again has educated us otherwise. They have said paradoxically this virus causes AIDS by killing T-cells. I don't know the explanation for that or no answer for that.

Another peculiarity about this virus is that unlike all other viruses known to me -- in fact, all other microbes known to me -- this virus is said to discriminate heavily between boys and girls and among those between heterosexuals and homosexuals. HIV, paradoxically, prefers men in this country, at least, with an absolute majority of 92 percent. That's the CDC's statistics, not my work. And even now, seven years into the epidemic, when we always hear that this is a rather permissive and liberal country, the virus should have made it out of these groups into the general population. But it hasn't.

Now perhaps there is one very last comment that I would like to make that raises a question about this virus being the cause of AIDS. Basic logic has it that viruses that are pathogens that are responsible or made responsible, held responsible, for disease have to be at least present, if not active, when they are responsible for the disease, and they should be present in all cases of the disease. This is called Koch's postulate, Koch's first postulate. If that one isn't met, you don't have to worry about the second, the third, and the fourth of Koch's postulates.

Now paradoxically, the CDC guidelines of September '87 stipulate exactly what you have to do or what you can do if you want to diagnose an AIDS patient, if there is absolutely no laboratory evidence for that virus, using the most sensitive techniques that biochemistry or biotechnology has to offer. And it stipulates in the statistics that about 25 percent of the cases of the 1987 AIDS vintage, like approximately 3000 cases, fit only the revised guidelines, which means there is simply no evidence for the virus.

[Slide.]

I made a slide here of this paper from the CDC which appeared in the Journal of the American Medical Association. This is a computer disk which they offer you free, how you go about it when you want to diagnose an AIDS patient when you can't find the virus.

See, this is easy when it's positive. Then you just follow Dr. Gallo's or Dr. Fauci's advice. You have an antibody positive test, and if something happens to that person, it's an

AIDS case, whether it's an airplane accident or a disease or diarrhea. That's easy.

[Applause.]

When it's unknown or inconclusive, then the CDC provides help. This is in the table. And when it's totally negative, you can still win. There are still possibilities here or here. That fits in your Mac computer.

So I would conclude, then, from what I have said, unless all of these problems can be solved, the AIDS virus cannot be the cause of AIDS. But unlike my competitors, I'll keep an open mind, and I'll wait for their answers, the answers from Dr. Fauci or Dr. Gallo or Dr. Broder, and I have been waiting for a year almost now. They didn't come yet, but maybe they're preparing them.

So in terms of recommendation, I could only say we could probably make tremendous savings in spending on the study of this virus, about a billion dollars, and all of this money could be made available for the study of AIDS, the disease that we have to deal with.

Thank you.

[Applause.]

[The prepared statement of Dr. Duesberg is included in the Appendix.]

DR. LILLY: Thank you, Dr. Duesberg. You have made your usual and very charming presentation. Most of the scientific community enjoys your iconoclasm.

I would like to speak briefly to the seven points that you made on your slides. In so doing, I would like to recommend that as I do every few years, it would perhaps be good if you were to sit through our graduate course in animal virology. In fact, all of your hypotheses are subject to exceptions. There are indeed other viruses that do those things.

Your first point was that all known viruses are biochemically active when they cause disease and you give polio and hepatitis as an example. HIV apparently is not active. Hepatitis virus, one of the ones you mentioned is indeed biochemically active when it causes hepatitis, but it is not in any traditional sense that we know, biochemically active when it causes liver cancer, which it does, a long time after the initial infection, after a very long latent period.

DR. DUESBERG: Can I answer to this?

DR. LILLY: No, not yet.

[Laughter.]

DR. DUESBERG: That's what I suspected.

[Laughter.]

DR. LILLY: I didn't interrupt you, did I?

DR. DUESBERG: No.

DR. LILLY: Your second point was that all known viruses when pathogenic infect and kill more cells than the host can spare or replace. That is a difficult statement because in fact we do recover to full normal health after many viral infections. On the other hand, what you seem to be worried about there is you are not satisfied with the explanations that people have for why T-cells are killed. I don't think anybody is. That is one of the things that we don't have an explanation for. I don't think that means HIV is necessarily not the cause of AIDS.

In fact, most viral infections that I am aware of do spare at least some cells among the target population in the body.

Your third point was that all known viruses produce primary viral disease after a short latent period of one to two months. They act quickly or not at all. That contradicts the review in which you first proposed that, in which you pointed out that some people pay attention to the existence of a primary HIV induced disease, which is a little bit like a brief and not terribly noticeable case of mononucleosis. I'm perfectly willing to accept that HIV is an acute virus in causing that disease and perhaps in a sense like hepatitis, like herpes virus, then goes to sleep in some sense for a long period of time and then is capable of being reactivated.

Point number four is that all known viruses cause disease in the absence of or prior to immunity. I would simply like to point out that herpes lesions, the initial herpes lesions probably occurs and certainly occurs in the absence of an immune response. On the other hand, herpes, as most people who have it, know that virus also becomes latent and is capable of being reactivated later in the face of a very strong immune response.

Point number five, HIV is a retrovirus and retroviruses don't kill cells. That is indeed classically true.

Here again, your point there is we don't know the mechanism whereby HIV is responsible for killing T-cells and I agree with that point. We do not know that mechanism. I think almost everybody is willing to agree that it might be secondary, that the virus does not do it directly, it has an indirect mechanism for doing it. It could even be a co-factor.

Point number six was no known virus discriminates between men and women nor between heterosexuals and homosexuals. We heard a great deal of testimony this morning about AIDS in women. We have a great deal of dates about AIDS in Africa and the Caribbean as a disease of heterosexuals. The fact that it came into the United States and Europe largely in a founder population is very simple and straight forward.

Your seventh one states that Koch's first postulate for identifying a causative pathogen states that the pathogen must be present in all cases of the disease. I can list a large number of diseases for which I don't think you would take exception to the cause, measles virus is widely accepted as the cause of measles. Measles virus is not demonstrable in all cases of measles. Syphilis, spirochete that is thought to cause syphilis, is not isolatable in all cases of syphilis.

When we come to your conclusion that HIV is not the cause of AIDS, you may be right. There is a slight possibility that HIV is not the cause of AIDS. The evidence to date is in fact circumstantial. But, there is an awful lot of it. I think that even a small number of years before the institution of the polio vaccine, there were still people who were saying that polio virus was not the cause of poliomyelitis, that it was proven essentially by the fact that people were able to make a vaccine that actually protected, a polio virus-derived vaccine that protected against the disease, poliomyelitis.

That was the final proof and probably the only real proof that polio virus caused poliomyelitis. I think that will undoubtedly stay true in the case of AIDS and the connection between AIDS and HIV.

Dr. Duesberg, you and I have been very good friends and I desperately hope that we will continue to be very good friends. You have an awful lot of experience with retroviruses as molecules in tissue culture. I wonder if you have very much experience with viruses as pathogens in animals?

DR. DUESBERG: Is that a question?

DR. LILLY: Yes.

DR. DUESBERG: There was a monk in Czechoslovakia, a Catholic monk. He had very little experience with genetics.

DR. LILLY: He had a lot of experience with peas, and what he published about was peas.

DR. DUESBERG: He had an open mind, although he was a Catholic monk. It seems to me that you are a teacher of undergraduate virology. I am teaching graduate virology at Berkeley. I think I could answer some of your questions if I had the time.

DR. LILLY: I agree that this is a very poor forum for this discussion. We are not going to satisfy it here and now. I want to make the point that there are in fact people who like Dr. Duesberg, do not have any personal stake in the answer to this question, who disagree with his answer to it. I do not have a personal stake in whether HIV causes AIDS or not. It seems to me there is a great deal of evidence for it.

I would like to say also that I really appreciate Dr. Duesberg's iconoclasm in that iconoclasm is very good for the scientific community. It is very good for us to be forced to re-examine the fundamental principles, the principles that we think are fundamental. They may not be fundamental in fact.

For that reason, I rather regret that this has come to be a forum, a very superficial one, we will not settle the question today for this, and I should say one of the reasons I regret is because I heard Dr. Duesberg make a presentation a couple of weeks ago to a group of people, to an audience in which a large percentage of the audience consisted of people who were HIV infected and some of whom were asymptomatic, some of whom were symptomatic.

The person who sat down beside me, who I came to know very shortly, was a man who had said he had just before been diagnosed. I sat and listened to Dr. Duesberg through the filter of my conversation with this young man who was very upset. I realized that this young man was not understanding the points that Dr. Duesberg was making. He was not a scientist. What he was hearing was the experts don't know anything, they are fakes, they are frauds, you are on your own, and that was devastating information.

For that reason, I regret that it has become a public question, although I realize that Dr. Duesberg did not make it so.

DR. DUESBERG: I would like to address this one point. You said yourself that I may even be right and the evidence is circumstantial. In the meantime, people are taking AZT, which is clearly a killer. It is one of the most toxic --

DR. LILLY: You don't seem to want to let me finish because I had a question to ask you. I was going to end my presentation with a question to you.

Since HIV is "bullshit", what should the scientific community be doing?

DR. DUESBERG: The exact quote is "cock and horse shit." That is what the nation's leading AIDS researcher said that in Spin Magazine.

With regard to AZT, even if the virus were the cause, AZT could be efficient if the virus were actively making DNA at the time when this drug is delivered, but there is no evidence for that. In fact, even Dr. Gallo and other laboratories that cost about $1 million a month to run are unable to detect DNA synthesis at the time AZT therapy is used. In the face of what you just said, the evidence is circumstantial, I wonder how good a public health policy that really is.

DR. LILLY: Do you think measles virus causes measles?

DR. DUESBERG: Yes.

DR. LILLY: Dr. Lee?

SPEAKER FROM THE FLOOR: I would like to address something.

DR. LILLY: I'm sorry. We have a very tight schedule. We are already over time for this session. We are going to have to maintain the protocol for these hearings. It is impossible for us to be able to entertain comments from the floor. We would be pleased to receive anything in writing to the Commission. We are serious about taking them into account.

Dr. Lee?

DR. LEE: Dr. Solomon, I commend you for your early reports on the VietNam vets and drug abuse. I take care of a number of those people who have ended up being HTLV positive with very aggressive lymphomas and they are a particularly sympathetic group.

I wanted to ask you a question about stress. I'm sure you don't have an answer but I would like to hear your thoughts. Stress is with all of us. When we look at stress today in the cancer world, we never could find anyone who didn't have stress. At least it was my theory that the best way to deal with stress is to deal with the cause of it. As long as you don't go back and deal with the cause of it, you are constantly dealing with the symptom.

When you are trying to get a handle on stress, have you found any way to measure it?

DR. SOLOMON: I don't like the word "stress" because stress refers to something external. I much prefer the term "distress." There are various forms of emotional distress, which result from external events not being adequately coped with or old issues within the person, not having been resolved. These can lead to emotional distress of various forms. All distress isn't the same, just as the immune system is not uniform and isn't uniformly suppressed or enhanced.

In my research and in that of others, there are a number of studies to show that different forms of stress or distress can affect immunity in different ways. I would say that in humans, depression, particularly helplessness and powerlessness and feelings of despair and grief, which certainly are relevant to the HIV epidemic, are particularly damaging to immune function. Of course, how this is related to clinical illness is sometimes open to question.

In humans, there are studies to show that bereavement, depression, even examination stress, are all reflected in some aspects of immune function and that certain things such as social support can buffer the effects of those stresses.

I do prefer to look at how the person deals with stress, and how it is affecting the individual, rather than what the event is.

DR. LEE: There is no question that it affects disease adversely, but we all have it at high levels almost daily. Really, if somebody in this audience were to stand up and say they are they without stress, I would love to meet that person and talk to them.

But the question is, can you measure the stress so that it is meaningful to us?

DR. SOLOMON: Yes. I have been impressed that psychological measurement really isn't that much less accurate than immunologic measurement and that we indeed to have tests for anxiety, for depression, for a variety of emotional states and traits and for coping that indeed can be quantified and correlated with physiological measures and clinical status.

DR. LEE: Thank you.

DR. LILLY: Dr. SerVaas?

DR. SERVAAS: I want to thank the panel, particularly Dr. Levy.

You are interested in keeping people with AIDS alive six years longer and there are so many differences of opinion among infectious disease experts on what is and is not immunosuppressive and how immunosuppressive is alcohol and how much, since you are talking about diet, how much alcohol is too much in order to maximize longevity.

I wondered if you could tell us in addition to nutrition what you know about smoking and taking aspirin and all the other things that we now advise the HIV positive individuals to do or not to do.

DR. LEVY: As far as chronic effects, I think alcohol doesn't have a particular effect on immunity until you get into an advanced alcoholic state and already have liver disease. Acutely, you do have diminished immune responses, perhaps for 24 hours after heavy drinking, you may have diminished immune responses. I think it is extrapolating but one would imagine that you are more vulnerable during that 24 hours and you are allowing perhaps a step up in the advance of this virus which does progress and have a very slow advance.

Although there is not hard evidence, I'd say it would be advisable for people to cut down on alcohol consumption.

DR. SERVAAS: How much?

DR. LEVY: I would have to do some research. I would have to look at that. Apparently, with breast cancer, there is a suggestion that as little as one drink a day is a risk factor. Something quite modest might be something to look into.

As far as smoking, heavy smoking is thought to impair immunity upwards of two packs a day over an extended period of time, but I believe moderate smoking hasn't been shown to have much of an effect.

DR. SOLOMON: I might add that heroin is extremely immunosuppressive because of its intermittent use, unlike methadone, which is a steady dose, and which does not appear over a long period of time to be immunosuppressive. Thus, it is much more adaptive for a person to be on methadone maintenance than to be taking other forms of exogenous opiates, like heroin. Drug effects on immunity vary. I am not cocaine advocate, and I think cocaine abuse might be a worse epidemic even than heroin. Its effect on immunity, however, is less than heroin. Again, it is specific to the particular drug.

DR. SERVAAS: Thank you.

DR. LILLY: Mr. Creedon?

MR. CREEDON: I am very interested in the nutritional and the other psycho-social factors involved in this disease. I notice that Mr. Hannan and Dr. Sonnabend are still here, and I would hope if it were possible in your clinical trials to include these factors. I think it could have significant benefits, not only as the Admiral has said on a number of occasions that some of the things that we are learning and some of the things that are being brought to our attention could be useful not only in the war on AIDS but looking forward to other types of medical problems.

I think that if anything, the pyscho-social aspects and the nutritional aspects may have been neglected and we might have a basis here for establishing an approach to scientific inquiry that would be the start of a movement that could be significant.

CHAIRMAN WATKINS: I would agree with that. I think it would be very important if we could have some kind of a concept on how this might be reflected, how this might be picked up. It is the kind of things we would like to note in our report. We have already put emphasis on psycho-social factors and we don't know enough about the nutritional impact. We have asked many questions to witnesses who have come before us about the kinds of things that Dr. Levy talked about and haven't received very satisfactory answers, perhaps we need to know a lot more.

MR. CREEDON: Maybe they could work with Mr. Hannan.

CHAIRMAN WATKINS: Mr. Hannan, could you indicate whether you would be willing to at least receive representation from these two to see how they might have some kind of an impact on trials as an adjunct to what you are already doing.

MR. HANNAN: Of course.

MR. CREEDON: I would like to ask Dr. Duesberg one question. Recognizing the state of scientific knowledge or reported knowledge or whatever, what recommendations if any would you have for the Commission? You have a question, you are a respected scientist, a number of the witnesses that appeared before us today, including Dr. Sonnabend, and yesterday, expressed similar doubts about whether HIV is the culprit, and yet the whole scientific community is lined up on the other side.

What do we as a Commission do? Do we ignore you or do we suggest that a certain amount be spent on other research? What do we do?

DR. DUESBERG: You are the only one who hasn't done that so far. You have not ignored me. You have asked me to come. We have to find the cause of AIDS, and I think Frank Lilly would be satisfied if we found the true cause. I think we would

have to have better reporting to do that. We are told that something is antibody positive in any of a number of diseases, that I, admittedly, not being an M.D., cannot possibly reconcile from my narrow perspective of a molecular biologist, as being caused by one agent. In fact, whoever coined the word "AIDS" showed more wisdom, because AIDS means acquired immunodeficiency syndrome. "Acquired" doesn't mean infectious and "syndrome" doesn't mean a disease entity. It is a collection of old diseases.

There is dementia, diarrhea, weight loss, pneumonia, pneumocystis carinii, Kaposi's sarcoma, lymphoma, these things couldn't possibly all be caused by one agent. They couldn't even be explained on the platform of immunodeficiency.

If you are immunodeficient, at least from what I know, you don't become stupid. You don't develop dementia. There are models like that, people born without immune systems and kept alive in sterile "bubbles," they are not stupid. There is a mouse model for that, which was specifically developed to test whether immunodeficiency increases cancer incidence. It doesn't. They do not develop any more tumors than any other laboratory mice. One of the key symptoms of the disease is Kaposi's sarcoma and lymphoma and dementia now.

Maybe antibody is a good marker to know about but we should not just call it AIDS. We need to know who gets dementia, who gets Kaposi's sarcoma, who gets lymphoma and who has diarrhea and who has just weight loss.

DR. SOLOMON: There are many similarities between the immune system and the central nervous system. We now know there are a number of similarities in so-called messenger substances that communicate between nervous cells and lymphokines or cytokines that communicate in the immune system. This is the basis of Candace Pert's work, in which she has basically in her Peptide T research, tried to develop a treatment for AIDS and has tried to block a receptor site for a neuro peptide through which the virus may enter the cell.

We know there are similarities. We know there is involvement in the brain of macrophages and some neurons also have the T4 receptor site. When Dr. Duesberg says how could the virus cause dementia, there are a number of ways the virus could cause dementia because other viruses, such as measles virus, affect both lymphocytes and the nervous system.

MR. CREEDON: Thank you.

DR. LILLY: Dr. Walsh?

DR. WALSH: I don't have a question; I do have a comment, however. I would first of all reassure any of you who may have been in doubt that the compelling evidence of the cause of AIDS I think is well known and also the fact that continuing research is going on and will continue to go on -- and that is how we are finding also the mutants and the various strains.

One thing I would hope, and Dr. Duesberg certainly is entitled to his theory and his opinion, but I would hope that you would press your theory within the scientific circles and not carry this uncertainty to the public in order to sensationalize something that isn't worth -- at this point -- talking about.

By that I mean, whether you are invited now -- not only on "Good Morning, America" but on several other shows, to have the scientific integrity to resist until you have something more substantial to say, rather than causing the dismay or despair among those people who are susceptible to the depths that they can be thrust by uncertainty.

As Dr. Lilly has said, you are a respected scientist and I think you keep your theories in scientific discussion until they are proven; don't confuse the public; don't confuse these poor people who are suffering with this disease. It is very, very unprofessional.

VOICE FROM THE AUDIENCE: It's been a year and they haven't answered him. One year ago. he wrote it, and they haven't answered him. Where is the scientific community's response to Dr. Duesberg? You should be ashamed of yourself for saying something like that, Dr. Walsh.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: What I would like to share or express is that while I find it very difficult as you heard earlier to accept any theory based on a distinction of this virus between whatever label someone happens to carry -- their sex or their sexual orientation -- I don't agree with that. I think that this is everyone's disease and we have to stop thinking of it as such a selective virus.

I have to say that I think that it is really important that we negotiate that fine line between a catechism of AIDS where no unpopular theories or outside concepts are entertained, and getting diverted or going astray on issues that mislead us in some way. We don't know everything about AIDS, I don't think, so I think we do need to keep that aliquot of open mind and if Dr. Duesberg's theories have merit, the evidence will accumulate and accrue.

On the other hand, it is difficult because we are trying so hard to get all of the information accessed and all of the answers, and there are majority opinions and majority reports, so I would just urge for a balance where we can listen, have an open mind -- but not toss out what we have achieved.

DR. LILLY: Ms. Pullen?

MS. PULLEN: Dr. Duesberg, if you believe that because of the things you say about viruses AZT could not be working to arrest this virus in any way, how do you explain that in many cases it appears that AZT in some way has prolonged life and improved health of individuals who are taking it, at least for a period of time?

DR. DUESBERG: That is not for me to say. I can only say, on the basis of antiviral therapy, it cannot work. If it helps, all the better for Dr. Broder. I would like to see the data. What I have seen hasn't convinced me of what you are saying, but maybe he has those data. I haven't seen them. But it can't hurt a virus that doesn't make any DNA, that is for sure.

And I know one thing also for sure. This stuff is used for sequencing, as Dr. Broder proudly advertised yesterday. He said he finds it aesthetically pleasing that he is sequencing DNA in human bodies. What he is saying is he is chain terminating and killing cells. That he does very successfully and I understand that people need red cells, transfusions -- they need other transfusions because it is killing cells. It is developed for chemotherapy: it is a killer. That is what we know.

It may work like chicken soup; I am not an M.D. There is a mystique. I don't know how aspirin works, I don't know how cocaine works and I don't know how AZT might work in addition to what it does for sure: namely killing cells that incorporate that drug. That is what it is designed for.

DR. LILLY: Admiral Watkins will close out the session.

CHAIRMAN WATKINS: To Dr. Levy and Solomon, could you give us any idea of how effective CDC or NIH has been to date in collecting any data on co-factors and -- that is one question -- and the other one is, what would you -- looking into the government agencies, who do you think would be the most effective, and who should perhaps we look at to charge with additional research on co-factors?

Could either one of you or both of you respond to those two questions?

DR. SOLOMON: I would like to comment perhaps in addition to Dr. Levy about this. The situation has improved recently. Initially, NIH would not look at anything psycho-social as related to its biomedical and immunological studies. And in contrast, NIMH wouldn't fund anything biological. For example, our attempts to get money to do very expensive immunological testing in conjunction with our psychosocial studies work were consistently thrown out by NIMH.

This is now changing, thank goodness. But I think that perhaps this separation of institutes between NIH and NIMH has been a problem and that there needs to be coordination among the various institutes: Infectious Disease, CDC, NIMH and perhaps a greater coordination could be arranged among these so that a more integrated approach to research could take place.

CHAIRMAN WATKINS: Thank you. Dr. Levy?

DR. LEVY: I would agree with Dr. Solomon's comments. Recently ADAMHA has begun to fund co-factor studies, although they are just beginning and I think there are not that many yet funded. They are interested in psycho-social influences, including drug and alcohol, as co-factors in the development of AIDS.

I think if you throw in nutrition, the division that Dr. Solomon was talking about between NIH and NIMH becomes more of a problem, because then I really don't know -- I have thought of this -- where would one submit such a grant? It is hard to say.

The study sections are not set up with the expertise to properly evaluate such studies.

CHAIRMAN WATKINS: Would the two of you be willing to team up and send me a letter, a specific letter saying what you think is needed and from your vantage point, how you think that collaborative effort could be enhanced and what you would do to enhance it, because I think it keeps coming up in these discussions and it keeps getting sloughed off, perhaps without any conclusion. I would like to try to put some steam into that engine and see what we can do to bring about a much better dialogue on this particular subject.

Thank you, very much, panel members for being here. We will go to the next panel now, and I would like to turn over the chair now to Dr. Theresa Crenshaw, to deal with the entire session this afternoon on behavioral research.

So, Dr. Crenshaw, if you will take the chair, please, and our first witness will be Dr. Thomas Coates for a very brief

introduction before we go on to Dr. June Reinisch, Dr. Voeller and Dr. Gagnon.

Behavioral Research

DR. CRENSHAW: I would like to begin the hearings on behavior and sexuality, so if those of you who are going to stay to hear those hearings could gather, we will get started.

We have such a very brief period of time to deal with the subject. I know it has been a long day and it will be a little bit longer, but I would like to very briefly create a setting here for you wherein a disease that is primarily transmitted through sexual behavior we need to draw on experts who have a long history and reputation in understanding the complexities of human sexuality to put many of the things that we need to know in order to act responsibly and plan the future into perspective.

The first is going to give us an overview of behavioral research and the possibilities in modifying sexual behavior -- Dr. Thomas Coates, who is Co-Director of the Center for AIDS Prevention Studies at UCSF.

Thank you, Dr. Coates.

DR. COATES: Thank you, Dr. Crenshaw.

First, let me introduce myself and say a few words about my background, because I think it is very important for the points I am going to make. I am a psychologist. I am an associate professor in the Department of Medicine at the University of California, San Francisco. I direct the Behavioral Medicine Program in the Department of Medicine there. I am also on the attending medical staff of the University of California hospital. I believe that those capacities straddle, sometimes uncomfortably as straddling always is, the worlds between the behavioral and the biomedical sciences.

I would like to actually make two general points in this opening session, and I was asked to make some statements about the role of behavioral research in health problems generally and the kinds of contributions that behavioral research can make and the kinds of questions that can be answered. I would like to do that.

But I would like to precede that by saying that ironically -- you know, your comments are very well taken -- AIDS is fundamentally not a viral disease. AIDS is fundamentally a behavioral disease. The modes of transmission have been well

described and there is some uncertainty about other specific modes, but the major modes are well known.

Yet it is ironic that we continue to spend precious little money on prevention and especially on prevention research.

Let me draw some comparisons. The National Heart, Lung and Blood Institute, which is where I have received my funding for the last 12 years I have been involved in cardiovascular disease prevention, an enterprise that has paid off well. All one needs to do is look at the dramatic fall in deaths and disability due to cardiovascular disease over the last 20 years to realize that this research has paid off.

The NHLBI spends $132 million annually on prevention research and on behavioral research.

The National Institute of Mental Health's current budget for AIDS prevention research is $5 million.

The total PHS budget that was requested for AIDS research, the original PHS budget that was requested for AIDS research in 1988, was on the order of $900 million -- $412 million for research, including only $28,000 to ADAMHA. In essence, we have the ratio between traditional biomedical and behavioral research being 4:1, and within the prevention arena, again the ratio being about 10:1 between programs and research.

It is vital that we support more research in this area and it is vital that this be placed at the NIMH and I think it is vital that this Commission make a strong statement to ADAMHA that they need to support behavioral research.

Now what can behavioral research do? Now that we want to support it, does it have any place?

[Slide.]

I'd like to use this little schema to talk about the relationship between the relationship between biomedical and behavioral research and to point out the major questions that are relevant here. I like it because it divides the world into four boxes and it is always simpler when you can deal with four boxes instead of the complexity of reality as it is. Nonetheless I think it is useful.

Independent and Dependent Variables, Biomedical and Psychosocial Variables -- the upper left hand quadrant being the domain of the traditional biomedical sciences; that is, the effort is to find the lesion or the agent that produces a

biological outcome and somehow to take care of that agent either through a procedure or through a chemical.

The lower right hand quadrant defines the domain of the traditional behavioral sciences. That is, we are interested in outcomes in terms of cognition, in terms of affect, in terms of behavior and we want to know what other psychosocial variables are related to those conditions.

The interesting arenas are on the other diagonal; that is, moving first to the lower left hand quadrant, we are asking about the influence of biomedical variable on psychosocial variables. Here is where behavioral research becomes quite important. We can ask this in a number of dimensions. What is the influence of the virus either in a primary way or due to secondary infection on people's cognition, on their behavior, on their affect? Can we, in fact, through various biological means modify people's cognition, behavior and affect?

It is probably the one arena in which modern psychiatry has advanced remarkably over the last 20 years, and that is by finding better ways to intervene chemically to modify major problems such as schizophrenia and the major affective disorders.

The other arena is the arena you have just been considering, and that is, "Do psycho-social variables in fact influence the biological variables?" We can ask about that in two different ways. We can ask about behaviors that are directly related to disease, behaviors such as smoking tobacco, ingesting drugs, behavior such as nutrition and exercise and certain kinds of sexual behaviors that are related to certain kind of biological outcomes because they introduce the disease process or make the disease process more rapidly. We can also ask about affective states which influences biological outcomes and ask questions about the potential of intervening on those psycho-social states to modify the biological outcomes.

Now the problem is, when we get to the area of AIDS research and we get to the area of sexual behavior research and to IV drug behavior research, we want to somehow put these in a special category. I will submit, and my testimony later I think will provide evidence, to submit that these behaviors are under the control of variables that influence many other kinds of behaviors. So therefore the objective becomes one of describing those determinants and deciding if we can intervene on those determinants.

Let me go back to an important model, and that is the important model used by the National Heart, Lung and Blood Institute and the important model used by the National Cancer Institute in its War on Cancer.

Again, in both arenas there has been a long, 10-20 year history where the progression has been from describing the range of behaviors related to those diseases in the population and in various sub-populations to developing studies that will describe the determinants of those behaviors in various populations to describing, to developing intervention studies that will hopefully modify those behaviors and look at disease outcomes as a result.

Let me make real explicit two biases that pervade the scientific world that inhibit the progression of this kind of research. I think they are important biases. They are important scientific biases which have inhibited an effective response to the AIDS epidemic.

The first is that somehow behavioral research is a poor second cousin to the so-called "hard sciences." It has been very interesting for me in my cardiovascular research history and now in my AIDS research history to venture into other people's sciences and to realize that they have the same problems that my sciences do. The variability around a single measure of immune function or immune status is I think well known, just as the variability of a single blood pressure measurement is well known.

I would submit that the behavioral sciences can be just as "hard" and as theoretically driven as the biomedical sciences.

The second point I would submit is that the tradition in our academic institutions is that so-called "basic research" that is translated to mean "laboratory research" somehow has more credibility and believability than the clinical field trial. As anyone knows, both are need to carry on an adequate and to develop an adequate knowledge base.

The last comment that I would make with regard to this issue, and it's not intended necessarily as a criticism but I think just as an observation. I think that this committee also operates in a culture that shares the norms of the larger culture and I think it is interesting in a three day hearing that this session is coming at the end. I think that tells it all. Thank you.

DR. CRENSHAW: Thank you very much.

What we might do with the next few minutes is ask questions before the next panel takes place. We just have a few and bear in mind that Dr. Coates will be available later for additional testimony, additional questions.

Dr. SerVaas?

DR. SERVAAS: Do we have your testimony in writing?

DR. COATES: I was told that I didn't need to prepare this particular opening segment of testimony in writing. My testimony later in the hearing will be in writing and it does make some of these same points.

DR. SERVAAS: You will be testifying again?

DR. COATES: I will be testifying on behavior change, particularly in gay and bisexual populations, the reasons for those behavior changes and a program of research that I think is needed at the NIH to promote that activity.

DR. SERVAAS: I'm sorry, I haven't done my homework, but I am just curious. You are a cardiovascular researcher, clinician?

DR. COATES: I am a behavioral scientist; I am a psychologist by training. My appointment is in medicine. I run a subspecialty clinic in the Department of Medicine. My research prior to AIDS was done in cardiovascular disease prevention and, since 1983, I devote a considerable energy to AIDS prevention -- which I think is the primary research agenda in AIDS.

DR. SERVAAS: Well, I am so happy you are here because I can't agree with you more that we should be spending a bigger part of our budget on prevention. Certainly if we can do for AIDS what we did in cardiovascular work, that is an excellent point. Thank you.

DR. CRENSHAW: Mr. Creedon?

MR. CREEDON: No questions.

DR. CRENSHAW: Dr. Walsh?

DR. WALSH: Dr. Coates, I -- just as you, I am somewhat astonished that in all of our hearings we have heard relatively little about behavioral research despite the fact that we have had pleas from some behavioral scientists early on.

But in one of our earlier hearings, the Director of the National Institute for Mental Health appeared before us and, while it was not earmarked money per se, he did make the statement that at least in the area of drug abuse, which astonished me, that he had not had sufficient requests to use the funds he already had.

This didn't make any sense to me at all.

I wondered whether there is such a vigorous earmarking between behavioral research money just for AIDS or whether the Institute of Mental Health funding could be used, since so much of it is involved with behavior in drug use and so on. Do you have any awareness of whether that line is so rigidly drawn at NIMH?

DR. COATES: You mean -- I am not sure I understand your question.

DR. WALSH: The funding that would be available -- like if they have given only $5 million for behavioral research studies in AIDS --

DR. COATES: Annually.

DR. WALSH: That is a drop in the bucket.

DR. COATES: Exactly.

DR. WALSH: But if they have given $160 million or whatever it is for behavioral research in substance abuse, is there any way we can get that funding combined so that more could be directed towards AIDS behavioral sciences?

DR. COATES: In AIDS prevention, yes.

DR. WALSH: Actually, AIDS-related diseases.

DR. COATES: In AIDS-related diseases as well. There are two problems here. One is my look at the portfolio of research for the National Institute on Drug Abuse lists approximately nine studies aimed at various populations for AIDS risk reduction and then there are community demonstration projects in six cities.

I think that is a drop in the bucket as well.

The difficulty also comes in the structure of the NIH and ADAMHA and it is somehow divided by body parts and diseases and doesn't seem to have a central nervous system that allows it to communicate among its body parts and diseases. I think there is incredible need for better coordination.

As an example, research is vitally needed on the intersection of IV drug use and sexual behavior, which is to be a major mode of transmission. It seems like that is a perfect point of intersection for cooperation between NIDA and NIMH.

As another example, and as I am you will find out from the next panel, research in sexual behavior, just describing it in the population as well as understanding its determinants for

various sub-populations does not reside within the purview of any one institute. The National Institute of Child Health and Human Development is interested in adolescents and young adults principally from a fertility perspective, which is important but no one has the mandate to develop and implement a program of sexual behavior research. I think there should be that.

DR. WALSH: This concerns us a great deal because you know we keep talking about the greatest weapon we have is education and then we talk constantly about counselling and yet the answer to all of that rests in behavior research.

DR. COATES: Indeed.

DR. WALSH: In how you find the answers. I think it would be very helpful to us when you do have your written submission that you give us some very good specifics.

DR. COATES: Indeed. I will.

DR. WALSH: I think we can have an influence on that, I really do.

DR. COATES: Let me give another example that I think this committee can address. That is, a structural problem in the relationship between the NIMH and ADAMHA. When NIH coordinating committees are set up, frequently they don't involve folks from ADAMHA. If ADAMHA is invited there, they are invited as observers only. I think that is not the way. Again, it is a reflection of the biomedical view of behavioral sciences.

Ironically, however, the biomedical scientists are saying, "This is a behavioral problem." Even if you have got an efficacious agent -- and I think we have got examples -- we know that penicillin works for syphilis and gonorrhea except for penicillin-resistant gonorrhea -- delivering it is still a problem. We know that we have an effective vaccine for hepatitis. Delivering it is still a problem. So the behavioral and the biomedical really needs to be combined. Condom efficacy may not be a problem. Compliance with techniques to make condoms effective may be a problem.

DR. WALSH: Well, since that is our prime weapon for the next 10 years, based on everything we have heard so far, it seems absolutely backwards to me. We will need your help.

DR. COATES: Indeed. Thank you.

DR. CRENSHAW: thank you very much, Dr. Coates. We look forward to hearing from you again a little later. I would appreciate if the next panel would come and join us.

DR. CRENSHAW: We will be hearing first from Dr. June Reinisch, Director at the Kinsey Institute, and after that from Dr. Bruce Voeller, from the Mariposa Research Foundation, and then from Dr. John Gagnon from Princeton University.

I want to first apologize to all of you for the brevity that you are faced with during this testimony and I hope that it turns out to be just a preview of an expanded, in- depth look into all of the issues that I know you will just touch on today.

So because of the brevity, let me not add to it by taking any more of your time. We look forward to your comments.

DR. REINISCH: Thank you, Dr. Crenshaw.

My name is Dr. June Reinisch and I am Director of the Kinsey Institute for Research in Sex, Gender and Reproduction at Indiana University. I am also a professor in the Departments of Psychology and Psychiatry. In addition, my staff and I author an internationally syndicated column which appears across the United States and in eleven countries around the world. The column is based on current research data and provides readers with facts, not advice.

First, as this is the first time that the testimony on sex behavior has been brought before the commission, I want to express my deep concern for the lack of adequate time to present information on this most sensitive area of human concern, which is essential to the control of the spread of the AIDS virus. It is impossible to make comprehensible recommendations or propose model solutions without providing the background information on the history of sex research and what we know and don't know. I hope that additional sessions of the committee in the future will be devoted to the complexities of these crucial issues and I hope that you will permit me today to take a little additional time from my question and answer period to speak so I can provide at least a minimum of these kind of data. I want to share data with you, new data and old data.

Sex research, that is who is doing what, with whom, how often, and under what circumstances, and information on the attitudes which related to these behaviors will provide the essential foundation upon which effective programs of behavior chance, so necessary to stemming the tide of the AIDS epidemic, must be built.

This yet-to-be-collected information will also provide crucial information for conducting research on the efficacy of barrier methods to block infection with HIV and assist in the

identification of appropriate subjects for such biomedical solutions as testing vaccine.

The sexual behaviors that place individuals at risk for infection by the AIDS virus are not new. Nor are they limited to the cultural post-sexual revolution America. Despite the beliefs of some that behaviors related to HIV transmission are the product of Western civilization in the second half of the Twentieth Century, even a cursory examination of the archeological and ethnographic record reveals art, artifacts, literature and ephemera which reflect the ubiquitous panhistoric omnicultural nature of the behaviors implicated in the transmission of the AIDS virus.

Much of the very limited research on human sex behavior has been plagued by a number of serious limitations, resulting in most cases from a general lack of both public and private research support for scientific investigation into human sexuality.

Despite these shortcomings, I have selected among the best small, usually government or foundation funded scientific studies and the large, usually commercially supported surveys to gain at least a limited perspective on the patterns of sexual behavior, but only in white, middle class, relatively educated Americans.

Based on these data, some preliminary insight can be gained into the prevalence of risk-related behavior, such as heterosexual and homosexual anal intercourse, fellatio, cunnilingus, extra-marital contact, group sex, bisexuality and the use of prostitutes.

I will be referring to data from 16 studies, beginning with the original Kinsey research.

I must emphasize here that very rough estimates from these data can only be made to white, middle-class, usually urban Americans between 20 and 45 years of age and not to the numerous ethnic, racial, social and sexual orientation and age groups which comprise the United States.

Secondly, all of these data are flawed. There has never been a scientifically designed, face-to-face interview study of the American population. Had there been such publicly funded research describing the major subgroups in our society we would be much closer to behavioral control of this epidemic than we are today.

[Slide.]

I think the prevalence of monogamy in our society is one of the issues that we are all concerned with, since we know that the number of partners has something to do with the transmission of this virus.

Here you see a number of studies on the extramarital affairs of husbands, and as a conservative estimate we can say that approximately 40 percent of the American population who is married and who is male has had at least one extramarital affair.

You will see we have considerably more information on females than males because of the surveys conducted regularly by women's magazines like Redbook, Ladies Home Journal, and Cosmopolitan.

One of the enduring beliefs in our culture is that women are much less likely to be involved in extramarital sexual interactions. Although it does appear that husbands ar more likely to participate in extramarital affairs, wives are not far behind.

[Slide.]

Our conservative estimate from the data that are available: about 30 percent.

Why are the bars so uneven? It indicates the variation in methodologies used, the biased or small samples involved, the different levels of scientific expertise involved in the designs of these studies. Nevertheless, even if the most conservative estimate from the 1940s are taken -- in this case 20 percent of wives involved in extramarital affairs -- it is clear that we are dealing with a significant portion of our population.

[Slide.]

The next behavior about which we have some but by no means adequate information is anal intercourse, the behavior most implicated in the sexual transmission of AIDS in this country. This is a behavior which most people believe is not common in the heterosexual community.

[Slide.]

Here, from a few studies on heterosexual males, in heterosexual anal intercourse we have a conservative estimate of 20 percent, which you will see in the next slide probably is too conservative because when we look at the data on women, we find out that conservatively 35 percent of women have had at least one experience with heterosexual anal intercourse.

[Slide.]

Sexual prostitutes is also been suggested as an avenue of transmission of the virus into the general population -- heterosexual population. Prostitutes appear to be infected not by their customers but via shared needles during IV drug use and perhaps more importantly from sexual behavior with their IV drug using husbands and lovers.

Our conservative estimate of use of women prostitutes by the general population is 35 percent.

We are all concerned about the question of the spread of the virus from groups with a high prevalence of the virus to the larger "heterosexual" population. Comprehensive descriptions of sex behavior in all segments of our society will provide answers to these questions. We don't have the answers.

We all know about IV drug users and the gay community and would like to believe that the majority of our population is isolated and thus safe from the at risk groups. The data that I am going to show you now, present to you now, show that this is really not true.

[Slide.]

If you ask homosexual men have they ever had heterosexual intercourse, two-thirds to three-quarters of homosexual men report from various studies over time that they have had sexual intercourse at least one time with women and one-quarter to one-third of homosexual men report that they have been married for some time in their lives.

When we look at the general male population, we see that approximately one-third of the general male, American population has had at least one sexual encounter with another male following puberty. When we ask gay males about their interactions with married men, Kinsey showed as others have that 70 percent of gay white males have had sex with a married man at least once and 20 percent of these have had six or more married male partners. We are not isolated from each other.

A recent Institute study of cross orientation sexual behavior in lesbian women sheds additional light on the inaccuracy of sexual orientation labels for predicting actual behavior.

[Slide.]

In a sample of 300, nearly 300 lesbian women from around the United States, nearly three-quarters who currently label themselves as lesbians, had at some time previously labeled themselves as heterosexual or bisexual. Approximately 20 percent

had been married or co-habitated with a man. One-quarter reported that they had always labeled themselves as lesbian.

Behavior across sexual orientation boundaries in terms of intercourse with men -- these supposedly safe lesbian women who are supposedly the lowest risk group in our culture, approximately three-quarters of lesbian women had sex with a man since age 18. One-half of the currently labeled lesbian women had had sex with a man since 1980; that is our banner year for the beginning of the AIDS virus in large amounts in this country. One-quarter of the women who reported that they had labeled themselves as lesbians had had sex with a man always labeled themselves as lesbian, and that is the middle pie, had had sex with a man since 1980 and one-third of all the lesbian women reported that at least one of their male sexual partners was a man who had sexual experience with other men. In most cases they were men who labeled themselves as "homosexual."

[Slide.]

Depending on whether a woman knew she had had a male sex partner who was what we would like to call "behaviorally bisexual," since even if they called themselves "homosexual" they are obviously having sex with women, we asked was there any difference in the frequency of high risk sexual behaviors, depending on what kind of a partner you had -- at least the partners you knew about. The left bar -- 41 percent of the population from the general population surveyed in various ways since 1974 reported having had anal intercourse at least once. There is no information as to their knowledge of their male partners' sexual interactions with other males, but from our experience it is unlikely that many would know, since American men and women talk very little about sex, and homosexual behavior is a particularly taboo subject.

Of lesbian women whose male partners as far as they knew were only heterosexual -- that is the middle bar -- 24 percent had experienced anal intercourse, while of lesbian women who knew at least one of their male partners had homosexual contacts, 45 had anal intercourse. Other studies are now showing us as well that women who have sex with behaviorally bisexual partners are more likely to have anal intercourse. We also expect that lesbian women are more likely to know of their male partner's homosexual contacts than are heterosexual women.

Another way we think communities are safe from infection is through geography.

[Slide.]

In my last slide -- I think Americans believe that if we are separated by distance from the cities identified as having high risk of infection then we are safe. We asked our subjects about trips to New York, San Francisco, Los Angeles, Houston, Washington, D.C., Miami, Chicago, Newark, Philadelphia or Dallas -- the ten top CDC cities for AIDS infection since 1980 -- had they visited and had they had sex with a partner from that city at that time. On the right bar, 29 percent said they had had sex with a resident of one of the ten high risk cities. Eleven percent said they had sexual contact with -- remember these are lesbian -- with a male resident. At the right bar, of these lesbians or bisexual women who had sexual contact with a male in one of these cities, for 49.5 percent it was a first contact with a new sexual partner. Again, this is since 1980 -- and remember that this is based on the lack of information that we have about Americans of all sorts. Everybody has been considering lesbians to be the group who is at lowest risk for infection with HIV.

Although all too scarce and flawed, and this is just a little of the data I'd hoped to present today but there isn't time -- research conducted during the past 40 years describing American sex behavior nonetheless alerts us to our grave lack of information in this vital and the fact that none of us or our families or friends are really isolated from or completely safe from this threat.

We all live in overlapping communities of risk. With self-control and modification of sexual practices serving as the only protection against sexual transmission of human immunodeficiency virus (HIV), a precise understanding of sexual behavior in the various ethnic, racial, social, age and sexual orientation groups which constitute our society and an appreciation of the methods, procedures and techniques necessary to derive accurate data are essential in the identification of at risk groups and in the design and implementation of educational programs directed towards attitudes and behavior change.

What are my suggestions for guidelines for future research?

First, we are a heterogeneous society and when it comes to sex, this factor is even more meaningful. We must accurately identify, acknowledge and target for research and education our subcultures. For example, American Blacks are not a homogeneous group. They minimally include Haitians, Caribbean Blacks and Afro-Americans. Our American Hispanic group culture includes Cubans, Puerto Ricans and Mexican- Americans. They are not the same. For example, the Mexican culture in America is based on the Mestizo culture of Mexico, a mixture of AmerIndian and Spanish culture. In that culture, male anal intercourse is only considered homosexual if you are the receptive partner. If you are the insertive partner, you are considered heterosexual.

Heterosexually, anal intercourse is used to maintain vaginal virginity before marriage and as a contraceptive method after marriage.

This is only one tiny example. We cannot believe that we understand any one group just because we have some information on white, middle-class Americans, which is by the way also inadequate.

Secondly, in any survey research we must over-represent, we must over-sample ethnic, racial and subcultural groups.

Thirdly, interview schedules and questionnaires must be developed by as wide a variety of individuals representing as many subgroups as possible.

Fourth, interviewing should be conducted by interviewers matched to subjects on at least sex and race, if not age.

Fifth, and perhaps most important, vernacular -- that is, the language of the culture -- must be used instead of sanitized, often incomprehensible language. That is, explicit language and visual aids targeted to specific groups must be permitted if meaningful sex behavior research and effective behavior change programs are to be developed to halt this dreadful epidemic.

I have interviewed women seven months pregnant, sitting with me at the table, and I have asked them whether they have had vaginal intercourse and they have answered me, "no." And when I asked them, "Well, how did you get pregnant?" they have other words in order to describe the activity that caused them to become pregnant, but "vaginal intercourse" is not one of them. They don't understand the word "vagina" nor do they understand the word "intercourse" because they come from a different cultures and we have many cultures in this country.

Finally, the limited data available demonstrate that these behaviors are not rare, that they are universally practices, many of them at substantial levels in the heterosexual community. Although there is no doubt that practicing abstinence assures complete safety from sexual transmission of the virus, even some individuals who have dedicated their lives to God are not successful in maintaining sexual abstinence. As I am sure you are all aware, there are more than 20 reported cases of AIDS in Catholic priests.

We must develop techniques for helping people to practice all sexual behaviors with care and thoughtful self-control. To do this, we must appropriate major public funding

for research describing American sexual behavior and developing behavior change strategies that are succinctly targeted and explicit about sex and drug use. To draw limits for or to deny funding to groundbreaking research cripples us in our search for the weapons with which to fight this devastating disease.

DR. CRENSHAW: Thank you very much, Dr. Reinisch. You did a remarkable job of covering an enormous amount of territory in a high speed, very condensed period. We will save questions for all of the panel members until the end of the presentations.

Dr. Voeller?

DR. VOELLER: I am Bruce Voeller, I am President of the Mariposa Education Research Foundation, and our main area of research and education being in the field of human sexuality, with particular emphasis based on my training as a physiologist and biochemist in the area of physiology of human sexuality and prevention related to that.

A group of us at the University of California Mariposa Foundation and University of Southern California have the principal Federal contract for the testing of the efficacy of condoms and spermicides, both in laboratory work and in clinical trials. We have already completed a comparable study for the British Government in that field. That is something of my background. I also am the one who gave AIDS its name.

Dr. Reinisch and I agree that at some levels, there was not sufficient time under the circumstances for us each to lay out an array of things to tantalize you with what might be more interesting broadly if there were more hours to hear from us, so she presented an array of information of the sort you just heard and I repeat, to tantalize you, to wet your appetite for what is really behind all of that and Dr. Gagnon will present additional related materials.

I want to look back just a little bit and specify what I think some of the problems are and what we need and why we need it.

Kinsey and his colleagues published their original volume in 1948, the first being on men and the second on women in 1953. In those two words, such a high standard of scholarship was set, that they could not be lightly dismissed. Kinsey and his colleagues thrilled researchers on the one hand by their daring and by the accomplishment and quality of it on the other hand shocked the public and its leaders.

Their careful, skilled interviewing revealed a vast chasm between what Americans thought that they did sexually and what they actually did. On the other hand, Kinsey and his

colleagues established truly the first substantial database on the very sexual practices and the pure extent of sexual expression, total sexual outlet.

On the other hand, Kinsey and his colleagues in doing that, demonstrated how ill informed were those who advised the public on sexuality and how oblivious they were to their ignorance. It is as true today as it was half a century ago, despite the much eventide sexual revolution, I might add.

Few know the persecution that Kinsey and his colleagues, and I know no better word or more accurate word than "persecution" to describe it, few know how much they experienced. Denunciation by physicians and ministers and priests, denunciation by politicians, by statisticians, even a major congressional investigation was launched against Kinsey and the Institute with all the public attendants related to that. As a consequence, they lost all their funding. They had been supported by the Rockefeller Foundation throughout the early days of the project, until the publication of the volume on women, and the notion that women could be sexual, as Dr. Reinisch has so clearly demonstrated in her slides, and it was more than the public or Congress could bear.

What lies behind all this? Someone neglected, because of the enormous press surrounding the Kinsey publication, two very distinguished Yale professors, Ford and Beach, published another book, "Patterns of Sexual Behavior," in 1952, a couple years after the male volume by Kinsey, a year before the female volume. They did that at the same period but they were somewhat eclipsed by the Kinsey celebrity, as far as the public was concerned.

Ford and Beach compared sexuality in some 200 cultures around the planet, and among a wide range of animals, looking at in essence the evolutionary history of sexuality through species including a wide range up through primates. One of their major conclusions was that of all these nearly 200 cultures which they reviewed, our culture, the Euro-American culture, was one of the three most sex-phobic on the planet.

Why then would we expect to have a high premium on scholarship in human sexuality? Dr. Reinisch outlined some of the things we know and which bear on the issue of AIDS and related social issues. The great point, however, is we have a shocking lack of such information.

Those of us who do research are all too aware, those of us in the area of human sexuality, that our colleagues look at us with suspicion, even those of us who are doing basically physiological research, never mind those who are in the more behavioral aspects of it.

At universities today, not much has changed from the Kinsey days. We have entire schools of journalism at most of the major universities in this country. We have whole schools, not just departments, schools of home economists, athletics, on and on. Cornell University even has a distinguished school of hotel management. There is not one department of human sexuality or research on sexuality in this entire country with the exception of the Kinsey Institute linked with the University of Indiana, although a private corporation, and the Masters and Johnson Institute and a few others which are small, independent units. We do not have major institutions at our universities to investigate and to make social and public scientific commentary upon the great issues that face Americans.

It is quite extraordinary that our sexuality enters our awareness throughout the day repeatedly. Our social crises in this country and throughout the world linked to sexuality with unwed mothers unable to provide for and educate the next generation of Americans; crises in sexually transmitted diseases, the most recent of which is but AIDS, and in all likelihood is but the forerunner of additional diseases which may be equally devastating if not more so if we don't learn the lessons which we better be learning, and I feel we are not.

To me, it is fascinating that so little study of one of the most central aspects of our personal lives is so ignored, that its implications on our social, political and moral lives has been so unstudied in terms of evidence and data on human sexuality and indeed, it obviously represents the very core of our evolutionary past, present and future as a species on this planet.

I would like to turn to "sexpertise" as a part of that, I alluded to it. We know so little about sex actually that every newspaper reporter, every rabbi and priest, every politician and every physician, even though they have never been trained because there are no courses or very few in medical schools and not a requirement to take the ones that do exist, every one of these people considers himself or herself an expert on human sexuality. The main people to whom the public turn for their information, their counseling and the like.

It is a rare person, indeed -- I've had the privilege, having served on most of the Federal commissions on AIDS, with FDA, CDC, NIH over the years, since 1982, one after the next, I have had the privilege to work with a few people out of that grand total of literally hundreds of researchers and physicians who make up those commissions, who have really genuinely knuckled under and begun to learn about human sexuality. June Osborne, who several of us have become good friends with, because of her keen awareness of the lack in her training, her willingness to go out and begin to learn. Roger Edles of the University of

California, June Osborne is the Dean of the School of Public Health, University of Michigan. Roger Diedlestein is the former Dean of the School of Medicine at UCLA, School of Public Health. Again, he have taken the time to learn that his training didn't provide him that. Most of the other people I've met on these commissions do not know these things.

For example, the heads of all the major organizations dealing with blood were debating all the issues concerning making safe the blood supply and we turned at one point, and having been on that commission over the years which June Osborne chaired, we turned to the issue of why it is that even though 90 percent of hemophiliacs are infected with the AIDS virus, or at least with HIV, they seemed at that point to develop clinical symptoms as well as their spouses than did people who contracted the disease in other ways.

A part of the problem in looking at whether there was some underlying physiology that might be instructive and interesting for everyone, it hinged on why was it that some hemophiliacs seemed never the less to go on apace with the development of clinical symptoms and the like. Until after sitting for nearly two hours, I pointed out that some of those hemophiliacs might well be homosexual and I could guarantee some were, and indeed, some of them were probably addicts as well.

The head of one of the major institutions turned to me and said that was an outrageous suggestion, was I suggesting there were homosexual hemophiliacs, and I said, well, I happen to know several.

You see why my central point, and I think you are beginning to see the drift of my argument, why I feel that it is so essential that we make people aware that they are trying to paint the landscape of the course for the future of our handling of the crisis, they are painting a technical portrait but they are color blind. They lack a full palette when they don't know about human sexuality.

I suggest that it is understandable in the context I've tried to paint, of Ford and Beach's identification of us as such a sex-phobic culture and with the evidence of it in terms of the research that is tolerated in this country, never mind funded, that we put ourselves into that position and it should be no surprise that we find ourselves where we are.

That discomfort is acceptable and understandable, to allow it to drop at that is not.

In the present AIDS crisis and what I am sure will be subsequent similar crises, we must learn more about human sexuality and put it to work. That is absolutely essential.

In the levels of physiology, as you will see from the statement here, Drs. Masters and Johnson, two months ago we prepared a statement and sent it along to the Commission, a joint statement. There is a three page summary statement that I hope you have been provided. We outline what we think needs to be done. The sum of it basically is that we think and feel strongly that it is critically important at this point that the nation make a commitment and that the interagency rivalries and the like which undermine that going forward automatically be dealt with appropriately but that a major national commitment be made to collecting and gathering the information of all kinds to human sexuality, in our culture and elsewhere, and this must include surveys, as June Reinisch put it, of who is doing what with whom and how often, and we need to know the physiology that relates to that. We need to know what all the physiology aspects are and we must have data banks on everything from T-cell information which has been so critical in the particular crisis we are addressing now, through such things as what are the components of semen.

Within the AIDS crisis, for example, at this point, we don't even know, and I say this from the standpoint of someone doing research on condoms and spermicides so that we don't know whether we are in the ball park or not in a certain sense, we don't know at this point in time such fundamental cellular physiology related to sexuality as to what the component in semen is that is infectious, is it virus bound to the head of the mobile or modal sperm, so it can swim throughout the female reproductive system vaginally or anally in either men or women, is it white blood cells that have been infected with the virus, we don't know simple answers to things like that, yet we are asked to identify whether or not different spermicides from around the world will be effective in preventing the sexual spread of the AIDS virus.

We need to have databases that collect all that range of information, behavioral all the way through the most elaborate array of physiological information. We need to have that data ongoing, not an one time shot just to address the AIDS issue and then go our ways, and the belief that is that and we have solved the problem.

We need to have an ongoing research database of the highest quality and with the highest priority placed upon it and the funding related to that to know what is happening with our people in all of the subcultures Dr. Reinisch alluded to, throughout this country and in turn throughout the world.

We have great arrogance, not even knowing what is going on in our own country and offering solutions and recommendations in such detail that we often do to the rest of the world, which is so sexually and culturally different from us.

The point basically is if we don't have a commitment at this point to building such a database, utilizing it, in the moral life, the social life, the political life and the health care of this country, we can expect the AIDS crisis to grow and become worse. We will have lost enormous time as indeed we have lost by not having had that commitment to such a database all along prior, and we will be in a terrible position when additional threats come to us.

Thank you.

[The prepared statement of Dr. Voeller follows in the Appendix.

DR. CRENSHAW: Thank you, Dr. Voeller.

Dr. Gagnon?

DR. GAGNON: My name is John Gagnon. I am a Professor of Sociology at Princeton University this year. I'm normally a Professor of Sociology and Psychology at the State University of New York at Stoneybrook.

I probably have spent the largest portion of my professional life doing sex research. I am this year the President of the International Academy of Sex Research. I come to you, third, which unfortunately extracts most of the things I was going to say, the least of most of my laments about the status of the field.

Let me just reiterate what was in my written comments with two additions. I think Dr. Reinisch and Dr. Voeller both pointed out the lack of data. That is we are absent for a period of nearly 40 years only very fragmentary pieces of research that have been done, and if you look across the entire spectrum of research, what we see is this enormous lack of data.

We have no data which give us any baseline information on where the epidemic may be taking us. We have great difficulty understanding the likelihood of transmission, for instance, if we don't have data on what people are doing sexually.

Let me make another point. The kind of data we need for transmission may not be the kind of data which we need for behavioral change. You may need data on partners, sexual techniques and other kinds of things to map either analytically or empirically what the epidemic is going to do.

In behavioral change, you have to understand a great deal more about those lives and much more about the way their sexuality fits into their general life.

A second point, why we are all here is really about AIDS and we are once again, as this culture tends to be, interested in sex because it appears to be driven by a problem which we have. We are interested in sex among adolescents because we are worried about teenage pregnancy or the sexuality of communities where there are large numbers of STDs and we are interested in their sexuality.

It is quite different to be interested in people's sexuality because you want to understand their sexuality, not because you have a problem about it. One of our difficulties is that we let the problems drive our research all the time, rather than attempting in some sensible way to keep constant monitoring or understanding of where sex fits into the lives of people who currently are not in trouble. That does not predict they will not be in the future.

The lack of the research tradition in sexuality really has a number of consequences. Some of you can see the simple consequences and the fact that we frequently don't even know how to ask the questions appropriately to get reliable and valid answers. More complex, I think we have a situation in which sexual research is interdisciplinary research. We have very weak traditions and collaboration between sociologists and biologists.

A second question is the research is not cumulative, we don't add on to what we have done before. We have sporadic outbreaks, so that Kinsey appears as sort of a media villain, Masters and Johnson appear as sort of media heroes, so what we do is we don't have a good sense of a long term cumulative tradition which trains graduate students, which has some density of people constantly working in the field, and it is really necessary to have a tradition of work going on, so that young people can be trained and replace people who are not doing work any more.

I think this has a deep impact on biomedical research. Much of the research which we report right now about AIDS is a combination of biomedical research combined with behavioral research. The biomedical research frequently is very strong, very robust. The behavioral research, asking people about their lives, which goes on with that biomedical research, frequently is very weak. That is because nearly everybody thinks they can do sex research. Not only does everybody think they know everything about it, as Dr. Voeller said, but everyone thinks they can design a question, they can ask questions and get good answers, and in fact, if you ask simply about behavioral change items, the reliability and validity of those items, have you changed your behavior in the last "x," we frequently do not have any sense of the validity or reliability of those items.

I wanted to suggest a number of recommendations to you. I think we need more sex research and I think we need a lot of it. I think we need a number of things to go with it. We desperately need research quality control. Dr. Reinisch has used surveys done by women's magazines, men's magazines, and we all know the defects of that research.

The American people want information about sexuality and they are willing to read it in Redbook instead of reading it from reliable people. The fact that we don't fund sex research doesn't mean that people don't want to consume information about themselves, and that people in society have a right to know about the sexual life of their society. They have a right to know, we tell them all about their voting behavior.

I think one of our crucial issues is really research quality control. We really have to begin to establish ways of upgrading the quality of work which is done in sexuality in society. That can be done a number of ways. They are not very expensive. Maintaining peer review, this work that really involves kind of research coordination. I don't mean that essentially we need an AIDS czar, no one should be deciding every question everybody should ask.

At this moment, at least four or five major studies concerned with AIDS surveys are now being planned with very little interconnection between what is going to be asked, what should be asked, how can it be asked, all of those require investments in research methodology. I'm not sure I have a number for this but I would think at least one or two percent of all granting money in social and behavioral sciences should go to methodological research. That is we should be spending money -- it is much worse to believe we know something and be ignorant than to know that we are ignorant and frequently in this area, we have spent all of our time being systematically - - you read the numbers but you can't believe them.

I think if one looks very carefully, for instance, at the document which was given to this Commission on what the incidence of the virus is in the population, all of those numbers have to be taken with an enormous grain of salt. They are not sample populations. They are peculiarly gathered together. Whatever numbers you get from that are numbers which you have to play with very carefully.

Let me suggest two other things. One is training. The epidemic is going to be with us for a while. We need to train the people to replace the people who are currently doing the work. Training grants are essential. They might be interdisciplinary. They have to work between both medical schools, colleges of arts and sciences, people have to know about

virology. I think such things can be done. We have done it in the past. I think that is absolutely essential.

Finally, there is a question of data archiving and sharing. One of the problems in science is what makes you famous and gets your name on an article first, that is that is what makes you a great scientist, but it also makes people hoard their data. Data which is gathered with public funds ends up being -- they hold the data until they can publish. Indeed, the New England Journal of Medicine will not publish data which in fact you have handed out reprints of at a scientific meeting. It encourages a situation in which both data and knowledge is restricted and as part of that kind of strange relationship in science, which is awards are given to individuals, but the work is really done by collectivity, that the scientific advances is never the work of one person, but awards, like the Nobel Prize, are always given to one person.

Data archiving, data sharing, I will tell you about what I see to be a real tragedy. The National Institute of Drug Abuse had a large data archive of surveys which were on surveys of drug abuse. They held that archive together in an university. They stopped funding that archive some years ago. We now do not know whether or not we can put that archive back together. That would have been baseline data on large aspects of drug abuse in society.

Finally, I think I want to say a couple of other things. I think sex research is meritorious in itself. I think it is perfectly good to be curious about sexuality and to tell people about it. I think it is as good to be interested in that than it is to be interested in the secrets of the gene or the workings of the atom. That is that research about this can be driven by your interest and understanding why people do it, not because you have a virus in the world. Indeed, asking questions from the point of view of only the virus will distort your interest in sexuality. Sexuality itself becomes the problem. The virus is the problem. Sexuality is not the problem.

I think that our failure to do such research in the spirit of understanding and social enlightenment really is a fundamental ambivalence about sex in society which Dr. Voeller talked about.

Social research has a peculiar character. It is consequential to the lives of people in society. The atom does not care if you are wrong. The atom does not care if you misconstrue what it is doing. If you are wrong in the social and behavioral sciences, institutions and organizations gather together to respond to what you are doing. If you think that IV drug users are absolutely out of control and indeed are hardened sinners, and you believe they will not adopt health care

practices, you then design programs to treat them which acts as if they will not tender to those practices. If you think that gay men are narcissistic and that is why they have sex with other men, what you will do is you will act towards them and you will create programs which in fact are based on that misconception of who they are. That is the helping behaviors that have occurred among gay communities providing social support belies every single argument about narcissism among gay men.

I know people who have given much of their lives for their friends. They have given up promotions at universities. I know very few other people I can say that about.

I think we need to understand sexuality from the point of view of the actor and we need to include those people who are doing the sexual things as part of our understanding of them. We don't want to dominate people's lives on the outside. That is one of the careless aspects of science. Science is a powerful instrument and we frequently overwhelm our subjects by telling them why they are doing things. We need to hear their voices as well. I think we need increased participation by the subjects in research.

I don't have any immediate recommendations on how many millions you would spend and I don't want to be that kind of a immediate supplicant and leave a grant application on your desk. I think we need to spend some money. I think we need to think about it fairly quickly. I think we need to do those things in the scientific community which will get research on line quickly so we can get data back quickly. That may involve sort of shaking up the scientific establishment about how it allocates funds.

Thank you very much.

[The prepared statement of Mr. Gagnon follows in the Appendix.]

DR. CRENSHAW: Thank you.

I would like to open the discussion for questions now. I would like to lead off by asking you to comment on the misperception of sex research and sex therapy as in a vacuum of genital phenomena without connection to the emotions or the rest of the human being. Perhaps we can put it a little better in context before we begin with the additional questions.

DR. REINISCH: I believe you are asking about the perception that sex research is not concerned with the emotional and love values. I don't think that has ever been the case. It is just that in any kind of scientific endeavor, one has to very carefully define what one is going to look at. I think there is

no question that questions regarding emotions, attitudes and values are a very important part of sex research.

Kinsey asked questions regarding that although people said he didn't, he did, and there are both books, and so have many other sex researchers who have had the opportunity to interview people about this subject.

One has to keep in mind that sex behavior itself, a very firm and careful description of it in our country today and I hope continuing, is essential to many of our major problems. I know people aren't mentioning this here but I would like to mention it, the fact that AIDS is a very major problem. We have other very major problems that relate directly to sexuality and had we been studying them, we would be dealing with them better today than we are.

Teen pregnancy is another one. We spent over $16 billion a year on families begun by teenage girls, every year. We have been doing that for 10 to 15 years already in this country. $16 billion. The problem is a sexual one. We don't understand the sexuality of adolescents. We don't understand how to deal with them and help them to be more responsible in the context of their families, in the context of their communities, religions and so forth.

At the heart of it lies their sexual behavior. We just don't have the data to make these programs. I want to make it really clear that what you are going to hear after us, from the panel on behavioral change, it is really not possible to make completely effective programs without knowing what people are doing because you can't educate them. You can't train them unless you know what they are doing.

DR. CRENSHAW: Without the baselines.

DR. REINISCH: Exactly. I think we have to ask people simultaneously about their behavior as well as about their attitudes, their emotions, their feelings, their responsibilities with regard to sexuality. That can be done. There is no problem with that.

DR. CRENSHAW: Thank you. Dr. Lee?

DR. LEE: My father told me when I was very little that the most important thing in the whole world was sex and if I saw avalanches, bankruptcies, wars, unhappiness, buildings falling down, if I got to the bottom of it, it would be sex. Dad, you were right!

[Laughter.]

I am glad that we have you people here.

When we get to your area in AIDS, it seems that what we are really focusing on is multiple sexual partners, and promiscuity. That's the dangerous thing, sexually, for us all. If we look at your interconnecting circles and if one is promiscuous, that "funnel" opens up very dramatically, particularly in certain communities. When we listened to Dr. Davis talk, if really 20 to 40 percent of the women in a community are HTLV-positive, and one is having sex with large numbers of people, you have a bad set of problems.

What do we do about this? Do you have any ideas on how we approach promiscuity? We certainly can't do much about sexuality. It is here, like hunger and need for shelter. But, what can we do about promiscuity? Is there a relationship between some sort of societal or family breakdown, the subunits of our society? Are we seeing social breakdown with increased promiscuity? When you look at animal behavior under these conditions, that happens.

DR. REINISCH: I don't think we have any evidence to support the fact that there is increased numbers of partners at this time in history. Again, one of the problems is we don't have the research to support that. People have all kinds of ideas, myths and beliefs about sexuality, including the one that somehow our society is becoming more "promiscuous." I put it in quotes because we don't have the definition.

The second Director of the Kinsey Institute used to define it as one more partner than I've had.

[Laughter.]

DR. REINISCH: That is really not a joke, we just really don't know the answers to what does that mean, what does the average person do, in what country, in what community, under what circumstances. Are you promiscuous if you have three husbands and each one of them dies and so you fall in love and marry another one. If you have had four partners in your life, does that make you promiscuous or equivalent to being promiscuous.

Again, I have to say we would love to be able to answer your question, Dr. Lee, and what we need is the appropriate research data, not just from one community, we have multiple communities here. We can't do a national survey. It is impossible. We have to survey the different cultures and different groups of our society probably separately. We would then be able to answer your question, and then we would have to do it over time, so that we could tell you whether there has been a change.

Everybody was very upset about Kinsey's data because he showed in the 1930s and 1940s that 50 percent of women were not virgins when they were married and that extramarital sex was going on at a rather high rate in both males and females in the 1930s and 1940s.

We really need to have good research over time to be able to answer your questions. I'm sure there is no doubt that family upset and the problems that we are having with divorces and so forth are important, but I can't tell you how they are important. I would like to be able to do that because then we could move in with programs to mediate what is being lost or hurt.

DR. LEE: We know how they are important. They are important because we see terrific social damage and we are now seeing AIDS, you are increasingly at risk if you have multiple sex partners.

DR. REINISCH: And you are not responsible. The limited data we have seems to show that if you are responsible about your sexuality, then the number of partner is not that important.

DR. LEE: Is that right?

DR. REINISCH: Yes, responsible sexuality is the thing we are talking about. As you said, we can't stop sex on this planet. It has been tried by many groups around the globe, or to limit it or make certain things illegal. There are times in our own history when certain behaviors would be punished by death. It didn't stop people from doing them.

We need to talk about responsibility.

DR. LEE: I can understand that.

DR. REINISCH: And so does your dad. We need to really be talking about responsibility and how we are going to train people, to educate them, to understand how to be responsible in their lives. If that means abstinence, that's great. If it means monogamy, that's great. If it means using condoms and spermicides in the appropriate ways, that also will help us stop this epidemic.

DR. LEE: In the inner city, underclass communities, where we are seeing single parent households, teenage pregnancies, illegitimate children at a very high rate, where we are finding the highest percentage of HTLV positivity, the highest percentage of drug abuse and what appears to be a breakdown in the system, that is what I was referring to.

DR. REINISCH: Teenage pregnancies and sexual abuse of children is not limited to the underclass; that's one thing we really do know and research has told us. Sexual abuse of children and incest and teen pregnancy is found in large amounts throughout our society at every level.

DR. GAGNON: I think we have to sort of segregate out the kinds of problems, I think we have to distinguish between child abuse and STDs and that kind of thing. I think there is one crucial issue here. It seems to me that what you point out is perfectly true, but what we may be seeing here is simply in addition, a disease burden of the poor. That is HIV may be added to the sexually transmitted disease process, to teenage pregnancy, even though it is widely distributed, it does exist there.

It seems to me that what is happening is we are losing a portion of society because we do not extend medical care to them. I would argue there is considerably more movement out of the underclass than most people think, it is not an iron wall between poor people and the rest of us, but I think the real point is there is a kind of failure to respond to the poor in society and that a whole series of structural issues other than sort of responding to the HIV issue, and they really have to be taken into account here.

I think drug addiction and teenage pregnancy all have to do with the kind of failure to face what the poorest portion of this society are living like. I think it links to HIV but if you asked me how to change it, I wouldn't be talking about simple disease control.

DR. VOELLER: I would like to comment a little on that too, and that is we have to go back a bit and look too -- for example, using gay men or using racial minorities in this country. But take gay men as an instance: If you deny gay men all of the buttressing strengths that society provides for heterosexual relationships, that is to say everything from double fares and insurance rates -- well, fare rates on airplanes and insurance rates for cars, all the way through religious documentation and validation of relationships all the way through what families think about those who are same sex couples versus cross sex or two gender couplings -- if you don't provide the routes of support, economically, socially, psychologically and the like, then you shouldn't be too surprised if you have gay males acting at a certain period in time with a different behavioral outlet or expression than what the general society thinks is appropriate.

I would suggest however equally if you have a look at the behavior of male populations which are heterosexual -- and our armed forces are a great case in point -- in the First World

War all the textbooks of syphilology point out that one of the major studies of American troops in France showed that 60 out of every 100 men every month were absent from duty because of syphilis or gonorrhea, which they didn't get by toilet seats. The point is that when you have no support for relationship of diverse sorts I've said and you have male societies, whether they are heterosexual or homosexual, you get a high sexual outlet. If you want to address some of those problems, you are going to have to look at changing those factors -- which is going back deeply -- just as are those issues related to solving our problems with poverty and the related social and political problems that, in turn, creates. You can't ignore those. They are not easily solved and they won't be solved during the course of this crisis. But it is an opportunity for the commission to address some of those issues and lend its support to the forces which would see those remedied.

DR. LEE: We are not going to ignore those issues.

DR. CRENSHAW: Dr. SerVaas?

DR. SERVAAS: My question is for Dr. Reinisch. I'd to like to know what the Kinsey Institute or you know about the number of teenagers who are sexually active and you are having intercourse and at what age. How many ten-year-olds, eleven-year-olds, twelve-year-olds? Could you give us the really bad news about that? The Children's Better Health Institute wants to know.

DR. REINISCH: Dr. SerVaas, we do have those data at the Institute, which we could provide you. I'm sorry I didn't get the question in advance.

But let me just say that children are -- there are several places in this country where there are pre-teen pregnancy clinics, and I have talked to youngsters who are on their second pregnancy before they become a teenager, so that we know that this is certainly happening very early. By I believe about age 16 the average American adolescent has become sexually active in terms of having his first intercourse.

It is very important to understand that in the few studies that are available, many of them done at the National Institute of Child Health and Human Development, it appears that education not only lowers the pregnancy rate -- and in fact the repeat pregnancy rate -- in one study from 60 percent for second pregnancies to 2 percent, but it also appears to delay first intercourse significantly. So, unfortunately there are many people in this country who believe that sex education is actually going to make children more sexually active and is going to make them more involved sexually and in fact the data that are available, and we should have a lot more -- I agree with you,

show us the exact opposite -- that with the proper education, with the proper availability of contraceptive materials, with education in a context of values, morals, the religious community of that community [sic] that children will make the right decision but they can't do it from ignorance. I can't think of a time in the whole history of human development that ignorance was better than knowledge.

DR. SERVAAS: I had one other question to you, and that is, in the Orient, do you how many homosexuals there are percentage-wise in the Orient?

DR. REINISCH: Well, it appears from the little work again that has been done around the world, that the percentage -- and again the question is "how does one define homosexual?" -- is that any man who has had one interaction sexually with another man? Well, Kinsey and other studies have shown in this country that it is about 37 percent of all men.

Are we talking about men who choose only to be with other men, exclusive? That is a small percentage. That is more like 4 or 5 percent, as far as we could tell. Our guess would be, and again we could use data from around the world -- is that the percentage would probably hold pretty constantly in most societies, even when -- and there are societies that have been discussed by anthropologists particularly in New Guinea in which young boys are -- the ingestion of semen directly from another male is part of their masculine development and every male does that for six to eight years during their childhood in order to become fertile. That is what the belief of the society is. And yet the percentage of homosexuals is no different than that in our culture once they are allowed to marry and have families.

So it appears that the percentage, from the little we know and again we would like to know a lot more -- is probably relatively, of those who are exclusively homosexual or wish to be, and some people don't act -- is relatively consistent throughout the world, but again that comes from very limited data.

DR. SERVAAS: Thank you.

DR. CRENSHAW: Mr. Creedon?

MR. CREEDON: I wonder how or what kinds of surveys would we have to do to get an accurate picture of the sexual activity of people in the United States -- I mean there is about 250 million people, whatever. The activity is probably different in San Francisco and New York than it is --

DR. REINISCH: Absolutely, that's right. It is not just social group, it is not sexual orientation group, it is not

just ethnic group. In fact, two things that groups tend to differ on the most are food and sex. There is where you find in fact an enormous amount of difference.

Yet -- also geographically --

MR. CREEDON: That is what I'm saying. How extensive would the surveys have to be? And secondly, the followup question is, how reliable would they be? In other words, people have feelings of privacy about their sexual activities and how honest are the answers that are given? I can see some people taking them kind of as a joke or say, well, they are going to confound the experts or whatever. But how reliable would the data be and how extensive would the surveys have to be to get reliable data?

DR. GAGNON: Part of the question is very technical. That is, if you have small phenomena -- that is if you have phenomena which occur at the rate of 2 and 3 percent in the population, then your sample sizes have to go up substantially in order to get accurate estimates if there is a population estimate. If you have a population rate at which you may have one or two percent --

MR. CREEDON: I am willing to concede that everybody does it -- over a certain age.

DR. GAGNON: No, no. You don't want to concede that. First of all if you look at some of the data there is a fairly large proportion of the American population which is not terribly sexually active and may in fact be active only with their spouses. I think it tends to -- the problem is the question really asked is precision and size. I would think that probably if you wanted to do a national sample of sexuality in society in which you got decent estimates -- there are two different questions here -- decent estimates of rates of behavior, assuming that people responded correctly, the sample sizes would be about 15-18,000 people.

And you would then need, if you wanted to look at the stability of that behavior, because that is really what is crucial -- how often do people change their sexual networks, how often do they change their partner (add them or drop them), you probably need to re-interview those people some time later.

DR. VOELLER: That is what I meant about ongoing --

MR. CREEDON: The second question is, the assumption--

DR. GAGNON: The second question is, can you get people to answer. It looks like we have done fairly well on a large number of fairly hard to do studies. The National Opinion

Research Center and other people have in fact done research about highly sensitive issues and have gotten decent answers in those studies.

Now I think the problem with the question you raised, which is the problem of response rates and will people tell you the truth -- the reason I can't give you a hard answer on that is that no one has ever let me do the research to find out.

You can do studies which are designed methodologically carefully in which you can get decent estimates on response problems. Such surveys are within the ken and within the skills of the social science community. It is only our unwillingness to do them and pay for them which in fact leaves us ignorant about it.

I think we know a lot more than we think we know and we know how to do certain kind of things actually quite well and I think we could solve those problems.

DR. VOELLER: Just to carry on with that, I agree and I think though that many people including in research, especially those who have not been trained in interviewing techniques and who now are doing extensive interviewing of gay men, of heterosexual populations in the AIDS crisis do not know how to conduct a proper interview and have no idea of the limitations of what people are willing to talk about.

I have long felt that the onus of the word "homosexual" is not really on "homo," which is what a lot of us have come to believe, but rather on being identified and labeled "sexual" in our culture. In fact, the presumption -- and I have heard this again and again from those doing studies on the sexual histories and the factors amongst gay men -- that lead to becoming infected in the first place and, if infected, going on to develop various clinical symptoms -- you know, the whole notion of co-factors and the like. The point is that many researchers believe that if you get a gay man to begin talking, he has already identified himself as "homosexual," he will then open up and tell you anything you want.

The fact of the matter is there are all kinds of sexual practices that are done by gay men and heterosexual couples which are even within gay circles are considered to be shocking by some significant portion of the population. This led to Centers for Disease Control, for example, to put an utterly undo emphasis upon "fisting" as a cause and source of the spread of AIDS early on in the epidemic.

We have seen that again and again and again. Take that example a step beyond: if you were to go to any of the so-called "leather" or "S/M" bars here in the city of New York, even

tonight, certainly over the past years when the crisis was developing you would discover that many of them, as they approached those leather bars over in the west dock areas and the 20s for the most part now, that many of those men would pull out a red handkerchief and put it in their left rear pocket of their blue jeans or whatever. The left means that they are an insertive partner in the act. Put in the right pocket, it would mean they were the receptive partner in the act.

Now in the first place, within the gay community the act of fisting is rather shocking to a fair proportion of the population to begin with, so the men don't put the handkerchief in, many of them, until they get near or at the door of the bar. Neither do they want to go into the bar and seem like they are shy about it, so they quickly at the door or in the block preceding it, put it in their pocket, in the wrong pocket, ofttimes, suggesting that they are only insertive partners -- which as June Reinisch said concerning Black, Hispanic and some White populations -- if you are the insertive partner, that is considered macho and heterosexual. Whereas if you are the receptive partner, even within the gay community, there is a carryover of that aura.

So that when researchers begin -- the interviewing techniques are exceedingly critical to getting the information that you want to have. Heterosexual anal intercourse, which may be a significant future route and already beginning route for the spread of the disease here as witness the work done at Einstein, for example , heterosexual anal intercourse is something that most people are unwilling to talk about.

In the one survey that has been done on this, it has been published by Dr. Bowling in San Antonio with a very large population of women and updated currently to some 2,000 interviewed women, he finds that only by the third interview do most of the women who acknowledge heterosexual anal intercourse as a frequent practice in their lives, acknowledge it. It takes three interviews. And having met him I could assure you he is a very easy person to talk with and confide in compared to some physicians.

He also surveyed his colleagues in obstetrics and gynecology and found that almost none of them was willing to ask such a question of their ob-gyn patients. So you see, in many levels at which the problem is impossible.

MR. CREEDON: -- would be very difficult to get --

DR. REINISCH: Well, Mr. Creedon, I think that it can be done and I think it is going to cost money to do it properly. That is, it cannot be done over the telephone, it can't be done with sending out questionnaires to people. It has to be done

face-to-face in face-to-face interviews by experienced -- not just experienced interviewers, but interviewers who have experience dealing with sexuality. People cannot be trained in two or three weeks to be comfortable and good at asking sexual questions. We are going to have to use our population I believe of sex therapists and sex researchers and graduate students working with sex researchers and sex therapists to be our interviewers across the country. They will then get some additional training. But I think that you can't just take somebody who is an expert in asking people about their taxes and about what kinds of soup cans they have on their shelves and then train them in two weeks or even four weeks to question people about this very sensitive behavior.

I would also like to undo -- and by the way I think that the interviewers have to be matched, as I said, for sex, for ethnicity if possible, for racial group and probably for age in order to get the best answers. Within a face-to-face interview there are ways of checking to see if somebody has given you misinformation. That was done in the Kinsey Institutes interviews and has been since then.

But the most important point I guess I would like to make as we get close to the end here is that we cannot be stopped, sex researchers and the people who are coming next or the people for behavior change programs -- for using explicit language, vernacular, the language of the people to whom you are speaking and for whom you are trying to educate in the education and research and questioning.

Up to this point the government has been very strong in interfering with the use of the language of the people in research and in behavior change programs. Until we can speak to people in the language they understand, in the words that they understand and use every day, we will not be able to find out what it is they are doing and what it is they want to do in the future and what their attitudes and values are. So I make a very strong plea here that the commission influence the powers that be in our government to allow researchers to use the language that is necessary to answer these questions and to train our people.

DR. CRENSHAW: Dr. Walsh?

DR. WALSH: One of the things that we have learned during these months is to have a sort of pessimistic outlook for the answer to the current problem in the near future. We are constantly told education is the secret weapon, education will lead to behavioral modification. You all have added to my pessimism now because you have indicated really that we don't have much of a foundation or base of knowledge to go on.

Now to help us, what would you do or suggest? I personally believe the educational programs for behavioral modification -- overall I am talking about -- that are being sponsored are a total failure. Certainly, except in -- you know, where you networking with the gay community in San Francisco and so on where it has been successful -- the problem seems to be that there are great differences of opinion on where you begin and what you tell them, what you have got to work on, what you have got to work with.

We see the incidence of sexually-transmitted disease on the increase. We see the problem in the minorities, which is making this into a real social crisis, as I think Dr. Gagnon re-emphasized, among Blacks and Hispanics.

What can we suggest for the near future on what you do know that we could do that would result perhaps in the improvement of the educational programs that are being put forth by our government? How can we persuade the churches, the Black churches and the Hispanic churches in particular, to become more involved? And what kind of material can we give them, based on what you know? That would help us. I realize you can't answer all that in the time allotted, but that is the kind of information we really need, because you yourself say if you are going to do the right kind of survey, it is not only going to have to be a large one, it is going to take a long time to do it correctly --

DR. REINISCH: Not with enough money. It probably could be done in a year if enough money is provided.

DR. WALSH: But I think we just have to have something because huge amounts of money are already being wasted on educational pamphlets that are used to --

DR. CRENSHAW: Dr. Reinisch, may I ask a favor of the panel? We are out of time, but this is one of the most important questions we could address, and if what you could do is give the very briefest of answers and then elaborate on it for us in writing so we can introduce it into the record and give it some careful attention.

DR. WALSH: Because we need it desperately.

DR. REINISCH: Thank you, Dr. Crenshaw, and thank you for the question, Dr. Walsh.

I think what I just said before -- one of the reasons that many of these programs are not working is because permission has not been given across the board to use the language and the explicit means that are necessary to educate people. You can't talk about sexual acts without some kind of

visual help, so that people know what you are talking about. You need to also use, as I said, the language that will communicate to them, and neither of things has been permitted in most areas, so many times you are speaking to people, as I just mentioned before -- "vaginal intercourse" is not a word that everybody in our society understands. The word "penis" is not used in many parts of our society. So even the best planned brochures and education programs without the proper language -- it is like speaking a foreign language even though those people speak English.

One thing that would help, that could be done immediately, is a strong voice from this very important commission telling the government that they must permit the use of the language of the people in these training and research programs. That would make a big difference and maybe some of those programs that are not working would begin to work just with that kind of change.

DR. GAGNON: Can I speak to that? I think that one of the things you also have to add here is that we can discuss whether programs work or don't work, but one of the reasons why there is debate over whether they work is that no one designs an evaluation procedure such that you would know whether they work at the end. When you give money for programs, you must assign money to evaluation so that we don't continue to build a series of square wheels.

What we systematically do is we do a program -- you see this in medicine -- we don't do a careful design. You don't know whether the effect is a placebo effect or there is no effect, or what effect you want -- and it seems to me that you have got to build the methodology in so that you don't repeat the errors you have already made.

DR. VOELLER: I'll be real quick. The one thing I would ask would be, because of the important of the question you pose and import of sex researchers can have to say in addition to those who are specifically going to follow us on this program, I really wish there would be a way -- if you have to invent it -- to have some serious time devoted to a longer consideration of the issues of sex research at the physiological, the survey, and behavioral -- all levels we have only touched on.

DR. CRENSHAW: Than

DR. LILLY: I am going to ask Dr. Voeller a question which under any decent of circumstances would elicit a two-hour lecture. I am wondering if you could say briefly and succinctly what your research into condoms has consisted of and perhaps what kinds of things you are finding.

DR. VOELLER: Well, first, let me just say that there are two separate studies at the laboratory level. We are doing the major study that is funded by the government, and the Consumers Union, who we have been collaborating closely with, are doing a separate study of the strengths, weaknesses, the flaw levels and rates and so forth of condoms.

We are looking at roughly some 35 different brands, but only testing a very large lot -- doing all of the international and American standards, in contrast with the FDA, which only does one of all those tests in screening all the lots that are manufactured or distributed in this country.

We are also looking at HIV leekage through those condoms and we find great variation. We find, for example, the different brands of condoms, if you total up the score -- I should say the lot we have looked at -- a large lot where we tested a thousand individual condoms in a particular lot of a particular brand. But the scores, when you tally up all values in a weighted formula, can range from zero to 100, and we have condoms that go all the way from 22 to 98 and a half. And they vary in their HIV leakage. I would also add that we believe that a lot of the data that has been put out, the pilot anecdotal studies, frankly, on laboratory testing of condoms, are deeply flawed -- giving both false negative (that's reassuring data) and false positives.

The clinical trials will be begun once we have completed the condom testing. We are doing similar studies with all of the major STD agents including HIV, by which I mean syphilis, gonorrhea, herpes, the lot -- we are looking at all of those and seeing what the most effective spermicides out of roughly a dozen different kinds from around the world, which ones are the most effective.

DR. CRENSHAW: Thank you so much. I would like to end this panel just with the comment that ordinarily under ideal circumstances, before we can educate the public in a responsible way, we need to educate the professionals and the experts -- and we haven't had a chance to touch on this today, but educating the educators is one of the gravest challenges that I see in our efforts to get responsible information to the community at large. It seems that we are going to have to somehow figure out how to do it all at the same time. But thank you very much. We will be in continuing contact and you will receive written questions to help us further.

Risk Behaviors: Research and Interventions

DR. CRENSHAW: I'd like to welcome our next panel and look very much forward to the comments. I want to preface it by saying that in a world where information about sexual baselines

and so importantly, changing sexual behavior has become an urgent priority. We need answers today that we were perhaps not aware enough, thoughtful enough or active enough to fund research on yesterday.

In that context, I know we are asking a great deal of you, you have learned and you have a lot to present to us that has been under funding conditions and opportunities to do the very studies that we are asking for definitive answers about today, but let's see what we can find out and what we can do to close that gap.

Dr. Patrick Carnes?

DR. CARNES: My name is Pat Carnes. I am Program Consultant to the Sexual Dependency Unit at Golden Valley Health Center, which is a 450 bed mental health and addiction complex just outside Minneapolis, Minnesota, and one of my roles there is also to serve as the Clinical Director of their Institute for Behavioral Medicine.

I was struck today as I was listening to the Commission listen to the various testimonies about sort of the constant themes, issues around research, around terminology, about lack of information and yet having an extreme urgency to all the questions. I found myself as I listened wanting to do parenthetical comments and to leap in, as I noticed there were a number of other people wanted to do.

I was even struck as June Reinisch was talking about the problem of terminology, remembering in our sexual addiction unit, one of the hospitals we worked with where we changed the word "indecent liberties" because we couldn't get patients to respond to the words "indecent liberties." We changed it to "grab a feel," and we had lots of people who said they did that but would not respond to "indecent liberties." We changed the hospital admit form to have "grab a feel" on it which worked fine until the Joint Commission of Accrediting Hospitals came by and asked how we got grabbing a feel onto the hospital admit form.

[Laughter.]

It represents a lot of issues and I think one of the things I would like to present to you is I think much of what you are dealing with and the themes you are trying to address has to do with the lenses that you use. The lenses I want to talk to you about today is one that will give you a different perspective but also an alarming one.

One of the things I want to talk to you about is the role of addiction and sexuality, and not just what most people associate in terms of addiction, thinking of chemical or alcohol

abuse, but I want to talk to you about other forms of addiction, specifically sexual addiction.

If I could have my first slide, please.

[SLIDE.]

DR. CARNES: What I have done on the slide is you have a normal curve and one of the things is that it helps give a sense of what we are talking about in terms of sexual addiction or sexual "prowesslessness." If you think of sexual behavior as a normal curve, one of the real accomplishments in the field of sexology over the last 35 years has been able to give people permission, whether they have had less experience or more sexual experience, to understand that there is a great amount of diversity in sexual experience and also a range in terms of how much sexual experience people have.

On the far left, there is an area in which we have made a great deal of success in terms of working in sexual dysfunction, where somebody's inability to function sexually has affected their life. We are talking about pre-orgasmic conditions, inhibited sexual desire, or impotence, for example.

That we have talked a lot about and there is still a lot of work to do but we have made a great deal of progress.

On the far right is a group of people who we have until Jim Orford's article in 1978, received very little attention in the professional literature. It is a group of people who literally get to a point in their sexuality where it is not having more sexual experience, it is an area where people lose the ability to set boundaries around their sexual behavior. This inability to stop their behavior, even though they can see significant consequences and even risk their lives and not be able to stop their behavior, is destructive to their life and is an obsessional illness that we have come to understand under terms like hyper sexuality, sexual addiction or sexual compulsivity.

[SLIDE.]

DR. CARNES: One of the things that helps when you think of that curve, one way you can think about sexual behavior and thinking of it as an addiction is to compare it to eating disorders. Unfortunately, what happens with sexual addiction is people immediately compare it to things like chemical dependency, where they think of an abstinence model. The fact of the matter is it is more like an eating disorder and if you think of the normal curve in terms of eating disorders, you have some people who eat more and some people who eat less. You have a group of people on the far left who literally, their inability to eat

leads to self starvation which we call anorexia, and on the far right, is a group of people who compulsively overeat. There are 34 million obese people in our culture, 14 million morbidly obese.

When a person goes to treatment for an eating disorder, they don't give up eating, they learn how to eat differently and to monitor their rituals and learn about what healthy food is for themselves. The same thing is true for sexual addiction.

People who are admitted to hospitals, in-patient or out-patient units for sexual addiction, usually have not had sexual experience as most of us would experience it, because of the nature of their obsessional illness. The fact of the matter is that many of them, starting when they were very small, entered into a world where the actual experience of sexuality was not something that they incorporated. It was more what happened in terms of their obsession.

One of the things that has happened in the field is we have started to notice that along with sexual addiction, other addictions start to be associated, for example, compulsive over eating women tend to be hyper sexual whereas compulsive non-sexual or anorexic women tend to be compulsively non-sexual.

It would not be unusual, for example, to see a family in which a husband is an alcoholic. He has been sexual with two of his daughters for eight years, has a pornography collection that is extremely large and has been having compulsive affairs for years. His wife is 325 pounds. He is physically abusive of his wife. His wife is physically abusive with the kids. One of the kids is psychotic and another is learning disabled.

It would not be an unusual thing to see within that marital dyad as he gets further out of control in terms of his sexuality, his wife would be more and more compulsively non-sexual. In other words, try to almost balance the marital equation.

What we are understanding in the field of addictions is many compulsive disorders co-exist.

[SLIDE.]

DR. CARNES: For example, in a national survey we just completed, of people who are recovering from sexual dependency, we found that 42 percent of them were also alcohol and drug dependent; 38 percent had some form of eating disorder; 27 percent reported compulsive work; 26 percent reported compulsive spending and 5 percent reported compulsive gambling.

One of the things that is happening in the field of addiction is we are starting to understand how out of control behavior then impacts in terms of working with one another, why is it, for example, a person who achieves alcohol sobriety will suddenly find that their sexual behavior will start to get out of control or even escalate far beyond the baseline that it had before the sobriety was achieved.

A number of models are used to try to make sense of the relationship among addictions. I have one example, a model that takes the addictions and divides them into three categories, the arousal addictions, which would be like gambling, sex, stimulants, drugs and high risk behaviors. The satiation addictions like over eating, depressant drugs and alcohol, and the fantasy additions like drugs, marijuana and a whole category of mystical and artistic preoccupations, that also goes in the same type of obsessional illness.

What the authors do then is they do an analysis of nine hormones that govern the electro-chemical interactions in the synapses of the brain in terms of looking what we call in the field cross tolerance effects. For example, at Golden Valley, 38 percent of our admissions are eating disordered. We know that when they achieve some sexual recovery from their illness, that 50 percent of them are going to find their urges to binge eat are going to increase and 50 percent are going to find that their urges to binge eat are going to decrease. We don't know how that process works yet.

I simply put it up there to show you that we in the field of addiction are starting to understand that no addiction is isolated, that they are intimately connected with one another.

One of the things that is real significant also in the research is that we know sex addicts, in the national survey we just completed, sex addicts have at least one addict, either sibling or parent of another variety, 87 percent of those have another addict in the immediate family.

[SLIDE.]

DR. CARNES: To summarize what some of the symptoms of sexual dependency are is to take a look at where a pathological relationship exists with sexual behavior, which makes mood alteration a higher priority than family, work, friends and values. A sex addict has developed or cultivated the ability to metabolize and to achieve a sexual high on specifically highly focused fantasies and rituals to the extent that they would sacrifice in order to preserve that behavior, their family, their work, their friends and their values.

Another characteristic very important to the recommendations I am going to make is these are literally people who lose contact with reality through denial and delusion. We have patients who have whole periods of their lives that they can't remember. The fact of the matter is, as one of their characteristics, they lose control despite obvious serious life consequences and even risk to life. In other words, they will see there is going to be disaster to their marriage, to their family or their work or even to their life, and they will not stop their behavior, which is very important in terms of thinking about the AIDS epidemic.

[SLIDE.]

DR. CARNES: Some of the questions that are frequently asked about the origins of sexual dependency, there are many different things, and this is another category that the Commission has to deal with, the fact that we could talk for many, many hours about how sexual addiction starts. One of the things is that we are getting very good at being able to pinpoint when it starts. We know that most people who are sex addicts have experienced a fair amount of abuse in growing up, about 81 percent of them have been sexually abused, 72 percent physically abused and 97 percent have experienced some form of severe emotional abuse.

In terms of the sexually abused, what we have learned of sexually abused victims, that the men have pretty much -- most of their sexual abuse has occurred between the ages of 5 and 8 and their out of control sexual patterns are already identifiable by that age. Women have an onset somewhat later, between 10 and 13/14. The reason that sexual abuse plays such a high role in sexual dependency is the fact that what happens when your care givers are sexual with you when you are young, you misidentify that all care and nurturing has to be sexual. Part of what happens for sexually dependent people as they mature, they look to sex as a way to navigate their life.

In fact, one of the assessment tools we use is when a patient starts to use medical language to describe their sexuality, like my tension reliever, my pain reliever.

[SLIDE.]

DR. CARNES: This is from a survey of sex addicts anonymous. There are many different types of recovery programs around the country. This particular survey was done in 1982. The behaviors that were identified as key to the kinds of behaviors involved and part of their addiction range from masturbation, heterosexual behavior, homosexual behavior, bestiality, right up through sex offenses, such as incest, child molesting and rape.

What is significant about this is each of these behaviors reached an extreme, for example, in masturbation, 45 percent of the men and 33 percent of the women had masturbated to the point of injury.

What is important for our purposes, I took two pieces out of a survey we have just completed that I think the Commission can see that will kind of dramatize for you why I think it is important to look at the connection between sexual dependency and AIDS.

[SLIDE.]

DR. CARNES: If you look at the differences here, men and women, for example, paying for sex, you will notice that men are more likely to patronize saunas, massage parlors, with 30 percent of the sample saying that was part of a frequent occurrence, as part of their addiction. Paying for sexual activity, 47 percent, which is considerably higher than the figures June Reinisch gave you as typical of our culture, participation in phone activity, et cetera. In terms of receiving money in exchange for sex or receiving drugs in exchange for sexual activity, 24 percent of the women and 24 percent of the men.

A different thing happens if you take a look at relationships in sex, if you just take having many relationships at the same time, 40 percent of the men in the survey, 79 percent of the women, having successive relationships one right after another, 37 percent of the men but 74 percent of the women, having one night stands, 62 percent, 86 percent, all of these ratings are part of where people have talked about an extreme level of functioning, behavior having a great deal of power over their lives.

Engaging in sex with anonymous partners, 55 percent of the men, 48 percent of the women. Swapping partners, 13 percent of the men, 19 percent of the women.

Just one statistic about women. There was not one woman in the survey who was faithful to her spouse within 90 days of their marriage.

[SLIDE.]

DR. CARNES: Physical consequences. This is one of a whole battery of physical consequences that happen to these people, ranging from continuation of sexual behaviors despite the risk of disease or infection, 65 percent of men, 60 percent of women; venereal diseases, 38 percent of the men, 45 percent of the women, et cetera.

The one that I want to bring to your attention is the one that in the sample, sample of people who had been in recovery programs, in other words, they had been through a treatment program for recovery, and most of them, five to six years. Even in this sample, we found 3 percent of our sample had AIDS or AIDS related complex. The thing that I want to underline for you and make clear is we are looking at a population who has a very, very high risk because of the amount of behavior they have and lack of discrimination and the denial they live with in terms of their behavior.

We estimate that the size of this population is between 3 and 6 percent of the population was right under where eating disorders and alcohol are.

I have four recommendations for the Commission.

--One, in order to promote recovering individuals so that they are less vulnerable to the threat of the disease or AIDS, is to promote identification and diagnosis. The key vehicles would be the National Institute of Mental Health, the National Institute of Alcoholism and Alcohol Studies, National Institute of Drug Abuse, to sponsor education about sex addiction with professionals who treat related disorders, including alcoholism, drug abuse, eating disorders and sexual dysfunction.

--Two, we need to support researchers who are documenting the role of sex addiction in the transmission of AIDS. There are some very excellent research in progress right now. People are struggling for financing, to figure out how to do that better.

--Three, we need to develop a study of the incidence of AIDS in medical facilities currently treating sexual addiction, both in-patient and out-patient facilities, so we can see if the current people who are coming into the hospital, what the rate of incidence of AIDS exists in those populations.

--Four, I think given the seriousness, it is like we have two major illnesses that are sort of colliding. We have a subset of our population who literally cannot control or make judgments about their sexual behavior. They are one of the most vulnerable risks in terms of spreading this illness, at a time when we are really concerned about the epidemic nature of the spread of AIDS.

One of the things that I think is very important is that we put some effort into really studying this population and promote successful recoveries. We do know that in this particular survey, since we are looking for successful recoveries, 77 percent of the 400 people in the sample said they

had been able to turn their lives around where they had five years of no behavior that was dangerous to them.

That success is possible. We need to understand better how they do it and how can we help people who have the same problem.

Thank you.

[The prepared statement of Dr. Carnes follows in the Appendix.]

DR. CRENSHAW: Thank you. Dr. Friedman?

DR. FRIEDMAN: I am Sam Friedman with Narcotic and Drug Research, Inc. of New York City, which is associated with the New York State Division of Substance Abuse Services.

Given the probability that we are not going to have either a vaccine or therapy for AIDS in the near future, prevention of the spread of the virus is crucial if we are going to get this epidemic under control. Given the fact that much of heterosexual transmission is from IV drug users to other people, then we have to get some kind of control on that, if we are going to stop the spread of the disease, to groups that haven't been heavily at risk previously.

We do not unfortunately have adequate knowledge about how to mount these interventions. What I am doing here today is chiefly to talk about research issues involved.

We need to learn how to affect risk and transmission behavior. This behavior is deeply social behavior, not just psycho-social but social. Transmission involves an interaction between at least two people in which the virus can be exchanged. The context that leads to contaminated syringes being shared, for example, can involve small group pressures, it can also include wide ranges of broader social factors such as those involved in racial differences or particular laws in a jurisdictions that may affect drug abuse.

These factors are hard to study, are complex. In spite of chemical dependency, in spite often of no education among IV users, in spite among many drug users of alienation from social institutions, the common stereotype that says they haven't done anything and can't do anything to protect themselves and others in this epidemic seems to be wrong. We have abundant evidence that people have tried to protect themselves and have tried to protect others. Some of this has been presented to you by my colleague, Dr. Des Jarlais, at a former meeting of this group.

Complexity is also indicated by comparisons between gay men and their attempts to get this epidemic under control and the activities of IV drug users. IV drug users have been much less able to organize than have gay men.

On the other hand, in New York City, there is an organization called ADAPT, of ex-users, some current users and health professionals. In the Netherlands, there is what they call the Junkiebonden, the drug users unions that have been coming to terms with issues on AIDS. I have done some studies of those.

The complexities of all these issues pose difficult methodological and research problems, which I want to focus on for a minute. Most research in this field has focused on what helps the individual to reduce his or her personal risk of becoming infected. It has been based heavily and at best on the experimental model from psychology as a model, which means it looks at individuals as the unit of change and that it assumes that history is irrelevant. That is what works at one point in time and at one place during the epidemic is going to work at other times and places.

When I say this has been much of the best research, I'm not saying that is the best research that should be done. We need additional kinds of research to get beyond this.

We need to focus on reduction of behaviors that potentially transmit HIV to others. This involves a different set of motivations than personal protection. Many IV drug users, for example, are more willing to listen to outreach workers when the issue is raised in terms of protected their loved ones, than when the issue is raised in terms of self protection.

We have to look at prevention efforts that take seriously the fact that risk behaviors are social. We are beginning projects to change the values of IV drug users and their partners to reduce transmission and to help them to develop ways to implement such protective ideas as groups, working with groups of people in the street, for example, to develop ways in which they can ritualize and set up norms by which they will protect each other and support each other, for example, if changes in their sex lives lead to break up of relationships.

We have to look at risk and transmission behaviors as historical events. At the beginning of the epidemic, few drug users believed in their own vulnerability to AIDS. Since then, more acceptance has occurred and considerable reduction in risk and transmission behaviors. Later on, we may well encounter a subculture perhaps only part of the drug users, of despair, about protection against AIDS. Each of these periods involves different contacts for the individual and for the group who is

confronted with a given intervention, so we would expect reactions to differ in accordance with the history of the epidemic and the psychological experimental behavioral model of research doesn't really deal adequately with this.

I might add in response to a question Dr. Lee raised earlier that virtually no research is being funded that I know of on how some of our more fundamental social structures may affect risk behaviors.

Decisions about research are often taken by medically trained persons and many of you here on the panel are medically trained persons, often superb medical scientists are involved in this. They make these decisions about what programs should be set up, about which proposal should be funded, about which article should be published and similar crucial decisions, on the basis of what they know and on medical research training.

Their input is useful but social scientists have developed understandings and techniques that go beyond what people are taught in medical school and we have to develop ways in which those understandings and techniques are brought into these decisions.

The history of national research policy just prior to AIDS becoming a major recognized threat is a warning to us, I think. Good social science in AIDS is rare, as it has been pointed out both by the National Academy of Sciences and the American Foundation for AIDS Research.

This is due in part to the restriction in social science research funds in the early 1980s. When AIDS hit as a result, we had less research into drug use and its prevention, into sexual behavior and into the methodologies for studying these topics. We also may have as a result of these and due to a lack of enrollments in social sciences, a serious shortage of social researchers needed for doing the research we need.

We have trouble recruiting those that do exist into the field of AIDS research, I might add. A lot that needs to be done gets left undone.

Another problem that we have in research that has been alluded to in the previous panel is that we have to examine and test some ideas that are controversial in order to protect the health at this stage, the public health. In Sweden and in Germany, methadone treatment, for example, is extremely controversial. In Sweden, in spite of basically not believing in it, they have doubled methadone treatment, to the point where 30 percent of the heroin users in that society now have slots available.

In Germany, they routinely have syringes sold over the counter and have made sure that pharmacists are actually selling them. In the United States, controversial issues include syringe exchanges and giving methadone without supportive services and counseling.

Here, it is important to understand that although it is sometimes argued that there are contradictions among various projects and goals, for example, between methadone and becoming drug free, or between teaching people how to inject more safely and entering drug abuse treatment, our experience in prevention efforts and our research alike show that these programs support each other. Syringe exchanges, for example, in Europe, do not reduce treatment admissions. In New Jersey, when they set up a program to teach people how to use bleach to sterilize works, one of the major effects of this was people went increasing to demand treatment, out of drug abuse treatment centers.

We have to do research in controversial areas if we are going to deal with AIDS. America has always been a country noted for taking risks, except in this epidemic, maybe not. Federal agencies are inhibited in sponsoring various kinds of research. CDC innovative research projects have been hindered by requirements that local committees approve educational materials, numerous bodies of the Federal and state governments have called for syringe exchanges to be tested out. So far, nobody has been willing to put the money behind it, even in jurisdictions where it is legal to do this.

We have places in some states in this country that would like to do syringe exchanges in the context of a funded research project, but we can't get Federal agencies to fund it so far, although some are thinking about it.

I have some specific suggestions about research management. We are reaching a point where we cannot train medium and high level researchers in AIDS at the rate we need through normal channels. We need a way to bring established researchers, good researchers from other fields in social sciences, who have not been doing AIDS research, into our ongoing projects.

I would propose a senior level equivalent of a post-doctoral program, appropriate persons might be approached, associate professors who want to change the area they focus on or who have sabbaticals. Stipend levels might be on the order of $35,000 to $50,000 a year. This would let us train people to become project directors, senior analysts and methodologists and principal investigators without having to give them line authority and research grants while they are being trained.

It might also help us to reduce the serious paucity of minority researchers in this field, which is important when we

are researching behaviors that lead to disproportional infection of minorities.

Expansions in research funding that have occurred in the last couple of years have not been matched by funding agency infrastructure expansion. That means, for example, at NIDA, that researchers have not had adequate support by staff, because the staff are overloaded and have much too much to do. In some of my supportive material, I give you some details on that for NIDA.

AIDS research moves fast and often when we get a project set up and funded, we discover that it may be a small project to begin with, and then we discover four months into it that we need a massive infusion of funds very quickly. There is no convenient mechanism in Federal funding at this stage to do that.

We need more top level social scientists in this field and funding help will do that but also any publicity you can give and anything you can do to help the prestige of social scientists who are involved in this research will be helpful in recruiting such people.

Funding, by the way, in this area, remains inadequate. NIDA has massively increased its funding and all the rest of it is still inadequate. The big community demonstration grants which are essential and critical to research, each one of us is probably under funded at this stage. We are getting roughly $1 million a year and it is not enough for interventions that have both an intervention component and a research component. I'm not criticizing NIDA when I say that. The money just isn't available.

In addition, the other aspects of research into drug use and AIDS are not getting adequate funding and we need it desperately.

The research that has been done suggests the following interventions to reduce AIDS among IV drug users and their partners and I guess this is answering the question asked to the last panel. We need to prevent initiation of IV drug use by people. We don't know how to do that. We need a lot of research. We have been doing a little bit. It may become one of the big fields that needs additional funding effort.

We need a rapid and sizeable expansion of drug abuse treatment systems. We have capacity for maybe 10 percent of the IV drug addicts and considerable waiting time, months, to get into treatment. We need improved levels not only of funding, they need space, facilities, staffing, people in this field are being worked to death, the counselors and such. Research shows

that better provision of these facilities leads to improved changes in behavior, less risk taking and such.

Outreach to IV drug users and their partners has begun but needs expansion and it needs additional innovation on how it should be done including research, of course. This should include individual educational outreach. It should include efforts to promote safer injection, it should include giving out materials on an experimental basis, and bleach is one, condoms is another, syringe exchanges has been suggested.

We also need efforts to mobilize the small groups in the subculture for AIDS prevention and perhaps even to organize organizations akin to the gay groups from IV drug users and ex-users and the partners of IV drug users.

Finally, given the extent to which AIDS is disproportionately impacting blacks and hispanics, we need special programs that involve minority community organizations and institutions.

This is the end of my presentation. If you want to ask me about evaluation of what is effective in the way of interventions, I will welcome that.

[The prepared statement of Dr. Friedman follows in the Appendix.]

DR. CRENSHAW: Thank you very much.

Dr. Karen Hein.

DR. HEIN: I am Dr. Karen Hein. I am a physician specializing in adolescent medicine and I am the director of the nation's first adolescent AIDS program, at Montefiore Medical Center in affiliation with Albert Einstein College of Medicine.

In my few moments, what I would like to discuss is the impact of the epidemic on adolescents. Why adolescents? Which adolescents? And what to do for and about adolescents?

I will give you data to support the following three points:

1. We have the opportunity to turn back the clock to 1981, to learn by what we have done and what we haven't done, about what we could do for adolescents.

2. We are at a unique point in this epidemic. Only about one percent of the case of AIDS are in adolescents, but many more are in the direct path of this epidemic.

3. There are critical differences between adolescents and children and adolescents and adults. It is these differences that we have to focus on in our planning in the next year or two.

To help in this planning, I want to briefly review a profile of the epidemic in adolescence to say that there aren't many cases, but there a few factors that could make all the difference.

First of all, of the 500 cases in young people ages 13 to 21, remember that these are AIDS cases. The latency period may be on average about seven years, with latency as long as 12-15 years, so that many cases of people in their twenties are really people infected in adolescence.

Secondly, we don't know much about the prevalence of HIV infection in adolescents. Some information from the Job Corps, from the Peace Corps and the military data do suggest that in epicenters where HIV infection has spread to other populations, that the adolescents are involved at this point.

Lastly, rates of sexually-transmitted diseases other than HIV are very alarming in adolescents and continue to be well into the eighties.

If I may have the first slide, we'll now look at a profile of the epidemic among New York adolescents to see what the relevant factors are that we can learn for the rest of the nation.

[Slide.]

Here we have a pie graph showing the breakdown by risk group for 114 cases of adolescents reported to the New York City Department of Health.

The important features are, first of all, that the largest group are in fact the male homosexual and bisexual adolescent -- again 13 through 21 years of age. However, this piece of the pie, 44 percent, is actually a smaller percent than the nation as whole.

The second piece, the IV drug abuser accounting for 23 percent of cases in adolescence, is again smaller than the nation as a whole and somewhat comparable to adults in New York.

Most important, however, is this wedge -- the female partners of high risk males, accounting for 11 percent of adolescent cases. This is far higher than adults. If we look at the females alone, this accounts for 42 percent of all the female adolescent cases in New York.

Lastly, the pie piece that represents the blood product recipients again differs in New York as compared to teenagers in the nation. This is eleven percent of the pie in New York, but if we look at the nation, the young hemophiliac male, the 11 to 17 years old in the nation, this piece of the pie would account for 80 percent of such males. In New York City many, many more of the cases are related to behavioral factors.

[Slide.]

Now let's take a quick look at the breakdown of New York AIDS cases in children, adults, and adolescents to make the points about the differences in these three age groups. Again, the male homosexual or bisexual is a large piece of the pie, but adolescents are somewhat less -- this is a less common risk behavior than in adults. As far IV drug abuse goes, the majority of parents of youngsters born with HIV infection are of course IV drug abusers. Again, the adolescent and adult populations are not too dissimilar one from the other.

But here is the biggest group. In the nation, only 4 percent in adult are attributed to heterosexual spread, but a much higher percent in adolescents and, again, blood product recipients for the nation -- adolescent males, largely hemophiliacs, but in New York City this is not a very prominent reason for HIV infection, at least as reported in AIDS cases.

Now if we are going to talk not about New York City adolescents because what do they represent vis-a-vis the rest of the country, I am going to show you a conceptual model to help you think about all the adolescents in the country, some 25 million between the ages of 13 and 19. They represent many, many different kinds of adolescents. This is a conceptual model that I have developed to help you understand the degrees of risk among the adolescent population, from those teenagers at no risk to those who are at immediate risk or who are already infected.

The circles do not represent actual numbers of teenagers again, but are in relation to the degree of risk. In the inner circle we have the teenagers who are not at any risk at the moment. They tend to be young, virginal, live in a place where the virus isn't, have not received a transfusion and don't use IV drugs.

Perhaps in the question-answer period we can -- I have some slides about the rates of sexual activity among adolescents in the country. But at any rate there are still issues, even for this group. They are three.

First of all, they may be the "worried well." How are they going to live and grow up in an atmosphere of concern and to not have undue concern and anxiety.

Secondly, they need information about casual contact, so that they can develop sexually and emotionally healthy in ways that don't put them at risk for this epidemic.

Lastly, they need support for their current sexual decision, namely abstinence.

In the next group we have those teenagers who are sexually active but not at risk at the moment. That may be because they are living in a place where the virus isn't -- because at the moment geography is destiny. Still there are issues for them -- the fact that they can't know their partner, that they might want to reconsider their sexual decision, and lastly that contraceptives in general are important for them and condoms in particular. They are separated by a dotted line from this group of teenagers at risk right now, many of whom have been infected already.

These teenagers can be infected from any one of eight potential sources: adults, homosexuals and bisexuals, IV drug abusers and their partners, or some teenage gay males, by sexual teenage drug abusers or teenage partners.

In our program we now have examples of every one of these circles. Decisions for them include the decision of whether or not to be tested, to know the serostatus of their partner, the need for condoms, reconsideration of their sexual practices, and -- for the females -- to decide to continue or to become pregnant.

Currently there are very few to almost no services that are specifically geared to help the adolescents really in any of these categories, but particularly in the outer ring. In our program, the first six HIV positive teenagers had 50 sexual partners, one of them had none and one had 28, to give you a feel for the range of what infected adolescents look like now.

I would like to now conclude with some of the recent responses to the challenge posed by adolescents in this epidemic -- if I can have the lights up.

I am going to mention by name only, but in the written material there are descriptions of nine responses, all of which can be viewed in the sense of a recommendation.

The first has to do with network. There are two task forces that exist so far in the country on a volunteer basis, one on the East Coast and one on the West Coast, to specifically bring together agencies in health, education, and direct services for teenagers.

Our own adolescent AIDS program again is the first, but hopefully will be followed by others to spread the knowledge and experience and care for adolescents around this country.

Secondly, the use of adolescent resource groups. Focus groups have been used by the health department in this city and others to screen and evaluate educational material. There have been hotlines developed by teenagers for teenagers, and peer counselling models where young people are used to help to educate and help change behavior in other youngster have also been developed and are not currently -- we don't have information about their effectiveness in AIDS but we do on their effectiveness in some other chronic illnesses.

Educational materials, books and pamphlets and videos and certainly curricula are coming out at a very impressive rate. However, cost, distribution problems, access problems and again the lack of evaluation are very pressing concerns.

Fourthly, analysis of available data, as I have shown to you, drawn from the Centers for Disease Control and the New York Department of Health, are available for teenagers. But if we lump them with children or adults we are going to miss some of these key differences that could help us in planning,.

Fifthly, surveys of AIDS knowledge, attitudes and beliefs have been conducted in a pilot way, particularly in four communities -- New York, San Francisco, L.A. and Boston. These can become the NIDAs for longitudinal studies and for more widespread studies.

Importantly, to link my comments with the former panel, the best questionnaires are those which include questions about behavior, not just about knowledge, attitudes and beliefs.

Sixthly, condom distribution schemes for adolescents are just beginning to be planned. Mass condom distribution campaigns have been promulgated here in the City through the Major's Office of Adolescent Pregnancy. But other such distribution campaigns have existed for adults in other parts of the nation.

We don't know very much in the seventh recommendation, about what HIV infection looks like in the adolescent population. I have showed you AIDS cases. We don't know about the progression of this illness in adolescence, the percent of asymptomatic versus symptomatic co-factors, whether they'll look like little kids and die quickly, often of bacterial common infections or like the adults with rare cancers. These are unanswered questions at this time.

Eighthly, there are some new funding initiatives, but they are buried. NICHD, NIDA, NIMH, MCH -- all may have funds available for teenagers but there is no way to report to you how much money is available or just where, because adolescents are usually lumped with children or with adults.

Lastly, the ethical and legal issues are perhaps the most pressing at this point in time and something that the commission should embrace and carefully weigh and consider. There are mandatory testing policies in place now in the Job Corps, the Peace Corp, the military and for dependent minors of families in the State Department who are going overseas.

The impact of these policies has not been looked at, but there are many instances now of a terrible fallout of these mandatory testing policies on the lives of teenagers. For example, military recruits in the City of New York who were found to be positive are told that they are positive, not enrolled in the military, given the number of the New York Department of Health hotline and that is it. There is no attempt at this time to link them with appropriate services to help them or their family.

In this ethical and legal dilemma, the whole question of parental notification of results or parental requirement for testing are issues that really need clarification.

So in conclusion, the history of the AIDS epidemic's impact on adolescents is a very brief one in that this commission is one of a handful of places in which the adolescent issues have been aired. The IOM report made reference to adolescents, the Surgeon-General's workshop in April, the June House Select Committee hearings on Children, Youth and Families -- but these are it.

In March there will be a National Invitational Conference to focus on the issues of AIDS and adolescence. But we are only at the beginning of learning about the impact of this epidemic on adolescents. If we don't consider their special needs, then we may repeat the mistakes that we have made that have led to the situation in the adult male homosexual, IV drug abusing community.

The next two years will make all the difference in the lives of our young people. Thank you.

[Applause.]

[The prepared statement of Dr. Hein follows in the Appendix.]

DR. CRENSHAW: Thank you very much.

Dr. Coates?

DR. COATES: Thank you.

In addition to what I have already told you I would also like to mention that I sit on the National Academy of Sciences Committee on AIDS and Social and Behavioral Research and we will be issuing a report in October. Hopefully, many of the recommendations coming out of that committee will dovetail with many of the recommendations coming out of this committee.

I also speak here on behalf of the American Psychological Association, which, as a member of the association I can say I am extremely proud. It is one of the few associations -- one of the few professional associations that responded early and loud with attempts to deal with the AIDS epidemic, both within its membership and on behalf of its membership to other important bodies.

I guess I would like to start off by saying -- and I'll try to be mercifully brief and not read my testimony, which contains the major substance of what I want to say to you. I think I would like to start off by saying that I think that the most important agenda in behavioral and social research with AIDS is prevention.

Now if one can take that as a given, one has to think that many things in life are crazy. "Crazy" is not a word that I like to use, for example, around the National Institute of Mental Health -- they are kind of sensitive about that word. But it is crazy that this Commission is sitting here in 1988. It should have been convened with regard to the AIDS epidemic in 1983 or 1984. But it is even crazy that it took an epidemic like AIDS to bring a Commission like this together.

As you have heard, many, many, many, many times over and over and over again, AIDS is only the last in a series of sexually-transmitted disease epidemics that this nation has faced and it has been a very serious, serious health problem that we as a national have failed to come to grips with.

Herpes, Hepatitis B, syphilis, chlamydia -- and you can go on down the line -- along with unplanned pregnancy, unwanted pregnancy and teenage, which have been with us for a long time.

So therefore my first recommendation to this committee is that it recommend loud and strong that the federal government -- and the group of the federal government that I am most intimately interested in, and that is the research arm -- never again allow sex research to be put under the table.

One of the biggest advantages of the AIDS epidemic is that sex again has come out of the closet and we can talk about things like condoms and anal intercourse and even vaginal intercourse in public. There needs to be in place a permanent mandate to the National Institutes of Health or to ADAMHA that they maintain a sharp focus on sexual research, much as we would not allow them to go out of the business of doing cardiovascular research, much as we would not let them go out of the business of doing cancer research, we cannot let them go out of the business of having a coordinated and concerted program of sexual behavior research.

Now, still continuing my theme, and that is commenting on the craziness of the world, I think another institutional establishment issue that needs to be addressed is that no one on your committee, and I respect your credentials, is a behavioral scientist. We have seen this over and over and over and over and over again. And I am not just sort of pulling for my own kind -- but if these are behavioral issues, why isn't there behavioral science expertise on your committee? I am sure we could look through the ranks of the PHS committees.

In the early days the CDC convened a consensus conference on the issue of antibody testing. Behavioral scientists were invited only after the APA sat on its hind legs and screamed, "This is a behavioral issue."

There was a planning meeting on the issue of condom efficacy at the NIH. There was one behavioral scientist among 12 people. This is another institutional issue that needs to be addressed -- that behavioral science and behavior change expertise needs to be included at the highest levels and the NIH and ADAMHA -- the brain and the rest of the body if you will -- needs to learn how to talk to one another. We always have difficulty on a personal level; I guess there's no reason to believe that the government wouldn't have the same problem. But it is an absolute necessity.

Now with regard to the issue of prevention, I have already made my first recommendation to you earlier, and that is that the national priorities need to be changed. It is critical and essential to spend as much or more money on AIDS prevention and intervention research as on biomedical research.

Dr. Bowen, in an article in <u>The New York Times</u> last Sunday, indicated that it was his opinion that the spread of the epidemic, particularly among heterosexuals, was not a major issue and not a major problem. Myself and most scientists that I talk to wonder if he has data that the rest of us don't have. We simply don't know. And in the face of that lack of knowledge we must continue with prevention efforts for that reason, for the reason that I mentioned -- that this is not the only

sexually-transmitted disease that we are interested in, and because we as a nation have taken it upon ourselves as one of our fundamental values that we have concern for our international neighbors.

You know, it is ironic that one of the policies that the Administration wanted to put in was testing of immigrants for antibodies for HIV. At least in terms of reported cases of AIDS, we are the reservoir of disease.

[Applause.]

We should perhaps think about helping people not to go out with the disease, at least not to carry it into other populations. Mexico, South America, have yet to grapple with this awful problem. We know what is going on in Africa and what may happen in the South Pacific.

So I think for these reasons we need to carry on a full and complete program of prevention research.

I think there are two interesting and important indicators on the potential spread of infection among other populations. One is the system of surveillance that is now being done in several major cities with regard to testing blood for antibodies to HIV. Of course the figure in New York is about 1 in 60.

The other interesting set of data are the armed forces recruitment data, where they are looking at monthly trends in HIV antibody among individuals who are coming to the armed forces recruitment centers to seek entry into the military. There has been no change in those trends -- and this is in the CDC Report to the Domestic Policy Council. There has been no change in those trends since the beginning of that surveillance system over a period of about 18 months and that is, they continue to find that about one and a half in 1000 are infected. This is reported in the July issue of the New England Journal of Medicine.

Interestingly, in three boroughs of New York, in Essex County, New Jersey, in Washington, D.C. and San Francisco the prevalence is one in a hundred -- and that hasn't changed over time.

The male to female ratio is 1:1. The Black to white ratio is two and a half to one. I submit that we have a very serious problem here and one of the recommendations I am going to make is that the Department of Defense, because it has discovered these individuals and, as Dr. Hein said, they are given a referral number to the Departments of Health, that we conduct a very serious set of research programs on these individuals both to determine their risk factors, to determine their behavior once

they are tested for antibodies, and to help them deal with this awful information.

Given that I am such a keen advocate of prevention research, I guess the major question is, "Can we achieve the changes necessary to stop the spread of the epidemic?" It is an issue of impact effectiveness. Can we get enough people to change enough behavior over enough period of time so that in fact the spread of the infection is limited?

I am sure you have heard about the San Francisco experience, but I think the experience there is very compelling and our experience shows us that it can. There are four behavioral studies, and all of them point to the same conclusion, and that is somewhere between six and eight percent, depending on the sample, of the men in those samples continue to practice unprotected receptive anal intercourse.

Anal intercourse was a very favorite activity of the gay population. When we began our baseline studies, 50 to 70 percent of our samples were practicing that activity. This was in the very earliest days of the AIDS epidemic. This is an incredibly remarkable change and suggests that perhaps it can be done elsewhere.

I am sure, as you have heard from the San Francisco Men's Health Study, that the rate of new infection at least in that one study is less than one percent.

The other important issue with regard to this unique population -- and then we will talk about how it might be generalized to other populations -- is that these changes are being sustained over time. Believe me, having devoted my career to health behavior change, this has never happened before.

I was asked to be interviewed by a reporter from Der Spiegel and I couldn't fit him into my schedule. I said "Come on over to my house at night. I will give you a glass of wine. I'll get some German wine. We'll drink, you know, and you can interview me."

So he came in the door -- he smelled of cigarettes. And so we got into my rap and he said, "Well, how can anyone -- yes six to ten percent is remarkable -- but how can anyone engage in a behavior that is so lethal when they know the consequences?" And I said, "Well, let me tell you something. The most preventable cause of morbidity and mortality in the United States today and in Western Europe is tobacco." It is responsible for some 300,000 to 500,000 deaths annually and, as I am sure you know, is related to heart disease, all kinds of cancers, osteoporosis and even wrinkles. Even though it causes wrinkles, people still smoke.

The Surgeon General of the United States, Luther Terry, published the first Surgeon General's report on smoking and health in 1964 -- 55 percent of men smoked. How many men smoke today? Between 30-35 percent. So the changes observed in the gay population are remarkable, incredible and need to be studied.

I was once called by a reporter -- a producer rather -- from "20/20." This was a couple of years ago. She said to me, we are interested now in looking at the heterosexual angle and I am interested in asking you what kind of data that you have. I said, well, the studies I am doing -- and I should have put this in context; I am from the Centers for AIDS prevention research at the UCSF and we have several studies with many populations but at that point we were primarily studying gay and bisexual populations -- and she said, well, we are really not interested in the homosexual angle, we are interested in the heterosexual angle.

I wanted to ask her how heterosexual angles differed from homosexual angles but I decided not to. I asked her instead -- or I told her instead -- that AIDS is fundamentally a human disease and the variables that control behavior for one group of individuals probably can be looked at and thought about for their potential application to other groups of individuals.

Now what about my three specific research priorities?

The first question and the burning question I am always ask is why do high risk individuals continue to practice high risk behavior? And it is important to put this into context. We want to segregate sexual behavior and we want to segregate IV drug using behavior and somehow make them special. The fact that so many of our men change suggests that probably the variables that control many other health-related behaviors control these behaviors as well.

We have been doing in-depth studies, and why do men in our samples continue to practice high risk behaviors? We know that those who are younger have a harder time changing their behavior. We know that those who are Black have a harder time changing their behavior. We know that those who receive antibody testing under conditions of confidentiality, anonymity and with appropriate pre-test and post-test counselling are assisted in changing their behavior. We know that there are certain personal characteristics -- a feeling of personal susceptibility, a sense of efficacy -- we know that those individuals change behavior.

So the second recommendation I want to make is that the government, the NIMH needs to fund additional studies to describe the meanings and the characteristics of sexual behavior and IV drug using behavior, especially comparing those who have failed

to change with those who have changed, so that we can understand better how to intervene with these populations.

"Meaning" is a very important term and let me caution you against the use of one term and that is the term "promiscuity." We are really talking about multiple partner sex. If we go into another culture, the Maori culture of New Zealand, multiple partner sex is the norm and people are not homosexual or bisexual or heterosexual, they are sexual. They enjoy a natural reality and I think we need to be careful about our language between we need to truly understand various populations.

Now of course descriptive studies are not enough and I think at the same time that we are engaging in a program of descriptor studies, we need to engage in a concerted program of intervention studies.

From our cardiovascular prevention research studies, we know some of the elements of behavior change. We know that people need to have information. They need the information. It needs to be personally appealing. It needs to be in language they can understand.

People also need skills and this is where education generally breaks down. If you really want someone to engage in protected sex, then they need two particular kinds of skills and this is an issue we are going to have to face. This is a hot political issue. They need to know how to use the condom and they are not easy to use. And they need to be able to engage in the complicated social skills to negotiate the use of that condom and we have to be willing to teach them.

The third thing they need -- the third key element of education programs -- is specific attention to community norms, methods for shifting the norms of the community so that when one individual comes in contact with another individual they both expect that they are going to want to do whatever they want to do safely.

Therefore the third recommendation that I am making is that the NIMH in collaboration with other relevant agencies undertake controlled studies of the efficacy of community intervention programs in reducing high risk behavior. This is clearly what happened in San Francisco. It was a community based program that included strong leadership from within the gay community. It used up-to-date, state-of-the-art market research techniques to identify messages and communications channels. It used a variety of communications channels, gay and straight media, face-to-face, health professionals' education, workplace education -- whatever avenues could be used to reach the population.

It was not afraid to teach skills. It was not afraid to use specific techniques to change the norms of that community and it involved broad scale, grass roots participation.

Now the final set of studies that I want to recommend is at the National Institute of Mental Health and it needs help in having the nerve to do this: In collaboration with other relevant agencies support a coordinated set of studies aimed at programs with high risk populations or avenues of interventions. What I am suggesting is a program that has been used very successfully by the National Cancer Institute. They are not afraid of smoking despite the tobacco industry. We can't be afraid of sex despite our squeamishness. That is, this coordinated set of studies -- that they fund five to ten investigators to work on specific populations, bring them together and help them move their studies along. The populations that need special attention are still gay and bisexual, who comprise 66 percent of the cases of AIDS and 80 percent of the estimated individuals who are infected with HIV but not yet diagnosed with AIDS. That is from the CDC Report to the Domestic Policy Council.

Special emphasis needs to be given to minority gay and bisexual men -- there is one study -- one study -- from the NIMH focused on Black gay men -- that is unconscionable given their high rate of disease -- and to homosexual youth; IV drug users and their sexual partners; adolescents -- especially minority adolescents; persons presenting for treatment at sexually transmitted diseases clinics; individuals identified as positive for antibodies of HIV at the armed forces recruiting centers; ethnic minority women; and prostitutes and others in the sex industry.

I propose that programs of research be developed in each of these areas. A minimum of five to seven studies should be funded to reflect national distribution. The investigators should be encouraged to request money for at least five years and the best methods of science should be employed to plan the studies and to evaluate outcomes.

This total program is cheap, believe me. It will cost around 200 million dollars over a 7-10 year period of time. The initial start-up cost for the NIMH would include a $60-70 million allocation for FY89, some $10 million to $20 million more than they are requesting. I think it is important. I think it will address AIDS. I think it will address many other problems.

Finally, we all recognize that we are working in a delicate arena. We are not working with smoking or exercise or weight reduction where people can agree on the kinds of changes that need to occur. We are working in the area of sexuality and we all have deep feelings about that. I think we need to provide

an agenda of research and philosophical discussion where we can begin to come together on some of our deeply held value differences with regard to sexuality itself, and with regard to appropriate programs and targets for intervention. The issue is scientific. The issue has to do with the health of the nation. The issue is also moral and we need to have forum for resolving this problem.

Thank you.

[The prepared statement of Dr. Coates follows in the Appendix.]

DR. CRENSHAW: Thank you, Dr. Coates. We have a few moments for questions, not nearly enough, as usual. But I want to highlight the importance of the content and type of material that has been shared with us today.

We are looking, perhaps for the first time, at really forceful intervention and prevention techniques and it is quite different to talk about education and its importance and prevention, and to implement and to actually do something, especially for our adolescents, who are now an apparently low risk group but an ultimate target for sexually-transmitted diseases.

So I would like to begin the questions with Dr.

DR. LILLY: I will try not to be hoggish, but I have a great many questions for each of the panelists.

Dr. Carnes, I was surprised at one datum in one of your slides that suggested that three percent of some group of so-called sex addicts had developed AIDS. Given the association between sex and AIDS, I found that surprisingly low. I am also wondering, is the criterion for sexual addiction merely numerical?

For Dr. Friedman, I would like to know -- do you know of research relevant to the question of whether needle availability actually encourages in any sense whatsoever drug use?

For Dr. Hein, can education in schools adequately be effective in reducing HIV infection? Is the school sufficient to the need? For example, in New York City, where there is at least to some extent education on the subject, do you have an evaluation of that?

Dr. Coates, one thing you said quite startled me. I would have thought exactly the opposite, but again this is a subject that I know nothing about. You said that younger people

and Black people have a harder time changing their sexual behavior than older people. I would have thought it would be exactly the opposite.

And then, also for you, given the fact that there is a significant portion of the population that just doesn't want sex discussed at all, again on the theory that if you discuss it, people are going to rush out and do it -- how do we cope with that attitude?

I rest.

DR. CARNES: Can we take them in order?

DR. CRENSHAW: Go ahead, and I think we are going to have to depend on a lot of supplemental written information for this, so that all our panels can ask something.

Go ahead.

DR. CARNES: I think that makes sense. The question about the three percent -- the point that I was making about it is that that particular study, which has about 400 people in the sample -- were people who had entered recovery programs for their sexual addition five to seven, eight years ago. So the point was that even in that sample we had three percent who had AIDS, even though their sexual behavior had been modified significantly over the last five to eight years.

What I was trying to demonstrate with the slides is that how terribly at risk these people are. One of the things that we need to take a look at it are alcoholism units, our eating disorder units, to train people to help identify the people who are coming in now, so we can get a different baseline so that current statistics are available. Our hunch is that it is extremely high and I maybe didn't make that as clear as I could.

DR. LILLY: Thank you for that.

DR. CARNES: The second criteria question about what does it take to -- obviously, as it was in alcoholism, it isn't how many drinks you drink -- it is not the same issue. There is a very elaborate diagnostic framework both for outpatient, inpatient and a number of different ways of looking at it from a private practice and I would be happy to supply the committee with those kind of diagnostic criteria.

DR. LILLY: Thank you.

DR. FRIEDMAN: On whether or not needle availability encourages IV drug use, there have been no comparative area

studies, for example in looking from city to city to see about availability and IV drug use. That would be a useful thing to have happen.

On the other hand, this has its greatest policy relevance perhaps to syringe exchange proposals. On that there have been studies on the effects of the Dutch syringe exchange. They are not definitive yet, but the Buning study indicates that it leads to decreased needle sharing and that there is evidence in the Buning and in the Van de Koeke study that there is lower frequency of IV drug use among the people attending and getting syringes through the exchange than among the people who do not come to that.

Finally, the other way in which this could impact is in terms of does it decrease treatment admissions. The theory might be that if you can get sterile syringes, you are not afraid of AIDS and therefore you don't go for drug treatment.

There is no evidence of this from any of the many countries that now have needle exchange programs and the study as I mentioned before of the Amsterdam Exchange decisively show that there at least there has been no such negative impact nor any influx of new IV drug users in large numbers.

DR. HEIN: To answer your question about the curriculum, curriculum is a good first step. Schools are where most kids in this country spend their days. It is fine. However, who is teaching the curriculum and what is the content? Do teachers have the time? Do they have the sensitivity and knowledge? What about parents? They have the responsibility. Do they have the non-judgmental ways to present the information. Friends? They certainly have a powerful influence. Do they have the judgment or the knowledge? Doctors -- from the question that you submitted earlier? Doctors: There is a network of adolescent clinics to help young people in a variety of health issues. These and the school-based clinics are obviously good ways to begin.

So the answer to your question: There is nothing wrong with school curriculum. Many of them -- most of them haven't been evaluated, but why should we stop there? We should only start there. I could anticipate Dr. SerVaas's question from the previous panel on rates of sexual activity in teenagers. If we could have Slide No. 6, a quick answer to your question on rate of first intercourse among teenagers in the country.

DR. LILLY: I am not sure that we still have the capacity to show that slide, at this point --

[Slide.]

DR. HEIN: Okay, in your materials then, in the article on "AIDS in Adolescents," there's for the nation, basically showing you for rapes among White and Black adolescents, ages 15 through 19 in three different sample periods in the 1970s. The point is that the rates went up, that they are high. Eighty percent of Black females in urban areas have had intercourse by 19, 60 percent of females. The biggest increase were among the White female.

And the next slide -- what about various population of adolescents?

[Slide.]

Here we have three curves, for a detention center (New York's only through the 1970s); urban group homes; and the national survey of Sorenson. Now for all young people who have had intercourse by 19, this shows what percent at different ages, and to make the point, among the detention center population, the average age of first intercourse was 12. For the national as a whole, the average age of first intercourse for people who had had intercourse by 19, was around 16 -- 15/16.

So, yes, early intercourse among certain groups and certainly sexual practices among adolescents need to be understood and then adolescents helped with knowledge, information, and most importantly let's not leave out services.

Services: we talk about adolescents as if we could only educate them our job is done. The point is the virus is there and we have to help the people that are already infected and their partners in curbing this epidemic.

DR. COATES: So, Dr. Lilly, it looks like everybody is rushing out and doing it anyway, so I think the appropriate answer to your question is that if they are rushing out and doing it under conditions where we are afraid to talk about it, what might happen under conditions where we really can talk abut it?

I submitted to the committee with my testimony a very lovely study published -- Murray Vincent, Dr. Murray Vincent was the senior author -- published in JAMA in the summer and I think it is an excellent example of what can be accomplished. This was in South Carolina and they engaged in a two-year community intervention program analogous to the kind of program that I suggested happened in San Francisco. They were able to cut the number of teenage pregnancies by one-third of the original rate, and compare it to adjoining counties where this didn't happen. This involved a process whereby church leaders, family leaders, workplace leaders, and school leaders got together, dialogued about the appropriate objectives, equipped teachers and parents with the ability not only to talk about these things but also to

teach skills, so that people really understand how to negotiate these very complicated social interactions.

The Centers for Disease Control, as part of their education programs, have conducted extensive focus groups with adolescents. Their experience probably would fit most people's here. If we were to take a poll in this room of everyone's first experience with intercourse, I think many people would say, well, it just happened. Now that doesn't take into account the fact that we may have fantasized it for years before it "just happened," but it points to the fact that people, when they are beginning to engage in something that we as a society consider a very important activity and a very important way of relating to another individual, we fail to equip people for the ability to do that.

What that means is that we need to start much younger, both with information about sexuality but also with the social skills. People don't have to have sexual relations if they don't want them. They should have the social skills and the abilities to deal with those things. That takes education.

So I guess I would say that the data really point to quite a contrary event. I would think we could delay onset of first intercourse and that in fact may be an important event because of the STDs and the unwanted pregnancies that are associated with that.

If we were willing to bite the bullet and start educating in an appropriate way, people would have the ability to deal with it. We wouldn't say, well, gee, if we talk about driving cars, people are going to go out in the street and start driving cars, so we better not talk about it; let's just let them sort of do it when they are ready, it would be a worse disaster than it is.

Why don't we deal with this very important arena in a sensible way?

Now in terms of resolving those cultural values, I think it is going to take dialogue. These are deeply held values and I think we need to stop sort of firing volleys across the chasm of our heterogeneity and think about ways of bringing groups together to think about this is a serious way. I know of no other way or admit that in fact we are a heterogeneous values that we can tolerate.

DR. CRENSHAW: Dr. Coates, you just made a very important point that I think is usually not in focus and that is giving adults or adolescents knowledge and information without teaching them comfortable and workable social skills to

implement them with is leaving out the major step that enables them to practice what you are preaching.

I would like to ask especially Dr. Hein to send me in writing your best recommendations for how we can access and highlight attention to the adolescent and teenage population, because one of the things that I am simply committed to try to accomplish on this Commission is to reach that population as all the others while they are still low and before we are reacting like we have to all of the other disasters.

Dr. Walsh?

DR. WALSH: I do not have any questions. I am just closing with a very brief comment, and that is you all are preaching to the choir when you tell us that we need behavioral science research. We are all in favor of it. It simply provides us again with the problem of priorities, of what we are going to recommend, and I can assure you that we are going to take that into consideration.

In regard to the membership of the Commission, remember, none of us campaigned for this job. If everyone who should be on it could be on it or would be on it were on it we would have a commission as big as the Congress and then we would only talk to one another and we wouldn't come to any conclusions.

This way, at least we are able to come to all of you, all of the groups -- the high risk groups, all of the people with varied skills -- and pick your brains the best we can. And believe me, we are trying to do that job as honestly as possible so that we can give you a real fair shake with our recommendations

DR. COATES: We look forward to the concert.

[Laughter.]

DR. CRENSHAW: Mr. Creedon?

MR. CREEDON: I would like also to thank the panel members for very interesting material.

Just one question to Dr. Hein, a simple question. I got the impression you were saying the adolescents you want to target are from age 16 on. I would think it would be a lot younger than that.

DR. HEIN: No, I didn't mean to give that impression, because again with the age of first intercourse, what is it and with --

MR. CREEDON: It has to start earlier --

DR. HEIN: -- understanding of sexuality certainly preceding puberty. We are really talking about older children as the Surgeon General suggested, in the age range of about eight on up.

MR. CREEDON: Okay, I agree. Thank you.

DR. CRENSHAW: Dr. SerVaas?

DR. SERVAAS: I just had one quick question. It is: on your adolescents, it was very disturbing to me that we didn't have physicians to whom to refer these AIDS-positive adolescent children. Would you tell the children they are positive for the HIV infection and then give them a hotline number? You really don't have --

DR. HEIN: That is the current procedure for all of the military recruits in this country. Now we would hope that as a result of the commission and other caring people, that this will change. The military has to define their area of responsibility to do screening and caring for the people who are enrolled, not for the recruits. So certainly here is a very good example of the kind of quick response the commission can make to help again the rates among the military recruits and adolescents in certain parts of the country, who as Dr. Coates has said, are incredibly high.

DR. SERVAAS: And then how many adolescent cases do you have?

DR. HEIN: Well, again, it depends on how you define cases. Our first HIV positive six kids had 50 partners. Do we include them all in our cases or not? So little do we know about the rates of HIV positivity among adolescents right now that that is not a question that is easily answered.

Certainly we at the moment again have opened our doors to any high risk adolescent to an HIV positive or their partners. But very few people have the resources, time or skills to be able to encompass this kind of counselling for adolescents. There is a network there of adolescent health clinics, of doctors comfortable with adolescents but they have not been freed up as was suggested for their retraining and re-tooling to enable them to do the kind of counselling and followup that is now required.

DR. CRENSHAW: Dr. Lee, I understand you have a quickie to wrap up us with.

DR. LEE: To reassure Dr. Coates -- when we organized our study and our report, in the very beginning, one of the

places we went was to the Institute of Medicine, and we are in very heavy discussion with Dr. Roy Widdus, Dr. Heather Miller, and the ongoing behavioral modification conference that they have been holding there, and we will be privy to their report.

For Dr. Coates, a fascinating group of people very pertinent to our study, that population you have identified, and I notice your background is extremely unusual and I might ask Mr. Creedon to take note of your background because I would think it would be very helpful in doing polls and statistical evaluations of sexual behaviors in the population.

DR. CRENSHAW: I'd like to thank all of you very much for coming and speaking with us. I am sure you feel as breathless as we do in terms of the ground to be covered and the opportunity that we had. I think it is clear that we need baseline data. I think it is clear that we need behavioral research and behavioral intervention programs with evaluations that are adequate to measuring the outcome of these efforts. I hope that we will have this just as a beginning and not as a completion of dealing with the issues, of understanding them and of coming to grips with them as I think we must do.

Thank you again very much, and thank you to the earlier panel, whom I see still with us.

[Applause.]

[Whereupon, the meeting was concluded.]

APPENDIX

Opening Statement Thursday, Feb. 18, 1988

Admiral James D. Watkins (Retired)
Chairman
Presidential Commission On the HIV Epidemic

Good morning to our distinguished guests and panelists, to my fellow Commissioners, and to our audience.

Today we begin our hearings on AIDS research and drug development. Research and drug development is the last of the four areas we identified as topics to be addressed in our interim report, which we will deliver to the President in about two weeks.

Research and drug development is a complex arena with many unanswered questions. It stimulates controversy and impassioned discussion among all of us, and reflects the fear of a society confronting a fatal disease for which there is no known cure.

Last November two PWAs appeared before our Commission in Florida to talk about the need for further research and drug development. Unfortunately those two PWAs, James Sammone and Patrick Haney have since died of AIDS. I have talked with the fathers of these two young men who have, in turn, dedicated their lives to furthering AIDS research. It is on behalf of persons like James Sammone and Patrick Haney that we begin our work today.

Today we will hear the frustrations endured by those seeking drug therapies when so few drug therapies are available. We will examine the drug development process and the drug approval process. We will hear from people divided in their opinions about what our society has done and what our society should do to expedite the development and availability of drugs for persons infected with HIV.

Our witness list includes all parties involved in the drug development process: persons infected with the HIV, the basic researchers, the regulatory agency responsible for approving new drug treatments and the pharmaceutical companies. Their research efforts will benefit all of us, in terms of both prevention and treatment.

The witnesses who will speak to us represent the best and the brightest in research and drug development. They also represent the essential leadership which must be brought to bear in order to ensure a wider range of drug therapies and expedited availability of effective drugs.

Now I have the honor of handing the gavel to Dr. Frank Lilly who will chair these hearings. As a New Yorker and chairman of the Genetics Department at Albert Einstein College of Medicine, Dr. Lilly is right at home. In addition to being a New Yorker, Dr. Lilly's expertise in retroviruses uniquely qualifies him to chair this set of hearings.

TESTIMONY: PRESIDENT'S AIDS COMMISSION

FEBRUARY 18, 1988

Frank J. Rauscher, Jr., Ph.D.
Senior Vice President for Research
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90 Park Avenue
New York, New York 10016

Mr. Chairman and distinguished members of the panel. You and your task are critically important for this Nation and others as to prevention, detection, cure and rehabilitation of AIDS.

My name is Dr. Frank J. Rauscher, Jr. and I presently serve as Senior Vice President for Research, American Cancer Society. I believe you have my CV. My background, in brief is as follows: I evolved through 10 years Academia, 18 years National Cancer Institute, NIH and now 12 years American Cancer Society in the private or voluntary sector. During this time I have also advised and served on Boards of Industry, and other Institutions - here and abroad.

I have been asked by one of the most innovative and productive scientists in this country, Dr. Frank Lilly - a member of your commission to comment on the good and not so good processes of "planning" - and eventual outcome, people benefit wise.

I will do this briefly and then be most pleased to try to discuss any questions you may have. I was trained as, and am a microbiologist - specifically as a virologist, in the retroviruses that now have to do with the induction of AIDS and other diseases.

In 1964 I was appointed head of the Special Virus Leukemia Program (SVLP) which I believe was the first major new program of the National Institutes of Health that attempted to include planning as a major component of program implementation and evaluation.

At that time, during the middle of a budget year, the National Cancer Institute (NCI) received a supplemental appropriation of $10 million with a mandate from Congress to determine whether viruses were responsible for any human neoplasm and to devise means for prevention.

While that charge was not fulfilled fully until Gallo, et. al discovered the relationships of HTLV-1 and a form of adult leukemia in the early 1980's, the technology coming out of that program provided the intellectual and technical base for what is now being done with AIDS and HIV. Parenthetically, Dr. Lilly was one of the first scientists supported by that program.

In terms of planning, a small number of NCI staff together with advice from outside peer scientists, with approval and overview of the National Cancer Advisory Council attempted to do the following:

- *Access history and state of the art in viral oncology.*
- *Determine what "critical path" might be followed to attain the objective quickly and economically.*
- *Identify and solicit people and institutions to do the work.*
- *Peer review, monitor and report.*
- *Update a "rolling" 5 year plan.*

These sub-objectives were accomplised but I believe a tactical mistake was made

in that the contract rather than the investigator initiated grant mechanism of funding was chosen to support projects in this program. It conjured up the image of "big brother" telling scientists what to do, how and when. Also, the program did not have direct budgetary, staffing or reporting priority as the National Cancer Program does now. Nonetheless in retrospect I believe it was a highly successful program. This in terms of its potential and now realized impact on high incidence or traumatic diseases that people fear most, Cancer and AIDS.

In 1970-71 President, Nixon, Congressman Rogers and Senator Kennedy committed this Nation to a "Conquest of Cancer Program" with all needed funds and with special bypass budget and reporting authority to the Executive and Congress. I was appointed the first director of what came to be known as the National Cancer Program (NCP-NCI). In my tenure through 1976 we committed about $3.5 billion in the quest for improved prevention, cure and rehabilitation. I believe a relatively small sum and very well used.

At about the same time (1970) over 1000 American and International Scientists were convened to "plan" this attack. This followed the "Yarborough report" (Senator, Texas) in which a panel of experts judged that there was sufficient available knowledge and technology, which if properly and widely applied, would result in more meaningful benefit to people than then realized. I believe that was and is true.

But in his "State of the Union" message and in comments made later, the President surmized that if this Nation could hit the moon, we ought to be able to "cure" cancer. His conviction and goal were laudable but it burdened the program with overpromise and overexpectancy. We did not know then where the moon was nor how many there were.

I urge you to plan but not to make that serious mistake.

I believe that planning is important, inexpensive and could be effective. It gets people together to think and the process is impressive to the Executive and Congress. It is an invaluable tool in reporting to OMB and to the Authorization and Appropriation Committees of Congress.

I believe firmly in the issues of Relevance, Priority, Need, Who and How as regards to planning;

Relevance: The project (grant/procurement) must have a reasonable chance of helping to attain the program goal.

Priority: Issues of merit and urgency. Money and talent are finite. No Nation can do everything. Peer review is fallible but must choose the best bets now. Reevaluate every 2 years.

Need: If its already being done well don't start a new program. Duplicate by all means; different minds bring different and probably beneficial approaches to a common goal. I do not think that overduplication (waste?) is a problem.

Who: Get the best regarding track record and promise. Motivate, twist arms; whatever.

How: For the most part review, fund and monitor investigator-initiated grants. Secondly, (this can be tricky) solicit people and institutions to do work (research, reagent production, etc.) agreed upon as top priority by staff and outside peer review.

Mr. Chairman this concludes my written statement. I thank you for this opportunity and will be pleased to try to answer questions and to submit additional information for the record.

THE FEDERAL ROLE IN AIDS RESEARCH: NIH

Anthony S. Fauci, M.D.

Director, National Institute of Allergy and Infectious Diseases
Coordinator of NIH AIDS Research

Summary of Testimony to the
President's Commission on the Human Immunodeficiency Virus Epidemic
February 18, 1988

The National Institutes of Health (NIH) is a prominent partner in a coordinated national effort to discover and evaluate promising approaches to the understanding, treatment, and prevention of human immunodeficiency virus (HIV) infection. Rapid progress has been made thus far, due in large part to the extraordinary basic science research foundation developed over many decades. The recognition of AIDS as a distinct entity, created the need for intensive scientific study directed specifically at this new disease. The current NIH budget reflects this surge in AIDS research, and at the present time, virtually all of the NIH Institutes and Divisions are involved to a greater or lesser degree in AIDS research. Several important mechanisms have been established to provide coordination for NIH-wide AIDS research activities, as well as with other Agencies of the Department of Health and Human Services (DHHS) Agencies, Federal Agencies and International Organizations involved in efforts to combat AIDS.

FUNDING

Over the roughly eight year period since the identification of AIDS, federal funding for AIDS has grown dramatically to meet this enormous challenge. The estimated total Public Health Service (PHS) AIDS budget for Fiscal Year 1988 is roughly $951 million. Of the five Agencies that comprise the PHS, the NIH AIDS budget represents by far, the largest percentage of the PHS AIDS budget. During Fiscal Year 1988, NIH spending on AIDS research is expected to reach almost $468 million. The budget has grown steeply since the less than $3.5 million spending figure noted in 1982. At present, the NIH AIDS budget represents approximately 7 percent of the total NIH budget obligations. Not suprisingly, there is considerable range in the AIDS budgets of the different NIH Institutes, based upon the nature and scope of their AIDS activities. For example, The National Institutes of Allergy and Infectious Disease (NIAID) is a major component in the NIH AIDS effort, with an estimated budget of $223 million for Fiscal Year 1988 which represents roughly 35% of the NIAID's total budget obligations.

NIH AIDS funding can be broken down by funding mechanism. This year, roughly 87% of the budget will support extramural programs, which includes research project grants, research centers, research training, R & D contracts and research management and support. The remaining proportion

(13%) will be used to support NIH intramural activities.

It may also be helpful to look at NIH AIDS funding by functional categories, which correspond roughly to the areas of scientific endeavor to be discussed below. Anticipated NIH AIDS funding by category for Fiscal Year 1988 include: (1) pathogenesis and clinical manifestations, $140 million ($99.6 million in FY 1987); (2) therapeutics research, $162.5 million ($122 million in FY 1987); (3) vaccine development and evaluation, almost $53.4 million ($26 million in FY 1987); (4) public health control measures, $17.5 million ($12.7 million in FY 1987); (5) patient care and public health needs, $2.4 million ($232,000 in FY 1987); multidisciplinary AIDS research, $4.7 million (2.6 million in FY 1987).

NIH AIDS RESEARCH EFFORTS

The NIH is responsible for funding and carrying out basic and clinical research on the acquired immune deficiency syndrome (AIDS). The NIH AIDS research efforts can be divided into five major scientific categories: 1) epidemiology and natural history; 2) the etiologic agent; 3) pathogenesis; 4) the development and testing of anti-retroviral therapies and immunologic reconstitution; and 5) vaccine development and evaluation. Significant advances have been made in each of these categories, often at a pace unprecedented in the history of biomedical science.

Epidemiology and Natural History

A substantial body of knowledge now exists about the epidemiology and natural history of the disease. However, since the disease was only first recognized in 1981, much remains to be learned about specific features of HIV infection and the course of infection over the long term. While the major responsibility for surveillance and epidemiologic studies rests with the Centers for Disease Control (CDC), the NIH has many important efforts in this area. The NIH has performed and continues to perform research complimentary to that of the CDC in utilizing cohorts of prospectively followed AIDS patients and healthy individuals practicing high risk behavior as sources for basic and clinical research studies. NIH is conducting a number of epidemiologic studies to examine the natural history of AIDS, the biologic characteristics of the virus and the host response to HIV infection. These studies include the prospective Multicenter AIDS Cohort Study (MACS), begun in 1983, involving approximately 5,000 homosexual men in four cities in the United States, as well as studies in Africa and the Caribbean basin to define viral and host factors of HIV infection in those regions. Other research investigations underway include the study of heterosexual transmission in specific populations, and the study of women and children at high risk for developing AIDS, including prostitutes, pregnant women and children of women with HIV infection. Ongoing surveillance studies of NIH employees working with AIDS patients or HIV specimens confirm the low risk of transmission in these groups.

The Etiologic Agent and Pathogenesis

In a remarkably short period following the recognition of AIDS, NIH-supported research led to the discovery and identification of HIV as the etiologic agent. Since that time, the virus has been isolated and cloned; its genes have been identified, fully sequenced and thier functions delineated. Insights into the pathogenesis of the disease (how the virus destroys the body's defenses) have occurred at a dramatic pace, although the precise mechanisms remain to be determined. We can anticipate major advances in this area in the near future. This research is ongoing at the NIH and at many NIH-supported research sites.

Drug Development and Testing

A major NIH effort has been directed toward the discovery and development of anti-HIV drugs. The NIH is pursuing two basic approaches: (1) the screening of large numbers of existing compounds for activity against HIV, (2) targeted drug development using information gained about unique properties and critical functions of the virus to design agents that interfere with the life cycle or with structural components of the virus.

Rapid advances are being made in both these areas. New approaches to screening, both in the test tube and in animals bearing human host cells infected with HIV, are being actively explored. Azidothymidine (AZT), the first and, at present, only drug licensed for use in AIDS was discovered through in vitro screening. NIH recently initiated the National Cooperative Drug Discovery Groups (NCDDGs), which represent an innovative, coordinated effort to utilize top scientists and the capabilities of universities, pharmaceutical companies, research institutes and other organizations, in collaboration with the federal government, to discover and develop potential new AIDS therapies through the stage of preclinical testing. Begun in 1986, 18 NCDDG's are now established at research centers across the country. Projects include: targeting of drugs to infected cells; studies of physiochemical effects of drugs on cell structures; the development of immunotherapies; studies of the antiviral effects of natural products and synthetic compounds; studies of the biophysical properties of HIV and cell proteins; the development of animal models for AIDS; and new biochemical prescreening assays. In addition, NIH recently awarded six program project grants to facilitate the organization of multidisciplinary research groups to study the structural and biophysical properties of HIV and related viruse. The NIH intramural program has also developed a targeted antiviral effort utilizing a structural biology approach. The purpose of such efforts is to develop drugs specifically targeted to virus based upon knowledge of its structure.

The NIH has undertaken an enormous effort to evaluate potentially effective therapies for persons with AIDS. An important early achievement occured when NIH scientists, in collaboration with the Burroughs Wellcome company, established that the drug AZT had anti-retroviral properties and is effective in prolonging life in patients. AZT is currently being studied alone and in combination with other agents in a variety of categories of HIV infection. However, it is not a cure and is not without significant toxicity. NIH is committed to the discovery of a less toxic and hopefully curative agent for persons with HIV infection.

In order to rapidly and carefully investigate potential therapies, NIH has established an extensive clinical trials network in which studies are underway to determine the safety and efficacy of antiretroviral and immunomodulatory treatment approaches in persons infected with HIV, as well as specific therapies (including prophylaxis) for the opportunistic infections and malignancies associated with HIV infection. Clinical trials of promising agents/therapeutic approaches are being conducted both in the intramural programs of the NIH and at academic institutions participating in the AIDS Clinical Trial Group program (ACTG). Overall goals are: (1) to ensure that high priority investigations are undertaken by quality researchers using rigorous scientific standards and structured protocols; (2) to develop new agents from preclinical studies to final FDA approval; and (3) to provide timely information to guide physicians in selecting appropriate treatment.

The ACTG program represents a major clinical initiative in the evaluation of experimental treatments for HIV infected individuals. This effort began several years ago with the establishment of 19 AIDS Treatment and Evaluation Units (ATEUs) at medical centers throughout the country, funded through NIH contracts to undertake clinical investigations of a number of therapeutic agents.To complement that effort, the NIH then developed the Clinical Studies Groups (CSGs), establishing 17 additional clinical investigation sites located in areas of both high and low endemicity for infection. These sites of clinical investigation (i.e. the ATEU's and CSG's) have been coordinated into a unifying, cooperative group structure, the ACTG program.

As of early February, 1988, accomplishments of the ACTG Program include:

- o 26 active protocols (4 completed with regard to patient accession; 22 still accessing patients). Approximately 15 additional protocols are in final stages of review or approval.
- o 18 agents under study:
  - <u>Anti-HIV Therapies</u> (alone or in combination, include AZT, ddC, acyclovir, AL-721, Foscarnet, Desiclovir, Interferon-alpha, Interferon-gamma, IL-2, Tumor necrosis factor)
  - <u>Biological Response Modifiers</u> (Interferon-alpha, Interferon-gamma, IL-2, Tumor necrosis factor)
  - <u>Therapies for Opportunistic Infections</u> (Aerosol pentamidine, DHPG, Trimetrexate, Amphotericin B, Fluconazole, Trimethoprim-sulfamethoxazole)
  - <u>Therapies for AIDS-associated Malignancies</u> (Radiotherapy, Doxirubicin)
- o Soon to be tested (Ampligen, Ribavirin)
- o To date, over 3,000 patients have been entered into studies.

Clinical trials of promising therapeutic agents are also ongoing in the intramural programs at NIH. In addition, the NIH intramural program has recently undertaken a very unique study of identical twin bone marrow transplantation and syngeneic lymphocyte transfusion in HIV infection. Such immunological reconstitution is still in the highly experimental stage. However, this approach in combination with specific anti-retroviral therapy provides the potential for a two-pronged attack aimed at suppressing virus

replication at the same time that damaged or destroyed immune function is rebuilt.

Vaccine Development and Testing

The development of a vaccine against HIV infection has assumed a prominent position in the strategies for prevention and control of AIDS, yet remains one of the greatest challenges in combatting the epidemic. NIH has mounted a major effort in the search for an AIDS vaccine based on a sound scientific approach. The recently proposed NIH Plan for AIDS Vaccine Development and Evaluation represents a comprehensive plan outlining coordinated efforts and active participation by government, industry and academia to foster the expedited development and testing of AIDS vaccines. The plan includes basic research, preclinical development and clinical testing.

Difficulties in the development of a safe and effective vaccine against HIV include the complexity of the viral organism, the antigenic variations of isolates, the lack of a clearcut delineation of protective immunity, and the paucity of suitable animal models. Vaccine testing and evaluation is a stepwise process that must be carefully designed to ensure that vaccines are safe and elicit an immune response (immunogenicity). After safety and immunogenicity are demonstrated in laboratory and animal tests, the vaccines are clinically evaluated in humans.

In early 1988, the NIH will begin funding several National Cooperative Vaccine Development Groups (NCVDGs) to foster collaboration among academia, industry and governemnt and facilitate the development of an AIDS vaccine. These multi-institutional, multi-disciplinary consortia will consist of experienced investigators with a range of skills needed to explore the various experimental approaches to AIDS vaccine development. Research conducted by the NCVDGs will include basic studies, developmental studies, scale-up and production, evaluation in laboratory animals and appropriate clinical trials.

The NIH is also expanding its capacity to test candidate vaccines in existing Vaccine Evaluation Units, funded by NIH and located at six medical research centers nationwide. These have been supplemented to prepare for AIDS vaccine testing and will serve as a national resource for the early evaluation of candidate AIDS vaccines in clinical trials (phase I and II testing). Future plans include further expansion and establishment of additional Units to meet the anticipated needs for AIDS vaccine trials.

In October 1987, NIH began the first FDA approved Phase 1 clinical trial of a candidate AIDS vaccine at the NIH Clinical Center. This study is expected to involve 81 healthy volunteers. Companion trials have now been approved to begin at the NIH funded Vaccine Evaluation Units, where a total of 72 volunteers will be studied. These trials represent an important first step among many necessary to determine whether this or another vaccine will be safe and effective enough for general use. NIH is prepared to be flexible and respond rapidly in the event that new and promising information on potential vaccine candidates becomes available.

COORDINATION

In order to further strengthen AIDS research, NIH has instituted a number of mechanisms to improve coordination, both throughout NIH and with the broader research community. Areas of coordination include: (1) NIH Interagency coordination, (2) Advisory groups, (3) Intramural scientific coordination, (4) International coordination and (5) Industry/Academic coordination.

NIH AIDS Coordination

In order to ensure coordination of NIH-wide AIDS research activities, several steps have been taken. The position of NIH AIDS Coordinator was created in 1986. I am presently serving in that capacity, in addition to my role as NIAID Director. An NIH AIDS Executive Committee has been established to provide guidance and direction for NIH-wide scientific, planning and resource allocation decision-making and facilitate effective coordination of efforts. The membership of the committee, co-chaired by the Director of NIH (Dr. Wyngaarden) and the NIH AIDS Coordinator (Dr. Fauci, Director of NIAID), is comprised of the Directors of those Institutes which are currently involved in AIDS research, as well as principal staff from the Office of the Director, NIH. The Committee also links the activities of NIH with other components of the Public Health Service (PHS) through the PHS Executive Task Force on AIDS.

To further enhance NIH research activities, Secretary of Health and Human Services, Dr. Otis Bowen recently established the AIDS Program Advisory Committee, consisting of the Director of NIH as chair, and thirteen members selected by the Secretary including nine individuals knowledgeable in the basic science, biomedical and clinical care fields underlying advances in AIDS research, as well as four representatives of the general public. The purpose of the Committee, which is to have its initial meeting at NIH on February 26, 1988, is to advise the NIH on all aspects of AIDS research, identifying opportunities for further research and recommending initiatives that should be undertaken to advance knowledge in the diagnosis, prevention, and treatment of AIDS.

In addition, multiple other advisory groups exist to provide coordination in areas relevant to NIH based or funded AIDS research. These include: (1) Institute councils (NIAID and NCI have established specific AIDS subcommittees), (2) Technical review committees, (3) Ad hoc advisory groups on specific issues/topics, and (4) the Institute of Medicine.

NIH intramural research activities are coordinated with guidance from a number of sources, importantly the NIH AIDS Executive, as well as such groups and activities as the NIH Scientific Vaccine Development Committee, Intramural Targeted Antiviral Development Program, DCT Decision Network Committee, AIDS Clinical Drug Development Committee, and the NIH Bimonthly AIDS Science Report.

The NIH has an active interest in close coordination with the

international health research community in the global effort to combat AIDS. At the present time, the NIH has collaborative activities with the World Health organization (WHO), the Pan American Health Organization (PAHO), the Carribean Epidemiology Center (CAREC), International Collaboration in AIDS Research (ICAR) and the Fogarty International Center.

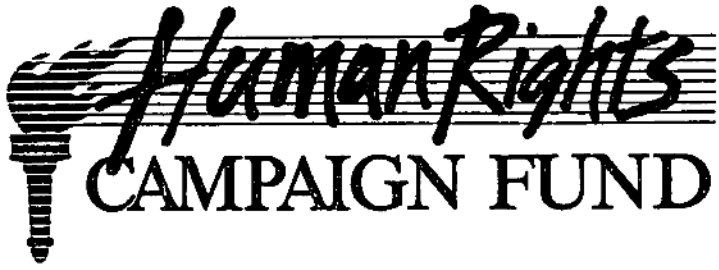
The NIH has also stimulated a number of innovative programs to foster industry and academic collaboration, in close coordination with the federal government. A number of these projects were described earlier in the discussion of drug and vaccine development and evaluation. Importantly they include the National Cooperative Drug Discovery Groups (NCDDGs), the AIDS Clinical Treatment Groups (ACTGs), The National Cooperative Vaccine Development Groups (NCVDGs), the Vaccine Evaluation Units. and individual collaborative agreements with industry.

Government-Wide AIDS Coordination

The NIH represents one of five agencies comprising the U.S. Public Health Service, Department of Health and Human Services. The other PHS Agencies include the Centers for Disease Control (CDC), Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), the Food and Drug Administration (FDA), and the Health Resources and Services Administration (HRSA). The Public Health service has placed the fight against AIDS at the very top ot its public health priority agenda. Coordination of AIDS activities within the PHS and throughout the federal governement is a major concern. I will now briefly describe some of the mechanisms in place to strengthen coordination at this level.

The PHS Executive Task Force on AIDS was established in May 1984, and serves as a major coordinating and focal point for all PHS and DHHS AIDS activities. The mission of the group is to advise the Assistant Secretary for Health on AIDS related issues, to coordinate AIDS activities among PHS Agencies, provide a forum for achieving concensus on AIDS issues, develop operating strategies for PHS AIDS activities and provide a conduit for AIDS information sharing among members. The Task Force is chaired by the Assiastant Secretary for Health, Dr. Robert E. Windom and co-chaired by the PHS AIDS Coordinator, Dr, Peter Fischinger. Members of the Task Force include Agency Heads and represenatatives of the PHS Agencies and the Office of the Assistant Secreatry for Health (OASH).

To facilitate improved communication and collaboration throughout the Federal Government, the Public Health Service established a Federal Coordinating Committee on AIDS Information, Education and Risk Reduction. First convened in December 1986, the Committee is composed of seven Federal Departments (USDA, DOD, DOED, HUD, DOJ, DOL and DOS), six independent agencies (Action, AID, EPA, OPM, USIA, and VA), and three offices within the Executive Office of the President (The Domestic Policy Council, the Office of Management and Budget, and the Office of Science and Technology Policy). The Departments and Agencies all have constituencies, networks, and issues that make them crucial in coordination of government-wide AIDS efforts. From a broad perspective, the committee is responsible for identifying government-wide issues, information/research/resource needs and gaps, and appropriate goals in the effort to combat AIDS.



Statement

Of

Vic Basile, Executive Director

Human Rights Campaign Fund

Before The

President's Commission On The HIV Epidemic

February 18, 1988

New York City, New York

1012 14th Street, N.W. Suite 607 Washington, D.C. 20005 202/628-4160

Mr. Chairman and members of the Commission:

My name is Vic Basile and I am the Executive Director of the Human Rights Campaign Fund, which lobbies in Washington on behalf of the nation's gay and lesbian community. I want to thank the Commission for this opportunity to present our views on the federal AIDS research effort, and some suggestions for improving the management of that effort.

There must be an urgent response to this crisis from the federal government, and from every sector of society. The importance of prevention is obvious, given the present lack of effective treatment for HIV infection. Tragically, prevention has become very controversial as common-sense measures have come under ideological attack from the uninformed and the uncaring.

The necessity for medical research should be equally obvious, as experts predict that 1 1/2 million or more Americans may already be infected and more are being infected each day. Research in the natural history of the infection yields increasingly frightening results, with many knowledgeable people now predicting that most, if not all, of those infected will become seriously ill and die prematurely unless effective treatments are developed.

In the next two days you will hear from other witnesses who will inform you of the widespread use of alternative therapies for AIDS, ARC, and HIV infection. I have here models of two medicine cabinets. One is full of bottles, to represent the myriad drugs under investigation as therapies in HIV infection,

which have not been licensed by the FDA. Many of them are in widespread use in the community.

In the other is one bottle, representing AZT, the one drug licensed by the FDA for treatment of HIV infection. This single drug still represents the great majority of the AIDS clinical trial work being performed by the NIH. The space between, you could say, represents the tragic chasm between hope and reality for 1 1/2 million Americans infected with HIV.

I speak as one who, like most gay men and lesbians, counted as friends many of the 30,000 Americans who have already died from AIDS. I have attended funerals just in the last month for two friends: Jim Kamel and Dan Bradley, former president of the Legal Services Corporation. It was painful to lose them, as it was painful to lose many friends before them--more now than I care to count. But that pain is magnified many times as I look around me at so many other friends who are living and struggling each day with AIDS, ARC, and HIV infection. If there is not rapid progress in medical treatment, we will lose them and so many others.

To add urgency to this need, there are many promising signs that an intensive effort will yield solutions in the near future. Nobel laureate Dr. David Baltimore, speaking to the National Academy of Sciences in September, said that developing therapies for HIV infection is a relatively simple scientific problem--compared, say, to cancer. He stated that the "research menu," while enormous, "is well defined and lends itself to directed

management." Similarly, Dr. William Haseltine of Harvard Medical School said in December that he is "convinced we can prevent and treat this disease. It's a question of applying, in a systematic way, the knowledge and the opportunities that we have."

Dr. Baltimore's remarks are included with our written statement. I will submit to the Commission copies of our compendium, MEDPAC, which is a compilation of both scientific and lay reporting on AIDS research. This compilation reveals that progress in AIDS research has been rapid and--most importantly--that there are numerous promising candidates on the horizon to treat HIV infection or its most serious consequences. The only issue is how quickly can promising candidates be transformed into therapies available to infected people and their physicians?

In his remarks to the NAS, Dr. Baltimore went on to say [emphasis added]:

> We all know that science and testing take time. . . . Therefore, our only response to a concerned public is that we are doing everyting we can as fast as we can. To make that argument, we ought to be able to say that <u>we are working at crash program speed with an integrated and comprehensive plan</u>. Can we say that today?

I'm afraid we can't. Granted, we have made progress; a few years ago most of the nation felt it could ignore this disease as somebody else's problem, and federal funding of research efforts was woefully inadequate. Today serious money is at last being

devoted to AIDS, and the entire federal establishment appears to recognize the need for increasing the effort. What is still missing, though, is a sense of urgency that permeates the federal establishment--beyond the laboratories where AIDS research is actually conducted--a recognition that we are in the midst of a crisis.

We believe that the political establishment, and this Commission, can be most useful in improving the management of federal research efforts, so that increased resources can be translated as quickly and efficiently as possible into greater scientific effort.

A model for such efforts is the Accelerated Solicitation-to-Award Process, or ASAP, plan that has been prepared recently by NIH. This plan provides for the review of grant applications within 6 months of submission. It requires new "fast-track" procedures whereby some steps in the process are taken concurrently rather than serially, and other steps are eliminated or abbreviated. This requires additional resources in some areas--particularly certain support staff--and it also requires the cooperation of other government agencies and the private sector.

This type of plan needs to be developed on a coordinated basis in all the federal agencies involved in any way with AIDS research. As a first step, the Executive Branch should establish an Interagency Task Force to audit all federal agencies involved in the research effort (NIH, FDA, OMB, OPM, GSA, etc.), identify

impediments to the efficient and effective expenditure of funds previously appropriated, and document future needs for consideration by the Executive Branch and the Congress.

There is also an immediate need for greater resources, particularly space and personnel. Medical researchers are demanding more nurses, technicians, and analysts in order to proceed with desired scientific research. Because of outmoded pay scales, senior NIH scientists are leaving the institution. There is a shortage of adequate facilities for medical research: laboratories, extramural research centers, and office space. The Commission should recommend several steps to correct these problems.

Federal personnel policies must be revised to attract and retain senior scientists, nurses, technicians, analysts and other scientific and medical professionals in numbers necessary to meet present and projected needs. Institutions involved in AIDS research should be exempt from personnel ceilings. It is not adequate to exempt AIDS research from personnel ceilings if the net effect is to require other functions to absorb cuts without corresponding diminution in responsibilities.

The Executive Branch should conduct an inventory of facilities and develop a plan to meet those needs, including proper and suitably located laboratory space, biocontainment facilities, office space, hospital beds, and out-patient space as well as instruments and equipment.

The largest gap in the national AIDS effort may be the lack

of collaboration with private industry. Several mechanisms for closing that gap can be found in the Stevenson-Wydler Federal Technology Transfer Act, which can facilitate consortium arrangements between private industry and federal research institutions. The NIH and its member institutes have just begun to use this law to develop and take advantage cooperative agreements with industry, and has not yet promulgated implementing regulations. All affected agencies should explore the potential use of this law in AIDS research.

The federal research effort must learn from community-based networks for alternative AIDS therapy. The planning of federal drug-development research must include the active participation of knowledgeable representatives of HIV-infected people and their health-care providers. They can provide essential information about the medical needs of the affected people, the impact of trial design on them, and measures they are taking that will make different trial designs more or less useful. The same mechanisms can then be used to disseminate the results of research rapidly to them.

We cannot ignore the international dimensions of this pandemic. The U.S. must assume a more prominent role internationally in marshalling our enormous scientific resources to assist in the global fight against AIDS. Through vigorous participation in the efforts of the World Health Organization, the U.S. can work to ensure that the research and development of new drugs, and in the future a vaccine, is carried out with as

much cooperation as possible. Other populations in the world are experiencing AIDS as an epidemic that is different from and perhaps represents the future of our own. Our scientific community needs to learn from these various medical experiences in order to be more full certain of the results discovered in the United States.

Legislation responsive to the needs of effective research management should be passed by the Congress or, where possible, implemented by Executive Order. Congress has taken three small but significant steps to expedite research objectives. In the FY 1988 Continuing Resolution, Congress directed NIH to process grant and contract applications within six months of submission, as the NIH has prepared to do in its ASAP plan; it required OPM and GSA to respond to resource requests for AIDS research within 21 days; and it directed the expansion of clinical trials for promising, experimental drugs.

Legislation is currently pending in both houses of Congress that addresses these concerns in a comprehensive fashion. These bills--S. 1220 and H.R. 3825--would require the expeditious approval of research contacts, prompt responses to priority requests for allocations of funds, services and personnel, expansion of clinical trials, greater collaboration by government and industry, increased international efforts, and bringing on-line needed research facilities. H.R. 3825 would also create mechanisms to encourage community-based research initiatives, and to incorporate their successes into the federal structure. These

bills should be passed and signed into law as soon as possible.

It is important to note, however, that all of these measures can be implemented through administrative actions. We do not need to wait for Congress. We do not need to wait for a resolution of the controvery around testing, discrimination, or education.

All that is lacking is the will to act, and to act now. The Human Rights Campaign Fund urges this Commission to call on the President to implement the measures we have described. Such action by our highest public servant would command instant attention and support. This Commission can present this critical opportunity to the President. We can together embark on this course today.

Thank you.

AIDS Products In Development

Anti-virals

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
AL-721 *(AL-721)*	Ethigen (Los Angeles, CA)	ARC, PGL	IND approved Phase II
Betaseron *(interferon beta)*	Triton Biosciences (Shell Oil) (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC	IND approved Phase I/II
Cytovene *(ganciclovir)*	Syntex (Palo Alto, CA)	CMV	NDA Pending (Orphan Drug)
DDC *(dideoxycytidine)*	Hoffmann-La Roche (Nutley, NJ)	AIDS, ARC	IND approved Phase I/II
(dextran sulfate; UA001)	Ueno Fine Chem. Industry (Osaka, Japan)	AIDS, ARC	IND approved Phase I
Foscarnet *(trisodium phosphonoformate)*	Astra Clinical Research (Hopkinton, MA)	HIV infection, CMV retinitis	IND approved Phase I/II
HPA-23	Rhone-Poulenc Sante (Monmouth Junction, NJ)	HIV infection	IND approved Phase I
Ornidyl *(eflornithine)*	Merrell Dow (Cincinnati, OH)	PCP	NDA pending (Orphan Drug)
Peptide T *(octapeptide sequence)*	Peninsula Labs (Belmont, CA)	AIDS	IND approved Phase I
Reticulose *(nucleophosphoprotein)*	Advanced Viral Research (Miami, FL)	AIDS, ARC	IND submitted
Retrovir *(zidovudine; AZT)*	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv. ARC	NDA approved
		pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV, neurological involvement, in combination w/other therapies	IND approved Phase I/II
Rifabutin *(ansamycin LM 427)*	Adria Labs (Dublin, OH)	ARC	IND approved Phase II
(trimetrexate)	Warner-Lambert (Morris Plains, NJ)	PCP	IND approved Phase III
Virazole *(ribavirin)*	Viratek/ICN (Costa Mesa, CA)	AIDS, Kaposi's sarcoma, ARC	IND approved Phase II/III
Wellferon *(alpha interferon)*	Burroughs Wellcome (Rsch. Triangle Park, NC)	Kaposi's sarcoma, HIV, in combination w/Retrovir	IND approved Phase I
Zovirax *(acyclovir)*	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, ARC, in combination w/Retrovir	IND approved Phase I

Immuno-modulators

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
ABPP *(bropirimine)*	Upjohn (Kalamazoo, MI)	Advanced AIDS, Kaposi's sarcoma	IND approved Phase II/III
AS-101	Scientific Testing (National Patent Development, Bar Ilan University, Israel) (New York, NY)	AIDS	IND approved
Ampligen *(mismatched RNA)*	DuPont (Wilmington, DE) HEM Research (Rockville, MD)	ARC, PGL	IND approved Phase III
(anti-human alpha interferon antibody)	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC	IND approved Phase I
Carrisyn *(acemannan)*	Carrington Labs (Irving, TX)	ARC	IND submitted
Colony Stimulating Factor *(GM-CSF)*	Sandoz (East Hanover, NJ) Genetics Institute (Cambridge, MA)	AIDS, Kaposi's sarcoma, ARC, HIV	IND approved Phase I

Provided as a Public Service by the Pharmaceutical Manufacturers Association

Immuno-modulators

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
CL246, 738 *(CL246, 738)*	American Cyanamid (Pearl River, NY)	AIDS	IND approved Phase I/II
(gamma interferon)	Genentech (S. San Francisco, CA)	ARC, in combination w/TNF (tumor necrosis factor)	IND approved clinical trials
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL	IND approved Phase III
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL	IND approved Phase II
Imuthiol *(diethyl dithio carbamate)*	Merieux Institute (Miami, FL)	AIDS, ARC	IND approved Phase II/III
IL-2 *(interleukin-2)*	Cetus (Emeryville, CA)	AIDS, Kaposi's sarcoma	IND approved Phase II
IL-2 *(interleukin-2)*	Hoffmann-La Roche (Nutley, NJ) Immunex (Seattle, WA)	Kaposi's sarcoma	IND approved Phase III
INTRON-A *(interferon alpha)*	Schering-Plough (Madison, NJ)	Kaposi's sarcoma	NDA filed
Isoprinosine *(inosine pranobex)*	Newport Pharmaceuticals (Newport Beach, CA)	ARC, PGL, HIV seropositive asymptomatic patients	IND approved Phase III
(methionine -enkephalin)	TNI Pharmaceuticals (Chicago, IL)	AIDS, ARC	Investigator's IND approved Phase I/II
MTP-PE *(muramyl-tripeptide)*	Ciba-Geigy (Summit, NJ)	Kaposi's sarcoma	IND approved Phase I
Thymopentin (TP-5) *(thymic compound)*	Ortho Pharmaceuticals (Raritan, NJ)	HIV infection	IND approved Phase I/II
Roferon-A *(interferon alpha)*	Hoffmann-LaRoche (Nutley, NJ)	Kaposi's sarcoma	NDA filed
(recombinant erythropoietin)	Ortho Pharmaceuticals (Raritan, NJ)	severe anemia assoc w/AIDS and AZT therapy	IND approved Phase II
Trexan *(naltrexone)*	DuPont (Wilmington, DE)	AIDS, ARC	early Phase II
TNF *(tumor necrosis factor)*	Genentech (S. San Francisco, CA)	ARC, in combination w/gamma interferon	IND approved clinical trials

--DRAFT--

TESTIMONY OF WILLIAM A. HASELTINE, PH.D.

TO THE PRESIDENT'S COMMISSION ON AIDS

FEBRUARY 18, 1988

GOOD AFTERNOON.

THE TOPIC THAT I SHALL ADDRESS TODAY IS THE PROSPECT FOR THE MEDICAL CONTROL OF THE AIDS EPIDEMIC. THE THREE TOOLS MEDICAL SCIENCE CAN PROVIDE IN THE BATTLE TO CONTROL THE AIDS EPIDEMIC ARE:

DIAGNOSIS - THE ABILITY TO DETECT THOSE INFECTED WITH THE AIDS VIRUS.

TREATMENT - THE ABILITY TO PROVIDE MEDICAL CARE FOR THOSE INFECTED.

PROPHYLAXIS - THE ABILITY TO PREVENT THE INFECTION UPON EXPOSURE TO THE AIDS VIRUS.

THE PROSPECTS FOR DEVELOPMENT OF THESE THREE FUNDAMENTAL TOOLS FOR CONTROL OF THE AIDS EPIDEMIC ARE BRIGHT. THEY ARE WITHIN OUR CURRENT TECHNICAL ABILITY - NOT NECESSARILY IN THE PRECISE FORM WE MAY WISH, BUT AVAILABLE NONETHELESS.

DIAGNOSIS

THE DISCOVERY OF THE ETIOLOGIC AGENT OF AIDS, A RETROVIRUS KNOWN NOW AS HIV, BROUGHT WITH IT THE ABILITY TO DIAGNOSE MOST INFECTIONS. DIAGNOSIS CAN BE RAPID AND ACCURATE. THE INTRODUCTION OF NEW, SIMPLE, RAPID AND EVEN MORE ACCURATE TESTS ARE ONLY MONTHS AWAY. SOON IT SHOULD BE POSSIBLE TO MAKE A PRELIMINARY DIAGNOSIS OF INFECTION WITHIN MINUTES AND A DEFINITIVE DIAGNOSIS OF INFECTION WITHIN HOURS.

ONE OF THE MOST SURPRISING AND UNNECESSARY ASPECTS OF OUR APPRECIATION OF THE SCOPE OF THE AIDS EPIDEMIC IN THE UNITED STATES HAS BEEN OF ABSENCE OF SYSTEMATIC-CROSS-SECTIONAL SURVEY DATA OF THE POPULATION. FOR THE PAST FOUR YEARS, IT HAS BEEN POSSIBLE TO GAUGE ACCURATELY THE EXTENT OF AIDS VIRUS INFECTION IN THE POPULATION VIA ANONYMOUS CROSS-SECTIONAL TESTING. WITHOUT SUCH INFORMATION, THE EXTENT OF THE PROBLEM IN DIFFERENT POPULATIONS IS CONJECTURE, THE RATE OF SPREAD OF THE DISEASE WITHIN AND BETWEEN POPULATION GROUPS IS UNKNOWN, AND THE EFFECT OF EDUCATION CONTROL PROGRAMS IS UNMEASURED. WE HAVE BEEN, AND TO A LARGE EXTENT STILL ARE, FLYING BLIND WITH RESPECT TO OUR KNOWLEDGE OF THE ~~DIAGNOSIS~~ DYNAMICS OF THE AIDS EPIDEMIC. WE SHOULD BROOK NO DELAY NOR ACCEPT ANY EXCUSE FOR THIS DEPLORABLE LACK OF KNOWLEDGE.

THERAPY

TREATMENT OF THOSE INFECTED WITH THE AIDS VIRUS CAN BE DIVIDED INTO THREE CATEGORIES.

- TREATMENT OF THOSE WITH ADVANCED ILLNESS, THOSE WITH SEVERE DAMAGE OF THE IMMUNE OR CENTRAL NERVOUS SYSTEM FUNCTION.
- TREATMENT OF THOSE WITH DETECTABLE, BUT MILDER IMMUNE OR ~~CONTROL~~ CENTRAL NERVOUS SYSTEM ABNORMALITIES.
- TREATMENT OF THE INFECTED (HIV-SEROPOSITIVE) PEOPLE WHO HAVE NO SERIOUS SYMPTOMS OF INFECTION.

TOWARD CURATIVE THERAPY

UNTIL RECENTLY ATTENTION HAS BEEN FOCUSED UPON TREATMENT OF THOSE WITH SERIOUS DISEASE. PROGRESS IN EXTENDING THE LIFE EXPECTANCY OF SOME PEOPLE HAS BEEN MADE. SUCH PROGRESS IS ALL THE MORE REMARKABLE AS IT IS LIKELY THAT THE ~~PATIENT~~ PERSON WITH SERIOUS DISEASE WILL ULTIMATELY PROVE TO BE THE MOST DIFFICULT TO TREAT. ATTENTION IS NOW TURNING TOWARDS TREATMENT OF THE INFECTED BUT ASYMPTOMATIC PERSON.

OVER THE PAST SEVERAL YEARS WE HAVE DEVELOPED A MUCH BETTER UNDERSTANDING OF THE NATURAL COURSE OF HIV INFECTION. THE GREAT MAJORITY OF THOSE INFECTED ARE VERY LIKELY TO DEVELOP SERIOUS, AIDS VIRUS-RELATED, LIFE-THREATENING DISEASE WITH TEN YEARS OF INFECTION. THE GOAL OF TREATMENT OF THE ASYMPTOMATIC HIV INFECTED PERSON IS TO RETARD, AND HOPEFULLY TO PREVENT, THE DEVELOPMENT OF SERIOUS DISEASE. IT MAY NEVER PROVE POSSIBLE TO FULLY REVERSE THE DAMAGE DONE BY THE AIDS VIRUS, BUT IT MAY VERY WELL PROVE POSSIBLE TO PREVENT THE DAMAGE ~~FOR~~ FROM EVER OCCURRING. I LOOK FORWARD TO THE DAY WHEN DIAGNOSIS OF INFECTION OF HIV IS SIMILAR TO A DIAGNOSIS OF DIABETES - WITH PROPER AND CONTINUAL MEDICAL CARE, THOSE INFECTED CAN LOOK FORWARD TO A NORMAL, FULL TERM LIFE.

I BELIEVE SUCH TREATMENTS ARE WITHIN OUR ABILITY TO ACHIEVE GIVEN OUR CURRENT BIOMEDICAL SKILLS. SYSTEMATIC, INTENSE, CO-ORDINATED APPLICATION OF EXISTING SCIENTIFIC AND MEDICAL RESOURCES IS VERY LIKELY TO BE UP TO THE TASK. GIVEN APPROPRIATE RESOURCES AND COMMITMENT OF GOVERNMENT, INDUSTRY AND ACADEMIC INSTITUTIONS THE PROBLEM CAN BE SOLVED.

I BASE THIS OPTIMISM ON CLOSE OBSERVATION OF THE DISEASE ORGANISMS ITSELF. MY SPECIALTY IS MOLECULAR BIOLOGY - THE TAKING APART OF THE AIDS VIRUS BIT-BY-BIT - AND ITS REASSEMBLY - TO SEE HOW THE VIRUS WORKS IN DETAIL. THE

MORE WE STUDY THE VIRUS, THE MORE WE ARE CONVINCED THAT IT IS VULNERABLE TO MANY DIFFERENT KINDS OF ATTACK. BOTH CHEMICALS AND SUBSTANCES KNOWN AS BIOLOGICAL RESPONSE MODIFIERS - INTERFERONS, GROWTH FACTOR, INTERLEUKINS AND CYTOKINES HAVE BEEN SHOWN TO INTERFERE WITH VIRUS GROWTH. AT LATEST COUNT, THERE WERE MORE THAN FOURTEEN DIFFERENT POINTS OF ATTACK. ADDITIONALLY, THERE ARE MULTIPLE WAYS TO MOUNT EACH ATTACK.

ENLIGHTENED SCREENING

HOW CAN NEW DRUGS THAT ACT AGAINST THE AIDS VIRUS BE FOUND? SUCH DRUGS ARE DISCOVERED EITHER BY A PROCESS I SHALL CALL "ENLIGHTENED SCREENING" OR BY RATIONAL DRUG DESIGN. SCREENING, OF COURSE, MEANS SIFTING THROUGH MANY CHEMICALS LOOKING FOR ONE THAT STOPS THE AIDS VIRUS. THANKS TO ADVANCES IN BIOTECHNOLOGY, THIS PROCESS CAN BE VASTLY SPEEDED UP. SCREENING PROGRAMS FOR EACH COMPONENT PART OF THE AIDS VIRUS ARE BEING DEVELOPED. IT IS EXPECTED THAT BY THE END OF THIS YEAR TWENTY THOUSAND COMPOUNDS WILL BE EXAMINED. NEXT YEAR IT IS EXPECTED THAT MORE THAN FORTY THOUSAND NEW COMPOUNDS WILL BE EXAMINED.

THE DISCOVERY OF AN ACTIVE COMPOUND MARKS JUST THE BEGINNING OF THE DRUG DISCOVERY PROCESS. GIVEN ONE ACTIVE COMPOUND, A TEAM OF CHEMISTS CAN, IN A

SINGLE YEAR, MAKE HUNDREDS AND SOMETIMES EVEN THOUSANDS OF SIMILAR CHEMICALS - EACH SLIGHTLY DIFFERENT. FROM SUCH A COLLECTION OF COMPOUNDS MAY EMERGE ONE THAT HAS PROPERTIES BETTER THAN THE ORIGINAL THE PROCESS OF TAKING A LEAD COMPOUND TO DEVELOPMENT AS A DRUG IS A FAMILIAR ONE FOR ALL LARGE PHARMACEUTICAL FIRMS.

RATIONAL DESIGN

THE TOOLS OF MODERN MOLECULAR BIOLOGY, BIOCHEMISTRY AND MEDICAL DISCOVERY HAVE OPENED NEW HORIZONS FOR DRUG DEVELOPMENT. WE ARE ENTERING THE ERA OF RATIONAL DRUG DESIGN. MOLECULAR BIOLOGY AND BIOCHEMISTRY CAN PROVIDE VIRTUALLY UNLIMITED QUANTITIES OF PROTEINS OF THE AIDS VIRUS. THE POSITION OF EACH ATOM IN SPACE RELATIVE TO ONE ANOTHER CAN BE DETERMINED BY X-RAY CRYSTALLOGRAPHY OR 2-NUCLEAR MAGNETIC RESONANCE. THE INTERACTION OF EACH MOLECULE WITH KNOWN DRUGS CAN BE STUDIED. PREDICTIONS FOR NEW DRUGS CAN BE MADE. SUCH NEW DRUGS CAN BE CHEMICALLY SYNTHESIZED AND TESTED. THIS IS NO PIPEDREAM, ALREADY THREE COMPONENTS OF THE AIDS VIRUS HAVE BEEN PRODUCED IN ABUNDANCE AND CRYSTALLIZED. THE COMPLETE STRUCTURE OF THESE PROTEINS SHOULD BE AVAILABLE BY

THE END OF THIS YEAR OR THE MIDDLE OF THE NEXT. THE STRUCTURE OF OTHERS WILL FOLLOW SHORTLY.

WITH MODERN TECHNOLOGY, THE AVAILABILITY OF NEW ANTI-VIRAL COMPOUNDS IS LIMITED ONLY BY RESOURCES, AND THE INTEREST AND IMAGINATION OF THE SCIENTIFIC COMMUNITY. WITHIN A YEAR OR TWO THE PROBLEM OF DRUG SELECTION WILL BE A FORMIDABLE ONE AS THERE WILL BE AN ABUNDANCE OF CANDIDATES.

~~I HAVE BEEN~~ WE ARE WITNESS TO THE BIRTH OF A LARGE, ACTIVE, IMAGINATIVE CO-ORDINATED DRUG DISCOVERY PROGRAM. OVER THE PAST TWO YEARS, VIA A VARIETY OF FUNDING MECHANISM, THE NATIONAL INSTITUTES OF HEALTH HAVE FORGED AN ALLIANCE BETWEEN INDUSTRIAL, ACADEMIC AND GOVERNMENT LABORATORIES TO FOSTER PRE-CLINICAL DRUG DEVELOPMENT. THE PROGRAM IS A MODEL OF ITS KIND AND HAS ALREADY ENGAGED SOME OF THE BEST SCIENTISTS OF OUR TIME. THE PROGRAM IS NOW EXPANDING. IN MY OPINION SHOULD EXPAND STILL FURTHER OVER THE NEXT FEW YEARS.

THE PACE OF DEVELOPMENT OF NEW THERAPIES

IT IS THE PACE OF THE DISEASE ITSELF RATHER THAN THE PACE OF DRUG DISCOVERY THAT WILL ULTIMATELY DETERMINE HOW RAPIDLY CURATIVE THERAPY CAN BE DEVELOPED. THE TIME BETWEEN INFECTION AND FIRST SERIOUS SYMPTOM IS TYPICALLY BETWEEN TWO TO

FIVE YEARS OR MORE. THIS LAG PERIOD MEANS THAT EVALUATION OF THE EFFICACY OF TREATMENTS DESIGNED TO EXTEND THE LATENT PERIOD WILL REQUIRE AT LEAST TWO YEARS. THE ONLY MEANS OF SHORTENING THIS PERIOD IS TO PLAN TRIALS USING THOUSANDS OF PEOPLE.

THE SHAPE OF THINGS TO COME.

IT IS LIKELY THAT THE BEST TREATMENT WILL INVOLVE COMBINATIONS OF TWO OR MORE DRUGS. COMBINATIONS OF DRUGS CAN REDUCE TOXIC SIDE EFFECTS. DRUGS CAN ACT IN CONCERT AGAINST THE VIRUS, MULTIPLYING THEIR EFFICACY WITHOUT EFFECTING NORMAL CELL FUNCTIONS. COMBINATIONS OF DRUGS CAN HELP PREVENT DEVELOPMENT OF DRUG RESISTANT STRAINS OF THE AIDS VIRUS. COMBINATIONS OF DRUGS MAY ALSO PREVENT DISEASE PROGRESSION AS WELL AS TRANSMISSION FROM AN INFECTED TO AN UNINFECTED PERSON.

PROPHYLAXIS

TO THINK OF PREVENTION IS TO THINK OF A VACCINE - A MEDICATION THAT ENABLES THE IMMUNE SYSTEM TO PROTECT US FROM DISEASE. VACCINES ARE IDEAL AS A PUBLIC

HEALTH MEASURE. ENTIRE POPULATIONS CAN BE PROTECTED BY A ONCE IN A LIFETIME - OR PERHAPS ONCE A YEAR AND MEDICAL INTERVENTION.

WHAT ARE THE PROSPECTS FOR AN AIDS VACCINE?

UNFORTUNATELY NO ONE CAN PREDICT WITH CERTAINTY THAT AN AIDS VACCINE CAN EVER BE MADE. THAT IS NOT TO SAY IT IS IMPOSSIBLE TO MAKE SUCH A VACCINE, ONLY THAT WE ARE NOT CERTAIN OF SUCCESS. I REMAIN CAUTIOUSLY OPTIMISTIC THAT GIVEN A SUFFICIENT EFFORT BY VIROLOGISTS AND IMMUNOLOGISTS, A VACCINE CAN BE DEVELOPED. INDEED, I AM VERY ACTIVELY ENGAGED IN VACCINE DEVELOPMENT. HOWEVER, IT IS CERTAIN THAT WE FACE SIGNIFICANT PROBLEMS.

THE EXTENT OF THE PROBLEMS FOR AIDS VACCINE DEVELOPMENT WAS HIGHLIGHTED BY THE FAILURE OF INITIAL VACCINE TRIALS IN ANIMALS. CHIMPANZEES IMMUNIZED WITH VACCINE CANDIDATES WERE NOT PROTECTED FROM AIDS VIRUS INFECTION. MONKEYS TREATED WITH A VACCINE CANDIDATE FOR THE SIMIAN AIDS VIRUS WAS ALSO NOT PROTECTED. FAILURE OF THE FIRST VACCINE TRIALS DOES NOT MEAN HOPE IS LOST. HOWEVER, IT DOES MEAN THAT THE ROAD AHEAD MAY BE LONG AND DIFFICULT.

WE HAVE NOW GAINED ENOUGH INSIGHT INTO THE WORKING OF THE AIDS VIRUS TO PERMIT INSIGHT INTO WHY VACCINATION MAY BE DIFFICULT.

THE FUNDAMENTAL REASONS FOR THE DIFFICULTY IS THAT THE AIDS VIRUS HAS EVOLVED TO CO-HABIT WITH THE HUMAN BODY IN SPITE OF THE IMMUNE RESPONSE. IT IS ONE OF A NUMBER OF VIRAL PARASITES THAT ESTABLISH LONG TERM RESIDENCE.

SPECIFIC MECHANISMS FOR EVASION OF THE IMMUNE RESPONSE BY THE AIDS VIRUS ARE OF TWO TYPES.

- THE STRUCTURE OF THE SURFACE OF THE VIRUS IS DESIGNED TO EVADE THE IMMUNE RESPONSE.
- THE LIFE CYCLE OF THE VIRUS PERMITS IT TO EVADE THE IMMUNE RESPONSE.

THE VIRAL SURFACE.

THE SURFACE OF THE VIRUS IS COMPRISED OF A PROTEIN THAT BINDS TO THE SURFACE OF THE UNINFECTED CELL VIA A SPECIFIC STRUCTURE - THE CD4 MOLECULE. INTERFERENCE WITH BINDING OF THE VIRUS SURFACE PROTEIN AND CD4 PREVENTS INFECTION.

PEOPLE INFECTED WITH THE AIDS VIRUS USUALLY MAKE ANTIBODIES THAT RECOGNIZE THE SURFACE OF THE AIDS VIRUS. HOWEVER, THESE ANTIBODIES DO NOT PREVENT GROWTH OF THE VIRUS AND DISEASE.

FEATURES OF THE SURFACE THAT CONTRIBUTE TO EVASION OF THE IMMUNE RESPONSE INCLUDE:

1. THE SURFACE PROTEIN IS COATED WITH SUGAR MOLECULES. THE SUGAR PROTECTS THE PROTEIN FROM ANTIBODIES.

2. THE REGION OF ATTACHMENT OF THE VIRUS TO CD4 IS PROBABLY DEEPLY RECESSED IN THE SURFACE PROTEIN. ANTIBODIES CAN NOT REACH INTO THE DEEP CD4 BINDING POCKET.

3. MOST OF THE WORKING PARTS OF THE OUTSIDE OF THE VIRUS ARE TUCKED AWAY - EITHER UNDER THE SUGAR COAT OR UNDER PROTEIN, HIDDEN FROM ANTIBODIES.

THE VIRUS LIFE CYCLE

THE LIFE CYCLE OF THE VIRUS ALSO HELPS IT TO EVADE THE IMMUNE SYSTEM. THE VIRUS CAN INFECT A CELL AND THEN LIE DORMANT, GIVING NO SIGN OF ITS PRESENCE. DORMANT INFECTIONS OF CELLS ARE MORE THE RULE THAN THE EXCEPTION.

(2) INFECTION OF SOME CELLS RESULTS IN FORMATION OF VIRUS THAT ARE CONTAINED ENTIRELY WITHIN THE CELL. IF THE VIRUS IS NOT PRESENT ON THE OUTSIDE OF A CELL, THE IMMUNE SYSTEM MAY NOT SEE IT. THE VIRUS MAY CIRCULATE IN A "TROJAN HORSE" LIKE STATE, INVISIBLE TO THE IMMUNE SYSTEM.

THESE ARE FORMIDABLE OBSTACLES TO OVERCOME. A LARGE SCALE-COORDINATED ~~TO~~ PROGRAM TO ADDRESS THESE PROBLEMS HAS BEEN DEVELOPED BY THE NATIONAL INSTITUTES OF HEALTH. THIS EFFORT IS NOW BEING EXPANDED. (4) THE DISCOVERY OF A NEW ~~M~~/MODEL SYSTEM - THE SIMIAN IMMUNODEFICIENCY VIRUS (SIV), WILL BE A GREAT HELP TO ~~FOR~~ VACCINE DEVELOPMENT STUDIES.

CHEMICAL PREVENTION

I WOULD LIKE TO END MY REMARKS ON A POSITIVE NOTE. WE MUST KEEP SIGHT OF THE GOAL. VACCINES ARE A MEANS TO AN END. THE GOAL IS THE PREVENTION OF INFECTION. IT WILL SOON BE TECHNICALLY POSSIBLE TO PREVENT INFECTION USING ANTI-VIRAL DRUGS - IN MANY CASES USING THE SAME DRUGS THAT ARE USED TO TREAT THOSE ALREADY INFECTED.

THE CONCEPT OF CHEMO-PREVENTION IS THE TREATMENT OF UNINFECTED, HEALTHY PEOPLE WITH ANTI-VIRAL DRUGS TO PREVENT INFECTION.

THE FEASIBILITY OF PREVENTION OF INFECTION BY ADMINISTRATION OF ANTI-VIRAL DRUGS HAS ALREADY BEEN DEMONSTRATED IN TWO RETROVIRUS ANIMAL MODELS. THE CONCEPT OF CHEMO-PREVENTION MAY BE APPLICABLE IN SEVERAL DIFFERENT SETTINGS.

- PREVENTION OF INFECTION OF HEALTH WORKERS AND SCIENTISTS EXPOSED TO THE VIRUS. NEEDLE STICKS, INJURIES, BLOOD SPILLS AND LABORATORY ACCIDENTS WILL CONTINUE TO EXPOSE MEDICAL AND SCIENTIFIC PERSONNEL TO INFECTION. ALTHOUGH THE RISK OF INFECTION IN SUCH SETTINGS IS LOW, IT IS MEASURABLE. TREATMENTS OF LIMITED DURATION WITH THE ANTI-VIRAL DRUGS MAY BE PROTECTIVE.

- TREATMENT OF NEWBORNS OF SEROPOSITIVE MOTHERS. THE RISK OF INFECTION OF INFANTS BORN TO HIV-INFECTED MOTHERS IS HIGH. ABOUT HALF OF BABIES BORN TO INFECTED MOTHERS BECOME INFECTED AND OF THESE, MANY DEVELOP SEVERE DISEASE WITHIN A YEAR. IT IS NOT KNOWN WHAT FRACTION OF THESE INFANTS ARE INFECTED BEFORE BIRTH OR AT DELIVERY. IT IS POSSIBLE THAT LIMITED DURATION WITH ANTI-VIRAL DRUGS COULD SUBSTANTIALLY REDUCE THE NUMBER OF CHILDREN INFECTED.

- SEX PARTNERS OF SEROPOSITIVE PEOPLE. SEX PARTNERS OF SEROPOSITIVE PEOPLE ARE AT RISK FOR INFECTION. SIGNIFICANT RISK MAY EXIST EVEN IF "SAFER SEX" IS PRACTICED. IN THIS CONTEXT, CHEMO-PREVENTION MEANS LONG TERM CHRONIC ADMINISTRATION OF ANTI-VIRAL DRUGS TO THE UNINFECTED PARTNER.

- HIGH RISK POPULATIONS. CHEMO-PREVENTION - ON A POPULATION BASIS - MAY BE APPROPRIATE IN POPULATIONS AT VERY HIGH RISK FOR INFECTION. THERE IS REASON TO BELIEVE THAT IN SOME PARTS OF THE WORLD AND IN SOME POPULATIONS, THE RATE OF INFECTION EXCEEDS FIVE PER CENT OF THE SEXUALLY ACTIVE POPULATION ANNUALLY. INFECTION RATES OF THIS MAGNITUDE CANNOT LONG BE SUSTAINED WITHOUT ENDANGERING AN ENTIRE POPULATION. UNDER THESE CIRCUMSTANCES, IN THE ABSENCE OF AN EFFECTIVE VACCINE, CHEMO-PREVENTION MAY BE ONE OF THE ONLY EFFECTIVE MEANS OF DISEASE CONTROL.

THE REQUIREMENTS FOR CHEMO-PREVENTION REGIONS ARE STRICT. THE TOXIC SIDE EFFECTS MUST BE MINIMAL AS THOSE TREATED WILL BE HEALTHY. CHRONIC AS WELL AS

ACUTE TOXICITY MUST BE EVALUATED, PARTICULARLY IF THE DRUGS ARE TO BE ADMINISTERED FOR A LONG TIME.

THE MEANS OF DELIVERY MUST BE SIMPLE. ORAL OR "SLOW-RELEASE" DRUGS ARE PREFERABLE. THE COST MUST BE AFFORDABLE TO INDIVIDUALS AND TO NATIONS.

THERE IS A SENSE OF URGENCY IN THE MATTER OF CHEMO-PREVENTION. AT PRESENT THERE IS NO EFFECTIVE MEANS TO PREVENT INFECTION OF THE NEWBORNS, OUR NEXT GENERATION. AIDS VIRUS INFECTION CONTINUES TO SPREAD RAPIDLY AND UNCHECKED IN LARGE POPULATIONS.

DRUGS, SUCH AS AZT, INTERFERON ALPHA THAT HAVE ALREADY BEEN APPROVED FOR HUMANS MAY BE USEFUL IN THIS CONTEXT. RESULTS OF CHEMO-PREVENTION COULD BE OBTAINED WITHIN ONE YEAR OF INITIATING THE STUDY.

SUMMARY

WE ARE NOT HELPLESS IN FACE OF THE AIDS EPIDEMIC. INDEED MANY OF THE ESSENTIAL TOOLS FOR MEDICAL CONTROL OF THE AIDS EPIDEMIC HAVE ALREADY BEEN FORGED. MEANS FOR ACCURATE DIAGNOSIS OF INFECTION ARE AT HAND, AND IMPROVED DIAGNOSTIC TESTS WILL BE AVAILABLE SOON. THE OUTLINES OF A STRATEGY FOR CURATIVE THERAPY HAVE EMERGED, IT IS LIKELY THAT PREVENTION OF DISEASE IN THOSE

ALREADY INFECTED WITH HIV CAN BE ACHIEVED PROVIDED ADEQUATE RESOURCES ARE MARSHALLED. IT IS LIKELY THAT MEANS TO PREVENT INFECTION CAN BE DEVELOPED IN THE NEAR FUTURE IN THE FORM OF CHEMO-PREVENTION. TO BE SURE, CHEMO-PREVENTION IS NOT AS DESIRABLE A MEANS FOR EPIDEMIC CONTROL AS IS A VACCINE. NEVERTHELESS, THE MAGNITUDE OF THE AIDS EPIDEMIC, AN EPIDEMIC WHICH THREATENS ENTIRE POPULATIONS IN SOME PARTS OF THE WORLD, MAY MAKE CHEMO-PREVENTION IMPERATIVE.

REPORT TO THE PRESIDENTIAL COMMISSION ON HIV INFECTION

18 February 1988

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The Immunology of AIDS: Unresolved Questions

I've been asked to discuss what is not known concerning the immunology of AIDS. Much, of course, has been discovered about how HIV, the etiologic agent of acquired immune deficiency syndrome, affects the immune network. In the five years that I've been involved in AIDS research, much has also been learned about how the body's various defense mechanisms attempt to cope with this invader. Even so, this would have been a considerably briefer presentation had I simply been asked to review all that is known about AIDS immunology.

I've divided my comments into five areas. (1) The entry of HIV into immunologically relevant white blood cells: the T lymphocyte, macrophage, and B cell. (2) The mechanisms by which certain T cells are depleted. This depletion is arguably the most important harbinger of an individual's progression from a viral carrier state to clinical disease. (3) Early qualitative immune defects, a period after HIV infection during which cell numbers may be normal, but cell function markedly curtailed. (4) The concept of latency, during which HIV is relatively silent within a cell, yet poised to be converted into a state of active replication. In this context I'll raise the idea of cofactors in the "rescue" of virus from the latent state. Cofactors are relevant to both experimental models of HIV infection and to pro-

gression of disease in humans. (5) Finally, I'll discuss the body's responses to HIV, including production of antibodies and autoantibodies, killer T cells and cell factors.

I. AIDS is initiated by entry of HIV into certain cells. This process requires a receptor. Receptor biology is an important issue in HIV infection, both in terms of drug or vaccine development, and in discussions of potential mechanisms of transmission. Portions of CD4 serve as a point of attachment for the virus. CD4 is a glycoprotein molecule found on the surface of helper T cells, macrophages, B lymphocytes, glial cells of the central nervous system, and perhaps other cells. HIV binds to CD4 by way of its own coat or envelope glycoprotein known as gp120. This binding is very strong. Its affinity is equivalent to that of CD4 for monoclonal antibodies raised against it. The troubling issue is that CD4 may not be necessary or sufficient for entry of HIV into all cells. For example, in the test-tube HIV can infect cell lines derived from human colon. Granted, these lines have messages--messenger RNAs--for CD4, but they are not putting the molecule out onto their surfaces, at least not in a manner one can detect it. Similarly, HIV can be introduced into other cells which don't have CD4, including endothelial cells which line blood vessels and Langerhans' cells of the skin. The gene for CD4 has been cloned and, when introduced into a human cell, is sufficient to render that cell infectable with HIV. When introduced into mouse cells, the CD4 gene also elicits production of high concentrations of CD4. Yet HIV cannot infect that cell. Clearly, the receptor

story is incomplete. Preliminary evidence has implicated an additional candidate, MHC class II (also known as HLA-DR or Ia). These molecules are much less restricted in their distribution in the body. They are found on everything from T cells and macrophages to activated endothelial cells and intestinal lining cells. These data are still tentative, as they are based upon relatively crude antibody blocking studies. But receptor-independent processes may also spread the virus. T cells infected with HIV form giant multi-nucleated structures known as syncytia, and these syncytia appear to be very sticky. That is, cells without CD4 receptors may acquire HIV as their membranes fuse with adjacent infected cells. Knowledge about these determinants are more than just academic exercises. Certain vaccine strategies, including design of anti-idiotypic antibodies, rely exclusively on structures that mimic the CD4 receptor. Recently, the CD4 glycoprotein product has been produced in abundance from the cloned gene. Its infusion into patients has been suggested as a possible AIDS therapy, blocking cell-to-cell spread of virus. This, of course, would only be valid if CD4 were the exclusive viral receptor. And if soluble CD4 did not itself disturb important immune functions. Finally, hypotheses as to how HIV can and can't be transmitted are often predicated on the need for direct interaction of HIV with a CD4+ cell.

Our knowledge as to why certain isolates of HIV infect helper T cells much more easily than macrophages, or vice versa, is also incomplete. Some experiments implicating the density of

CD4 on the cell surface have not been supported by other studies. The type of immune cell infected has relevance to treatment strategies. For example, AZT is the most potent anti-HIV drug in clinical use. Yet the concentration of AZT required to achieve a certain level of HIV inhibition in the test-tube varies with the type of CD4+ lymphocyte or immortalized T cell line chosen for study. Even more disturbing is the fact that at least one human macrophage-like cell line, U937, can be infected quite easily by HIV, unperturbed by the presence of any concentration of AZT in its culture milieu. Whether this resistance will hold true for normal human macrophages is unknown, and must be tested.

II. The mechanisms by which HIV kills cells must be completely understood in order to design ways of blocking them. The CD4+ T cell subset encompasses a variety of cells with helper and inducer immune functions. This subset has been quite accurately described as a conductor in the symphony of immune responses which protect the body from infections, cancers and other foreign invaders. Elimination of this cell type results in the profound immune defects characteristic of clinical AIDS. Indeed, there appears to be a direct correlation between the absolute number of CD4+ cells and development of AIDS. In one large cohort study of asymptomatic, HIV seropositive homosexual men in Los Angeles, 58% with fewer than 100 CD4+ T cells per mm3 developed AIDS within 18 months. Only 4% of asymptomatic men with greater than 500 CD4+ cells per mm3 developed AIDS within that same interval.How does this profound cell depletion occur, and why does it occur at different rates in different

individuals? In the test-tube, HIV can kill CD4+ cells by inducing the multi-nucleated syncytia I had mentioned earlier. These structures, which can trap up to 500 cells in one giant mass, have a limited life span. Certain HIV isolates may induce syncytia more rapidly than others. Those syncytia related to the newly described HIV-2 subclass, most prevalent in western Africa, may take an especially long time to die in vitro. Still, the phenomena is generalizable to all intact HIV isolates. It is dependent on expression of the HIV envelope component gp120. There is great debate as to how important this phenomenon is in the body, however. Syncytia can be identified in pathologic specimens, particularly in the brain, liver and spleen, but they are very rare. It has been postulated that CD4 forms complexes with HIV envelope intracellularly, and that these complexes are toxic to cells. However, certain cells which express little CD4 are killed quite efficiently by HIV. Other explanations have been offered to explain the depletion of CD4+ cells. Suppressor factors induced by infection of CD4+ T cells may amplify the virus's effect, circulating in the blood to inhibit the growth of uninfected T cells and their precursors in the thymus gland and bone marrow. Molecules on the surface of T helper cells may serve as targets for autoantibodies or killer T cells, both reported to occur after HIV infection. Any or all of these mechanisms are plausible explanations for the T cell depletion observed. Conclusive evidence for the importance of any one them in the body is still lacking, however. Without these data, rational protocols for immune enhancement are impossible.

III. Depletion of T helper cells, and consequent reversal of the CD4:CD8 helper-to-suppressor T cell ratio, is the most obvious laboratory manifestation of AIDS. Yet profound immunologic defects, found in the body and duplicated in the test-tube, occur early after HIV infection, prior to any measurable T cell depletion. This stage of HIV infection, conceivably more amenable to intervention, requires much closer scrutiny. Examples of such early defects include the inability of an individual to respond to skin test antigens in a reaction known as delayed type hypersensitivity, failure to generate specific antibody in a vaccine challenge, and inability of T cells to proliferate after exposure to foreign antigens. These abnormalities are often independent of CD4+ T cell number. In the test-tube they are not correctable by addition of T cell factors such as interleukin 2 (IL-2), or inclusion of macrophages or other accessory cells from non-infected individuals. Why does this occur? There is evidence that the initial steps of antigen recognition by T cells are intact. Infected T cells respond in certain ways to foreign signals, even if they can't proceed along the full cascade which describes normal T cell function. The exact nature of the barrier to complete responsiveness is unknown. Macrophages, one type of cell which can process antigens and "present" them to T cells, may be involved. Macrophages are qualitatively and quantitatively disturbed in HIV infection. The range of these abnormalities is large, although certain investigators question their significance to clinical disease. For example, in many systems T cell defects

are independent of macrophages. The contribution of macrophages, and other antigen-presenting cells, is a distinct issue which also requires further work. Finally, there are gaps in our knowledge of the way HIV interferes with different pathways of T cell activation. Alterations in an important T cell growth factor, IL-2, without changes in a cell's receptors for that hormone, have been identified. However, adding IL-2 in the test-tube has little beneficial effect. Indeed, in certain systems it may worsen the immune deficit. IL-2 has been used to treat patients with AIDS in experimental studies at the NIH and elsewhere. It has shown little efficacy, and has been linked to an unexpectedly high incidence of serious infectious complications. Another disturbing issue is that many of the signals, both antigen dependent and antigen independent, with which one would like to stimulate an infected T cell may instead provoke that cell to begin actively replicating virus, and eventually to self-destruct. This leads directly into the topic of viral latency, and questions as to the ways in which dormant virus is converted into productive infection.

IV. One of the more puzzling aspects of AIDS is the profound disturbance of immune function that occurs in the face of what appears to be very low levels of viral replication. Currently available techniques to detect virus-associated nucleic acid, known as in situ hybridization, demonstrate RNA or proviral DNA in less than one in ten-thousand target T cells or macrophages in blood or other tissues. It has been postulated that HIV-induced cellular factors, or gp120 shed from these few cells, greatly

amplify the effects of a limited infection. These phenomena cannot be demonstrated in all patients, however, and the concentration of viral gp120 required to produce an immune deficit in the test-tube is orders of magnitude greater than what is detected in the body. It now appears likely, albeit by no means proven, that many more cells are infected in the body, persisting in a dormant or latent state. These cells, producing very little viral protein or nucleic acid, and not actively replicating HIV, escape detection. Indeed, lacking a foreign protein target on their surface, they may not only escape detection by our hybridization assays, they may also escape whatever host mechanisms of viral clearance have been left intact. Evidence supporting this theory comes from serial examinations of T cell cultures exposed to very low levels of virus. The viral signposts one commonly searches for--reverse transcriptase activity, proteins, RNA--are not apparent, unless one further perturbs the system. Foreign antigens which the T cell had been primed to recognize, artifical plant lectins such as PHA (phytohemagglutinin), chemicals such as PMA (phorbol ester), or other viruses can all stimulate T cells, and concominantly activate the virus, within a short period of time. Active viral replication can now be quite easily demonstrated, as the latent HIV has been "rescued," or converted into a productive state. If one makes an analogy between this system and the situation in humans, many more lymphocytes and macrophages are almost certainly infected with virus than can be found by what are currently our most sensitive detection techniques.

Latency makes alot of sense from a virus's point of view. It can remain dormant and slowly propagate along with its host cell. As long as limited amounts of envelope protein gp120 are made, it will not kill the cell. The mechanisms by which HIV remains in this state are complex. They involve several genes which alter viral replication either by so-called cis-acting (e.g., the NRE (negative regulatory element) region) or trans-acting (e.g., tat and art) mechanisms, as well as one gene with diverse functions (3'-orf). This is outside of the scope of a talk on immunology. What is relevant is how signals as diverse as a herpesvirus or a plant molecule can activate latent virus.

There are certain sequences in a region of the HIV genome known as the 5'-LTR which serve as targets for viral and cellular regulatory factors. Binding of these protein molecules to this region markedly enhances the transcription of HIV. This region is sensitive not only to HIV's own proteins, known as trans-acting molecules, but to those induced by many T cell activation signals. What we don't know is the relevance of these cofactors identified in the test-tube to enhancement of HIV replication in humans. It is also unclear how one might design drugs that could interfere with HIV activation, without simultaneously interferring with activation of normal T cells attempting to combat the infection. The importance of this phenomenon to the immunology of AIDS may be illustrated by two recent, and very public examples.

A small, uncontrolled clinical trial of the T cell immune

suppressant cyclosporine was undertaken by a French group two years ago. One rationale was that HIV replicates actively only in stimulated T cells. Cyclosporine, by blocking this stimulation, might thereby retard the spread of HIV to uninfected lymphocytes. We now know that cyclosporine inhibits only one of the many pathways by which T cells become activated. This is technically known as the CD3-Ti pathway, and responds to stimulants such as PHA and antigen. In test-tube experiments using the HIV 5'-LTR, cyclosporine did indeed inhibit signals linked to CD3-Ti, but not those associated with several other activators.

Secondly, there has been much attention paid to possible infectious AIDS cofactors. The very variable and, in some instances, very long or indeterminate interval between infection with HIV and development of AIDS has been linked epidemiologically to intercurrent viral infections. One of these infections is HTLV-I. HTLV-I, like HIV, is a human retrovirus which homes in on T cells. Rather than killing T cells, however, it leads to their immortalization. A small percentage of infected individuals will develop a T cell cancer, either leukemia or lymphoma, after an incubation period that is measured in decades. Most people remain healthy. In Trinidad, where a high incidence of both HIV and HTLV-I infection exists, comparisons were made between the development of AIDS in asymptomatic homosexual men infected with HIV alone versus HIV plus HTLV-I. Of 34 men infected with HIV alone, 9% developed AIDS within a four year surveillance period. Of six men infected with both retroviruses,

50% developed AIDS within that interval. The numbers are small, but the difference was highly significant statistically. The phenomenon deserves close attention as in Trinidad only 6% of their HIV infected individuals also harbor HTLV-I. The situation is quite different in the United States. In one borough of New York (Queens), this figure was 27% of all drug abusers screened. In one city of New Jersey, it was 16% of all drug abusers screened. Granted, HTLV-I is a rare virus, and dual infection in the U.S.is probably limited to drug abuse populations of certain inner cities. But the phenomenon of HIV activation following exposure to products of other infections is not limited only to HTLV-I. In the test-tube, it can occur with herpes simplex virus, cytomegalovirus, and hepatitis B virus, all very common microorganisms. And these are only the ones that have been tested. Other experimental viral activators may also be relevant to human disease. The potential risk of immunization of HIV infected persons has been raised. In one case report, smallpox, quickly followed by AIDS, developed shortly after vaccination of an asymptomatic, HIV seropositive Army recruit with attenuated smallpox virus. Statistically, this and other anecdotes are insignificant. I would still argue that these are important and unsettled issues. The HIV/HTLV-I data, and analogies with test-tube activation of infected T cells, must be carefully explored in clinical studies prior to the widespread institution of experimental AIDS treatments, be they immune modulators such as IL-2, recommendations of "hypervaccination," or HIV vaccines. Paranthetically, these preliminary immunologic findings also

suggest avenues for improved HIV detection. Cell activation combined with more sensitive viral assays, such as the PCR (polymerase chain reaction) DNA amplification technique, could represent a valuable joining of immunology and virology. It might help to resolve the issue as to why techniques such as PCR alone could not detect HIV in some 40% of cultured cell samples derived from HIV seropositive individuals.

V. Against these odds one might think the host's immune defense is totally effete, but this is not the case. Humoral and cellular immune responses directed against HIV and its products do occur. Their relative efficacy, and how they might be amplified, are important unknowns. Serologic responses to HIV envelope and structural components have been extensively charted. The relevance of certain patterns which appear to distinguish the asymptomatic carrier state from AIDS-related complex and AIDS remains controversial, however. Newer insights have been gained by examination of antibody responses to enzymatic activities of the virus, but these associations are also tentative.

In terms of serologic information of use for vaccine development, it is unclear whether the consensus sequences of the viral envelope recognized by immunoglobulins from most infected individuals have any relevance for fighting the infection in the body. Most neutralization assays performed in vitro correlate very poorly, if at all, with the clinical situation. Until the appropriate neutralizing epitopes are defined, vaccine strategies may not be much more than "hit-or-miss" struggles.

It is also possible that antibodies play much less a protective role than do killer T cells primed to recognize and destroy HIV-infected targets. These cytotoxic lymphocytes, which bear surface molecules known as CD8, can be demonstrated in many infected individuals. They are most easily found at the early stages of disease. Vaccine strategies which attempt to incorporate both a B cell (antibody) and T cell (cytotoxic) component may have the best chances for success. Of course, more work in defining exactly what parts of the virus the CD8 lymphocte "sees" is necessary.

Other types of immune cells, including those involved in antibody-dependent cell mediated cytotoxicity (ADCC), natural killer cells, and macrophages, as well as their soluble mediators, the interleukins and interferons, deserve more attention. Finally, potential synergies between anti-viral drugs and these immune cell mediators must be explored in a systematic manner. A concerted effort aimed at joining the expertise of virologists and immunologists in examining the myriad effects of HIV on the immune network can only facilitate development of the anti-HIV drugs and vaccines we all urgently seek.

Testimony of Drs. Dierig and Waldthaler

TESTIMONY DELIVERED TO THE PRESIDENT'S COMMISSION
FEBRUARY 18, 1988 (SECTION IMMUNOLOGY)

I hope you don't mind if our English is far from being perfe

We are anaesthesiologists with an office in Augsburg, Wes Germany. Both of us spent years in an intensive care uni

Early in 1981, we treated a bisexual patient with a history of venereal diseases for possible sepsis. Since all blood cultures were negative, we decided to treat him with high dose IV Penicillin-G. The patient recovered within three weeks.

When the test for LAV/HTLV III became available in early 1985, we tested the patient to rule out any possible connection with the Acquired Immune Deficiency Syndrome. The test was positive. This led us to treat more HIV positive patients. Ten treatments in six patients were performed. Five patients are in excellent clinical conditions; one patient died during treatment because of pulmonary complications.

Clinical manifestations attributed to HIV infection disappeared. So we tried to correlate the immunosuppression attributed to HIV infection with immunosuppresion known in syphilis.

What we present here as clinicians is not a study, neither randomized nor double blind but a report of immunological changes by penicillin treatment of HIV positive patients.

Laboratory data and some interpretations are as follows:

In lymphocyte subpopulations no particular changes were noted with B and NK cells.

T4 (helper/inducer)-cells: In three cases an increase was seen, for example, from 93 to 383 per microliter and from 205 to 774 per microliter, in other cases an initial decrease and an increase after two months.

T8 (suppressor/cytotoxic)-cells: In four cases we noted an increase, for example from 956 to 1810 per microliter, in other cases a decrease for example from 905 to 344 per microliter. At the moment we are unable to differentiate between suppressor and cytotoxic cells but clinical improvements (for example the resolution of lymphadenopathy, skin problems and Herpes Zoster) suggests that the increase in T8 numbers may be due to an increase in cytoxic cells numbers.

Lymphotcyte mitogenesis assays with PHA, Con A and PWM all improved in three cases where they were performed, especially with PHA. The impairment of lymphocyte response to PHA is well known in syphilis, where acidic mucopolysaccharides coat immunocompetent cells inhibiting either cell to cell contact or the binding of mitogens to cell receptors.

Circulating immune complexes (CIC) of IgG and IgM class: In the cases where analyses of CIC's revealed presence of treponemal antigens, the CIC's dropped significantly.

Lysozyme: Increases were noted in all cases where it was measured; in one case, the increase was over two hundred fold.

Beta-2-microglobulin, which is a loosely bound part of the major histocompatibility complex 1, in our patients remained above normal range. The variable region of gp120 of HIV imitates antigenic structures of MHC 1. Treponema pallidum acquires MHC 1 antigens of the host. It should be discussed which of the two mechanism is responsible for the increased level of Beta-2-microglobulin in HIV positive patients.

Vitamin B12 and folate where measured because of anemia with high MCV, hypersensitivity to TMP/SMX and an increase of T4 and B cells after administration of potassium iodide. Vitamin B12 increased after therapy while total folate remained unaffected. In our analysis it was not possible to differentiate between dihydrofolate and tetrahydrofolate. Since treponema pallidum are not susceptible to sulfonamides and do not incorporate thymidine, they are dependent upon the folate cycle of the host. Trimethoprim blocks the dihydrofolate reductase while potassium iodide and heavy metals stimulate this enzyme. This could explain on the one hand the adverse reactions of HIV positive patients to trimethoprim and on the other the effect of potassium iodide and heavy metals in the treatment of syphilis. It is worth mentioning that potassium iodide was used for treating syphilomas and had some effect on Kaposi's sarcoma, as do high doses of IV penicillin.

A dilution of the HIV Elisa test was done in two cases. In both cases the titers dropped dramatically. In one case it dropped from 1:327,680 to 1:5,120, in the second case, it dropped from 1:2,621,440 to 1:10,240.

Finally a word on syphilis serology. After therapy we found an overall decrease in the most sensitive test, the TPHA and an increase in the most specific test, the IgG-FTA-Abs. After five treatments the VDRL test turned positive. In one case the TPHA and FTA tests, which had been positive for over 20 years, turned negative after treatment.

In conclusion: Many of the clinical manifestations and immunological disorders attributed to infection with HIV are indistinguishable from those found in the course of infection with treponema pallidum. As of this day, no definite pathomechanism has been found for any of the symptoms of syphilis. Since syphilis serology in HIV positive patients is not reliable and since there exists no criterion for adequate therapy, especially of late syphilis, it is imperative to rule out syphilis by all means in an HIV positive patient.

We conclude that:

1. A positive VDRL means active syphilitic infection.
2. A negative VDRL with a positive treponemal test means presence of treponemal antigen.
3. A negative VDRL and negative treponemal test do not exclude treponemal infection because specific antibodies may be hidden within CIC's and antibody specificity is lost over time.
4. Monoclonal antibodies may prove more helpful to diagnose syphilis. or nucleic acid hybridization may prove more helpful.
5. The safest way to rule out a treponemal infection would be diagnostic treatment.

Mr. Chairman, Members of the Commission, we appreciate the invitation to present this information to you today and we hope that it may contribute to a better understanding of some aspects of the HIV epidemic.

Recommendations for consideration by The Commission:

We suggest an investigation of which role treponemal infection plays in the HIV epidemic by:

1. Accelerated basic treponemal research on the interaction of treponema pallidum with:
   a. Mitrochondria (VDRL test; anemia in HIV positive patients).
   b. Vitamin B12 and folate metabolism (anemia, thrombocytopenia, reduced blastogenesis of immunocompetent cells, demyelinating disorders and hypersensitivity to TMP/SMX in HIV positive patients).
   c. Beta-2 microglobulin.
   d. B and plasma cells (Russell's bodies are found in both KS and syphilomas).
2. New diagnostic approaches in order to detect treponemal antigen in:
   a. Circulating immune complexes.
   b. KS by indirect immunofluorescence microscopy.
3. Making available facilities to treat HIV positive patients with high doses of IV penicillin-G (20 million units continuously IV over 28 days). NOTE: Detailed information about the regimen and results of its application is being prepared for publication.

It seems imperative that we reappraise the ~~diagnostic~~ procedures ~~of~~ in diagnosing treponemal infections in the antibiotic era and redefine "adequate treatment".

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Testimony of Dr. A. Arthur Gottlieb

TESTIMONY BEFORE THE PRESIDENTIAL COMMISSION
ON HIV INFECTION

FEBRUARY 18, 1988
NEW YORK CITY

Ladies and Gentlemen:

I am Dr. A. Arthur Gottlieb, Professor and Chairman of the Department of Microbiology and Immunology, and Professor of Medicine at the Tulane University School of Medicine, and Chief Executive Officer of Imreg Inc., a publicly held biotechnology company. I appreciate the opportunity to appear before you today and to give you some of my views on drug development in AIDS/ARC. My comments reflect my perspective and experience at the academic-industrial interface, and as the inventor and developer of IMREG®-1, an immunosupportive biologic.

I have presented to you a position paper by myself and Dr. Robert F. Garry, Associate Professor of Microbiology and Immunology at Tulane. For the moment, I wish to summarize some of the points made in that position paper. I might say that Dr. Garry's expertise is in virology, and that he and I were responsible for confirmation of the case of HIV infection that was seen in St. Louis in 1968, and is to our knowledge the earliest documented case of AIDS in the U.S.

The principal message I would leave you with today is that the national effort directed to treatment of AIDS/ARC needs to place greater emphasis on ways and means to correct the state of immune deficiency seen in patients with this disease. There is a need to ~~preserve~~ this objective with at least the same commitment as is being directed to the antivirals. It appears that some interest is developing in this area, but to date the development of immunosupportive drugs has clearly had a lower priority.

The emergence of HIV infection as a major world health problem is at once a challenge to the scientific and medical communities as well as a vindication of the investment which has been made in basic immunologic research over the last two decades, for without that information, our ability to understand and deal with this disease would be nil. The characteristics of the devastating disease states, AIDS and ARC are widely known, but it is well to emphasize that a principal feature is a defect in the capacity of the patient to mount immune reactions to specific antigenic challenges, as a result of selective progressive destruction of critical regulatory cells (T helper cells).

There are a variety of associated immune phenomena which occur in HIV infected individuals, and in a very real sense, this condition should be viewed as an acquired dysregulation of the immune system, the most prominent feature of which is a deficiency in the ability to mount specific immune responses. Reversal of these serious and complex immune dysfunctions does not occur spontaneously, and the disease in its advanced form has a high degree of fatality. The emergence of AIDS as a world public health problem of major dimensions poses a need for intense and comprehensive attention to all possible approaches to the treatment of this infection.

We now recognize that the original definition of AIDS, as promulgated by the Centers for Disease Control, was very narrow and reflected only a minor fraction

of the range of clinical and immunologic phenomena seen as a result of HIV infection. It is more logical to regard infection with HIV as being able to cause a deficiency of the immune system to a variable degree in each patient who is infected. That is, some individuals who have been infected with the human immunodeficiency virus (HIV) (previously referred to as the LAV/HTLV III) will have little compromise of immune function, while others will have a severe deficiency, and many will fall in between. In general, the more severe the immunodeficiency, the more likely the patient will experience the serious clinical complications of opportunistic infections and malignancies.

The most advantageous time to treat a patient with an immunosupportive drug is at the early stages of appearance of functional immunodeficiency.

It should be noted that although substantial information has been developed about the Human Immunodeficiency Virus, and the fine structure of its genetics, relatively little is known about the way in which this virus damages cells of the immune system and thereby leads to disease. We need to develop much more information concerning the pathogenic effects of the virus on the immune system at both a cellular and molecular level, and the regulatory abnormalities that result from HIV infection. For example, we have little information about the cells that are needed to trigger immunity against this virus, and we remain puzzled as to why initial infection leads to circulating antibody which is not protective.

In thinking about approaches to treatment of HIV infection, two initiatives come to mind:

(1) Development of anti-viral drugs that will suppress production of new HIV virus, or prevent infection of healthy lymphocytes by that virus, it being recognized that no technological means for eliminating the virus from the host DNA is possible, at the present time, or seems likely to be developed in the next decade.

(2) The development of biologics and/or drugs that ameliorate or modify the state of immune dysregulation with predominant immunodeficiency that is the hallmark of this disease. There is developing evidence that support of the immune system is possible in these patients. In my view, too little attention is being paid to this critical aspect of the problem. It is surprising that the repair of the immune deficiency in AIDS/ARC has, to date, been considered to be the least important aspect of treatment and control of this infection.

We submit that while extensive efforts have been undertaken in the area of development of anti-viral agents, there is too little effort being directed toward a comprehensive understanding of the pathogenesis of this disease, and the effects of HIV on the immune system. Such information would, of course, also be critical to development of vaccines. Moreover, in our judgment, there has been a lack of appropriate emphasis on the development of drugs and/or biologics which can modify or repair the immune deficiency. The drug development programs currently underway are weighted too heavily in the direction of anti-viral therapy. While there are some initiatives being undertaken in the area of immunosupportive drugs, the basis on which drugs of this type have been selected for testing under the NIH drug development programs has been unclear.

A consideration of importance as regards the development of immunosupportive or immunoreconstructive drugs is the apparent ability of the immune system of patients with HIV to undergo a process of immunologic compensation. For example, some patients with HIV infection manifest normal functional immune responses, notwithstanding an absolute reduction in numbers of their $CD4^+$ (T helper) cells. What appears to happen in these instances is that the remaining cells work harder to "take up the slack." While the remaining cells are capable of doing this, the immune system maintains a normal or near normal level of function. However, as more $CD4^+$ cells are destroyed, the compensatory capacity of the remaining cells becomes compromised, and immunological function declines. If a drug or biologic could stabilize a compensated immune system or prevent decompensation, that would likely be beneficial for the patient.

In this context, the development of drugs/biologics capable of moving a patient's immune system from a state of immune deficiency to one of more normal function would likely have an impact on this disease. Such a drug/biologic would not be a cure, since it would not eliminate the virus, but it could control some of the manifestations and course of the disease.

The specific rational for an immunosupportive drug in HIV disease is as follows:

(1) A principal feature of the disease is an immune deficiency.

(2) Although it is possible to design a program for development of anti-viral drug(s) for widescale application to all HIV infected individuals, such drug(s) are not presently available. The anticipated timetable for such drug(s) is a minimum of five years, with time frames out to fifteen years.

(3) It is clear that correction of the immune defect is a desirable objective, and it is reasonable to anticipate that improving immune function would reduce the frequency of opportunistic infections, and possibly malignancies in HIV infected patients.

While it is claimed in some quarters that an "effective" anti-viral would eliminate the necessity for an immunosupportive drug, since the immune system would regenerate on its own, it is important to point out that the ability and/or the period of time required for the $CD4^+$ cell population (or progenitors thereof) to be reconstituted in adequate numbers and function, once viral production is suppressed, is unknown. In this respect, attention should be paid to the possibility that bone marrow progenitor cells may be latently infected with HIV, and that such latent infection may well affect the ability of such cells to adequately reconstitute the immune system.

A further important consideration is the prospect that a drug having supportive effects on the immune system might enhance immune reactivity against strains of HIV virus which infect particular patients. That is, this might provide a means for enhancing the ability of the patient's immune system to react against the particular viral strains which have infected the patient. This concept of post-infection vaccination, which is possible owing to the long latent period seen in this disease, has been advanced by several researchers, and is an initiative that should be vigorously addressed, since:

(a) it might provide a means for possible protection of patients who have already been infected with HIV,

(b) it would be an extremely useful ancillary to a vaccine, if a vaccine were developed,

(c) it would reduce the need to come up with effective vaccines against multiple viral strains.

The development of immunosupportive drugs or biologics should be viewed as complementary to the development of anti-viral drugs for widescale application to HIV infected individuals. As developments proceed to find drugs which suppress production of new HIV particles and/or prevent infection of healthy $CD4^+$ cells by new viral particles, it is important to keep in mind the requirement that such drugs must be free of significant toxicity on either bone marrow precursors of immune cells, or on effector cells of the immune system. To date, we believe that there has been too great a concentration of effort on developing anti-viral therapy, and too little emphasis on learning about and correcting the disorders in immune function which are manifested in variable degrees in HIV infected patients.

I would now like to describe a case in point of development of an immunosupportive biologic.

If one views the history of biological response modifiers beginning with the interferons (late 50's) to the interleukins (mid 70's), the general approach has been to take these substances which had been found to have effects on viruses or immune cells in the laboratory and use them clinically to see if they had desirable effects.

The approach we have taken is to extract from cells of the immune system (generally, white blood cells) substances which could be shown in human test subjects to have important effects on the immune system -- in particular, substances that could strengthen the body's response against foreign substances such as tetanus toxoid (vaccine). We were able to systematically identify, isolate, purify and patent a group of such substances, one of which has now been designated as IMREG®-1. The immunologically active components of IMREG®-1 have been shown to be chemically related to the enkephalins, a group of important neuropeptides peptides. I might say that these developments began in 1980, and that it was necessary to look to the capital markets for the necessary commitment of financial resources over a reasonable period of time, in order to take these initiatives forward.

Our concept was that these naturally-occurring immunoregulators might be useful in diseases such as cancer, rheumatoid arthritis and other conditions in which a disordered immune system plays a role in the disease. From the outset, these substances were know to affect cell mediated immunity and therefore, it seems reasonable to suggest that they might have potential as clinical therapeutics. When we started, AIDS had not surfaced as the major public health problem that it is today. Indeed, it was only as a result of the recommendation of our Company's Scientific Advisory Board that we began to use IMREG®-1 in patients with AIDS/ARC, and we in fact had to divert resources from other initiatives in order to address the AIDS problem. We treated the first patient in 1983 and returned his ability to mount specific immunity In 1984, we began

larger studies which necessarily involved the absence of a placebo controls, as we were looking for some effect on immunity and needed to assess toxicity. We did see important effects on immune function, as well as clinically important parameters. In particular, these studies showed:

(1) Restoration of delayed hypersensitivity (capacity to respond to antigen injected under the skin) in more than 50% of patients who were unresponsive before treatment with IMREG®-1.

(2) Patients treated biweekly gained an average of three pounds.

(3) A decrease in the rate of destruction of $CD4^+$ T helper cells in patients treated biweekly.

(4) No toxicity was observed and there were no deaths on study.

Since patients at this stage of HIV infection display a progressive downhill course, we felt that the investment of our time, effort and the Company's money in a multicenter placebo-controlled trial of IMREG®-1 in AIDS/ARC patients was justified, and could not wait for application to an negotiations with NIH for support of such a trial, although an offer of cooperation from NIH would not have been declined Accordingly, such a trial has been undertaken, and has essentially been completed. One hundred fifty (150) patients have been enrolled and randomized in a 2:1 fashion. We expect to have the results of this trial and a judgement of the efficacy of IMREG®-1 in AIDS/ARC will be made by an independent review group by the end of March

I might say that these developments have been undertaken completely on our own resources, and in particular, not a single penny of federal support has been used.

Secondly, we have been able to conduct a placebo-controlled trial in this disease. One reason we were able to do so is that the trial protocol called for providing IMREG®-1 for six months to any patient who completed the trial, or reached an endpoint. We are now confronted by a very difficult question. Several of these patients who have completed the 6 month compassionate course (following their participation in the 6 month trial) are asking that they be kept on treatment. We do not have permission from FDA to do this, and we would hope that under the new federal regulations pertaining to experimental drugs, the FDA will see fit to permit these patients to continue to be treated.

PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

Statement of
Dr. Richard S. Ross
Dean of the Medical Faculty
Johns Hopkins University School of Medicine

February 18, 1988

The medical schools and universities are ideally suited to become the focus of major comprehensive programs directed at the control of the HIV virus epidemic. The programs should include public health education and, hence, the universities with both medical schools and schools of public health have special strengths. Clinical investigation to include evaluation of therapeutic agents is another area in which medical schools and teaching hospitals have unique expertise. Basic retroviral research must also proceed at a more rapid pace if new drugs and vaccines are to emerge for clinical trial.

The medical schools have people who have the necessary skills and interest in all these areas, and more importantly, can attract and train others. The limiting factor is lack of space. None of the excellent academic medical centers have space available in the quantity necessary to mount a comprehensive program. New space of a very special sort must be provided if the pace of research, education, and patient care for AIDS patients is to accelerate.

I propose that the comprehensive cancer center program of the early 1970s be taken as a model for a HIV centers program. Four or five HIV centers would be constructed in conjunction with major academic medical centers. Each center would have programs in prevention, education, clinical care,

clinical investigation, and basic retrovirus research. Such centers would provide a critical mass of experts in these various areas, and the interaction between the various groups would be extremely productive. Problems arising in patients could be taken to the laboratory for solution, and ideas developed in the laboratory could be brought to rapid testing in the clinic. The centers should be bound together by a coordinating mechanism so that concerted action could be directed at specific problems. For example, a new drug could be subject to trial using the same protocol in all the centers. A large number of patients could be studied in a short period of time by the same method and questions answered more rapidly.

Not all the available funds should be allocated to the comprehensive center program. An approximately equal amount should be made available to be allocated to institutions proposing quality research programs in one or more, but not all the areas in the comprehensive centers. For example, it should be possible to provide funds for the creation of a new P3 laboratory to encourage an established virologist to enter HIV research.

In summary, the critical need is for facilities, both comprehensive centers as well as other laboratories, associated with academic medical centers.

GMHC

The AIDS Service and Education Foundation

Testimony
Presidential Commission on the HIV Epidemic

Barry Gingell, M.D.
February 19, 1988

I have been asked to discuss my personal involvement with AIDS drug development and access. I am a physician and am currently the Director of Medical Information for Gay Men's Health Crisis, the nation's foremost private organization providing patient services, education and advocacy for people with and at risk for AIDS. For several years, I was a primary care physician and have treated many patients with AIDS and ARC. Over three years ago, I myself was diagnosed with AIDS.

My diagnosis in January, 1985 was, of course, a great shock to me. But, being a physician, I felt that I had a better-than-average chance of beating AIDS. I thought I would be able to access clinical trials and experimental drugs easily. I knew that some progress was being made in the search for effective antiviral drugs. But much to my dismay, I soon discovered that my search for experimental drugs would not be easy. I had waged a successful battle with PCP pneumonia, but the next hurdle, accessing antiviral and/or immune modulating therapies, proved infinitely more difficult.

I discovered that there was no centralized registry of trials of AIDS drugs, and so my search for appropriate clinical trials took the form of an endless series of telephone inquiries to researchers across the country. I was promised that I would be first in line for two different trials, one with Ribavirin and one with Foscarnet, in the Spring of 1985. By September, neither of the trials materialized, and I knew I was losing precious time. I learned that Ribavirin, a drug which was shown to have activity against HIV in vitro one year earlier, was available essentially over-the-counter in Mexico. And so I joined the other hundreds of patients in Tijiuana to smuggle in a drug that I hoped might stop the progressive damage that I knew was occurring to my immune system.

I was successfully maintained on Ribavirin for over 14 months without serious opportunistic infection. When AZT became available on a Treatment IND, I opted for it instead of Ribavirin, primarily because of the easy availability and apparent superior antiviral activity.

We now know that AZT exacts a very expensive price, both financially and in terms of toxicity. The magnitude of this toxicity is increasing with time. A recent study on the original cohort of AZT recipients who took the drug for one year provides us with the sobering figures: fully 40% of patients experience serious hematologic toxicity after one year, and 25% have to be discontinued entirely. The magic drug Retrovir which has been foisted on the public as a triumph against AIDS is actually turning out to be a cumulative poison. While it may prolong life in the short term, AZT creates its own set of serious hematologic problems, which may in fact contribute to the disease rather than moderate it.

Yesterday, none of the testimony focused on the serious limitations of AZT, and I feel that they need enumeration. First, as I have mentioned, AZT causes serious bone marrow suppression, resulting in lowered red and white cells in the blood. AZT-induced anemia is becoming quite commonplace, and some have expressed fears that the increasing number of transfusions associated with AZT may put a serious strain on the nation's blood supply. AZT-induced neutropenia may be a contributing factor for the increasing numbers of bacterial infections now being seen in AIDS. Second, AZT works at a stage of viral replication after binding of the virion to a susceptible lymphocyte. As mentioned in previous testimony, cell-to-cell transmission is an important way in which HIV is spread within the body. AZT has no effect on blocking cell-to-cell HIV infection. Third, it has been recently demonstrated that AZT is not effective in the monocyte-macrophage because this type of cell lacks the enzymes necessary to activate the drug. Thus, this cell which is already thought to be a reservoir for virus in the body, actually protects the virus within it from inhibition by AZT.

Because of these serious shortcomings of this drug, AZT should actually be considered only a prototype antiviral drug. However, fully 80% of patients in NIH-sponsored clinical trials are taking AZT. At the same time, many drugs which have shown promise either in in vitro studies or limited pilot studies and are less toxic than AZT are being ignored.

Ribavirin, the drug which I procured in Mexico in 1985, was shown to have in vitro anti-HIV activity in November, 1984. From preliminary studies (none conducted at NIH), Ribavirin seems to be less toxic than AZT. Why has it taken over 3 years to get a definitive study of this drug underway? What

does this kind of delay say about the process by which we are evaluating potential AIDS therapies?

A similar in vitro observation was made for AL721 in October, 1985 by Dr. Gallo at the NIH. This anti-HIV activity has since been confirmed by Dr. Laurence, who delivered testimony during yesterday's session. AL721, actually a food substance, seems to have no toxicity whatsoever. Yet these and other promising drugs are being overlooked by NIH while they exhaustively study their crude first attempt, AZT. These follow-up studies of AZT could be easily financed and conducted by Burroughs Wellcome which is making money hand over fist with the drug. Why are we devoting precious government resources on studying every conceivable aspect of AZT when we know its critical limitations? Why, at the same time, are other drugs are caught up in endless red tape or stymied by petty quarrels between pharmaceutical companies and governmental agencies?

As is typical for people taking AZT in the long-term, I reached the end of the road with the drug less than one year after starting it. Eight months after beginning AZT, my white cells progressively decreased to dangerously low levels despite dose reduction and culminated in a bacterial pneumonia which almost cost me my life. Since there is no alternative antiviral available to me, even through a clinical trial, I again have found myself in the situation I was in three years ago: searching for available, hopefully safe and possibly effective drugs. If I am to continue antiviral therapy, I must again procure a substance which is illegal and for which very little is known. There is no excuse for this ignorance given the long delays these drugs have experienced in the testing process. I would have hoped that by this time at least pilot studies would have been done on AL721, Ampligen, Ribavirin, and Dextran sulfate to assist me in my decision. They have not.

Based on my own experience and the experiences of other People With AIDS, I would therefore make the following recommendations to the Commission:

1. It is imperative that a comprehensive, up-to-date registry of clinical studies of AIDS drugs be created in order that patients and physicians might find appropriate clinical studies. Locating clinical trials must not be a hit-or-miss endeavor. A similar system, PDQ, exists for cancer trials and must be created for AIDS trials.

2. The NIH must expand clinical trials and lower the threshold for testing potential AIDS therapies. Substances which have passed toxicity studies and which are in widespread use must be tested in small pilot studies to confirm or disprove anecdotal data.

3. Community-based research groups should be given special consideration in designing clinical trials for AIDS therapies. These organizations represent large patient populations in all stages of HIV related disease who are generally eager to participate in clinical trials. By coordinating clinical trials with primary care, trials can be accelerated and patients' lives simplified.

4. Physicians and patients must be made aware of drugs which nave been made available through the FDA's new Treatment IND regulations. In addition, physicians must be trained on how to access these experimental drugs for their patients. At the recent conference in Washington sponsored by the FDA and the AMA, it was disconcerting that physicians left the conference as ignorant as they arrived as to the procedure for applying for drugs through Treatment INDs.

Thank you.

People With AIDS Coalition

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TESTIMONY OF

MICHAEL L. CALLEN

Founding Member,
People with AIDS Coalition (New York)
and
Member,
New York State AIDS Advisory Council

before

Presidential Commission on the
Human Immunodeficiency Virus Epidemic
RESEARCH HEARINGS

Friday, February 19, 1988
9:30 a.m.

My name is Michael Callen and I am a gay man with AIDS. I was diagnosed with cryptosporidiosis in the Summer of '82 and have been hospitalized several times since then with various opportunistic complications. I am one of the 15% or so long term survivors of AIDS recently reported in CDC researcher Dr. Rothenberg's long term survivor study.

I mention the fact of my long term survival to emphasize that I've been dealing with this epidemic a long time and I've seen a lot in the 5 1/2 years since I was diagnosed. I've witnessed the desperate scramble for treatments--any treatment. And seen friends fly around the world in search

of a cure, frustrated with the sluggish treatment research response here in the U.S.

Because my time is limited, I will focus on two points. One--and I sha'n't belabor this point--is that I do not believe HIV has been proven, by any respectable standards of classic scientific inquiry--to be "the cause" of AIDS. To that extent, I think this Commission is woefully misnamed. But I don't intend to take up that hot potato here--at least not directly. My point could be restated thus: the cause or causes of AIDS remain(s) unknown and we are senselessly limiting our search for treatments to drugs which are anti-retroviral because we arrogantly assume that we know the cause of AIDS.

If I understand the recent New York Times' series on AIDS, specifically Monday, February 15th's article entitled "Campaign to Find Drugs for Fighting AIDS Is Intensified," we are limiting drug trials to substances which, in the test tube, show some anti-retroviral effect. That is a lot of eggs to be putting in the HIV basket since other viruses which don't happen to be retroviruses may well be more important than HIV in making people sick with what we call AIDS. I think a CMV treatment would do far more good than an HIV treatment.

I asked FDA Commissioner Frank Young if anti-HIV activity was the litmus test used to prioritize substances to be tested and he denied that this was so. But the Times

article seems to suggest that my suspicion is correct. There are many substances which the People with AIDS community is clamoring for which aren't anti-retroviral, but which, anecdotally at least, seem to be making people feel better. Isn't this, after all, what the goal of treatment research ought to be?

My main objection to what I call the religion of HIV is that it oversimplifies what is a very complex disease. T-cell problems are only one small part of AIDS. There are the B-cell problems. And auto-immune components. Indeed, just about everything that can go wrong with the immune system seems to be going wrong and it seems simplistic to attribute everything to poor HIV. I fear that by limiting our search for treatments to anti-retrovirals, we are only pursuing one small portion of what we might be doing.

Lipid research is a good example of this. Lipids may or may not be anti-retroviral, but they seem to repair cell damage--something which certainly is happening in AIDS. Why has Dr. Fauci and the NIH only so begrudgingly begun trials? It's as if they don't want to believe anything does damage other than "the virus." Another example is PCP prophylaxis. Preventing the number one killer of people with AIDS ought to have been the #1 treatment priority. Instead, the AIDS community has brought it about largely through word of mouth. As a result, in nearly every AIDS practice in New York City, PCP prophylaxis is now standard procedure--despite the lack

of the kind of "proof" that NIH seems to be demanding. And I believe that PCP prophylaxis will, in a single stroke, save more lives than all the AZT in the world.

Before I end with my second and final point, let me acknowledge that I am unable to fulfill your request to recommend "improvements in the federal agencies" or to suggest "better working partnerships between the private sector and Federal, state and local public entities." I am as much at a loss as the government seems to be. Except for the Community Research Initiative, about which you will hear testimony tomorrow, I see no creative solutions to the log jam of federal treatment research other than the creation of a Manhattan project for treatments which would essentially pursue every reasonable lead with all due haste.

That said, my final point is this. One essential fact of human nature has been ignored in the design of federal treatment trials, and that is that desperate people--people who believe they are facing certain death--will lie and cheat and generally do whatever they have to do to stay alive. In a situation like AIDS where there are no proven treatments, getting into a treatment trial is viewed as the only chance one has to save one's life. In other words, we're losing the important distinction between providing access to drugs and the proper conduct of treatment research. They are not be the same thing, but with AIDS they are.

Much of the treatment research done so far--and in particular, I refer to the AZT trials--isn't very good research because it has been designed in academic, ivory towers, far from the real world. Placebo double-blind trials may be the quickest, simplest and cleanest way to get good data, but they are not the only way; and given the reality of AIDS, it is unreasonable to expect us to participate in placebo trials. As I said, there has been lying on the part of participants; some doctors have fudged lab tests to permit their patients to meet trial entry criteria; some people have had their pills analyzed to see who was on placebo and who was getting medication; and there's been just about every other kind of "cheating" you could imagine.

Before you blame us, put yourself in our shoes. Wouldn't you do the same if you believed your <u>only</u> hope was to get an experimental drug?

The central problem seems to me to be the placebo fixation of federal treatment research design. People with AIDS should not be asked to die for the greater good of research. <u>Death</u> should not be the efficacy measure of a drug.

I will end with one suggestion which connects the two points I've just made. There exists in the world a veritable arsenal of substances which one could lay out on a spectrum from herbs and lipids through highly complex and toxic synthesized chemicals. I would suggest that one can

construct two parallel lines and lay out each substance along those lines. One line would represent each substance's toxicity--at one end, substances like lipids and herbs which have no or low toxicity, and at the other end, substances like AZT which have staggering toxicity. Parallel to that toxicity spectrum would run a line along which one could estimate efficacy--and hopefully not just efficacy as an anti-retroviral. Rather, the question to be asked should be this: is there <u>any</u> theoretical reason to believe a particular substance will help <u>any</u> of the impairments found in AIDS?

Once one has laid all substances out along these two lines, it seems to me that the place to concentrate first is on substances with low or no toxicity which have some theoretical efficacy. Again, lipids provide a good example. Instead of blasting people with AIDS with the most toxic stuff we've got, let's start at the other end of the spectrum. Or, if we must, do both kinds of treatment research simultaneously.

As others have said, and I'm sure others will say, there ought to be many more clinical trials going on than there are.

The time for excuses is long past.

Thank you.

Testimony of Jay C. Lipner

My name is Jay C. Lipner. I am an attorney here in New York City. I am a partner in the law firm of Silverstein, Langer, Lipner & Newburgh. I volunteer my time to Lambda Legal Defense and Education Fund, the Community Research Initiative, and Gay Mens Health Crisis. (GMHC)

I am a member of the Subcommittee on Access to Therapeutic Trials of the New York State Department of Health AIDS Advisory Council. My legal background includes ten years of experience with federal/state income assistance programs, which familiarize me with federal litigation, rulemaking, and legislative analysis. I have also had three years of experience with toxic waste litigation, which involved daily and close work with the New York State Department of Health. I have worked in both New York and Washington, D.C.

I have been involved with AIDS as an attorney since 1982, when I first began to work with GMHC. I have had scores of clients with AIDS. I have visited them in hospitals when they were too ill to come to my office. I have seen people get sick and die, and have watched in growing frustration as the epidemic has grown. After five years of day-to-day exposure to AIDS, I thought I understood what it was like, but I was wrong. I did not gain that insight until I also became a person with AIDS.

I got sick with very little warning in March, 1987, when I developed pneumocystis carinii pneumonia (PCP). While recovering, I decided not to return to private practice. It is too stressful, and makes time and deadline commitments I no longer felt capable of meeting. I decided instead to volunteer my time as a lawyer to Lambda Legal

Defense on the issue of access to experimental drugs. I did this for two reasons: first, to utilize my skills and knowledge as a lawyer at a pace that I could manage; and second, to keep on top of drugs and treatments which might prove beneficial for myself.

My first lesson in drug education came soon. After I had recovered from PCP, my doctor strongly recommended that I begin taking AZT. I knew that AZT had possible toxic side effects, and was very anxious about starting it, but it did not seem that I had any viable options. As my knowledge grew, my concerns multiplied. I began to understand how the FDA's policy has limited the availability of drugs for people with AIDS and ARC. This is what I want to talk about today. I am testifying both as a person who has sought drugs for treatment use and as an attorney on behalf of Lambda Legal Defense. Lambda is the nation's oldest and largest lesbian and gay legal organization, and in recent years has been in the forefront of the nationwide fight against AIDS-based discrimination.

AZT is an anti-retroviral drug. It works by preventing replication of the HIV-virus. It does not help reconstitute an already crippled immune system. To accomplish this, one needs an immunomodulator. To date, however, no immunomodulator has been approved by the FDA for use in treating AIDS. The FDA has approved only AZT. And as time went by, I began to understand ;how the FDA's policy has limited the availability of drugs for people with AIDS and ARC.

As the Commission members know, before a drug may be sold commercially for a new treatment use, the manufacturer must obtain approval from the FDA. It does not matter if the drug is approved for use in other countries, or has been approved for a different treatment use. Each new or different treatment use must be approved by the FDA. This process is lengthy and complicated, and moves by stages through initial research, data on animal toxicity, and human trials, which progress in stages (Phase I to Phase II to Phase III). At any step along the way, the FDA may reject data without giving its reasons. Similarly, the FDA may also refuse to approve commercial marketing of the drug when trials are completed, again without giving reasons.

Drug approval is a risky and expensive game which can take 5 to 7 years or longer. The process heavily favors the NIH and large drug companies, which have the staff, the experience, and the budget to play the game by the FDA's rules. In the interim, until a drug has been approved for use, (or granted "orphan drug" status) there are only two ways for a patient to lawfully get drugs in this country: (a): participating in a drug trial or (b): asking for the drug on a "compassionate need" basis. Both these approaches had serious drawbacks. Drug trials are limited in their size and location, and have rigid inclusion and exclusion criteria. Compassionate use is viewed as a last ditch effort, and is used on a case-by-case basis for patients who are critically ill. It involves considerable paperwork on the part of the treating physician. What other options are open to people who have already developed AIDS? This is the question I started with.

Within a short period of time, I thought I had an answer -- a "treatment IND".

Treatment IND is the name FDA has given to a new policy set forth in regulations issued on June 22, 1987, in the Federal Register. These regulations purport to make experimental drugs more widely available to people with AIDS, and has been widely reported in the press.

The treatment IND regulations are not easy to understand because they are poorly written and raise more questions than they answer. These are the essentials: a drug company may apply to the FDA to sell a drug for treatment use even while that drug is still undergoing clinical trials. The manufacturer must be actively pursuing approval of the drug, and the drug must be intended for use in a life-threatening or serious illness. Life-threatening is defined in the regulations as including AIDS. A treatment IND may be granted for persons with AIDS as early as Phase II of clinical trials. A drug may be approved for persons with a serious illness once the drug has reached Phase III. Since the regulations do not define serious illness, it is not clear how a person with ARC would be treated.

Although the regulations stress that a treatment IND is to be used for drugs which have manageable or acceptable side effects, there is no standard for judging whether a drug has proved sufficiently effective to warrant treatment use prior to final approval. This is left solely and completely to the F.D.A. Commissioner.

Since the application must be initiated by the drug company, with no indication of the standard for approval, why would companies want to apply for a treatment IND? The answer is they wouldn't. It is not in their interest. It is not in their interest for several reasons: (a), the treatment IND would invite unwelcome scrutiny of interim pricing of the drug; the drug company loses control over the collection of data when the drug is taken outside the scope of a clinical trial, thus possibly jeopardizing their NDA; (b), a treatment IND would increase the number of persons receiving the drug, thus increasing the drug company's potential liability if someone gets sick while taking the drug; and (c), the application process would impose additional requirements of staff time, paperwork, and product procurement. For these reasons, and others, a treatment IND would be counterproductive, and might jeopardize ultimate approval of the drug. The fact that only government-sponsored drugs have been granted treatment IND status illustrates this problem. The large pharmaceuticals will not apply. Trimetrexate is an NIH sponsored drug. The interim of approval of AZT came <u>before</u> the treatment IND regulations, not as a result. It is thus not surprising, that eight months after FDA issued the regulations, little has changed.

Please let me give you a personal example of how FDA policy affects people with AIDS. I asked my doctor to try to obtain a drug called Imuthiol for my use as an immunomodulator. The drug is manufactured in France, and is being used there in the treatment of AIDS. The drug is in FDA-approved clinical trials in only six locations in this country,

none of which is in New York State. My doctor wrote to the manufacturer and requested that this drug be made available to me on a compassionate use basis. The company declined, citing its desire to complete the formal FDA approval process before making the drug further available. Other doctors also approached the company, but to no avail. At that point I helped to draft a letter to the company from Lambda Legal Defense and others requesting that the company institute a treatment IND for this Imuthiol. The company has not yet replied.

These efforts to obtain Imuthiol took months, and produced nothing. I am no closer than when I started. If I wish to obtain the drug, my only option at this point is to go to France and attempt to obtain the drug there. This would be difficult for several reasons. My only income is from Social Security and a private disability policy. A trip to France would be prohibitively expensive, depleting a month's income. I fear the trip would subject me to considerable physical stress, which I doubt would do anything to improve my health. Obtaining the drug in the United States is also out of the question. The clinical trials are closed. Even if they were open, I could hardly afford to commute to Texas, California or Arizona.

My dilemma, I believe, illustrates clearly how lack of access to drugs affects people with AIDS. AZT has proved too toxic for me to take at full dose. Even at half dose, I have required two transfusions. If I must take AZT, I want access to other drugs that will help repair my immune system. If time permitted, I could give you other examples of

drugs that might prove beneficial to me now or at a future time, but I hope this illustrates the point. This effort to obtain drugs is time consuming, stressful, and mentally exhausting, and I suspect that being a lawyer equips me better than most people with AIDS to deal with the issue. After several months of research on treatment INDs, I have concluded the FDA never intended the treatment IND process to work in any significant way beyond AZT. It was intended to obtain favorable press for the FDA, and in that, it worked. The conflict between the reality of the drug regulation process and the treatment IND regulations has wholly escaped television, radio, and the print media. Commissioner Young has made frequent statements to the effect that the treatment IND regulations mark a major change in policy, and the press has duly reported it. But there has been no major change in policy. What there has been instead is an effort by the FDA and the Reagan administration to create the impression that drugs have somehow become more available to people with AIDS. In the interim, the death toll from AIDS mounts daily.

If the FDA is truly interested in making drugs available to people with AIDS and ARC, it must restructure the treatment IND regulations. The FDA should begin by removing the emphasis on a drug's effectiveness. Efficacy is the standard to be used for final approval. If the same standard is used for a treatment IND, the regulation is meaningless. The appropriate question for the FDA should be whether the drug has manageable side effects. If the answer is yes, then persons with AIDS and ARC should have access to the drug while the clinical trials

proceed. The FDA's present policy does the opposite. It denies access to people who are dying because it is not clear the drug will work. This is absurd. The FDA's policy also fails to address the concerns of the drug manufacturers. Drug companies should be given financial incentives to encourage them to apply for a treatment IND similar to that given to orphan drugs. In addition, the FDA must provide assurances that application for and subsequent use of a treatment IND will not jeopardize final approval. Another means of providing incentives to pharmaceuticals to apply for treatment IND would be for the FDA to promise to give priority to those NDA's in which a treatment IND has been submitted. If these steps require changes in the FDA statutory authority, such changes should be undertaken immediately.

I hope the Commission understands my frustration in being allowed only five minutes to address such a complex issue, while Frank Young has two hours. I would therefore like to emphasize that while doing research on this issue, I have spoken and met with many, many people knowledgeable about the FDA process, including Commissioner Young. My consistent impression is that the FDA is in disarray, does not have clear policy on treatment IND's, and has placed its greatest emphasis on public relations. I believe such a conclusion is inescapable, for as we sit here discussing this issue, the situation remains as it was on May 22, 1987 when the regulations were issued.

I appreciate the opportunity to testify, and would welcome any questions members of the Commission may have.

Jay C. Lipner
February 19, 1988
New York, New York

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STATEMENT OF

FRANK E. YOUNG, M.D., Ph.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

U.S. PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE

PRESIDENTIAL COMMISSION ON THE HUMAN
IMMUNODEFICIENCY VIRUS EPIDEMIC

NEW YORK, NEW YORK

FEBRUARY 19, 1988

I am pleased to be here today to participate in the Commission's hearings on the development of new drugs and vaccines to treat and prevent the spread of AIDS. The Food and Drug Administration has an important role in the war against AIDS, and I am happy to describe that role for you today. I want you to know that we are committed to this battle, will modify our procedures to contribute in any way possible to win this war, while still assuring safety and effectiveness, and will divert whatever resources are necessary to ensure our responsiveness.

My testimony will focus on four main subjects today--how FDA regulates drugs, vaccines, blood products, and medical devices; the procedures we have put into effect to expedite the review of AIDS therapies and diagnostics; our accomplishments thus far in managing challenges posed by the AIDS epidemic; and our view of FDA's future role in assisting in the war on this terrible affliction.

I believe it significant that we at FDA have instituted new procedures for reviewing AIDS drugs, so that they are our highest priority, and new procedures for making investigational drugs more widely available to the desperately ill; reorganized our drug and biological review offices to better concentrate our efforts on those therapies; approved the first anti-AIDS drug, zidovudine, in record time, and human testing of the first two AIDS vaccines as well; and stepped up our efforts to ensure the

safety of medical devices, such as condoms and gloves, that protect against AIDS.

Nevertheless, it is equally significant that the challenges ahead that are posed by AIDS are tremendous. FDA is a crucial link in efforts to transfer AIDS research into therapy for patients. That research is growing at such a rapid pace that we are challenged to ensure that we have sufficient capability to oversee the testing of new AIDS therapies and the eventual approval of those that prove effective.

I want to expand upon those accomplishments and those challenges for the future. But first, let me note that AIDS is clearly too big an issue for any one Agency of government to handle, and that the Department of Health and Human Services, through the Public Health Service, has done a remarkable job of coordinating and supporting the efforts of its constituent agencies in their fight against AIDS. Indeed, I cannot overemphasize the importance of the efforts made by Secretary Bowen and Assistant Secretary for Health Windom in leading that fight. That coordination is assured by the work of the PHS Executive Task Force on AIDS, which is chaired by Dr. Windom, and to which FDA reports on every significant AIDS activity undertaken by me and my staff. Indeed, we rely on Dr. Bowen's and Dr. Windom's leadership on virtually a daily basis.

FDA'S RESPONSIBILITIES AND ORGANIZATION

As you know, the Food and Drug Administration's role in combatting AIDS is based primarily in its responsibility for the premarket review of new drugs, biologicals, and medical devices. To ensure that those products, once developed, reach AIDS patients as rapidly as possible, FDA has given the highest priority to providing the most timely and efficient premarketing review possible of promising new AIDS therapies.

To assure that AIDS products get that highest priority, we have implemented a number of management initiatives. First, last fall we divided FDA's Center for Drugs and Biologics into two new centers--the Center for Drug Evaluation and Research--or CDER--and the Center for Biologics Evaluation and Research. As the attached organizational chart shows, CDER is responsible for the review of most new AIDS drugs. Within CDER, the Center's Director, Dr. Carl Peck, created this month a new Division of Anti-Viral Drugs that can concentrate on reviewing the new therapies being developed to combat the HIV virus.

To complement our review of new drugs, our Center for Biologics Evaluation and Research, or CBER, is responsible for the review of new vaccines, blood products, AIDS diagnostic kits, and biological drugs (primarily the immunomodulators designed to strengthen the body's immune system). To better manage the boom

in new AIDS biologicals expected to result from developments in biotechnology, CBER's Director, Dr. Paul Parkman, is planning the creation of a new Division of Cytokine Biology, which will contain several laboratories capable of in-depth study of cell biology, immunology and other possible keys to understanding this deadly virus. I have also consolidated the coordination of all of FDA's AIDS-related activities under Dr. Parkman's able leadership, to ensure that issues dealing with AIDS are properly coordinated throughout the Agency.

FDA'S DRUG REVIEW PROCESS

Let me now summarize for you how the premarket review process operates and then discuss how we have modified our procedures to help people who are desperately ill with AIDS. Before clinical testing can begin for an experimental drug or vaccine, the sponsor or investigator must file an investigational new drug application, or "IND," with FDA. The IND must demonstrate, based on animal studies, that it is reasonably safe to test the drug on human subjects. This process is normally accomplished in 30 days with 95% of IND application; but for AIDS drugs we aim for just 5 days.

After FDA completes the IND review, the sponsor assumes the responsibility for the development of the drug. Clinical testing, whether done by the pharmaceutical company, an academic institution, or the National Institutes of Health, is normally

divided into three sequential phases. As the attached chart on the drug approval process illustrates, Phase 1 is the initial introduction of an investigational therapy into humans to determine safety. Phase 1 studies are designed to explore pharmacologic actions of the therapy, how the body breaks the drug down, and the side effects associated with varying doses. Phase 1 usually includes less than 100 patients, usually healthy ones, and may take a year to complete.

The second phase is the first controlled clinical study to evaluate the effectiveness of the drug for a particular indication and to determine common short-term side effects. A phase 2 study typically involves a few hundred patients. Most of the drugs that will fail do so in Phase 1 and 2. In fact, 90% of the drugs that are abandoned during IND research do so during Phases 1 or 2.

Once a phase 2 study is completed, the drug's sponsor has learned much about the drug's safety and effectiveness, and a larger controlled study using several thousand patients--phase 3--can be conducted. This large study can collect enough information to prove that a drug really works and can be safely marketed.

Once phase 3 testing is completed, the sponsor submits the test results to FDA in the form of a new drug application or biologic license application. FDA's medical officers, chemists,

statisticians, and pharmacologists review the application to determine if the sponsor's data in fact shows that the drug is safe and effective. Therefore, of the eight years that are typically devoted to the clinical study of drugs by the sponsor, about two years are required to review the drug.

To make this process more efficient, FDA has recently completed an extensive reform of the regulations governing the drug review process. The new regulations are intended to simplify and expedite the testing and application review phases of new drug development. Concomitant with those new regulations have been guidelines to help sponsors better plan their clinical testing and to encourage careful planning between FDA and sponsors--to ensure that testing will fully meet FDA's needs for safety and efficacy data.

Finally, we also recognize that there are times when a new experimental drug holds the promise of hope for desperately ill patients--such as AIDS patients. In those cases, it seems imperative that we allow desperately ill patients access to those drugs once a reasonable body of data exists. Although FDA has for years permitted some patients access to such drugs, last year we reached the conclusion that a formal provision should be written into FDA's regulations permitting expanded use of experimental drugs. These so-called "treatment INDs" will allow broader use during the second phase of clinical testing of drugs

for immediately life-threatening diseases. We developed criteria for determining whether a treatment IND is appropriate for particular drugs:

1) That the drug is intended to treat a serious or immediately life-threatening disease;

2) There is no comparable or satisfactory alternative or other therapy to treat that stage of the disease in the intended population;

3) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

4) The sponsor for the controlled clinical trial is actively pursuing marketing approval of the investigational drug.

For drugs intended to treat an immediately life-threatening disease, a request may be denied for treatment use if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug (1) may be effective for its intended use in its intended patient population, or (2) would not expose patients who receive the drug to an unreasonable and significant additional risk of illness or injury.

The drug AZT served as the model for these new regulations, when over 4,000 patients received the drug prior to formal marketing approval. And just last week we approved the drug Trimetrexate as a treatment for AIDS patients with Pneumocystis Carinii Pneumonia who cannot take approved therapies because of serious adverse reactions. We promise to bring breakthrough drugs to desperately ill patients as rapidly as possible. As you know, I have committed myself, not only to the development, but to the implementation of this process. Since the regulation was written, we have approved 3 drugs for Treatment INDs--Trimetrexate; Cytomegalovirus Immune Globulin for infections in renal transplant patients; and Ifosfamide and Mesna for a form of cancer. Additionally, we have fostered the administration of the drug ganciclovir--for CMV Retinitis-- to 1500 AIDS patients on a "compassionate IND" basis.

FDA'S PROGRESS TO DATE

Our efforts have already begun to produce real progress in assuring that FDA does its part in fighting AIDS. Let me summarize some of the accomplishments made thus far.

Drug Review

- A special classification, known as "1-AA," has been established for all AIDS drugs, to ensure that they receive the absolute highest priority in the drug review process.

- The first new drug application for AIDS--for zidovudine (formerly known as AZT)--received FDA approval in record time (3 1/2 months). This timeliness stands in sharp contrast to the 2 years or more the average new chemical entity spends in the review process. However, to accomplish such an expeditious review, FDA staff expended 8 manyears of effort, at a cost of $600,000, to review a new drug application 20 linear feet tall.

- FDA has received 179 applications for approval to test 120 new AIDS drugs, diagnostics and vaccines, and has approved 90% (154) of those applications thus far. The approved applications for human testing include:

  - 35 for anti-viral drugs
  - 4 for anti-neoplastics
  - 36 for diagnostics
  - 3 for AIDS vaccines
  - 45 for immunomodulators
  - 31 for drugs for opportunistic infections

- Furthermore, the number of these applications has been increasing markedly, as shown by the attached chart.

- It's important to point out, however, that 95% of those investigations are still in Phases I and II of clinical testing, and we know little of their true safety and efficacy.

- We are fortunate in having about a dozen anti-infective drugs that have already been approved by FDA, and that are proving useful against opportunistic infections in AIDS patients. Their presence has given physicians a small but important armamentarium against the ravages of the disease.

- Under the authority of the Orphan Drug Act, we have designated AIDS therapies as eligible for tax incentives and grants for products of limited commercial value. Thus far, 7 drugs for the treatment of AIDS, 3 for Kaposi's Sarcoma, and 4 for Pneumocystis Carinii Pneumonia have received "orphan" designation. Four grants for research on orphan drugs to treat AIDS have also been made.

Vaccines

On August 18, FDA granted permission for the first clinical study in humans of an experimental AIDS vaccine. That was an important first step in the development of a vaccine to prevent infection by the AIDS virus. The vaccine, manufactured by MicroGeneSys, Inc. of West Haven, Connecticut, consists of purified protein from the genetic material of the HIV virus, and was developed using recombinant DNA techniques similar to those employed in the manufacture of other recombinant vaccines. We approved a

clinical trial for a second AIDS vaccine in November. This vaccine, produced by Bristol-Myers Company of New York City, is made from vaccinia virus into which genes from the surface proteins from the AIDS virus have been inserted by recombinant DNA techniques. And most recently, we have granted an IND to the National Institutes of Health for NIH testing of the Bristol-Myers vaccine.

The Blood Supply

The initial screening test--the ELISA--was first licensed by FDA for commercial use in 1985, to ensure that the nation's blood supply is a safe one. In fact, the first three ELISA tests to be licensed were the result of extremely rapid concurrent review by FDA's biologics specialists--3 months or less--despite the complexity of the clinical trial data used to support the licensing applications. In all, we have approved 7 ELISA tests. In April 1987, FDA licensed the first Western Blot AIDS test kit for commercial use in validating initial positive screening tests for antibodies to the AIDS virus.

We believe use of the Western Blot method, in conjunction with the ELISA test, could help potential blood donors who have falsely tested positive by the ELISA method to be reentered into the blood donor pool. The two tests together have gone a long way toward assuring the nation that the blood supply is a safe

one.

FDA also has several new blood screening products under expedited review, either for marketing approval or for approval of human testing. Those include:

- ELISA tests designed to detect presence of the AIDS virus itself in blood;
- Screening ELISA tests using recombinant DNA technology;
- Detection tests for antibodies to other viruses similar to HIV (e.g., HTLV-1, HIV-2);
- Rapid immunoassays; and
- Blood sample collection kits for use by physicians for HIV antibody detection.

Semen Banks

We have also made just this month, in conjunction with the Centers for Disease Control, recommendations on semen banking and organ and tissue transplantation. Those recommendations have been provided to you for the record. They provide for the HIV testing of semen and organ and tissue transplant.

Medical Devices

FDA regulates four types of AIDS-related medical devices--barrier products, such as condoms and rubber gloves; commonly used clinical devices that could transmit HIV if not handled properly, such as dental drills and bronchoscope; modified clinical devices designed to minimize risk of transmission, such as "stick-proof" needles; and devices to treat AIDS, such as biostimulation devices.

For condoms, our primary goal has been to assure adequate quality of the products. We have increased our inspection of manufacturers and processors, and developed a program for testing both domestic and foreign-made condoms to ensure conformance with FDA's criteria for acceptability. If condoms are found out of compliance with our criteria, they are removed from the market. Because of these programs, we are observing increased quality control by manufacturers, and a concomitant reduction in the number of faulty condomsleaving the factory. Our program for ensuring the quality of rubber surgical and examination gloves is also underway and involves an acceptable criteria for glove quality. Although there is no evidence at this time that glove failure has ever contributed to a case of HIV infection, we are determined to ensure that gloves meet the highest possible standard for protecting health care workers from exposure to infection.

For devices that could transmit the AIDS virus, we are surveying the methods of disinfection to learn how sterilization procedures may be improved, and we are working with device manufacturers to improve device design in ways that would minimize risk. The development of devices intended specifically to minimize the risk of AIDS transmission, such as "stick-proof" needles, could be a substantial benefit to health care workers. We will be monitoring such devices to ensure that they actually do reduce transmission risk. Only one device has yet been submitted to FDA for approval of human testing as an actual treatment for AIDS--an electro-magnetic field generator device for treating AIDS-Related Complex. Results of that testing are not yet in, but we intend to give all such devices the most expeditious review possible.

Research

FDA staff are actively involved in AIDS research in several areas, much of it in coordination with our colleagues at the National Institutes of Health, who have the lead responsibility for AIDS research. It should be emphasized that our research is much different from that at NIH. FDA focuses on research that will facilitate our regulatory actions. Among our research are comparative analyses of diagnostic tests, methods to validate vaccine safety, studies of the basic immunologic defects associated with the disease, examinations of the biological and

chemical properties of natural interferons and their ability to modify the immune system, and efforts to develop in primates an animal model for AIDS research. We are also funding private AIDS research on the safety and efficacy of AIDS vaccines, on testing for HIV antibodies in blood donors, and other AIDS-related research. And finally, the Center for Drug Evaluation and Research is preparing a major new research effort focusing on optimizing dosages of AIDS drugs as they are developed.

Fraudulent Products

We have recently seen an increase in the number of fraudulent products intended for AIDS patients and those who fear coming down with the disease. So-called "treatments" include blue-green algae, injections of hydrogen peroxide, the food preservative BHT, pills derived from mice that have been given the AIDS virus, and herbal capsules that contain poisonous metals. For uninfected consumers, there are products such as a spermicide that untruthfully claims to kill the AIDS virus and the "Sani-Form," a piece of plastic to cover telephone mouthpieces that was promoted to protect against infection from public phones. The latter, of course, not only takes people's money, but erroneously promotes the idea that AIDS can be contracted by touching items handled by someone infected with HIV.

To counter these forms of fraud, we have mobilized our field

inspectional force to investigate those promoting fraudulent claims, prepared numerous major articles for health care publications, and initiated a public information program to alert AIDS patients and consumers against these fraudulent products.

Public Education and Information

Another part of our public education effort is aimed at improving the knowledge citizens have about AIDS and ways to combat the disease. For example, we have issued special publications of our FDA Drug Bulletin to physicians, distributed instructions on the proper use of condoms and surgical gloves, developed an award-winning information package for the medical community, and we publish a monthly update on AIDS drugs that are under development and review.

We have also stepped up our educational efforts aimed at helping people understand why there aren't more AIDS therapies being approved by FDA. You may know that some citizens, even AIDS patients, claim that there are effective AIDS drugs in existence, but unavailable because FDA will not permit their marketing. This is just not true. Thus, we are trying to improve public understanding of the drug approval process. I have brought with me copies of our recent publication on the drug development process, which is intended to help consumers understand that

drug development often takes eight or more years, yet FDA's review time occupies only a relatively small fraction of that time. We intend to ensure that our review time for AIDS drugs will take no longer than 180 days; AZT, as I mentioned earlier, was approved in 107 days. In fact, AZT's was the fastest review in recent times. And we must see to it that people understand that there is no backlog of AIDS drugs awaiting FDA review. Indeed, there is not one single new drug application for the treatment of the AIDS virus itself pending in the Agency today. Therefore, is important to emphasize that much of the frustration today is due to the difficulty in developing good AIDS drugs, and the length of time required to obtain an evaluation of candidates by sponsors (rather than delay by FDA). Furthermore, it is also important to state clearly that, if the past is a prologue to the future, 80% of the drugs now under investigation will fail to be safe and effective.

THE FUTURE

The task ahead for the public and private organizations trying to develop AIDS therapies is enormous. Indeed, finding effective drugs against any viral illness is extraordinarily difficult. One statistic illustrates that fact powerfully: to date, hundreds of antibacterial agents have been discovered, to cure virtually any bacterial infection; yet in all our years of experimentation, only seven antiviral agents ever reached the

stage where safety and efficacy are known.

Fortunately, the public and private research on AIDS drugs that has been underway since the early 1980s has begun to bear fruit. As I mentioned earlier, FDA has approved 115 applications for human testing of 81 AIDS and AIDS-related drugs, including 21 antiviral agents and 39 immunomodulators. As the attached graphs demonstrate, NIH research is growing in response to the AIDS epidemic, at a rate approximately equal to private research, which should cause a continued exponential growth in the number of Investigational New Drug applications for AIDS therapies.

As research increases for finding a treatment for AIDS, FDA's funding for product review must increase concurrently, so that we never become a bottleneck to the successful development of AIDS treatments. Indeed, I believe FDA should be a bridge between the scientists who do the research and the patients who need the products of that research. I commend Drs. Wyngaarden, Fauci, Broder, and others at NIH for their vigorous efforts to develop this research program, as well as the many other scientists within and outside government who are devoting such dedicated effort to finding a cure for AIDS. But we cannot be complacent. There is no cure for AIDS today.

Fortunately, we at FDA know something about building bridges. And over the years we have evolved five key elements for assuring

the expeditious transfer of new drug development to patients.

The first is the all-important initial communication with the sponsor. FDA staff, sometimes including myself, meet with new drug and vaccine sponsors to help them design their clinical trials.

Second, we continue that communication during Phase II and III testing, to protect against false starts and to assure that our expertise in designing clinical trials is provided to sponsors. This is particularly true of research being conducted by our colleagues at NIH, and in many small companies that have not traditionally been involved in drug development of this sort.

Third, we must--and do--always remember the crucial element of public confidence. Americans must know that the drugs and vaccines they use have been given the rigorous "stamp of approval" of FDA's scientists--that they can be confident that their therapies do work and are effective.

Fourth, we developed a way of getting a good product over that bridge before the span is fully completed. I'm referring to the Treatment IND regulation I mentioned earlier. With Treatment INDs, we can permit the use of promising experimental drugs for the desperately ill while clinical trials are being completed--as we did with AZT and are now doing with Trimetrexate.

Finally, FDA must have enough workers to build that bridge. As public and private AIDS research increases, demands will flow to FDA from drug developers for guidance in designing research protocols and for final product review. When that happens, as it surely will--and already is--FDA must be a catalyst and facilitator, not a rate-limiting factor slowing the movement of products across my theoretical bridge.

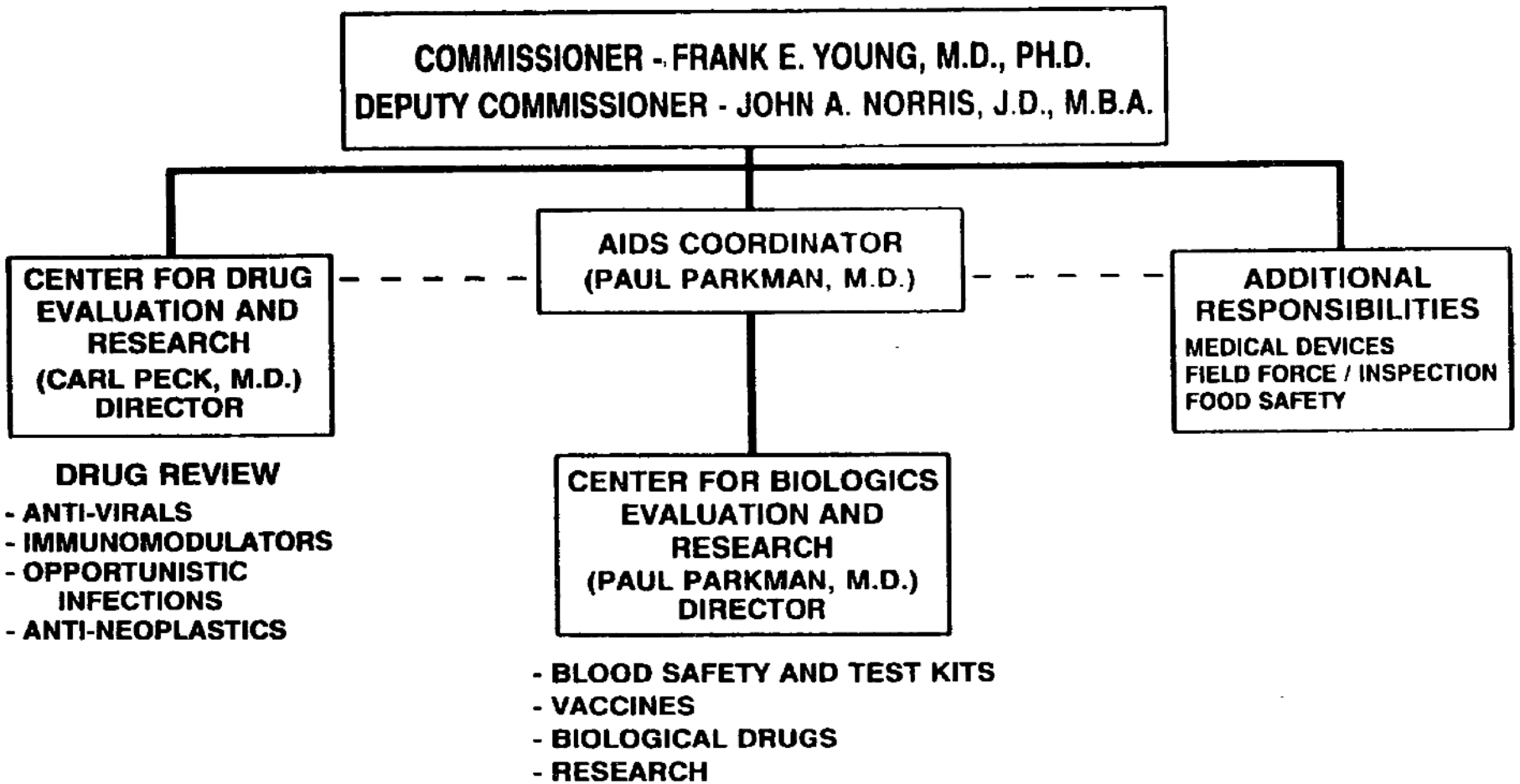
Although we readily devoted 8 manyears of effort over a 3 1/2 month period to the review of AZT, as I described earlier, our ability to "drop everything" to review new AIDS drugs is limited. In fact, if only the percentage of INDs that normally become applications for marketing--20%--reach that stage, we would be hard pressed, because of the overwhelming workload, to swiftly transfer the fruits of the research efforts, as we did with AZT, to the patients who so desperately need them.

We are working with Drs. Bowen and Windom within the Department of Health and Human Services to secure the necessary resources to prepare ourselves for the expected future demands for review of AIDS therapies. And we are reallocating resources within FDA as well, with the understanding that no more important priority exists than the war against AIDS. Finally, we are working closely with the Institute of Medicine and the Pharmaceutical Manufacturers Association to develop creative new solutions to

our substantial manpower recruitment and retention problems--solutions such as fellowship and physician training programs, improved automation, and assistance from academia. I welcome your suggestions for improvements in these areas as well. We stand prepared to implement your good suggestions.

Thank you.

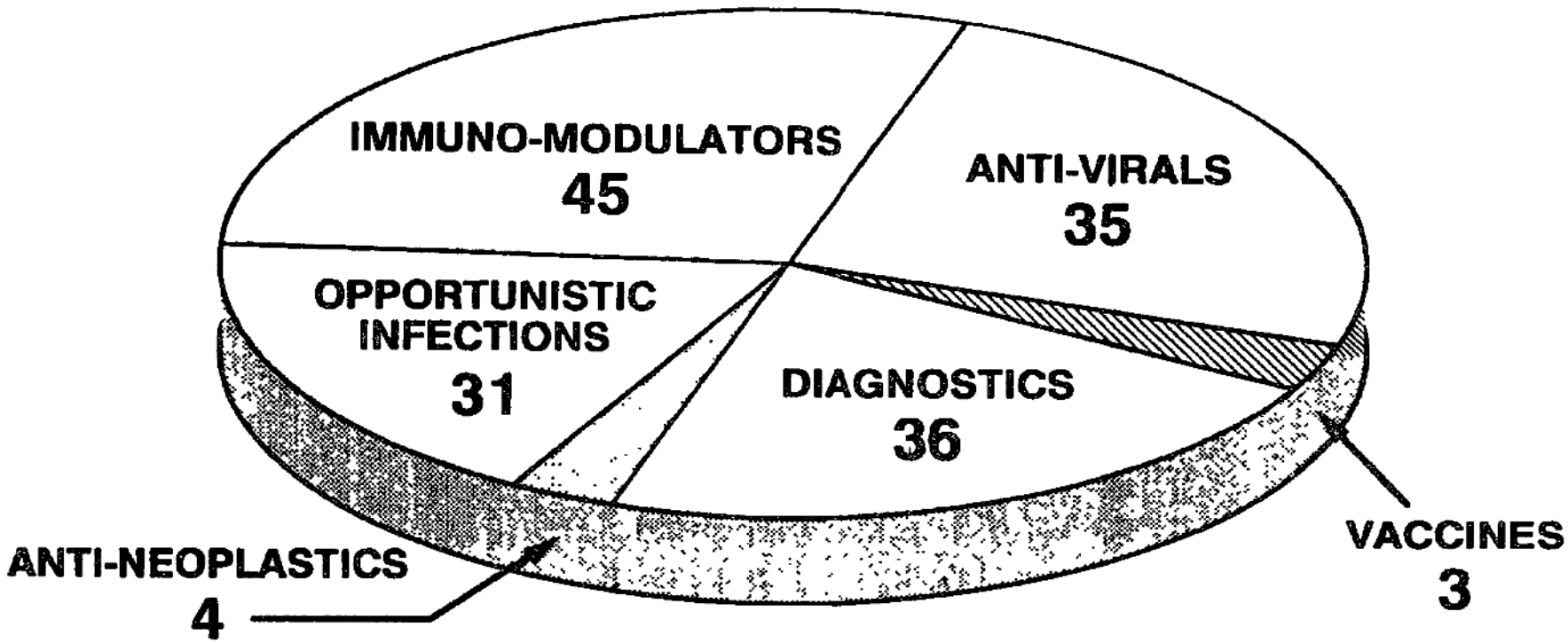
FDA COORDINATION OF AIDS ISSUES



AIDS INDs

TOTAL = 154

Approved As of Jan. 31, 1988



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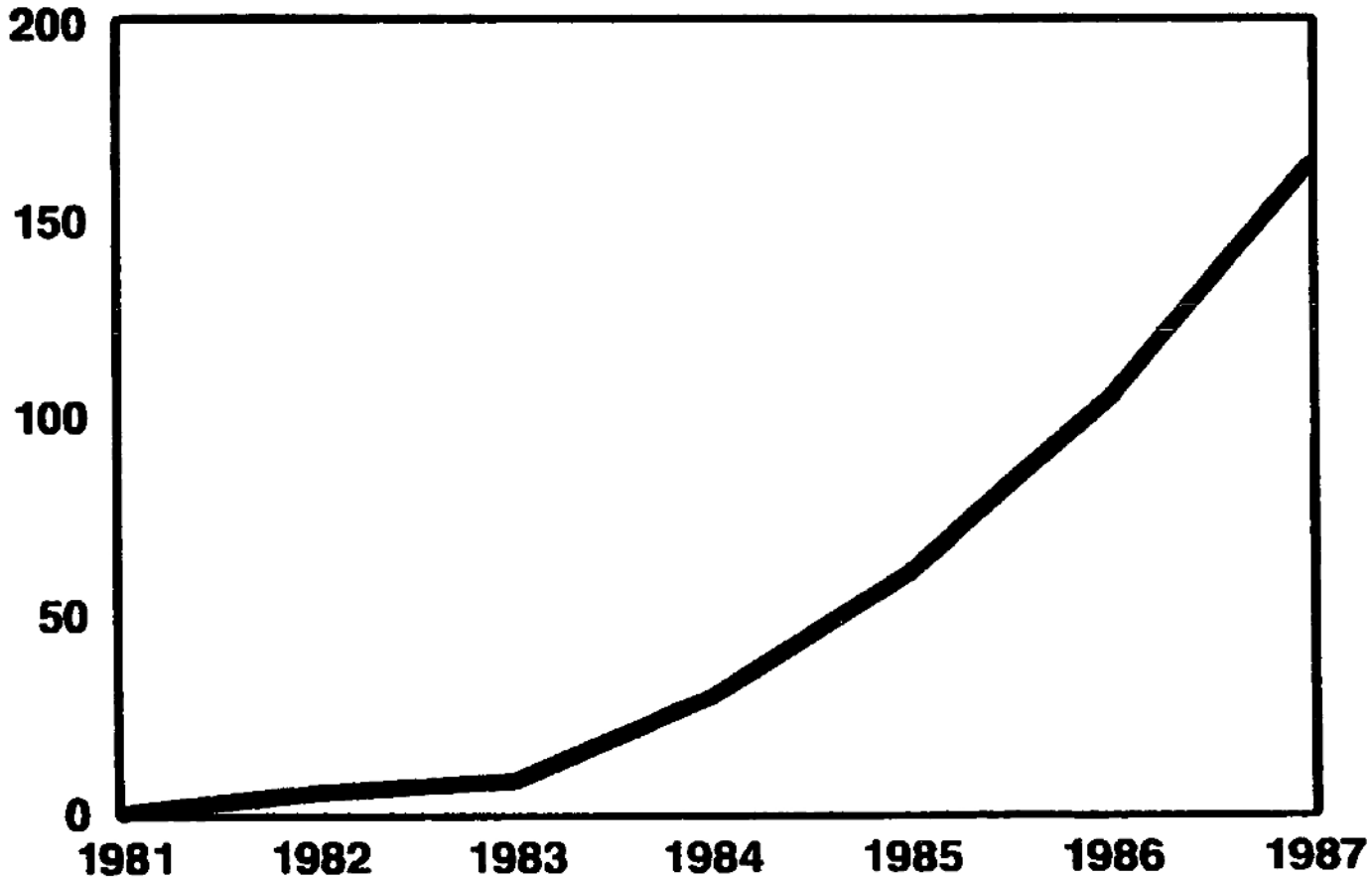
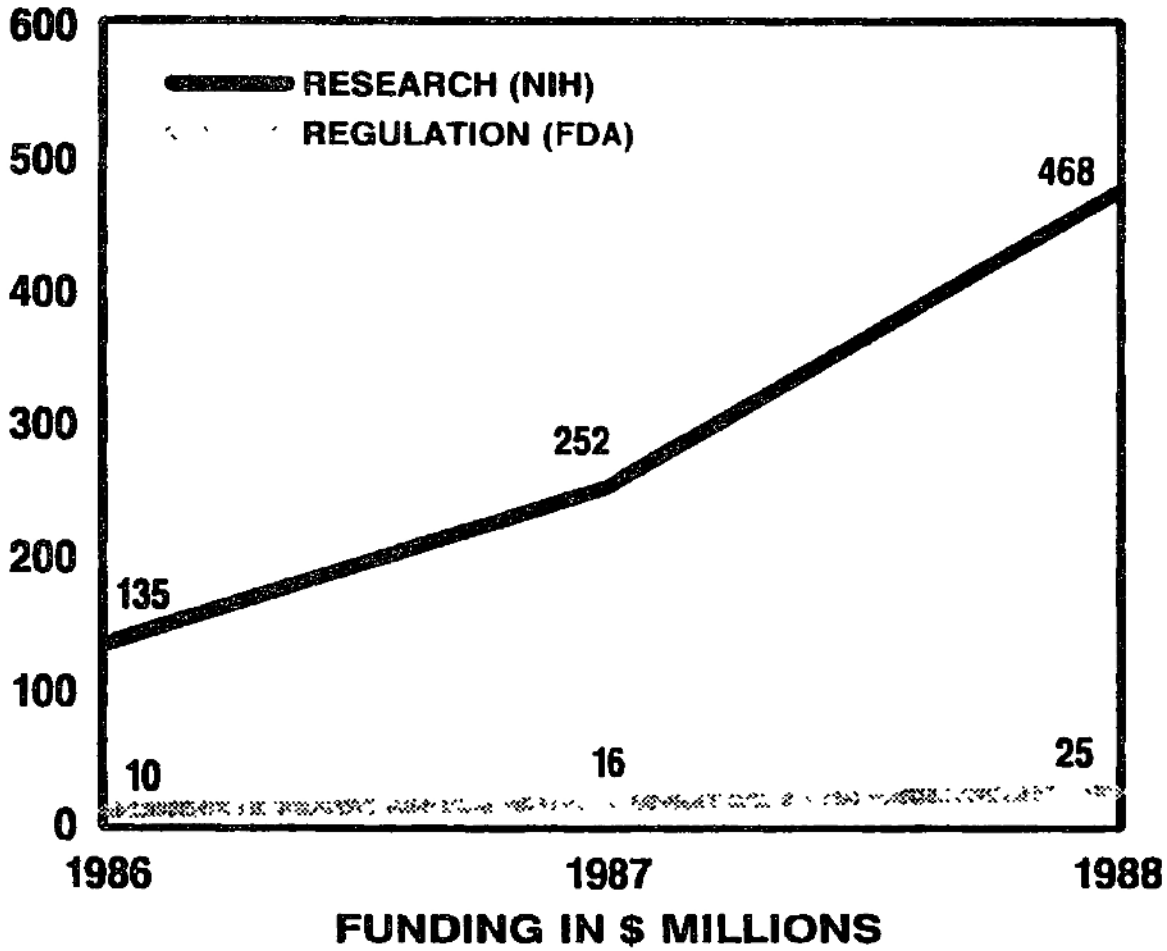
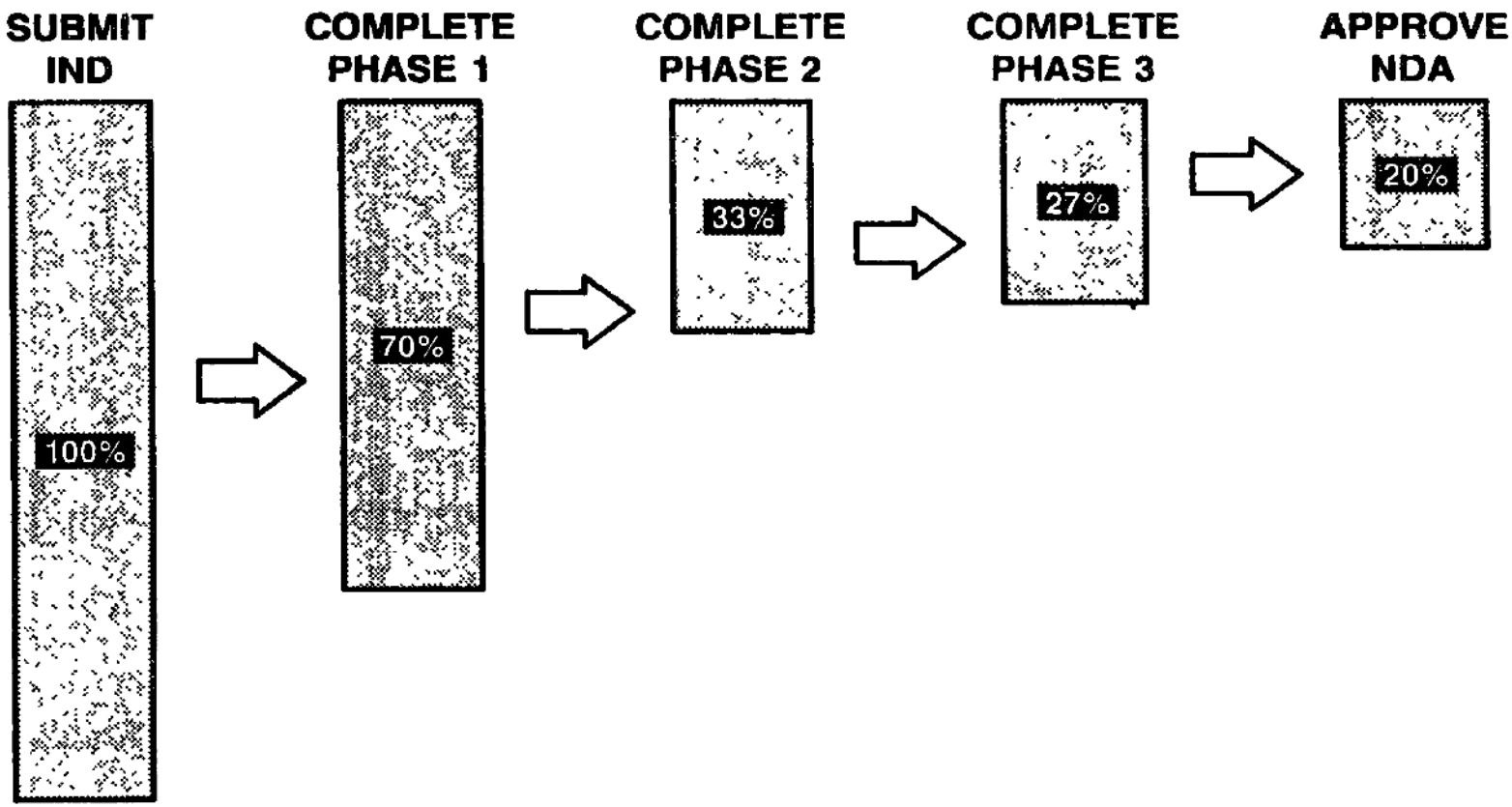


AIDS RESEARCH AND REGULATORY FUNDING



SUCCESS OF CLINICAL RESEARCH
(NCEs SUBMITTING FIRST INDs IN 1976-1978)



SUCCESS OF CLINICAL RESEARCH
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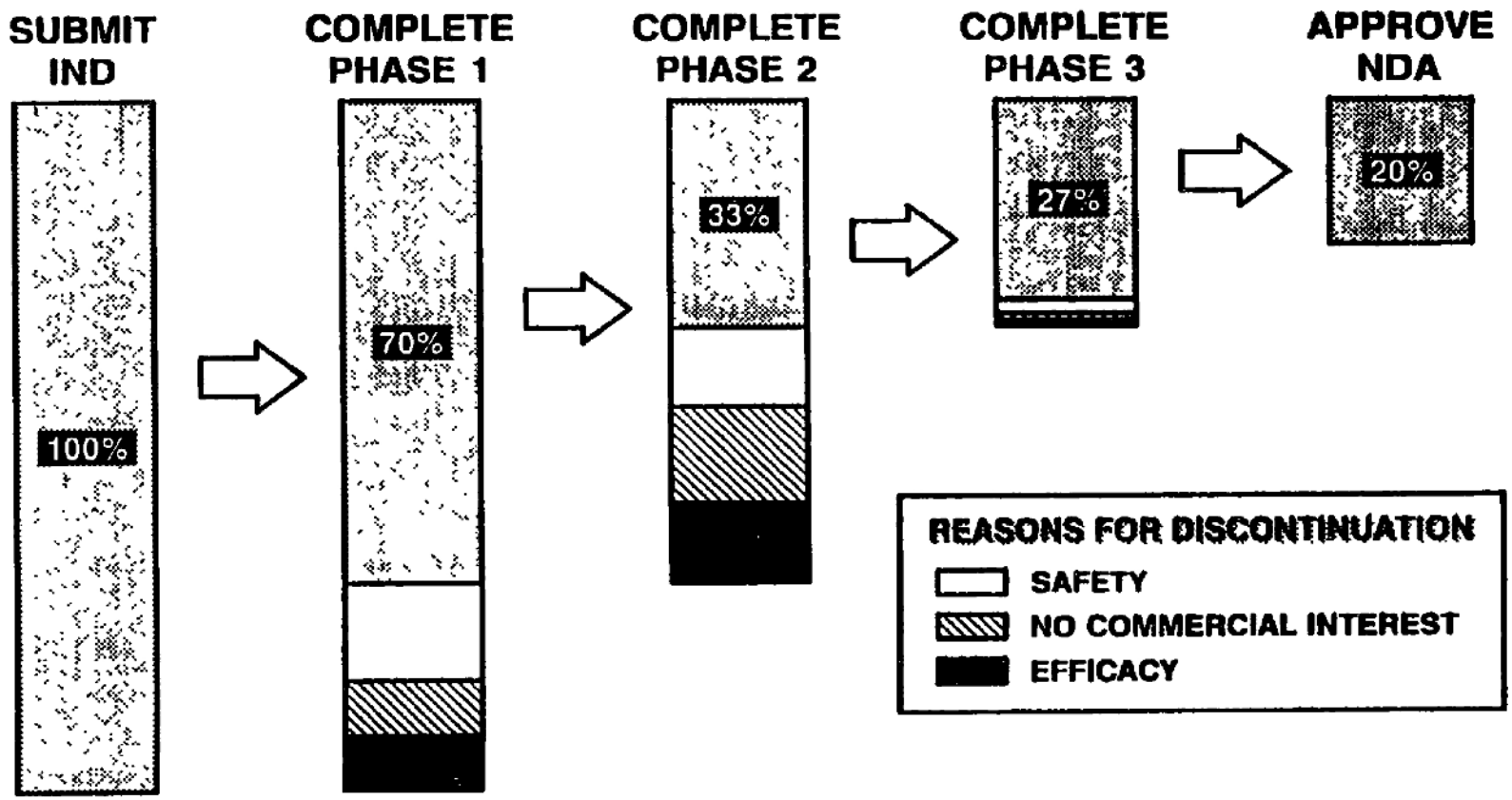


Statement

Pharmaceutical Manufacturers Association

GERALD J. MOSSINGHOFF
PRESIDENT, PHARMACEUTIAL MANUFACTURERS ASSOCIATION

BEFORE THE

PRESIDENT'S COMMISSION ON
HUMAN IMMUNE VIRUS EPIDEMIC

NEW YORK CITY, NEW YORK

FEBRUARY 19, 1988

Mr. Chairman and Members of the Commission:

I am Gerald J. Mossinghoff, President of the Pharmaceutical Manufacturers Association. PMA represents more than 100 research-based pharmaceutical companies that discover, develop and produce most of the prescription drugs used in the United States. I appreciate very much this opportunity to appear before the Commission to discuss our industry's intensive efforts to develop drugs to combat Acquired Immune Deficiency Syndrome (AIDS).

I will begin by providing a brief overview of the research-based pharmaceutical industry. Thereafter, Dr. Patrick Gage, Vice President and Director of Exploratory Research at Hoffmann-La Roche Inc., will discuss the challenges of viral research and federal/private cooperation; Dr. David W. Barry, Vice President

of Research at Burroughs Wellcome Co., will describe his company's experience in developing Retrovir (AZT), and Dr. George B. Rathmann, President and Chief Executive Officer of AMGEN, will concentrate on the role of biotechnology in the battle against AIDS.

Our companies recognize the urgency of discovering and developing drugs to stem the AIDS epidemic--one of the most serious public-health problems this country has ever faced. Never before have so many companies devoted so many resources in such a short period of time to combat a single disease. Fifty-five companies are developing, or have developed, a total of 77 products to diagnose, prevent or treat AIDS. This is shown in Appendix A of my statement, which is reproduced in the charts on display here today.

Despite this impressive range of activity, no one should under-estimate the enormous challenge of discovering and developing products to combat AIDS. According to our best scientists working in this area, there is insufficient basic scientific knowledge about viral diseases generally, and specifically about the HIV virus and its effects on the body, particularly the immune system. For more than three decades, scientists have been trying to develop drugs to treat viral diseases and only a handful of products with limited application have been produced.

In the relatively brief time since AIDS was recognized as a public-health threat, private companies have developed nine diagnostic tests, including screening tests to ensure the safety of the nation's blood supply, Retrovir to arrest the development of the disease and Pentam 300 to treat PCP. Just this week, the Food and Drug Administration, by granting a Treatment IND, approved the expanded use of another drug to treat PCP.

Contrary to what many people believe, our companies use their own funds to discover and develop new drugs. The government provides less than one-tenth of 1 percent of all the funds our companies use for this purpose. Last year, our companies invested a record $5.4 billion on research and development in all disease categories. This year, they will spend almost as much on all of their pharmaceutical research and development as the National Institutes of Health will spend on all biomedical research. (A more complete discussion of our industry's investment in research and development in all areas is provided in Appendix B of this statement.)

As a result of this enormous investment in research and development, private pharmaceutical companies discover most, and develop all, of the new drugs that are introduced on the U.S. market. In working to combat AIDS, each company is concentrating efforts in the areas it believes will be most fruitful based on its previous research and existing scientific capabilities. As I have noted, 55 companies are developing, or have developed, a

total of 77 products to diagnose, prevent or treat AIDS. The products now being developed include 15 antivirals, 22 immunomodulators (to strengthen the immune system), two anti-infectives, 17 diagnostics and 10 vaccines.

All of the products are listed in Appendix A, which is based on a detailed survey conducted by PMA. This Appendix specifies the manufacturer of each product, the proposed use of the product and the product's development status. Appendix A also describes the various phases of the drug-approval process the FDA uses to approve new drugs as safe and effective. Of course, not all of the products described in the Appendix will prove to be safe and effective. A number of them, therefore, will not be developed as testing proceeds, but other products will be discovered and developed as research continues.

To conquer AIDS, government, industry and academic scientists have worked well together, but the time has come to provide a more effective arrangement to accelerate the development of new therapies. The National Institutes of Health established a network of AIDS Testing and Evaluation Units (ATEUs) to facilitate the development of AIDS drugs. In creating the ATEUs, the NIH recognized that there was a finite number of AIDS patients suitable for clinical trials under FDA criteria, and a limited number of qualified clinical investigators and appropriate clinical facilities. The ATEUs have been useful, but, with the increasing number of AIDS drugs to be tested, it is

time to re-examine their role and administration.

To discuss this and other issues that inevitably will arise as AIDS-related research and development continues, there is a need for a forum where government, academia and industry can meet to assess progress in the battle against AIDS, resolve problems as they emerge and thoroughly discuss all relevant issues. The National Academy of Sciences' Institute of Medicine is uniquely qualified to provide such a forum. It is highly respected by the scientific and medical community. And the National Academy of Sciences was specifically chartered to advise the Government on critical scientific issues, which it has done very ably over the years. PMA knows first-hand that the Institute of Medicine already is deeply involved in the efforts to combat AIDS.

In responding to the AIDS epidemic, the FDA is acting swiftly and effectively. Officials at all levels of the agency--from Commissioner Frank E. Young on down--are working extremely hard in cooperating with our companies to hasten the approval of drug and diagnostic products to combat AIDS and its complications.

It has been suggested that the country needs a crash program to combat AIDS organized along the lines of the Manhattan Project to develop the atomic bomb or the Apollo program to land a man on the moon. We do not believe such an effort would be productive. Nor do we believe that a single person or government entity

should be given overall authority to direct the efforts to combat AIDS.

The Manhattan and Apollo projects were massive engineering enterprises that used existing scientific knowledge to accomplish specific programmatic objectives. One of the major difficulties with AIDS is that many fundamental scientific questions remain unanswered, as I have noted. To ensure that scientific research proceeds as rapidly as possible, the Federal budget must provide adequate funding to support all legitimate AIDS research proposals for such funding. In addition, research by private organizations should be encouraged, so a rich diversity of approaches will be pursued. Development and marketing of products is best accomplished by the private sector, which, as I have indicated, develops and markets all of the drugs and vaccines introduced in the United States. Establishing a single director or bureaucracy to decide what research should be pursued, and what discoveries should be developed, would be an enormously counter-productive step that would threaten the expeditious development of AIDS therapies.

SUMMARY

- The research-based pharmaceutical industry fully appreciates the urgency of discovering and developing drugs to combat AIDS, and has mounted intensive efforts to that end.

- Fifty-five pharmaceutical companies are developing, or have developed, 77 products to diagnose, prevent and treat AIDS.

- The industry supports the conduct of basic research, public and private, to gain scientific knowledge about the HIV virus and its effects.

- The Institute of Medicine should be designated as the forum where the government, academic scientists and private industry can meet to assess progress in the battle against AIDS, resolve problems as they emerge and thoroughly consider all relevant issues, including the role and administration of the AIDS Testing and Evaluation Units.

- The Food and Drug Administration should be encouraged, and provided sufficient resources, to continue its efforts to expedite the approval of safe and effective drugs and diagnostic products to combat AIDS.

- Diversity of research and development efforts should be preserved as the best way to ensure progress in the battle against AIDS.

Mr. Chairman, that concludes my prepared remarks. I would be pleased to respond to any questions that you and other members of the Commission may have.

Update:
AIDS PRODUCTS IN DEVELOPMENT
January 1988 *Presented by the Pharmaceutical Manufacturers Association*

Survey Tracks Progress in Development of AIDS Products

At least 77 AIDS-related drugs, diagnostics and vaccines are available or in development, according to the quarterly survey by the Pharmaceutical Manufacturers Association (PMA). Fifty-five companies are involved in the effort.

Two AIDS drugs and nine diagnostics already are approved and available. The drugs are Retrovir (zidovudine, Burroughs Wellcome), used to treat AIDS and advanced AIDS related complex (ARC), and Pentam 300 (pentamidine isethionate, LyphoMed), used to treat pneumocystis carinii pneumonia, a common opportunistic infection in AIDS patients.

The 77 products in the survey include 16 anti-virals, 22 immunomodulators, three anti-infectives, 26 diagnostics and 10 vaccines.

The survey, taken in January, showed an increase of 13 products over the last survey. New are the immuno-modulator gamma interferon from Genentech and the anti-infective fluconazole from Pfizer. Oncogen, Otisville BioPharm and Wistar Institute are developing vaccines. New diagnostics are the Cetus/Eastman Kodak SureCell to detect HIV antibodies and another product to amplify and detect HIV viral DNA; Cambridge Bioscience's two Recombigen tests for detecting HIV antibodies; Gen-Probe's test for detecting AIDS virus; Organon Teknika's Vironostika to detect antibodies to HIV antigen; Viral Technologies' product to detect HIV p17 antibodies; and RIBA HIV216, under development by Chiron to be marketed by Ortho Diagnostics.

Companies working on the 77 anti-AIDS products include many of the country's largest pharmaceutical firms—Abbott, American Cyanamid, Burroughs Wellcome, Ciba-Geigy, DuPont, Genentech, Hoffmann-La Roche, Merck, Merrell Dow, Ortho, Pfizer, Sandoz, Schering-Plough, Syntex, Upjohn and Warner-Lambert—as well as many small, highly-specialized research firms.

"The diversity of research on AIDS drugs is one of the most encouraging factors in the search for a remedy," said PMA President Gerald J. Mossinghoff. "Companies throughout the industry are pursuing widely differing approaches, greatly enhancing the prospects for discovery."

Thirty-nine products have progressed to clinical trials. Of the drugs, 11 are in Phase I testing, six are in Phase I/II, six are in Phase II, three are in Phase II/III, and seven are in Phase III. Exact status of six products could not be determined.

Phase I tests usually involve only a few people and are intended to determine the drug's pharmacological actions—its safe dosage range, how it is absorbed and metabolized, and its duration of action. Phase II and III tests involve increasing numbers of patients to determine the effectiveness of the product. If the testing successfully demonstrates the product's safety and effectiveness, the test data then are submitted to the Food and Drug Administration as a New Drug Application (NDA) for review and market approval.

For the average pharmaceutical, the process of pre-clinical development, clinical testing, and NDA review requires seven to 10 years, but the Food and Drug Administration has established special review procedures intended to speed review of AIDS-related drugs and vaccines.

A more detailed explanation of the drug approval process is included.

AIDS Products In Development

Anti-virals

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
AL-721 *(AL-721)*	Ethigen (Los Angeles, CA)	ARC, PGL	IND approved Phase II
Betaseron *(interferon beta)*	Triton Biosciences (Shell Oil) (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC	IND approved Phase I/II
Cytovene *(ganciclovir)*	Syntex (Palo Alto, CA)	CMV	NDA Pending (Orphan Drug)
DDC *(dideoxycytidine)*	Hoffmann-La Roche (Nutley, NJ)	AIDS, ARC	IND approved Phase I/II
(dextran sulfate; UA001)	Ueno Fine Chem. Industry (Osaka, Japan)	AIDS, ARC	IND approved Phase I
Foscarnet *(trisodium phosphonoformate)*	Astra Clinical Research (Hopkinton, MA)	HIV infection, CMV retinitis	IND approved Phase I/II
HPA-23	Rhone-Poulenc Sante (Monmouth Junction, NJ)	HIV infection	IND approved Phase I
Ornidyl *(eflornithine)*	Merrell Dow (Cincinnati, OH)	PCP	NDA pending (Orphan Drug)
Peptide T *(octapeptide sequence)*	Peninsula Labs (Belmont, CA)	AIDS	IND approved Phase I
Reticulose *(nucleophosphoprotein)*	Advanced Viral Research (Miami, FL)	AIDS, ARC	IND submitted
Retrovir *(zidovudine; AZT)*	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv. ARC	NDA approved
		pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV, neurological involvement, in combination w/other therapies	IND approved Phase I/II
Rifabutin *(ansamycin LM 427)*	Adria Labs (Dublin, OH)	ARC	IND approved Phase II
(trimetrexate)	Warner-Lambert (Morris Plains, NJ)	PCP	IND approved Phase III
Virazole *(ribavirin)*	Viratek/ICN (Costa Mesa, CA)	AIDS, Kaposi's sarcoma, ARC	IND approved Phase II/III
Wellferon *(alpha interferon)*	Burroughs Wellcome (Rsch. Triangle Park, NC)	Kaposi's sarcoma, HIV, in combination w/Retrovir	IND approved Phase I
Zovirax *(acyclovir)*	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, ARC, in combination w/Retrovir	IND approved Phase I

Immuno-modulators

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
ABPP *(bropirimine)*	Upjohn (Kalamazoo, MI)	Advanced AIDS, Kaposi's sarcoma	IND approved Phase II/III
AS-101	Scientific Testing (National Patent Development, Bar Ilan University, Israel) (New York, NY)	AIDS	IND approved
Ampligen *(mismatched RNA)*	DuPont (Wilmington, DE) HEM Research (Rockville, MD)	ARC, PGL	IND approved Phase III
(anti-human alpha interferon antibody)	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC	IND approved Phase I
Carrisyn *(acemannan)*	Carrington Labs (Irving, TX)	ARC	IND submitted
Colony Stimulating Factor *(GM-CSF)*	Sandoz (East Hanover, NJ) Genetics Institute (Cambridge, MA)	AIDS, Kaposi's sarcoma, ARC, HIV	IND approved Phase I

Provided as a Public Service by the Pharmaceutical Manufacturers Association.

Immuno-modulators

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
CL246, 738 *(CL246, 738)*	American Cyanamid (Pearl River, NY)	AIDS	IND approved Phase I/II
(gamma interferon)	Genentech (S. San Francisco, CA)	ARC, in combination w/TNF (tumor necrosis factor)	IND approved clinical trials
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL	IND approved Phase III
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL	IND approved Phase II
Imuthiol *(diethyl dithio carbamate)*	Merieux Institute (Miami, FL)	AIDS, ARC	IND approved Phase II/III
IL-2 *(interleukin-2)*	Cetus (Emeryville, CA)	AIDS, Kaposi's sarcoma	IND approved Phase II
IL-2 *(interleukin-2)*	Hoffmann-La Roche (Nutley, NJ) Immunex (Seattle, WA)	Kaposi's sarcoma	IND approved Phase III
INTRON-A *(interferon alpha)*	Schering-Plough (Madison, NJ)	Kaposi's sarcoma	NDA filed
Isoprinosine *(inosine pranobex)*	Newport Pharmaceuticals (Newport Beach, CA)	ARC, PGL, HIV seropositive asymptomatic patients	IND approved Phase III
(methionine -enkephalin)	TNI Pharmaceuticals (Chicago, IL)	AIDS, ARC	Investigator's IND approved Phase I/II
MTP-PE *(muramyl-tripeptide)*	Ciba-Geigy (Summit, NJ)	Kaposi's sarcoma	IND approved, Phase I
Thymopentin (TP-5) *(thymic compound)*	Ortho Pharmaceuticals (Raritan, NJ)	HIV infection	IND approved Phase I/II
Roferon-A *(interferon alpha)*	Hoffmann-LaRoche (Nutley, NJ)	Kaposi's sarcoma	NDA filed
(recombinant erythropoietin)	Ortho Pharmaceuticals (Raritan, NJ)	severe anemia assoc. w/AIDS and AZT therapy	IND approved Phase II
Trexan *(naltrexone)*	DuPont (Wilmington, DE)	AIDS, ARC	early Phase II
TNF *(tumor necrosis factor)*	Genentech (S. San Francisco, CA)	ARC, in combination w/gamma interferon	IND approved clinical trials

Anti-infectives

DRUG NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
Pentam 300 *(pentamidine isethionate, IV dosage)*	LyphoMed (Rosemont, IL)	PCP	NDA approved
aerosol dosage		PCP prophylaxis	IND approved Phase III
		PCP treatment	IND approved Phase III
(fluconazole)	Pfizer (New York, NY)	cryptococcal meningitis, candidiasis	IND approved Phase III

Diagnostics

TEST NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
HTLV3-EIA	Abbott Labs (N. Chicago, IL)	detects HIV antibodies	licensed
To Be Announced	Abbott Labs (N. Chicago, IL)	detects HIV antigens	pending FDA approval

Diagnostics

TEST NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
Envacor	Abbott Labs (N. Chicago, IL)	detects antibodies to core antigen p24 and the envelope antigen p41	pending FDA approval
Recombigen Latex HIV *(rapid HIV antibody test)*	Cambridge Bioscience (Worcester, MA)	detects HIV antibodies	pending FDA approval
Recombigen EIA HIV *(two-hour immunoassay)*	Cambridge Bioscience (Worcester, MA)	detects HIV antibodies	pending FDA approval
HIV ELISA	Cellular Products (Buffalo, NY) (Eastman Kodak, marketer, Rochester, NY)	detects HIV antibodies	licensed
SureCell	Cetus (Emeryville, CA) Eastman Kodak (Rochester, NY)	detects HIV antibodies	in development
To Be Announced	Cetus (Emeryville, CA) Eastman Kodak (Rochester, NY)	amplifies and detects HIV viral DNA	in development
RIBA HIV216	Chiron (Emeryville, CA) (Ortho Diagnostics, marketer, Raritan, NJ)	validates results of positive ELISA test	clinical trials
HIV ELISA Antibody Kit	DuPont (Wilmington, DE)	detects HIV antibodies	licensed
HIV Western Blot Kit	DuPont/Biotech (Wilmington, DE)	validates results of positive ELISA test	licensed
HIV p24 core antigen test	DuPont (Wilmington, DE)	detects HIV p24 core antigen	pending FDA approval
Rapid HIV antibody test	DuPont (Wilmington, DE)	detects HIV antibodies	clinical trials
VIRGO HIV ELISA	Electro-Nucleonics (Fairfield, NJ)	detects HIV antibodies	licensed
VIRGO HIV IFA *(immunofluorescence assay)*	Electro-Nucleonics (Fairfield, NJ)	detects HIV antibodies	pending FDA approval
LAV EIA	Genetic Systems (Seattle, WA)	detects HIV antibodies	licensed
To Be Announced	Gen-Probe (San Diego, CA)	test for AIDS virus	early research stages
To Be Announced	Hoffmann-La Roche (Nutley, NJ)	detects HIV antibodies	pending FDA approval
MGSearch HIV-160	MicroGeneSys (West Haven, CT)	detects HIV antibodies	clinical trials
ELISA	Ortho Diagnostics (Raritan, NJ)	detects HIV antibodies	licensed
Bio-EnzaBead *(HIV ELISA)*	Organon Teknika (Durham, NC)	detects antibodies to HIV antigen in serum or plasma	licensed

LEGEND:

AIDS—Acquired Immune Deficiency Syndrome.
ARC—AIDS related complex.
CMV—Cytomegalovirus. An opportunistic infection that can cause blindness and be fatal in AIDS patients.
CNS—central nervous system.
ELISA or EIA—enzyme-linked immunosorbant assay. Used to screen blood for HIV antibodies.
HIV—Human immunodeficiency virus. Previously called HTLV-III or LAV.
IND—Investigational New Drug.
Orphan drug—Indicated for rare diseases.
PCR—*Pneumocystis carinii* pneumonia. A common opportunistic infection in AIDS patients.
PGL—persistent generalized lymphadenopathy
Phase I—safety testing and pharmacological profiling in humans
Phase II—effectiveness testing in humans
Phase III—extensive clinical trials in humans

Diagnostics

TEST NAME	MANUFACTURER	INDICATION	DEVELOPMENT STATUS
Vironostika *(HIV Microelisa system)*	Organon Teknika (Durham, NC)	detects antibodies to HIV antigen in serum or plasma	licensed
To Be Announced	Syntex/Syva (Palo Alto, CA) Cambridge Bioscience (Worcester, MA)	test for AIDS antibodies	in development
To Be Announced	Syntex/Syva (Palo Alto, CA)	test for AIDS virus	in research
Fluorognost *(immunofluorescence assay)*	Thermascan (New York, NY)	HIV-1 antibody confirmation test	IND approved clinical trials
To Be Announced	Viral Technologies (Interleukin-2, Alpha-1 Biomedicals) (Washington, DC)	detects HIV p17 antibodies	in development

Vaccines

MANUFACTURER	INDICATION	DEVELOPMENT STATUS
Biotech Research Labs (Rockville, MD)	AIDS	early research phase
Ciba-Geigy (Summit, NJ) Chiron (Emeryville, CA)	AIDS	animal studies
Genentech (S. San Francisco, CA)	AIDS	early research phase
Institut Merieux (Lyon, France) Cambridge Bioscience (Worcester, MA)	AIDS	early research stages
VaxSyn HIV-1 MicroGeneSys (West Haven, CT)	AIDS	Phase I
Oncogen (Seattle, WA)	AIDS	Phase I
Otisville BioPharm (Otisville, NY)	AIDS	early research phase
Repligen (Cambridge, MA) Merck (Rahway, NJ)	AIDS	animal studies
Viral Technologies (Interleukin-2, Alpha-1 Biomedicals) (Washington, DC)	AIDS	IND submitted
Wistar Institute (Philadelphia, PA)	AIDS	IND submitted

The content of this chart has been obtained through government and industry sources (including FDA and NIH) based on the latest information. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly.

The Drug Approval Process

The U.S. system of new drug approvals is perhaps the most rigorous in the world. Here is how a drug is tested and approved.

Preclinical Testing. The promising agent is first subjected to extensive laboratory and animal testing to determine answers to two key questions: Is the compound biologically active? Is it safe? If the answers to both appear to be affirmative, the drug sponsor is ready to test in humans. This stage generally lasts from one to two years.

Investigational New Drug. Before human tests can start, the drug sponsor must file an Investigational New Drug (IND) application with the Food and Drug Administration (FDA), showing the results of all animal testing and how the drug is made. The IND becomes effective if FDA does not disapprove the application in 30 days.

Human Testing (Clinical). There are three phases of human testing, each involving larger numbers of people than the one before.

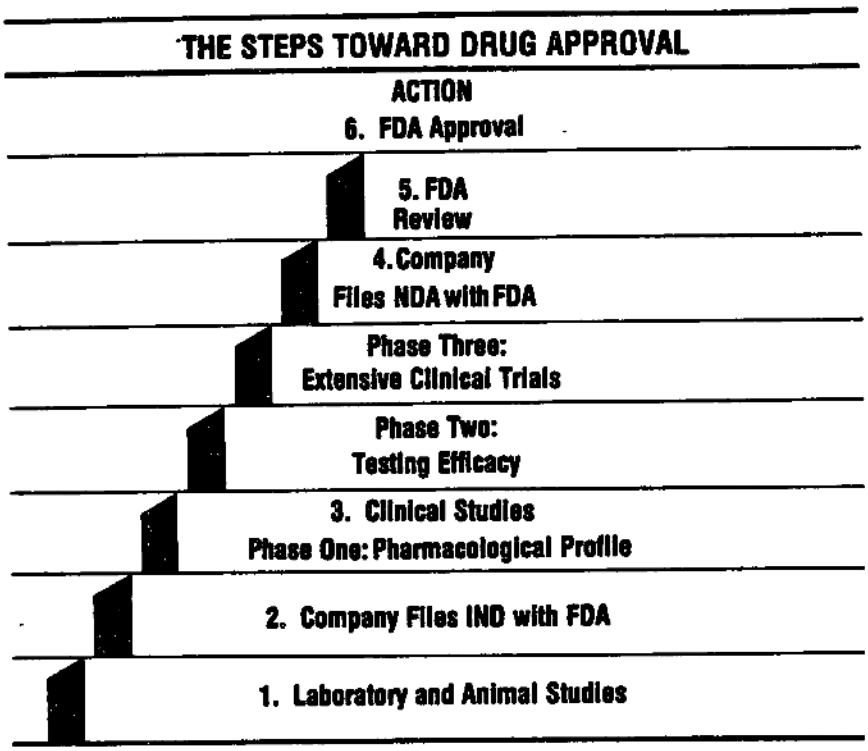
Phase I. Safety Studies and Pharmacological Profiling: This phase determines the drug's pharmacological actions, its safe dosage range, how it is absorbed, distributed, metabolized and excreted, and the duration of its action. These tests involve a small number of normal healthy subjects (not patients). Phase I clinical testing can usually be conducted in less than one year.

Phase II. Pilot Efficacy Studies: This phase consists of controlled studies in approximately 200 to 300 volunteer patients to assess the drug's effectiveness. Simultaneous animal and human studies continue to determine the drug's safety. Phase II clinical testing may require about two years to complete.

Phase III. Extensive Clinical Trials: Here the testing moves to larger numbers of volunteer patients — usually 1,000 to 3,000, in clinics and hospitals. The drug is administered by practicing physicians to those suffering from the condition the drug is intended to treat. These studies must confirm earlier efficacy studies and identify low-incidence adverse reactions. Phase III clinical trials last about three years.

New Drug Application (NDA). Following completion of Phase III, the drug sponsor must file an NDA with the FDA, containing all the information the sponsor has gathered. NDAs typically run into thousands of pages. The information submitted must include the chemical structure of the drug, scientific rationale and purpose, animal and laboratory studies, results of all tests in humans, formulation and production details, and proposed labeling. On average, the NDA review and approval process by FDA takes two to three years.

Approval. Once an NDA is approved, the company is required to periodically submit reports to FDA, including adverse reaction data and production, quality control and distribution records. For some drugs, FDA requires affirmative post-marketing monitoring, or additional studies to evaluate the long-term effects.



Pharmaceutical Manufacturers Association

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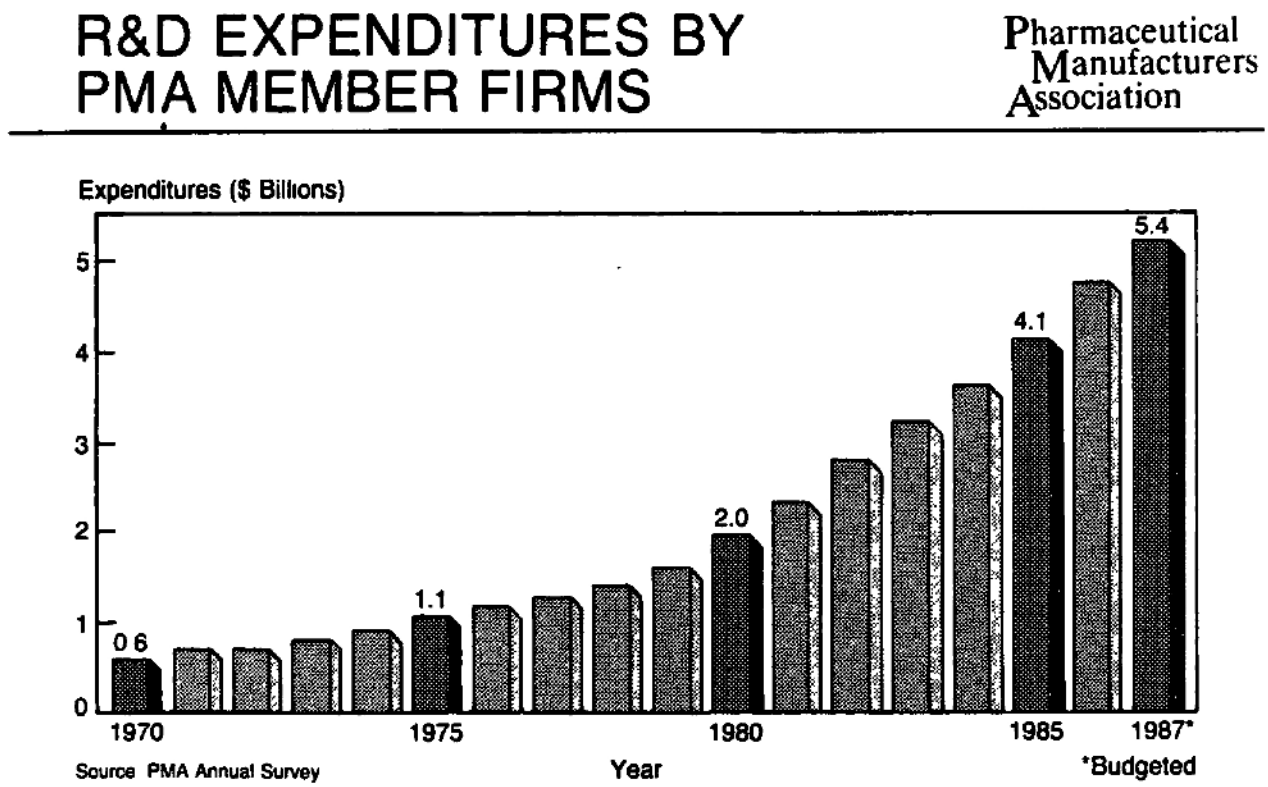
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

The hallmark of the pharmaceutical industry is its investment in research and development--to produce new and more effective medicines. "There is perhaps no industry that depends as heavily on new products--and thus on research and development --as does pharmaceuticals," according to the February 23, 1987 edition of Forbes. As the chart below shows, the research-based pharmaceutical industry has doubled its investment in research and development every five years since 1970. This trend continued in 1987, when the industry invested a record $5.4 billion on research and development--a 14.9 percent increase over the $4.7 billion spent in 1986.



To finance this mounting investment in research and development, pharmaceutical companies have used an increasingly larger proportion of U.S. sales revenues. From 1973 to 1980, the U.S. research-based pharmaceutical industry invested between 11.1 percent and 11.7 percent of U.S. sales in research and development. In 1981, the industry increased its investment to 13.1 percent of sales, and, in 1987, PMA member companies invested an estimated 15.1 percent of their domestic sales and exports in research and development.

Pharmaceutical companies have continued to increase their funding for research and development even though pharmaceutical research is an expensive, time-consuming and risky business. The average cost of developing a new drug is about $125 million, as shown in a new study--The Cost of Developing a New Drug--by Steven N. Wiggins, Rex B. Grey Professor in the Department of Economics at Texas A&M University. Thousands of new compounds are screened for each new molecular entity that eventually is approved for marketing. On average, it takes from seven to 10 years from the time a new drug is discovered until the drug is introduced on the market.

THE DEVELOPMENT AND USE OF AZIDOTHYMIDINE IN THE TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS

Written testimony to be given to the President's Commission on AIDS
February 19, 1988, New York City

DAVID W. BARRY, M.D.
WELLCOME RESEARCH LABORATORIES
BURROUGHS WELLCOME CO.
NORTH CAROLINA

Burroughs Wellcome Co. first became directly involved in efforts to discover and develop therapy for the treatment of the Acquired Immune Deficiency Syndrome (AIDS) and associated infections in 1980, a year before the illness was described as a syndrome by the USPHS Centers for Disease Control (8,9). The company's initial involvement was based upon the fact that many of the drugs used to treat the opportunistic infections associated with AIDS are manufactured by Wellcome. In that year, we began to receive a number of calls requesting intravenous Septra® for the treatment of adult patients with Pneumocystis carinii pneumonia (PCP). At that time the intravenous preparation of Septra was not approved in the United States for general use, but was available under a treatment IND program. Initially, we were somewhat skeptical of the increase in requests for Septra because, until that time, episodes of PCP generally occurred primarily in children who had received intensive chemotherapy for leukemia. Approximately a year later, epidemiologic studies showed that PCP was one of the prime manifestations of AIDS (8,9). In addition, we have supplied pyrimethamine (Daraprim®), leukovorin (Wellcovorin®), acyclovir (Zovirax®), DHPG (BW 759U, ganciclovir) and interferon (Wellferon®) to treat various opportunistic infections or tumors occurring in AIDS patients. Because of this involvement, scientists at Wellcome became familiar with the disease during the early 1980s. In addition, Wellcome has a long history of the development of antiviral therapy, including the development of Marboran® for the treatment of the complications of smallpox vaccination in the 1960s, trifluorothymidine (Viroptic®) for ocular herpes infections in the 1970s and then acyclovir (Zovirax®) for herpes infections in the 1980s.

In 1984 Drs. Francoise Barre'-Sinnoussi, Robert Gallo and Samuel Broder served as a catalyst to increase B.W. Co.'s involvement in the development of therapies for the disease syndrome known then as AIDS. They came to the Wellcome Research Laboratories to talk about the newly discovered retrovirus, termed HTLV III or LAV, which, at that time, had been cultured from nearly 50 AIDS patients (4,35). This virus has subsequently been termed the Human Immunodeficiency Virus or HIV. It was at this time that the decision was made at B.W. Co. to test some of our compounds for activity against the newly discovered retrovirus. In our research laboratories were several compounds which had been studied for antiviral and antibacterial activity and which were subsequently tested for activity against HIV.

Among those tested was a compound which was activated by cellular thymidine kinase; the compound was an analogue of thymidine with an azido group replacing the 3'-hydroxyl group of thymidine. This compound, known initially as compound BW 509U is now known as azidothymidine, AZT, zidovudine or Retrovir®. As a very close analogue of thymidine, the azido replacement does not interfere with efficient phosphorylation by cellular thymidine kinase (17,41). AZT had initially been synthesized in 1964 by Dr. Jerome Horwitz at the Michigan Cancer Foundation as a potential anti-cancer agent, but studies with the compound were abandoned shortly thereafter because of a lack of activity against animal cancers (23). Wellcome resynthesized it in the early 1980s and conducted a number of studies which showed that it was quite active against many aerobic gram-negative bacteria (14). Studies in November of 1984 with two murine retroviruses (Harvey Sarcoma Virus and Friend Leukemia Virus) suggested that it might be highly active against the human immunodeficiency virus. At that time Wellcome did not have laboratory facilities to test it against the AIDS virus, so it was sent to Dr. Broder at the National Cancer Institute in the United States, who confirmed its activity against HIV (31). Its mechanism of action against HIV is analogous to that against bacteria in that AZT must be converted to an active phosphorylated form. AZT is first phosphorylated to AZT 5'-monophosphate by cellular thymidine kinase (17). Subsequent phosphorylation by other cellular kinases yields AZT diphosphate and AZT triphosphate (AZT-TP). The latter is a selective inhibitor of retroviral reverse transcriptase (41). In addition, because the azido group prevents

the necessary 3'-5' phosphodiester bonds required for DNA elongation, AZT-TP also acts as a viral DNA chain terminator (14,43).

After confirming AZT's anti-HIV activity in February of 1985, Wellcome scientists conducted a rapid series of preclinical studies, including toxicology, pharmacology, and pharmacokinetic studies. These studies suggested that trials in humans should proceed. A Phase I study began in July of 1985, and was a collaboration between the National Cancer Institute and Duke University sponsored by Burroughs Wellcome Co. This study was conducted in patients infected with HIV who had been diagnosed as having AIDS or ARC. The results indicated AZT was well absorbed orally, with dose-independent kinetics observed over a fairly wide dosing range (29). AZT was shown to be 65% bioavailable (44), but in reality, may be as high as 100% bioavailable. This discrepancy results because there is a first pass metabolism effect in which a portion of the AZT is converted to AZT-5'-glucuronide as the result of glucuronidation in the liver (26). Both peak and trough levels that were above the <u>in vitro</u> sensitivity of the virus were achieved in these studies, suggesting that anti-HIV effects might be possible in man (27,31,33). In addition, it was found that AZT penetrated the blood-brain barrier quite well (26), suggesting that viral infections in brain could be treated (17). The significant glucuronidation of AZT may be an important factor since other drugs which are glucuronidated, such as acetaminophen, may have some effect on the metabolism of AZT (25).

When the Phase I studies were completed in January of 1986, we had a very difficult decision as to how to proceed. Traditionally, early clinical studies of new drugs proceed in a very regimented way. New drugs are typically tested in normal, healthy volunteers to evaluate safety and tolerance and then the new drug is examined in a larger number of patients to evaluate its efficacy and safety profile, usually in patients with milder stages of the disease in question. There are many reasons for this approach. The first is that any toxicity seen is likely to be milder in patients whose baseline physical status is relatively good. More importantly, the likelihood of therapeutic success in less ill patients is often greater in these patients than in those who are at a more severe stage of their disease. We know from experience

with antibiotics, for example, that many patients who are severely granulocytopenic secondary to intense cancer chemotherapy have infections which will often not respond to antibacterial agents which are known to be quite effective in less ill patients, simply because their illness is so advanced and their immune status compromised. In the case of AZT, however, Wellcome believed that there were two counterbalancing elements which required that a less classical approach be taken. The first was that there were a large number of people, possibly hundreds per week, dying of AIDS at the time the Phase I study was completed in January, 1986. Wellcome also believed that testing AZT in patients with advanced manifestations of HIV infection was the most vigorous test to determine its therapeutic index. If it proved to be effective in the most severely ill patients, while exhibiting manageable adverse effects, then it might be more beneficial in patients with milder forms of disease. We therefore made a difficult decision to conduct a double-blinded, placebo-controlled study in advanced AIDS and ARC patients in February of 1986. The results of this study have been published (15,36) so only a brief review and update of data gathered since then are necessary.

One of the most difficult and key issues in the study was the decision to administer placebo to half of the patients enrolled. This study was initiated at a time when the Phase I study had given only hints that the drug might be effective. Yet with hundreds of people dying, and the publication of the Phase I study which described potentially beneficial therapeutic effects in man (44), there arose a number of ethical and scientific questions concerning the conduct of a placebo-controlled study (5). Nevertheless, we believed that this drug must be proven, by classical clinical research methodology, to be both safe and effective, or otherwise many patients might be put at risk without knowledge of the actual benefits of the drug. In order to assure that the risk and benefits of AZT were evaluated adequately without withholding, for any longer than necessary, a promising therapy, it was agreed to appoint a Data Safety and Monitoring Board whose members would examine data from the ongoing study every two months and make recommendations about how to proceed. After analysis of various safety and efficacy parameters, the board of medical experts was to advise Wellcome whether one group was experiencing significantly greater side effects or greater benefit from therapy than the other group.

From this analysis, the board was to recommend whether it would be unethical to proceed.

In this study, 282 AIDS and ARC patients were entered at 12 university-associated medical centers in the United States between January and June of 1986. In order to have as uniform and comparable groups as possible between drug and placebo, narrow categories of disease progression were studied. For the AIDS component, only those patients who had experienced their first episode of PCP within the prior four months were entered in the study. ARC patients were enrolled if they had a number of symptoms including, among others, weight loss, sustained fever for over a month, and/or extensive oral candidiasis. All patients were required to have fewer than 500 CD4 cells and to have complete cutaneous anergy to four common antigens. The vast majority of patients had fewer than 200 CD4 cells. Patients with Kaposi's sarcoma, intravenous drug abusers and children were excluded from this study. The drug and placebo groups were quite comparable in a variety of baseline characteristics that were examined.

On September 19, 1986, the Data Safety and Monitoring Board recommended to Wellcome that the study should be terminated because a significantly higher mortality rate in the placebo group compared to the therapy group was found. Since patients were enrolled at different times, the length of time on drug ranged from 10 to 28 weeks, with an average of 17 weeks. Analysis of the data at that time indicated that, when compared to placebo, AZT recipients had significant improvements in the number of CD4 cells, delayed cutaneous hypersensitivity, weight gain, activities of daily living and neurologic function (15). In addition, AZT recipients had significant decreases (in many cases to an undetectable level) of previously circulating P24 antigen (10) and significant decreases in the frequency and severity of opportunistic infections. Most importantly, the probability of death within six months of initiating therapy was 22% for the placebo group and 2% for the drug treated group.

Symptomatic adverse reactions were extremely common in both groups (36). This may have been the result of the complicated nature of the underlying

disease. Nausea, myalgias, insomnia and headache, however, were somewhat more common in the drug treated group. The most significant toxicity was myelosuppression which was dependent upon dose and duration of therapy, as well as upon pre-existant bone-marrow reserve. Up to 45% of patients with poor bone-marrow reserve had significant decreases in either red cell and/or white cell numbers during the observation period. The incidence of such decreases in patients with better marrow reserve was only slightly higher than that in the same subset of individuals in the placebo group. The management of such myelosuppression was left to the judgement of the individual investigator. Although there was great heterogeneity of practice, the bone marrow suppression could generally be managed by dose reduction, dose interruption, transfusion or a combination of these approaches.

At the time the placebo-controlled portion of the study was terminated, all patients, including those originally randomized to receive placebo, were offered the opportunity to receive AZT in an unblinded fashion provided they agreed to continued follow-up by the original investigator. While most of the patients agreed to continue taking AZT, a small number elected to leave the study for a variety of reasons. Some, particularly in the original placebo group, were moribund and their physicians felt that their terminal status would not be improved by additional therapy. Other moribund patients originally assigned to the placebo cohort received drug for only a few days or weeks before expiring. Conversely, some patients originally assigned to receive AZT subsequently stopped taking it because of real or perceived adverse reactions. Some patients in both groups withdrew because of a desire to avoid the rigorous follow-up required.

Because of these factors, continued follow-up and comparison of the two groups has been particularly difficult. However, if comparisons are made in which patients who originally received placebo are considered only if they had received no AZT or AZT for less than three weeks, and AZT recipients are included if they received active drug until at least 2 months before expiring, the survival rate of the AZT treated group was 98%, 94%, 88%, 85% and 78% at 6, 9, 12, 15 and 18 months respectively since entry into the study, compared to a survival of 76% and 52% at 6 and 9 months in the placebo group. Survival

was even further improved to 91% and 84% at 12 and 18 months in those patients receiving prophylaxis for PCP in addition to receiving AZT.

Too few patients in the original placebo group remained after 9 months to provide meaningful comparisons. In fact, only four of the 28 patients originally assigned to placebo who did not elect to receive AZT after unblinding of the study, or who received it for less than 3 weeks were alive one year after initiation of the study, and all are now dead. Thus, comparison of survival of patients on AZT for greater than 9 months must be compared to historical controls. These comparisons are, however, less than ideal because historical groups may represent a significantly different patient cohort, and because of the very incomplete follow-up of individual patients in most epidemiologic studies which are used for this comparison. Also, most epidemiologic studies use spontaneous reporting of death or registration of death certificates specifying death from AIDS within a particular locale to make their projection of survival rates. Both of these factors lead to significant under-reporting of deaths (37). It is known that AIDS patients are a highly mobile population often moving to other locales from those where the original diagnosis was made. In addition, physicians do not always list AIDS as the cause of death on death certificates. For example, a study which made extensive efforts to track down purported "longer term survivors" of AIDS found that at least 58% of such patients, in fact, were dead (32,37).

With these caveats in mind, the best historical comparison to the original cohort of patients who were randomized to AZT in the study is a cohort of AIDS patients in New York City in 1985 who had their diagnosis made exclusively on the basis of PCP (37). Their minimum one year mortality from the date of PCP diagnosis was 51%. Mortality was probably significantly greater because only those patients who had AIDS listed as their cause of death on a death certificate that was registered in New York City were considered to be dead in the study. Because AIDS patients in the original double-blind, placebo-controll study began taking AZT about 2½ months after their initial episode of PCP, their 13% mortality at one year after diagnosis of PCP and 21% after entry into the study is one-fourth to one-half the minimal mortality reported in the New York study. For purposes of direct comparison, in the double-blind,

placebo-controlled study, the mortality rate of 12% in the AZT-treated AIDS patients at 9 months was less than one fifth the 61% 9-month mortality rate of the AIDS patients who did not receive AZT or who received it for less than three weeks. The higher mortality in this placebo group (61% at 9 months) compared to the New York passive surveillance group (at least 51% at 12 months) may be related to a sicker population in the AZT study, better follow-up and recording of deaths, or other unidentified confounding factors.

Future follow-up in the original AZT and placebo cohorts and subsequent relevant mortality comparisons will become increasingly difficult because of anticipated loss of patients to follow-up and because of the possible decision of some patients to discontinue drug for a variety of reasons. In addition, management of both adverse reactions and the prevention and treatment of opportunistic infections varies widely among centers, thereby making the patients progressively less homogenous. For example, some physicians continue to give full doses of AZT in the face of significant myelosuppression and treat anemia with substantial numbers of transfusions. Others used to more benign (curative) drugs with huge therapeutic indices, decrease or temporarily discontinue therapy when even moderate anemia or granulocytopenia occurs. Furthermore, the use of prophylaxis with Septra, aerosolised pentamidine or dapsone, each of which has been shown to substantially diminish the incidence of PCP (12), is not standardized in these patients.

The de'nouement of the original double-blind, placebo-controlled study in September of 1985 provided another opportunity to study a large cohort of patients. Wellcome set up a program, in conjunction with the National Institutes of Health, to dispense AZT free of charge to any AIDS patient in the United States who had had PCP at any time in the past, and who fulfilled minimum entry criteria. ARC patients were not included in this program because tne FDA was still analyzing data concerning them at that time. Approximately 4800 AIDS patients received AZT under this "treatment IND", "compassionate plea" or "named patient" program between October, 1986 and March, 1987 when the drug became available by prescription. The characteristics of

the patients in this study were generally similar to those of AIDS patients in the general population, with the vast majority being homosexual or bisexual. Nevertheless, a number of patient categories not well represented in the Phase II double-blind, placebo-controlled study did participate in this uncontrolled study. There were nearly 150 women and over 250 intravenous drug abusers. In addition, 424 patients were hispanic and over 500 were black. Although AZT was approved for general use in March of 1987, we were able to monitor the survival of these patients until September 15, 1987, when the controlled distribution program that was in place during that interval was dismantled. The amount of data that can be obtained during "treatment IND" studies is generally limited, but sufficient controls were instituted in this program so that mortality statistics are reasonably reliable, at least for a 9 month period. After adjusting for the fact that significantly sicker patients could participate in this program, overall survival data were very similar to that observed in the original placebo-controlled study.

The incidence of adverse reactions was somewhat less than noted in the original placebo-controlled study, and may have been the result of less intensive observation and management of the patients or less aggressive reporting of such reactions. Although significantly higher rates of death have been reported in untreated women and drug addicts with AIDS when compared to male homosexuals with AIDS (37), no such differences were noted if these patients were receiving AZT. Likewise, no differences in mortality were noted between black and white AIDS patients receiving AZT. Surprisingly, survival among hispanics was slightly higher than among whites or blacks, but it is unclear whether this is significant. The highest mortality rates were recorded during the first eight weeks of study, indicating the very advanced state of illness of many of the participants. Over 100 patients, in fact, died in the 1-2 week interval between the request for drug and its receipt in the pharmacy. The mortality rate of people who had acquired disease through blood transfusion was somewhat higher than those who had acquired infection by other means. This observation may have been the result of the more advanced age of such patients, as well as their poorer general state of health.

Certain prognostic factors of survival were noted in this study. Better survival was associated with higher hemoglobin and performance (Karnofsky) levels at enrollment, as well as the brevity of the period between the first episode of PCP and the initiation of AZT therapy. These data point to the importance of beginning therapy as soon as possible after the diagnosis of AIDS or advanced ARC is made.

Although a great deal of information about the usefulness of AZT has been gathered in a relatively short period of time, a very aggressive world-wide program of clinical research is being mounted to address many as yet unanswered questions. In the United States this program is being conducted in conjunction with the AIDS Treatment and Evaluation Units (ATEUs). The largest group of studies involves patients with different degrees of severity of HIV infection, including patients with advanced disease (AIDS), milder forms of ARC, lymphadenopathy syndrome and even those who are infected but who do not have obvious signs or symptoms of disease. Four studies, in fact, are being conducted in this latter "asymptomatic" group, with the largest involving 1500 patients randomized to receive one or two different dosing regimens of AZT or placebo. A placebo-controlled study will also be conducted in otherwise normal individuals, primarily health care workers, who have been exposed, by cuts or punctures, to HIV infected fluids. There is optimism that this approach may be effective, because animal studies have indicated that administration of AZT, if begun within a few days of challenge and continued only for a few weeks, may completely prevent the establishment of retroviral infection (38,40,42). In addition, the relatively brief period of therapy envisaged is likely to produce few significant adverse reactions in healthy individuals.

Studies will also be conducted in special patient populations, such as hemophiliacs, intravenous drug abusers and children. Preliminary data from children (6,34) indicate that their absorption, distribution, metabolism and excretion of AZT is similar to those of adults (44), as are the benefits and adverse reactions to the drug (6). Chronic interstitial pneumonia, common in children with AIDS, but rare in adults, may also respond to AZT therapy (2). Particularly striking improvements in neurologic function have been noted in pediatric patients (6). Additional studies concerning the effect

of AZT on abnormal neurologic function in HIV-infected adults will also be conducted. Although significant improvements in neurologic function in adults with AIDS and ARC have already been noted in controlled (15), as well as uncontrolled (45), studies, additional research is required to precisely define the degree of benefit and to further understand occasional neurologic adverse experiences associated with the use of AZT (3, 11). Likewise, the role of AZT in improving (19) or worsening (16,18) the thrombocytopenia often seen in AIDS patients will be examined.

Other studies will examine different dosing regimens of AZT to determine whether certain adverse reactions, particularly bone marrow suppression, can be mollified while maintaining full therapeutic efficacy if smaller doses are given, or if the dosing interval is lengthened. In addition, the use of AZT in conjunction with a variety of other medications will be examined for two distinct reasons. Certain drugs, such as acyclovir, ampligen, interferon, and several others have been shown to be synergistic in vitro with AZT in inhibiting HIV replication (22,28-30,39) but additional studies are required to determine whether an additive or synergistic effect can be observed in people. Additionally, some compounds such as GM-CSF and erythropoeitin may counteract the marrow suppressive effects of AZT (20). Some immunomodulators, such as interleukin II, may enhance immune function at the same time that AZT inhibits viral replication and such combinations are currently under study. The combination of ribavirin and AZT will not be studied because ribavirin has been shown to antagonize AZT's antiviral effect in vitro (43) and in itself can cause anemia (13,24).

Studies will also be conducted to determine the safety and tolerance of AZT when used in conjunction with drugs employed in the therapy of opportunistic infections. Such medications include trimethoprim-sulfamethoxazole, pyrimethamine and amphotericin B, as well as drugs to treat Mycobacterium avium-intracellulare (MAI) infections (7). This latter study is particularly important because MAI in itself produces bone marrow dysfunction (21) and severely complicates and compromises the use of AZT in AIDS patients. Anecdotal reports indicate that AZT induced marrow suppression is most severe and less prone to spontaneous reversal in MAI infected patients (18). In

addition, studies of the appropriate dosage adjustment in patients with renal and/or hepatic failure will be included as part of an extensive post-marketing surveillance program. Finally, intensive viral sensitivity studies will be performed to determine the potential of resistance development. Although years may pass before the results of some of these studies enable us to have a more complete knowledge of the full therapeutic profile of AZT, sufficient data already exist to indicate that it is a valuable weapon in the physicians armamentarium to improve and lengthen the life of patients with AIDS and advanced ARC.

It should be emphasized that the rapidity and success observed in the development of AZT as a treatment for AIDS and ARC is very atypical. The urgency and fear generated by the threat of HIV infection in the United States has fostered an atmosphere of extensive cooperation in identifying and developing new agents for the treatment of the various stages of HIV infection, as well as the numerous infections which complicate the infected patients' course. The spirit thus extant between certain individuals of the National Institutes of Health and National Institute of Allergy and Infectious Diseases, researchers and clinicians in those communities where HIV infection is prevalent, researchers of the pharmaceutical industry, and certain members of the Food and Drug Administration figured prominently in allowing the significant speed with which AZT became available to large numbers of HIV infected patients. Whether other promising agents become available in the marketplace with such rapidity awaits to be seen. However, future endeavors will likewise necessitate considerable cooperation among researchers in academia, industry and the government.

Development of AZT is also unlikely to serve as a precedent for the development of other compounds found to be active against this virus in the test tube. A historical review of drug development unfortunately reveals that the majority of chemicals exhibiting in vitro activity never become useful drugs. Some are simply not effective, either because the original test tube testing was less than stringent or because conditions which allow virus proliferation and its direct and indirect adverse effects in the human being are vastly different from those in the test tube. Ascertaining the reliability of in

vitro predictors of efficacy in humans becomes even more problematic when dealing with immunomodulating agents because compounds which increase the numbers or activity of immune cells may also merely increase the numbers or susceptibility of cells available for viral infection. More commonly, chemicals do not become drugs because unacceptable toxicity may be observed in experimental animals or humans that was not or could not be evident in initial tissue culture assays. Finally a myriad of other factors, including poor absorption following oral administration, rapid excretion, rapid metabolism to an inactive compound, poor penetration into the CNS, or even the inability to manufacture the material in large scale with consistent identity, purity and potency all mitigate against successful drug development.

Drug development in general, and anti-AIDS drug development in particular, is a labor- and money-intensive venture filled with many promising leads which usually lead to failure and disappointment. This general lack of success, however, should not lead to cynicism or disillusionment with the entire process but should evoke a healthy scepticism among patients who are using a variety of unproven nostrums. The drug development process requires a great deal of knowledge, skill, time and luck to ensure that a compound is a safe and effective drug. The last thing any of us wishes is the widespread use of something which proves to be, on subsequent careful examination, either useless, or toxic or both.

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Presentation for Presidential Commission on the Human Immunodeficiency Epidemic February 19, 1988

Developing a Drug: Ampligen - A Case Study

by William A. Carter, M.D. Chairman,
HEM Research

I am the Co-discoverer of Ampligen and have been the principal catalyst in its development over the last several years. I will briefly describe the environment in which Ampligen was discovered and nurtured to its present state of development. Dr. Mollica, Director, Pharmaceutical Research at E. I. DuPont, will describe present efforts at large scale manufacturing and the breadth of our jointly-sponsored nationwide clinical evaluation program. Dr. Lennox, principal investigator at one of our key participating hospital sites, will overview some of the tedious but very necessary tasks required to implement definitive studies of promising anti HIV-agents at the clinical level.

Ampligen was discovered by Dr. Paul Ts'o and myself in the 1970's while at Johns Hopkins University. The conceptual background was as follows: we were searching for a component common to various human virus particles which would be capable of stimulating <u>both</u> the body's immunological defenses and the antiviral mechanism at the single cell level. Earlier, work at Merck had suggested that double-stranded RNAs had a broad range of potential therapeutic

activity in this regard, but the products they developed there had unacceptable toxicity and low therapeutic ratios. Accordingly, very little clinical progress was being made with the primary required target of dsRNA-namely, untreatable human cancers.

Double-helical RNAs actually look like two-winding staircases which intertwine at a given frequency. I am sure you are all familiar with the shape of double-helical DNA and RNA (or Ampligen) is quite similar. The essence of our discovery was to produce little out-pouchings, or mismatches, in the molecular staircase which resulted in a dramatically different biological effect - a fragile molecule which nonetheless triggers a biochemical variety (termed "cascade") of host immune/antiviral responses and then would undergo accelerated biodegradation - hence its lack of any significant toxicity.

Ampligen is thus a type of artificial "virus", if you will, which we initially developed primarily for treatment of human cancers and only later (1986) did we recognize its broad-spectrum anti-HIV potential. Our earlier work in cancer was supported primarily by the NIH and we are especially indebted to the NCI, Dr. DeVita and his colleagues in the Division of Cancer Diagnosis and Biology for being long term believers and supporters of the scientific merit of Ampligen.

Thus, Ampligen was not an "overnight eureka" but rather a logical scientific discovery after years of laboratory research with concrete objectives. In the late 1970's and early 1980's, we began to expand cautiously the therapeutic potential of Ampligen by laboratory studies which suggested that many human viruses might also be susceptible to its unique immune enhancing/antiviral mechanism. This broad spectrum antiviral feature of Ampligen may ultimately prove especially important in people with HIV infection since often other viruses are isolated in these individuals especially as their immune statuses undergo further deterioration over time. Ampligen is thus a powerful probe of the potential role of other viruses in HIV-induced disease progression.

The development program of Ampligen is a model one in that the concept was developed initially in an academic environment. Hahnemann University in Philadelphia, working with HEM Research, was central to strengthening Ampligen's scientific underpinnings between 1980-1986 and I share with you here (a hardbound copy of Ampligen scientific article reprints) the productivity for just one 18 month interval. By 1986, a more entrepreneurial environment was necessary with the discovery of its anti HIV activity and the realization that hundreds of individuals, as opposed to dozens, would require evaluation before, during, and after Ampligen treatment. The entrepreneurial environment led ultimately to the HEM/Du Pont joint venture, the scope of which will be addressed by Dr. Mollica. DuPont was already committed

greatly to AIDS research. But suffice it to say that the intellectual freedom/entrepreneurial spirits still are "alive and well" in this joint-venture; the opportunity for innovation in manufacturing, clinical study design, etc. can flow from cooperative efforts of a large and a small company just as well as, and in some instances, superior to those of a purely academic setting.

We believe that the integrity of this scientific/medical effort to find an effective non-toxic HIV treatment cannot be short-cut. Short cut processes include avoiding the rigorous process of peer scientific review such as by going straight to the lay press with interesting new findings or by avoiding FDA sanctioned clinical studies. At the end of the day, such short cuts can only compromise the care that HIV-infected individuals will receive. Accordingly, we always first publish our data in recognized scientific journals and, after publication, provide only limited releases to the lay press which conform fully with both the spirit and the guidelines set forth by the FDA. Where possible, we try earnestly to present all data with a full biostatistical analysis so that the reader can evaluate for himself, or herself, the relative likelihood that the data will be reproducible overtime. Suffice it to say that we have found that our recent data (T4 cells, virus load, skin tests etc.) with <u>18 months</u> treatment experience in HIV treatment agree well with interpretations from a 1 month experience reported in <u>Lancet</u> 1987 (June); accordingly, no patients, no families, and no physicians

have been misled. Over 2000 patient study weeks data agree with pilot data because quality assurance mechanisms were in place both at the laboratory and clinical level from the beginning of our work.

We are acutely aware of the special needs of our patient population and working towards an Ampligen treatment program which will utilize community physicians in our research endeavors and we are making every effort to provide treatment in AIDS/ARC in non-hospital settings. Indeed, one of the great promises of the preclinical work with Ampligen, is the suggestion of Ampligen's potential as "base biological" treatment, is that it may increase the effectiveness of other anti-AIDS drugs. By allowing a reduction in dosage of potentially toxic, though necessary, therapies, Ampligen may thus be able to reduce dramatically the need for extensive hospitalization with its devastating effect on personal finances and morale.

We have established a close scientific contact with the FDA and especially the Bureau of Biologics within the agency has provided invaluable assistance in the accelerated development of Ampligen. Our own experience suggests a remarkable level of readiness on the part of the FDA to assist all manufacturers, whether small or large companies, in accelerating their clinical programs. Accordingly, we find no basis, whatsoever, for the occasional FDA "bashing" on the grounds that the Agency is proceeding "too slowly" to follow up possibly important therapeutic leads. To

the contrary, our concern is that pressure groups would cause administrative/scientific disruptions within the FDA: such changes, however, in the name of "progress" might only disrupt very effective working teams within the agency and thus produce new cadres which needed to get up on new "learning curves", explore new ways to collaborate, etc. In summary, we feel the agency is discharging its functions well and that regulatory mechanisms are already in place to accelerate the work of all manufacturers in the anti-HIV therapeutic arena.

As a senior scientist in the Ampligen development program, I am very much involved in all aspects of clinical and laboratory program. We are expanding our clinical programs as each month passes and plan a series of scientific manuscripts which combine rigorous laboratory and clinical data such as we published 8 months ago, in Lancet. At present, over 300 individuals (males) are enrolled in our HIV-treatment programs and we intend to include females as as an integral part of our future study plans. We are trying, with cooperation of the FDA, to compress a process which might normally require 8 years to, hopefully, 2 years.

In closing, all staff at HEM Research have made dramatic commitments to Ampligen recognizing the magnitude of the epidemic and the potential of our approach. This commitment, where our staff commonly work 60-100 hours per week, has been the key to our progress to date. A similar commitment has been made by

staff at E.I. DuPont and for further details I turn over to my colleague, Dr. Mollica.

Testimony of Ted Lenox, M.D.

I am Ted Lenox, M.D., an Assistant Professor of Medicine at New York Medical College at Valhalla, New York, and an attending physician in Infectious Diseases at Metropolitan Hospital Center, one of the city operated hospitals in New York City. I have been asked to describe my experiences in establishing and running the Ampligen trial at my hospital.

I was first approached with this project on November 2, 1987. By this time, the protocol had gone through the first of three IRB's needed to do research at Metropolitan. This is the first major obstacle to doing any research at my hospital. Because we are a medical school affiliate at a city hospital, we must submit protocols to New York Medical College, then to the Research Committee at Metropolitan, and finally to the Research Office at Health and Hospitals Corporation (HHC) headquarters. You can imagine how long this process can take. On a different project, it once took six months just to approve the consent form. Obviously, any revisions of the protocol must be resubmitted through the same channels. Dr. Gary Wormser, the chief of Infectious Diseases at New York Medical College and my co-investigator, had submitted the protocol to the college and had received approval after several amendments had been made and about four months had passed. I then became responsible for obtaining the necessary approvals from Metropolitan Hospital and from HHC. In ten working days, I had received written approval from the hospital and verbal approval from HHC. However, the written approval from HHC, which was necessary prior to enrolling clients, did not come until Dec. 10, almost a month later. I must say that this is an unusually short period of time and it is

indicative of the recognition of the importance of this particular protocol.

During this process, the second obstacle was to find the personnel to coordinate and essentially run the study. I was fortunate to know a registered nurse who has excellent qualifications and was interested. He has worked as a medical technologist, a lab supervisor in a major NYC hospital, and has counselled extensively for GMHC. He was hired quickly and recommended the second nurse who was hired. From previous experiences, finding qualified, interested personnel is not easy.

The nurses are primarily responsible for the day-to-day functioning of the study. They answer the telephone, screen clients and answer their questions, do the scheduling, draw the bloods, supervise other required tests, administer the infusions, and are ultimately responsible for collecting the data. I have with me one of three notebooks which we are required to keep on each client. The paperwork is phenomenal. The data is originally entered into a workbook and then has to be transposed into the more permanent case reporting forms. We have been told that the workbooks must be kept as the primary source of the data. We would like to hire an additional person just to handle the paperwork.

Counselling skills have been an invaluable asset in working with our clients, most of whom are still healthy and working daily. Because of this, many have been able to minimize the fact that they are HIV positive. Once they enter the trial they are reminded at least twice weekly that there is a real possibility of deterioration and they must face the idea of their own demise. One client reported nightmares for several nights prior to his

first infusion; they since have ceased. Other clients are extremely anxious and a calming force is important for them and for us if we hope to keep them in the study for nine months. The level of their anxiety is frequently heightened once they have entered the study.

A major obstacle was finding available space at the hospital, and this is still not entirely settled. Space is a premium at Metropolitan and we must compete with pre-existing clinics who need additional time and space. The space which had been allocated for us was later cut in half. The space which was promised by early January is still not completed and we are operating primarily out of my office which is also used by two infectious disease fellows. A more recent problem arose when we attempted to install telephone lines to support the printer to receive lab reports and the fax machine to receive the randomization data from DuPont. The city bureaucracy was in full force here. It took three weeks just to get the administrative approval to install the telephone lines. When we went to hook up the fax machine last week, the line was dead. To get someone to look at it requires a work order and the promise that "We'll get to it soon." We were informed on Tuesday, that because of construction in that area of the hospital, the electricity may be turned off for two weeks. Therefore in order to get the data we need to evaluate our clients we would have to phone directly. However, in order to do that we must request permission from my Department Office for each phone call, including collect calls. This can be a time consuming venture.

The next problem came with the recruitment of clients. As my own patient population is primarily IVDA's, we had to recruit

from outside our own population. I wrote letters to all of the local infectious disease attendings and used lists of resources published for PWA's and PWArc's and wrote to appropriate groups. Most of our referrals have come from private physicians. Several organizations have called us regarding the eligibility criteria and have promised to refer clients to us.

As of this morning, we have taken a minimum of 120 telephone calls, begun or completed active screening on 28 clients, eliminated 12, and have begun infusions for five with three more planned to begin next week. The total number of calls taken is misleading because a great deal of time can be spent counselling clients, some of whom decide to enter. Many calls request information or the clients are disqualified very quickly, e.g. women or IVDA's and have not been counted. Clients have decided not to enter for mostly three reasons: 1. an unwillingness to take a chance with a placebo; 2. an unwillingness to stop PCP prophylaxis or antiviral or immunomodulating agents several of which are used frequently in New York; or 3. the rigorous demands of the study, i.e. twice weekly infusions for nine months.

In conclusion, doing a research trial like this in a setting such as mine is full of frustration and disappointment and a lot of long hours. I have taken on this resposibility in addition to my clinical, teaching, and administrative duties with assistance from my colleagues in my division. My staff and I are encouraged at this early date by the very positive, appreciative response which we have received from our clients. We must never lose sight of the number of lives already lost to this epidemic and use whatever resources available to get effective therapy to as many people as possisble. We should never allow ourselves the

complacency of designing trials because that's the way it has been done before. We must continue to question whether it is still ethical to run placebo trials and when must we stop denying clients adjunctive therapy which may be beneficial. Must we define an endpoint as one in which the patient becomes seriously ill and accept the loss of lives as necessary?

I would recommend the following:

-that counselling support for the clients as well as the staff become a part of future research projects. All involved need emotional support to complete a long study

-an up-to-date clearing house for dissemination of available trials with information regarding the protocol eligibility requirements. I am aware that some are available, but these frequently have old or incorrect information.

-incentives to public institutions to encourage the development and implementation of research projects.

-the involvement of private physicians to assist in the development and implementation of research projects

-the inclusion of all persons at risk in future trials.

-the redefinition of endpoints to eliminate the necessity of expecting serious illness or further loss of lives.

Testimony of Joseph Sonnabend, M.D.

My name is Joseph Sonnabend. I am a physician and have been providing primary care for people with Aids since the beginnings of this epidemic.

I am grateful to have this opportunity to tell you about the Community Research Innitiative. Of the many emergencies that comprise the Aids crisis, the need to rapidly develop effective treatments is perhaps the most pressing. This means that we have to expiditiously test many different treatments and combinations of treatments simultaneously. This requires access to a large population of individuals with AIDS and AIDS Related Conditions, as well as an appropriate administrative structure that would insure the proper conduct of trials and the efficient gathering and analysis of data.

The Community Research Innitiative can fulfill both these requirements. Community based trials can tap into the large population of People With Aids who are seen in the practices of communtity physicians. These patients are in a relationship of trust with their physicians who are eager to participate in treatment research. Because this group of patients are largely white gay men the CRI is committed to actively reaching groups of patients who are under-represented in these practices. At its second meeting almost a year ago the CRI's Institutional Review Board addressed the issue of equitable entrance into treatment trials for all people with AIDS. I believe this kind of

responsiveness indicates an important advantage a community based research endeavor has in comparison with Medical Center based research. One only has to look at the demographics of the large multicenter AZT trial to see this contrast. There were virtually no women nor black men who were enrolled at any of the study centers.

As a community based organization sponsored by People With AIDS, the CRI is particularly sensitive to their needs. The importance given to the issue of equitable entrance is not the only example. The issue of pneumocystis pneumonia prophylaxis and the use of placebos in critically ill individuals are two further examples. Pneumocystis pneuemonisa is the most frequently occuring opportunistic infection in AIDS. This infecton is almost definately preventable although the kind of data that is needed to provide proof of efficacy has yet to be obtained. It is of course of great importance to systematically gather such data and provide proof of efficacy. It is also important that People With AIDS are not denied access to an intervention that will most probably prevent pneumocystis pneumonia while trials establishing efficacy are underway. The CRI is meeting both of these needs. A 200 person formal trial of aerosolized pentamadine for the prevention of pneumocystis pneumonia has been underway since the beginning of January at the CRI. Data obtained from this study which will last for a year will add to data gained from similar studies at the San Fransisco General Hospital in providing evidence regarding efficacy and longer term safety. At the same

time as conducting a systematic study on PCP prevention, the CRI, in considering other trials in AIDS patients requires that PCP prophylaxis is not denied to trial participants. Of course this means that the occurance of PCP can no longer be an end point when testing a particular AIDS treatment. The studies are therefore more difficult but certainly not impossible to design. I should also point out that the move towards PCP prevention has originated in the community of People With AIDS. It is largely in response to pressure from this community that the use of a life-saving intervention is now being offered to more individuals. The CRI has also shown that the wider availability of such an interventiuon is not incompatable with the systimatic gathering of data that is required to obtain proof of efficacy.

On the issue of placebo controll trials, the CRI is also responsive to the community of People With AIDS in resisting the use of placebos in trials where the life expectancy of the individual may be shorter than the duration of the trial. Of course there are places for placebo controlled trials but critical illness with a short life expectancy is not one of them. There are other ways to conduct controlled trials that do not require the use of a placebo. For example, the CRI is about to begin a blinded trial comparing two dosages of active lipids analogous to AL-721.

There is a further advantage that community based trials offer in comparison with those conducted in medical centers. This relates to the fact that People With AIDS who are trial participants are

now taking a number of interventions on their own innitiative. Since this would exclude them from entrance into the trial, these individuals are witholding this information. CRI trials are more likely to acknowledge this reality and design studies that will take this into account. Of course there will be some studies in which the use of specific treatments outside a particular protocol would make it impossible to interpret the results.

The conduct of trials outside medical centers is novel but not unprecidentad. I founded the AIDS Medical Foundation with Dr. Mathilde Krimm and one of our tasks was to conduct the kind of community based research that the CRI is undertaking. Our experience in establishing an Institutional Review Board and in approving and sponsoring trials in a communty setting indicates that such trials can be successfully conducted. In fact many of the CRI IRB members were also members of the AIDS Medical Foundation IRB and thus have experience in reviewing community based trials.

I'd like to end on a personal note. I am a microbiologist and until 1978 most of my profesional life had been spent in the rsearch laboratory with some clinical experience limited to infectious diseases in a hospital setting. It is from this background that I started to see patients in a private practice in Greenwich Village in NYC. Many of these patients were gay men who already had a variety of hemotologic abnormalities which in retrospect were the earliest manifestations of AIDS. Thus I have

had the opportunity to observe this epidemic from its onset. My views on AIDS have been shaped by this considerable practical experience and my research background. I believe that the cause or causes of AIDS remain unknown. The premature acceptance that HIV1 and now HIV2 cause AIDS has resulted in almost all resources being devoted to developing anti-retroviral treatments. The CRI is less likely to be constrained by such a limitation. The years since 1981 have been immeasurably bleak for us all. For all the above reasons, I believe that the CRI represents a very significant hope for the future and deserves all the help and support it can ~~get~~ receive.

A I D S
TREATMENT
N E W S

AIDS Treatment Access:
A Wish List, Some Problems, and Recommendations

Testimony of John S. James
Editor and Publisher, AIDS Treatment News

Before the Presidential Commission On the HIV Epidemic
New York City, New York, February 20, 1988

The biweekly newsletter AIDS Treatment News began as volunteer research and writing for an AIDS archiving organization in San Francisco. In little over a year it has grown to a circulation of over 3,500 almost entirely by word of mouth--an unexpected public response which illustrates the critical dearth of practical treatment information felt by patients and physicians alike. Researching treatment articles for AIDS Treatment News has provided an unusual opportunity to hear what this community would like to see happen, and where it sees the obstacles now.

People react to an AIDS diagnosis in different ways. Some resign themselves to dying and begin to prepare for death. Others ask their doctors to make the medical decisions for them, without their personal involvement. I do not have contact with these people and do not know how they feel about treatment research and access issues.

But very many persons with AIDS or other HIV infections do choose to involve themselves in decisions about their health care. They often become experts in the disease and potential treatments.

And most of these people come to feel abandoned and betrayed by society. They believe that many physicians, researchers, and officials have been quick to write them off as already all but dead--despite all the unknowns about this disease which make it impossible for anyone to be sure that death is

inevitable. The projected deaths of at least a quarter of a million Americans seem to have been accepted with surprising equanimity and surprisingly little sense of crisis or mobilization.

Oddly enough there seems to have been no professionally conducted survey asking the persons most directly affected by AIDS what they though about the issues of treatment research and access now before this Commission. Certainly the people I know have never been asked how they see the situation, what problems they find in the institutional response to the epidemic, and what improvements they would suggest.

A Wish List

Since we have no scientific survey information on what people with AIDS would most like to see done, we did the next best thing and interviewed Nathaniel Pier M.D., a physician with a large AIDS practice in New York City. We have found his statements about what is needed to be as close as anyone's to the beliefs of the persons with AIDS with whom we have communicated while writing AIDS Treatment News.

Dr. Pier proposed above all "That anybody diagnosed with HIV-related disease or immunodeficiency be given a full assessment of their situation and be allowed to choose to receive a therapeutic regimen or decline it. Theoretically, all five hundred thousand persons infected in New York should be allowed access to some form of therapy if they wished. To satisfy scientific needs, they could be enrolled in formal protocols. Otherwise clinicians should be allowed to use empirical regimens, with patients properly monitored.

"This way everybody would be given the optimal chance to save their lives and nobody would be allowed to twist in the wind. Furthermore, we could look at the results--and get a sense of what works much more rapidly than under the current system.

"Persons could use single drug treatments, or rational combinations based on the best judgment of experienced physicians.

"What we propose here is what is already done with cancer patients. Almost no one diagnosed in the United States today with cancer is denied an opportunity to participate in potentially lifesaving therapy. There is in place a widely accepted system for providing these experimental and established therapies to cancer patients. This system advances our knowledge of the treatments for this disease but is also a humane and compassionate way of caring for patients.

"To the argument that there are no AIDS treatments except AZT because no others have proven effective, we would answer that we are currently capable of choosing safe, rational approaches to therapies. In addition, people are using therapies anyway. Our proposal would allow them to do so under supervision, so this can be done safely and the data developed can be critically evaluated and thereby be helpful to others instead of remaining anecdotal."

Some Problems (See Lentinan Correspondence, Attached)

"It is clear that the best hope for people with immune deficiency or at risk for the illness is the rapid development and dissemination of safe and effective therapies. Until this goal is achieved, the most humane approach to dealing with AIDS and AIDS-related problems is to give people access to supervised therapeutic protocols. The main problem, therefore, is to develop such a system--a system that would allow rigorous scientific analysis of therapies and still incorporate anyone wishing to try to help themselves with experimental therapies.

"The present system for developing AIDS therapies has been painfully slow in starting. Access is so severely limited that the majority of people affected by this disorder are left without intelligent recourse.

"In addition it is unclear where the leadership for determining priorities in therapy development is coming from. It is also unclear how the decisions for prioritizing the various therapeutic approaches are being made. For people with AIDS it is unclear who is setting the timetable and who is supervising the large-scale effort to develop therapies.

"For the individual who must make decisions there is no centralized method of gaining access to the information that will allow him or her to choose the best course of action.

"How does the present system work? As an example, we submit correspondence relating to a potential therapy for AIDS which first was recognized in 1984. In spite of prominent AIDS researchers acknowledging the potential benefit of this therapy, no clinical trials on humans with HIV infection have been initiated since then. In addition, you will see that letters to the people vested with protecting the public health have gone ignored and unanswered. This has left the impression that they are inefficiently and callously dealing with this very important issue. We do not believe that this is truly the case. Nevertheless the letters have gone unanswered and the trials have not materialized."

Other Concerns

Lentinan. Dr. Pier's statement above concerns his two-year attempt to get this drug considered. We should point out that lentinan has long been used for cancer treatment in Japan, with complete safety. And a letter to The Lancet in October 20 (attached), signed by seven scientists including Robert Gallo M.D. describes its use in the successful treatment of two patients which retroviral infections (one with HIV, the other with HTLV-I).

In four years nothing has been done. Examination of Dr. Pier's correspondence with governmental authorities clearly illustrates the frustration and difficulty he experienced in attempting to get this potential treatment considered on its merits. Now we have heard that NIH has put lentinan into its highest priority category for investigation--without major new information, essentially on the basis of what was known four years ago. However the drug-selection process is secret so we only have hearsay and have not been able to confirm that lentinan has been placed into the high priority category, or that it was done without new information.

AL 721. The unhappy story of the repeated failures to test this drug properly and make benefits available is presented at length in the back issues of AIDS Treatment News, submitted into the record of this hearing.

We would add two points not covered in the newsletter:

(1) We have heard reliable information that AL 721 was used to treat one person with AIDS or ARC even before it was submitted to Robert Gallo's lab for the successful in vitro test against HIV replication published in the New England Journal of Medicine, November 1985. In other words there was one successful human test by early to mid 1985, a fact never publicly revealed until this testimony. The public was denied access to this information--compelling enough to some for them to get Robert Gallo involved in further testing--in the middle of a deadly epidemic.

(2) In yesterday's hearings one of the Commissioners asked FDA Commissioner Dr. Frank E. Young if a therapy might be developed to help overcome drug abuse, which is becoming so important in the spread of AIDS. AL 721 was in fact first developed primarily for that purpose. Theory, laboratory, and animal studies have suggested that it might be effective in reducing the symptoms of opiate or alcohol withdrawal, thus helping abusers to overcome their habits permanently. However to our knowledge no human study has been done--not

even a small, quick, inexpensive pilot study which would give some sense of whether it was worth proceeding with this potential medical intervention against drug abuse.

Trimetrexate. The important news about the approval of the first AIDS-related treatment IND has failed to acknowledge a major concern. Theory and laboratory studies suggest that the trimetrexate with leucovorin therapy now approved for pneumocystis pneumonia (when standard therapies have failed) would very likely also work against cryptosporidiosis, a severe and often fatal diarrheal illness of persons with AIDS. Cryptosporidiosis presently has no satisfactory treatment.

We have heard that even a leading gastroenterologist has been unable to obtain trimetrexate for compassionate use for treating cryptosporidiosis. We have also learned that the manufacturer, Parke Davis/Warner Lambert, has no plans to develop the drug for this condition.

The result is that this drug, already proven so safe in persons with AIDS that almost none of the (pneumocystis) patients had to have the therapy terminated, will never be tested for cryptosporidiosis under the current system, despite the immense benefit the discovery of a successful therapy for this opportunistic infection might bring.

Salk Polio Vaccine. The "old" Salk killed-virus polio vaccine (not to be confused with Salk's current work on an HIV vaccine) has recently been tried as a possible ARC or AIDS treatment. Although it is far too early to be sure it is effective, this therapy has generated considerable excitement among the physicians who have seen the results. In addition, according to an overview article which appeared in The Wall Street Journal on January 27, 1988, this possible therapy has also attracted unusual attention from some NIH scientists, who have determined that persons receiving repeated treatments with this vaccine have produced neutralizing antibodies against the AIDS virus. We have heard that Dr. Pitts is now collaborating with a university and a county board of health on a formal study, approved by his IRB--but that Dr. Pitts and a colleague must pay for the vaccine out of their own pockets.

We have also heard two reports that Connaught Laboratories Inc., the only company able to sell the Salk polio vaccine in the United States, has recently made it difficult for physicians to obtain supplies for use in treating AIDS--even though it is perfectly legal for physicians to use it for that purpose. One internist told us that the company refused to ship the vaccine unless he signed an affidavit that it would only be used to immunize against polio. And we also

heard that Dr. Pitts' group had to threaten a lawsuit in order to obtain supplies for the study cited above.

We have been unable to confirm these reports because Connaught has refused to discuss them.

It is widely believed in the AIDS community that companies do not on their own resist the development of new markets for their products. It is generally presumed that these cases reflect fear by the company of making enemies at the FDA, which may fear damage to the regulatory process from the development of a public demand for a drug outside of normal channels. Bureaucratic interests may be best served if the usefulness of a valid AIDS treatment is never discovered in the first place. Patients' interests differ. All this in conjecture, of course, as in these cases no one talks, and unless an insider reveals information nothing can be proved.

The polio-vaccine case is not at all unusual. In case after case, too numerous to list here, deliberate roadblocks and obstacles have impeded patients in obtaining treatments, and prevented research which could serve as early pilot studies to indicate whether or not an idea deserved further, more formal trials.

Recommendations

1. That either the Commission or another body investigate the problems cited above, and dozens of similar ones which we can bring forward, to find out what did happen, if there are indeed roadblocks to treatment and treatment research, and how these roadblocks could be overcome.

2. That the Commission arrange for a survey to ask persons with AIDS, ARC, and asymptomatic HIV infection what they think about current public policies regarding the epidemic, and how those policies might be improved.

3. That the Commission ask the FDA to provide guidelines to researchers outlining what studies would be required to qualify a drug for treatment IND or for approval. These guidelines should specify when it is and is not ethical to use placebos in persons with life-threatening disease, or to withhold use of previously proven therapies such as pneumocystis prophylaxis.

4. That the Commission recommend the creation of a public, computerized and printed registry of all human trials for treating AIDS and related disorders should be established. This registry should include pertinent information about each drug, and the protocols, in language that can be understood by a lay person. Registration in this database should be required for all government-funded protocols, and voluntary

registry of all others should be encouraged.

5. That the Commission recommend steps to make access to therapeutic trials equally available to all qualified persons. A system must be established for insuring fair access to everyone in need. A lottery might be suggested.

6. That the Commission suggest the creation of a confidential, voluntary registry of individuals affected by AIDS and related disorders, whereby these individuals can be notified automatically when there are new trials for which they can qualify. (This system could also help researchers recruit for their trials.)

7. That the Commission recommend the immediate expansion of funding for experimental trials organized and run at the community level, using the resources of private and community physicians, such as the Community Research Initiative in New York, and the Community Consortium in San Francisco.

8. That the Commission encourage the current attempts to share and disseminate reagents, materials, and scientific data within the scientific community, to speed the discovery of safe and effective therapies for AIDS.

9. That the Commission recommend the development of a system such as compulsory licensing which would prevent proprietary restrictions on data and access to drugs from impeding development of AIDS treatments.

10. We urge the Commission to recommend that individual patients and their physicians be allowed to choose to use safe experimental therapies under supervision, even before efficacy has been confirmed, if informed consent is obtained.

Testimony of John Scafuti

TEXT OF RECOMMENDATIONS PRESENTED BY JOHN SCAFUTI BEFORE THE PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC - FEBRUARY 20, 1988

Representing: Home Health Care Services, Inc. - Research Division, Aids Coalition Endowment (ACE), Aid Orlando, Florida Task Force (FTF), University of Central Florida Task Force on Aids, Orlando Gay Community Services (GCS)

My testimony is dedicated to the memories of three particularly motivated men who have preceded me here - Tom Jefferson, Patrick Haney, and Jim Sammone - they have all expired within the last two months, highlighting the urgency of our task.

I will present two sets of recommendations for expediting delivery of unauthorized or investigational new drugs at the earliest possible time. The first set of suggestions are made within the current framework of the drug approval system. I estimate this method of proceeding to be only half as effective as the second more comprehensive set.

Under the new regulations governing IND compassionate use treatments and IND protocols, a specific example is cited on page 19467, column two, next to the last paragraph, qualifying all stages of HIV infection as "immediately life-threatened", thereby clearing the way for even the asymptomatic patients to receive the most advanced treatments as soon as possible. With as many as 2,000,000 potential clinical subjects there should be no problems filling clinical trials - a requirement for consideration of IND compassionate use treatments.

In most of the current trials in progress clinical subjects are recruited from the most financially secure, and most pharmaceutically sophisticated patients. Both the FDA and the pharmaceutical companies fail to address the implications of this reality. These patients are much more likely to follow through with the full term of the trial but are not nearly as likely to adhere to the conditions of the trial. This results in a smaller subject population but questionable validity.

A far more fertile source of clinical subjects is in the very clinics where current care is significantly inferior - VA hospitals (See Enclosure #2), and free government clinics. This would offer some hope of advanced treatments to the underprivileged that doesn't now exist. While the populations in the trials would have to be expanded to allow for a higher dropout, the trials would be far more valid due to closer adherence to the testing conditions. There will be charges of bias against the underprivileged and of using them as guinea pigs. The truth is that their care will be significantly improved, they will enjoy a sense of contribution to society, and the financial burden for much of their care will be shifted to the private sector (the pharmaceutical companies). The test results whould be far more valid due to closer adherence to the conditions of the trial. In short, the positives far outweigh the negatives, regardless of the potential criticism.

RECOMMENDATIONS BY JOHN SCAFUTI (CONT'D) - FEB. 20, 1988

Under the new FDA regulations for IND compassionate use treatment protocols, a surprising possibility has emerged. By the time a drug has neared the end of Phase II (small controlled studies) and the four general criteria have been met allowing IND treatments to begin, there may be more liability to the physician, pharmaceutical company, and the FDA for not providing the drug than that which is associated with providing it. An interesting historical fact is that only one case has been tried where an investigational new drug was administered. The decision in all of the courts was consistently for the defendants. What this indicates is that early usage of promising new drugs for AIDS is likely to be rather non-litigious, while delaying usage, conversely, could attract significant class-action litigation (2,000,000 Americans with HIV infection currently qualify as "immediately life-threatened").

Two major defects in the IND treatment approach could, and probably will, nix the whole system. While the FDA seems to be bending over backwards to provide promising drugs at the earliest possible time, the pharmaceutical companies are not compelled to provide the drugs and the third party payors (Medicare, Medicaid, and private insurance) are not compelled to pay for the drugs. Historically the FDA has played a passive role. Even if they are now inclined to be more proactive, it will be some time before they will be capable of making that adjustment.

To make the system work the government must put the public interests of the ravaged populations above the proprietary interests of the pharmaceutical companies. The appropriate legislation accomplishing this must be enacted. Part of that same legislation should include a requirement that third party payors must pay for all IND treatment situations. Without this legislation the new FDA regulations are clearly worthless with only the very wealthy having any early opportunity to use expensive investigational new drugs such as Ampligen.

The next set of recommendations fall outside of the current health care and drug approval systems. Do not pursue a Manhatten Project for AIDS - the historical Manhatten Project had a narrow well-defined purpose. The scope and implications of this disease are far too broad and comprehensive to be dealt with in the same manner. Such a project would likely be biased towards strictly HIV theory, be focused on "magic bullets" rather than disease control, and would not adequately address multifactorial possibilities.

RECOMMENDATIONS BY JOHN SCAFUTI (CONT'D) - FEB. 20, 1988

Instead of the Manhatten Project the Congress or the President should literally DECLARE WAR ON AIDS and appoint "Joint Chiefs of Staff" under the Department of Health. This body should have the same power to fight AIDS as its military counterpart during wartimes. Represented on this committee should be: the Surgeon General, the Commissioner of the FDA, the head of the NIH, the Commissioner of Insurance, a representative of the pharmaceutical industry, and the head of the Department of HRS. Balancing the traditional government and bureaucratic bias in the composition just stated, it is essential that leaders of groups hardest hit by this epidemic be well represented on this panel: homosexuals, Blacks, hemophiliacs, and women. Since many of the anticipated decisions will be economic and based upon questionable statistical data, it is essential to include cost accountants and statisticians as well. At no time should the private representation be outnumbered by the government representation. A significant effort should be made to include HIV positive individuals whenever possible. No one has a greater inherent human right to make decisions affecting survival than those who are struggling personally to survive. This body would formulate strategy, implement policies, and serve as a board of appeal for conflicts which would inevitably arise.

Rather than trying to squelch the AIDS drug underground (those efforts would be miserably unsuccessful, ill-advised, and a huge waste of time, money, and energy); we should instead devise a strategy for gaining as much information as possible from that system. We must provide physicians with incentives to track and report the polypharmaceutical treatment strategies which are being followed by their patients. Most experts agree that ultimately a multifactorial approach consisting of combinations of anti-virals, immune enhancers and immune modulators will effect the greatest degree of disease control. Instead of fighting what is going to occur anyway, we could gain valuable insights for controlled combinational studies based upon subjective indications, which become apparent when the data is reported in huge numbers by physicians throughout the country.

To create incentives for this project, I propose the following: (1) Statisticians working with highly informed physicians and researchers who have an understanding of the polypharmaceutical possibilities would design computerized patient histories, regimens, baseline and maintenance lab data in the most convenient fashion possible. (2) Participating physicians should be given a prestigious labeling which could be recognized by the general public in advertising media (example: NDI - "New Drug Investigator"). (3) Provide participating physicians with the most sophisticated interactive data retrieval system to date, enabling them to know immediately as evolutionary advances in treatment possibilities are occuring. Also include a complete registry of all trials planned or in progress relative to any AIDS issue. (4) The government should pay the physician for his additional efforts on a per patient basis.

RECOMMENDATIONS BY JOHN SCAFUTI (CONT'D) - FEB. 20, 1988

The significance of creating the model described above cannot be underestimated. While there are very few reports of drug interations, there is no responsible tracking going on and extremely useful combinations may be going unnoticed. By expanding the subject population to enormous proportions we can validly include a large number of variables and still produce extremely valuable subjective indications for more controlled research. This offers the opportunity of leap froging current step-by-step traditional research.

These proposals are obviously not "business as usual." Imagine the progress we could make if they are implemented! It is long past time to drop a "business as usual" approach.

Several enclosures have been included which support the conclusions reached above:

Enclosure #1 - Example of Child Thriving with Unauthorized Drugs (with Exhibits $1A_1$ - 1F).

Enclosure #2 - Example of Inferior Medical Care in VA Hospitals.

Enclosure #3 - Example of Results Using Drug Prior to Marketing Approval - DHPG

SUMMARY OF RECOMMENDATIONS PRESENTED BY JOHN SCAFUTI BEFORE THE PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC - FEBRUARY 20, 1988

I. Recommendations Within Current Drug Approval and Research Framework
   A. Utilize 2,000,000 potential clinical subjects providing greater purpose to their lives and more advanced medical care.
   B. Current clinical subjects are too sophisticated, jeapardizing the validity of trials in progress.
   C. Use the VA, prisons and other government sponsored clinics for the primary source of subjects thereby raising the standard of care and shifting much of the cost to the private sector. These subjects will also yield more valid results.
   D. Actively push for early usage of drugs thereby avoiding significant possibilities of class-action litigation (2,000,000 Americans - all HIV+ are classified as "immediately life-threatened" by the new FDA regulations).
   E. Close the holes in the IND treatment system by:
      1. Requiring pharmaceutical companies to provide;
      2. Requiring third-party payors to pay.

II. Recommendations Outside of the Current Drug Approval and Research Framework
   A. Do <u>not</u> pursue a Manhatten Project. It is likely to be biased towards HIV theory only and too narrow to include broader concepts of disease control.
   B. DECLARE WAR ON AIDS!
      1. Appoint "Joint Chiefs of Staff" with representation from both government and private sector - include HIV+s. They should:
         a. Formulate strategies
         b. Implement policies
         c. Act as a board of appeal in disputes.
      2. Utilize data created from individuals using polypharmacy.
         a. Design model using input from staticians, physicians, and researchers.
         b. Make reporting simple but comprehensive.
         c. Assign a prestigious label to physicians participating in the reporting process.
         d. Provide participating physicians with an interactive data retrieval system.
         e. Provide a complete AIDS registry of trials in progress and trials planned.
         f. Pay the physician for his reporting efforts on a per patient basis.

III. Enclosures Supporting Recommendations Above

THE PRESIDENT'S COMMISSION ON AIDS
TESTIMONY
by
DR. HERBERT R. SPIERS
Saturday, February 19, 1988

Mr. Chairman and distinguished members of The President's Commission on Aids. Thank you for the opportunity of presenting this testimony on behalf of ACT UP --The AIDS COALITION TO UNLEASH POWER.

For us, AIDS is not only about health, it is about politics. This is a connection many of you may find difficult to accept. I first became aware of AIDS in the summer of 1981 when it was called "gay cancer." I now realize that I made a fatal error in my understanding then. I focused on the word 'cancer' and assumed that this new and mysterious disease would be dealth with in the same manner as Legionnaire's Disease, which is to say with great urgency from our medical establishments and the White House alike. It was not. It was a politically unpopular illness and not until a few courageous voices spoke out against the lackadaisical political and medical response to the by then already epidemic proportion of the disease did the true personal, social and cultural horror begin to stir the national conscience. This historical context is the framework by which we judge today's promises of fast-tracked drug developments and redesigned systems for clinical trials.

It is from within this tradition of neglect--even though perhaps benign neglect--that we are compelled to make sense of the fact that as of this moment a Person with AIDS has, in the entire breadth of this nation, access to only ONE ATEU trial testing a drug other than AZT, and at that there are only twenty-five slots available. This historical context prompts us to ask embarrassing and provocative questions. Is scientific methodology really the only reason that as of February 5, 1988 83% of all people enrolled in ATEU trials are on AZT? Are our scientific wits so dull that we cannot find effective alternatives to cruel and self-defeating double-blind placebo trials? Are woman, blacks, children, Hispanics and drug users somehow innately unqualified for drug trials--for they are woefully underrepresented in trials currently underway? Is the NIH really committed to a world-wide search for potential new drugs or is it too comfortably wedded to domestic products? Why must drug companies retest potentially life-saving drugs because the FDA fails to make its rules and regulations for the design of acceptable protocols clear and comprehensible?

In making answer to these and other questions the politics of drug development must be addressed. There is still a leadership vacuum in the fight against AIDS. Despite the noble intentions of political and bureaucratic functionaries, AIDS will remain a controversial issue on the national agenda until the Chief Executive of our country removes it from partisan and ideological

politics by personal moral example and by bold leadership. We have been told that AIDS is the nation's number one health problem, yet is four letter word was not once uttered in President Reagan's State of the Union address last January. Is this the type of example to set for his subordinates; does this demonstrate commitment and concern? Can the President not hold publicly an AIDS baby in his arms or avail himself of a photo opportunity to shake hands with a Person with AIDS to educate the public about compassion and how this disease is really transmitted? Let's start at the top; let's start with the role of the Chief Executive. Recommend to this President and the next to become truly involved in the fight against AIDS.

You know that the AIDs Treatment and Evaluation Program has not been a resounding success. After 18 months not a single report has been published. You've been told that it has been revamped and redesigned, that new committees have been added to expedite the testing of more and different drugs. Nothing could please us more than to see that happen. But we've had experience with the ATEU program first-hand and we know that if it is going to work it must, one, include participation from community physicians and, two, must win the confidence of the very people it seeks to recruit. This means outreach to AIDS communities in culturally appropriate ways such as designing clinical trials commensurate with nonwhite, non-middle class values. It means alternatives to placebo trials. And it means convincing people like Dr. Iris Long that genuine efforts are being made.

ACT UP is singularly proud of Dr. Long. There is perhaps no more informed person on drug treatments currently underway in this country than she. What we have learned about the problems with the ATEU program can be of use in preventing similar errors in the new program. Not content with simply a critic's role, Dr. Long and several other ACT UP people have undertaken a pilot project that will serve as a prototype for a national effort. We are developing our own data bank on drug treatments at all hospitals in the Greater New York area. Physicians and PWAs need up-to-date information about drugs and drug treatments and this information is nowhere available. Certainly, the government's databases, PDQ and CLINPROT are not the answer. In addition, ACT UP will demonstrate the importance of a Central Registry of clinical trials for researchers and physicians, another idea we strongly urge this committee to take under advisement.

For many of us, perhaps for many of you as well, there is still a mystery as to how drugs are selected for clinical trials by the NIH. Successes or failures notwithstanding, it has never been satisfactorily explained why AZT and not some other drug or drugs were put on a fast track approval process by the NIH and the FDA. Recent press reports once again testify to the inherent suspicion on the part of our great medical establishments to substances developed aboard. To ensure that domestic business considerations ould never be allowed to impinge upon drug selections we urge the creation of an Ombudsagency to examine the experience of other

countries in the search for new drugs to be tested. "The real problem," say Commissioner Young, "is where do you get the ideas nd where do you get the compounds from? That's the major block." ..andate imagination and creative research through such an Ombudsagency. To demystify the process of drug selection and to inspire trust and confidence within the various AIDS communities we make two recommendations: first, both the FDA and the NIH must make greater efforts in providing timely and current information that is organized and systematized. The above mentioned national database is indispensable in this regard, as are monthly and weekly publications and a National Hotline on drugs and treatments to which physicians and PWAs can make reference. Second, structure community physicians' and PWAs' participation in all drug review committees.

On Tuesday of this week, with not a little fanfare, the FDA announced that trimetrexate had been approved under a Treatment IND. Bravo. But questions remain as to liability and treatment costs within a Treatment IND protocol, and, in spite of a two day conference just this week, the regulations pertaining to Treatment INDs remain murky, prompting a number of informed persons to wonder whether pharmaceutical companies would indeed submit their drugs for Treatment IND approval. You've heard some glowing reports from the FDA Commissioner. Let's hope they come to fruition. But again we have historical reasons for being more than a little skeptical. Supposedly thousands of drugs have been examined, over forty are "in-the-works" yet only AZT is approved. What is the status of HPG, the only hope for people suffering from CMV infection: will r will not the Commissioner approve its release, or must the parent company put it back into trials causing further delay of the only drug effective against CMV retinitis?

And who in the government is willing to take even a modicum of responsibility for possible abuse of The Orphan Drug Act? The government grants exclusive drug marketing rights to companies, yet it refuses to monitor possible abuses of a federally created monopoly. In 1984, pentamidine cost $24.95 a vial. It now costs four times that amount. Who pays for this whopping increase? Individuals, insurers and, in a variety of ways, taxpayers, that's who. While the government granted a marketing monopoly to Lyphomed for penatmidine, the FDA's Office of Orphan Products Development says that it has no monitoring power. We all know too well the astronomical cost of AZT, another Orphan Drug Act product. This act was intended to induce companies to develop drugs that otherwise would go undeveloped without forms of financial assistance. A wise policy and within the tradition of Chrysler and Lockheed bailouts. But has it become a government handout? Perhaps it is time to consider a United States Drug Development Corporation that would be self-financing and would treat drug patents and marketing rights as part of the public commonwealth.

Time does not permit me to focus attention on other issues ·ith which we are concerned. For example, does the FDA's Informed onsent Regulation (21CFR50) which requires informing patients of

alternative therapies before signing them up for a trial mean making them conversant with drugs and treatments being used in a limited geographical area, or does it mean all drugs and treatments used throughout the country? Obviously, the answer to this question is of significant moral and legal importance. Discrimination, housing and health care, education are all part of the politics of AIDS. The National Leadership Coalition Against AIDS, a group of business leaders, recently suggested a bill of rights for Persons with AIDS and for seropositives. It's time has certainly come and I commend their idea to you.

I wish to close with that with which I began. We the woman and men of ACT UP are gadflies, the grassroots variety. That is why this commission, the White House, Dr. Young at the FDA, Dr. Fauci at the NIH, governors, mayors, representatives, counsel members, senators, health commissioners, candidates, and many other varieties of politicians and bureaucrats and their anointed appointees, find us buzzing about. We are driven by the Politics of AIDS and despite attempts to shoo us aside, to ignore us, spray us with invectiside, and all other means to dispel unwanted pests, or more accurately, those perceived to be pests, we will in the tradition of political gadflies keep you honest by ACTing UP.

Recent rhetoric would have us believe that the epidemic is over--at least here in the US. Tis a consummation devoutly to be wished. Still, one cannot help but wonder if the very same people who were so late in coming to the battle are now prematurely calling it at an end? For many here present this morning, the full effect of the politics of AIDS was brought home forcefully by the death in one's arms of a lover or a son, or the diagnosis of Kaposi's Sarcoma in oneself or in a friend. My mistake --the mistake of those most effected by this disease-- was to remain silent too long; quiet in the assumption that the health of the body politic was above the ideological issues of partisan politics. With our mouths closed we watched the deaths mount. In high school, we were taught that the price of freedom is eternal vigilance. Sad to say, in the Age of AIDS, many of us have learned that in our democratic society the price of health is perpetual pressure and an ever ready pair of vocal cords.

In fighting for the cause of human life, no price is too high. And so, even though some contend that the epidemic is over because, they believe, it has not entered the white middle-class, heterosexual population, we will continue to bring pressure to bear commensurate with the goal we are seeking: an end to AIDS, an end to dying.

My testimony, then, is a kind of pressure, delivered before you in the form of verbal pleading. We ask you to examine fairly, carefully, critically all the testimony that you have heard and received. Weigh it on the scale of scientific merit and reason; but also measure it with the rule of your own personal integrity. You will be making recommendations effecting who will or will not suffer, who will or will not die.

On this issue we cannot and will not ever be silent again. We ask that your officially sanctioned voices speak out with us.

Thank you.

Testimony for the Presidential Commission on the Human Immunodeficiency Virus Epidemic
February 20, 1988
New York, NY

Elinor M. Levy, Ph.D.
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Boston University School of Medicine
Boston, MA 02118

Each year we learn a little more about the natural history of HIV infections. We now know that following infection with HIV some individuals develop AIDS within a year, while others remain without any symptoms for at least 7 years. Similarly, we know that some individuals with Kaposi's sarcoma (KS) die within months of diagnosis, while others live longer than 6 years. At this point, however, we have little evidence to explain these differences, and therefore are unable to advise the estimated 1-2 million Americans infected with HIV how to maximize their longevity. Should they change their habits, their diets, their attitudes? There is evidence that suggests that each of these might influence progression of HIV related diseases.

I will concentrate my remarks on nutrition as a possible cofactor in HIV related disease. In general, malnutrition is associated with a significantly impaired immune response. The immune response is also sensitive to deficiencies and excesses of single nutritional elements, and to the quantity and quality of fat intake. Nutrition can be shown to affect susceptibility to a variety of infectious agents, and is implicated in the development of cancer. I have been involved in a pilot study of men with AIDS related diseases who have chosen to follow a macrobiotic regimen. This includes a vegetarian diet, a healthy lifestyle, and a sense of hope and control. The large majority report an improved in AIDS related symptoms. Additionally, those in the group with KS also showed an increase in their number of lymphocytes during the first 3 years after diagnosis, and 6/19 of these men are alive greater than 3 years after diagnosis with KS.

Research into nutrition as a cofactor for progression of HIV related disease is difficult for several reasons, among them prevailing research priorities, the complexity of study in this area, and certain methodological problems. Research priorities have focused on finding a cure and developing a vaccine, both worthwhile but still elusive goals. Only recently has their been a shift to include education to prevent HIV infection, and an interest by ADAMHA in the role of psychosocial factors, including alcohol and drug abuse, in AIDS progression. The group we have been studying is an example of the likely interrelationship between nutritional, psychosocial, and behavioral choices. Studies must take into account these interrelationships in order to interpret data correctly. Additionally there are methodological problems in accurately assessing nutritional status, particularly if absorption may be a problem.

I would recommend that the NIH foster more of an interest in nutritional and other cofactors through the organization of small workshops to bring together the multidisciplinary talents needed to work out design and methodological issues, and by encouraging research through RFAs. I would recommend that nutritional components be added onto ongoing "natural history" studies, and/or that new studies focusing on psychosocial and

nutritional cofactors be encouraged, including those with an intervention design. Finally, I would recommend that NIH create multidisciplinary review committees to properly evaluate these grant applications.

At this time I cannot given an estimated cost for implementing these recommendations, but suggest it would be a modest investment compared to what could be saved in health care and social service costs if onset of debilitating symptoms can be delayed or prevented. Although the state of our knowledge about the factors predisposing to the progression of HIV infection is not extensive, it is extremely likely that cofactors play an important role. There is an urgent need for research in these areas, so that accurate information can be used as a basis for more effective treatment strategies and educating persons at risk.

Submitted by Peter Duesberg, Ph.D.

PROBLEMS WITH THE VIRUS-AIDS HYPOTHESIS

① All known viruses are biochemically active when they cause disease (polio, hepatitis, etc.).

Paradoxically: HIV is inactive, latent, even in fatal cases of AIDS--no more active in AIDS patients than in asymptomatic carriers.

② All known viruses, when pathogenic, infect and kill more cells than the host can spare or replace.

Paradoxically: HIV actively infects <1 in 10,000 T- cells, even in fatal cases of AIDS.

③ All known viruses produce primary viral disease after short latent periods of 1 to 2 months.
Viruses act quickly or not at all.

Paradoxically: HIV is said to cause AIDS only after a peculiar latent period of 5 to 7 years.

Duesberg - 2

④ All known viruses cause disease in the absence of or prior to immunity.
This is why vaccination works--the ultimate weapon against viral disease.

Paradoxically: HIV is said to cause AIDS in the presence of or after antiviral immunity.
Antiviral immunity is diagnosed by the "AIDS test".

⑤ Unlike all other cytocidal viruses, HIV is a retrovirus.
Retroviruses do not kill cells. On the contrary, they depend on living cells to reproduce.
This is why retroviruses were the most plausible viral carcinogens in President Nixon's "War on Cancer".

Paradoxically: The retrovirus called HIV is said to cause AIDS by killing T-cells.

⑥ No known virus discriminates between men and women, nor between heterosexuals and homosexuals.

Paradoxically: HIV shows an absolute preference (92%) for men, even seven years into the AIDS epidemic.

Duesberg - 3

⑦ Koch's first postulate for identifying a causative pathogen states that the pathogen must be present in <u>all</u> cases of the disease.

<u>Paradoxically</u>: The CDC guidelines of September, 1987 stipulate that AIDS can be diagnosed in the absence of all laboratory evidence for HIV.

AIDS - HIV

Viral AIDS + non-viral AIDS AIDS - HIV

<u>CONCLUSION</u>:

Unless these problems can be resolved

HIV is not the cause of AIDS.

American Psychological Association

Advancing psychology as a science, a profession, and as a means of promoting human welfare

TESTIMONY OF

Thomas J. Coates, Ph.D.

Co-Director

CENTER FOR AIDS PREVENTION STUDIES (CAPS)

and

Associate Professor in the Division of General Internal Medicine

at the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

on Behalf of

THE AMERICAN PSYCHOLOGICAL ASSOCIATION

before the

PRESIDENT'S COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS

on the Subject of

BEHAVIOR CHANGE AND AIDS RESEARCH

February 20,1988

Admiral James D. Watkins, Chair

1200 Seventeenth Street, NW
Washington, DC 20036
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Summary of Recommendations

1. Change the national priorities. It is essential to spend as much or more money on AIDS prevention and intervention research as on biomedical research.

2. Fund additional studies to describe the characteristics of those who have changed in comparison to those who have found it difficult to change behavior so that intervention programs can be aimed at groups who have the potential to spread the infection to others or to be infected themselves.

3. The NIMH in collaboration with other relevant agencies, undertake a controlled trial of the efficacy of community intervention programs in reducing high risk behavior.

4. The National Institute of Mental Health, in collaboration with other relevant agencies (e.g, the CDC, the National Institute on Drug Abuse) support a coordinated set of studies aimed at programs with high risk populations or avenues of intervention.

In each area, a minimum of 5 to 7 studies should be funded to reflect national distribution. The investigators should be encouraged to request funding for at least five years, and the best methods of science should be employed to plan the studies and to evaluate outcomes. The studies should be designed to shed light on basic behavioral processes as well as to develop disseminable programs. The investigators should be brought together semi-annually to plan their studies and share their results. The best place to accomplish this research is within the NIMH, hopefully within the AIDS Branch to be established there.

I am Dr. Thomas J. Coates. I am Associate Professor in the Division of General Internal Medicine at the University of California, San Francisco, where I also Co-Direct the Center for AIDS Prevention Studies (CAPS). I am also a member of the Medical Attending Staff at the UCSF Hospitals and Clinics. In that capacity, I direct the Behavioral Medicine Unit, and have considerable clinical experience in counseling persons who are positive for HIV, and who have ARC and AIDS. These include males and females with a variety of sexual orientations and from a variety of ethnic backgrounds. Many have had to relinquish their jobs, their relationships, and their life.

I testify here also representing the American Psychological Association. APA'S involvement in AIDS stems from our membership's goal of responding to this epidemic with sound public health measures--a response that protects the public and ensures the mental health of persons infected with the AIDS virus. APA's members include clinical providers whose patients manifest the spectrum of HIV infection, from HIV positivity to AIDS related complex (ARC) to frank AIDS. We also include among our membership research scientists who are seeking effective means to promote lasting behavior change; who are examining the impacts of HIV antibody testing; and, who are analyzing the ramifications of AIDS for all segments of the population. APA members also include educators who are teaching the public about AIDS and safer sex, industrial psychologists who are addressing the issues of AIDS in the workplace, psychologists providing counselling and other services in the schools and individuals who are providing services both professionally and on a volunteer basis to the hundreds of local community-based AIDS service provider organizations across the country. Clearly, APA members are involved in addressing this dreaded disease from a variety of perspectives.

As an organization, APA has taken steps to respond to this crisis since the very earliest days of the epidemic. We have been at the forefront of lobbying for AIDS appropriations. We have worked to keep mental health providers aware of the unique aspects of this disease. In 1986, our Council of Representatives adopted a resolution on AIDS which deplores discrimination against those affected by the epidemic, condemns the use of the epidemic as a vehicle for prejudice, opposes the indiscriminate use of the antibody test, and calls for the confidentiality of patient records while recognizing the need for "large-scale identification of AIDS seropositive persons" as a major public health goal. At its most recent meeting in February 1988, the Council adopted a second resolution urging speedy action to incorporate information about AIDS and its transmission and prevention in those elementary and secondary educational programs that address human sexuality, drug use, and family issues.

In June 1987, APA established a Task Force on Psychology and AIDS that will examine more closely the behavioral aspects of this disease and direct the psychological response to the epidemic. In addition the Board of

Directors is currently considering a proposal to establish an Office on AIDS with an operating budget of approximately $160,000. The activities projected for this office include information dissemination to psychologists and the general public, technical assistance to the APA membership, work with other professional organizations to ensure an appropriate mental health response to AIDS, and continued advocacy around mental health, psychological and behavioral issues related to the epidemic.

In addition, APA has just received a $750,000 contract award from the National Institute of Mental Health (NIMH) to train health and mental health providers about the mental health aspects of AIDS over the next three years. Under the program design, a core of faculty psychologists will work with established community AIDS resource persons at sites across the country to deliver mental health training in locations with currently low levels of AIDS cases but high projections of HIV infection.

My testimony will focus largely on change in sexual behavior. Other experts on this panel will focus on IV drug using behavior.

The Center for AIDS Prevention Studies

The Center for AIDS Prevention Studies is a $13 million project funded in large part by the National Institute of Mental Health and the National Institute on Drug Abuse. Specific projects within the Center are also funded by the National Institute on Allergy and Infectious Diseases, the Department of Defense, and the University of California. The Center is a collaboration between the University of California (at San Francisco and Berkeley), the San Francisco Department of Health, and the Bayview-Hunters' Point Foundation (a minority community service organization) which some of you visited while you were in San Francisco. The Center seeks to complete studies that will identify determinants of high risk behavior in all of the various populations likely to be hit by AIDS. Our ultimate goal is to develop and test programs designed to reduce risk of HIV infection in these populations.

Prevention Is An Absolute Necessity

Prevention is the top priority for AIDS. The Centers for Disease Control reports that over 50,000 persons have been diagnosed and reported with AIDS in the US and Public Health Service estimates that 1.5 million persons are infected with this deadly and awful virus. The primary objective in our efforts to fight AIDS must be to prevent any more people from becoming infected.

The majority of the population is not infected HIV, and even the majority of high risk populations is not infected with HIV. Our greatest effort must be directed toward programs and research to prevent any more of the

population from becoming infected. Unfortunately, we are fighting the AIDS epidemic in the same way that we fight most diseases. We pour money into biomedical research to describe the virus, to develop cures for those who are suffering its ravages, and in developing vaccines.

This research is laudable and the progress that is being made is remarkable. However, the priorities are lopsided. The original unamended PHS Budget Requests for AIDS, Fiscal Year 1988[1] requested $412,365,000 for research (including only $28,326,000) to ADAMHA, and only $101,164,000 for Prevention. One dollar in four was to be spent for prevention when the most effective antidote to the spread of the AIDS epidemic is behavior change. **My first recommendation, therefore, is to change the national priorities. It is essential to spend as much or more money on AIDS prevention and intervention research as on biomedical research.**

We are fortunate in the spread of HIV that a relatively narrow set of behaviors seem capable of spreading the virus from one person to another. In the realm of sexual behavior, this includes anal or vaginal intercourse with the exchange of semen or vaginal fluid. Oral sex with the exchange of semen or vaginal secretions may also transmit the virus, albeit with a very low rate of infectivity. From an intervention perspective, we are fortunate. Campaigns to reduce the spread of AIDS can be focussed on one or few behaviors. This should increase their efficacy.

Our Current Research: San Francisco and the US

Are we able to achieve the changes necessary to stop the spread of the epidemic? Our experience in San Francisco shows us that we can.

Since 1984, we have been involved in studies funded by NIMH documenting changes in high risk behavior in the gay, bisexual, and heterosexual populations in San Francisco. (We are now beginning studies among adolescents, ethnic minority single individuals, and other high risk groups). These studies have been carried out primarily with two large groups recruited at the beginning of the epidemic; our total sample is around 1600 men.

Both studies show remarkable results. Men in San Francisco--gay, bisexual, and straight--have reduced their high risk behavior to a remarkable degree. The amount and kinds of changes in high risk sexual behavior among gay and bisexual men exceed anything documented to date in the public health education field or literature. The AIDS Behavioral

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[1] United States General Accounting Office. AIDS Prevention: Views on the Administration's Budget Proposals. Briefing Report to the Chairman, Subcommittee on Labor, Health, and Human Services, Education and Related Agencies, Committee on Appropriations, United States Senate, August 1987.

Research Study reported that only 7.2% practiced unprotected anal intercourse with secondary partners in 1986. The San Francisco Men's Health Study reported that only 5.8% of HIV negative individuals practiced this activity in 1985. Communication Technologies, a marketing firm working for the SF AIDS Foundation, reported that only 6% of their sample practiced this activity in 1986.In San Francisco, there is no new infection among gay or bisexual men.

Second, these changes are being sustained, and this is something almost unheard of in health behavior change. Cigarette smoking, the leading cause of death and disability in the US today, has proven remarkably resistant to change over the 24 years since Dr. Luther Terry published the first *Surgeon General's Report on Smoking and Health* in 1964.

What About the National Scene?

I and my colleagues at the University of California, San Francisco, have also just completed studies for the Office of Technology Assessment and the Hudson Institute. The topic of this study was changes in sexual behavior since the beginning of the AIDS epidemic. We completed an exhaustive survey of all of the studies currently being done in the US and Canada with regard to prevalence of high risk behavior and factors associated with behavior change in all populations for which data are available: gay and bisexual men, ethnic minorities, adolescents, and single heterosexuals.[2]

Evidence from a number of studies indicates that high risk behavior and seroconversion continues to occur in a number of localities including New York, Los Angeles, Washington DC and other places. Rates of syphilis continue to be high in certain localities among gay and bisexual men and among other high risk groups as well.

Why Do High Risk Individuals Continue To Practice High Risk Behavior?

One response upon hearing that gay and bisexual men and others are still practicing unsafe sex is to label them (e.g, "addicted," "homicidal") or to pass restrictive laws calling for conviction and incarceration. These probably do more to satisfy lawmakers than to stem the tide of the epidemic.

A more rational and helpful approach calls for understanding better the psychosocial determinants of high risk behavior and aiming educational programs at these determinants. For example, we and others have found several factors to be associated with continued high risk behavior. Among these are

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[2] Colleagues in this research are Ron D. Stall PhD MPH, Colleen C. Hoff, Joseph A. Catania PhD, and Mary Margaret Dolcini MA.

- those who use drug and alcohol use during sex are more likely to engage in high risk behavior

- men who are younger in age are more likely to engage in high risk behavior

- denial is always an issue; it has been a national problem since the beginning of the epidemic

- those receive antibody testing, and those who test positive once they are tested, are more likely to reduce high risk behavior

- a feeling of personal susceptibility and the feeling that one has the skills to negotiate safe sex are associated with decreases in high risk behavior.

This is just a partial list. **Therefore, my second recommendation is to fund additional studies to describe the characteristics of those who have changed in comparison to those who have found it difficult to change behavior so that intervention programs can be aimed at groups who have the potential to spread the infection to others or to be infected themselves.**

Descriptive Studies Are Not Enough

Can we afford to wait for the descriptive studies to be completed before embarking upon intervention research? The answer clearly is no. We need behavior change studies, but the need for behavior change is urgent. We need a broadly based and coordinated set of studies that will help us to identify strategies for various segments of the population that are useful and effective in preventing further infection.

We know already what the principles of behavior change are. For risk reduction to be effective, we first need to arm people with the **information** they need to make choices. We are good at disseminating information, and many of the programs now in place are continuing to pursue this objective.

More difficult to accomplish is the need to teach **skills. For people to change, they need to know how to perform the activities that will protect them from infection.** In the case of AIDS, this means that people need to have the technical skills to practice protected sex. It also means that they need to have the social skills to put them into place.

Finally, intervention strategies need to shift **community norms** so that when one individual decides that he or she wants sexual relations with another individual, both will expect that one or the other could refuse. If they decide to engage in sex, they will both expect that the other would want them to practice safe sex.

Research in Community-Based Programs

We mentioned before that behavior change in San Francisco has been important, significant, and sustained.

The changes observed in San Francisco, compared to those made in other cities, reflect the results that can be expected from concerted and systematic community organization and program focused on knowledge, skills, and shifting community norms. Six elements contributed to the success of the San Francisco risk eduction program:

- (1) a community-based program including strong leadership from within the gay community;
- (2) market research techniques to identify appropriate messages and communication channels for reaching the target audience;
- (3) programs to inform and motivate target audiences
- (4) specific methods to teach skills and to facilitate social and cultural change;
- (5) reliance on multiple channels of communication including print, broadcast, and face-to-face channels of communication;
- (6) broad-scale grass-roots participation.

Essential to this program was the fact that it built upon the strengths and issues of the community. Gay pride and survival, and a sense that this community needed to save itself because no one else would, were the underpinnings of the efforts. Non-discrimination and a pro-gay attitude were needed to bring the population into the movement.

My third recommendation, is that the NIMH in collaboration with other relevant agencies, undertake a controlled trial of the efficacy of community intervention programs in reducing high risk behavior.

The behavioral sciences are faced here with the need to impact high risk behavior with enough strength to prevent the virus from spreading. This means changing the behavior of enough individuals over a long enough period of time to prevent substantial spread of HIV. This requires the power and potency of a community program approach that attends to information, opportunities for teaching skills, and methods for shifting community norms.

Research in Change Strategies

The National Cancer Institute has, for the past 7 years, been sponsoring research in smoking cessation that could prove to be a useful model to prevent the spread of AIDS. Some 45 individual investigations have been funded to develop, implement, and evaluate various strategies for reducing smoking in various segments of the population. Investigators come together periodically to plan studies and programs, and to share results. I have been involved with this process with the NCI and I believe that it has pushed smoking cessation programs much further along than almost any other area of health behavior change.

My fourth recommendation is that the National Institute of Mental Health, in collaboration with other relevant agencies (e.g, the CDC, the National Institute on Drug Abuse) support a coordinated set of studies aimed at programs with high risk populations or avenues of intervention. High priority populations are

- gay and bisexual men who still comprise 65% of the cases of AIDS and 80% of the estimated individuals who are infected with HIV but not yet diagnosed with AIDS
- special emphasis within this group should be given to minority gay and bisexual men[2] and to homosexual youth.
- IV drug users and their sexual partners.
- adolescents, especially ethnic minority adolescents in areas where rates of sexually transmitted diseases and unplanned pregnancies are higher
- persons presenting for treatment at sexually transmitted diseases clinics
- individuals identified as positive for antibodies to HIV at the Armed Forces Recruiting Centers[3] These individuals may not enjoy the support of other individuals who are in the same situation and may need special programs to prevent spreading the infection to others.
- ethnic and minority women.
- prostitutes and others in the sex industry.

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[2] As of this writing, the NIMH is supporting only one study in this area, and this is a descriptive study of Black gay and bisexual men. No intervention studies are being supported, and no studies focused on Hispanic gay and bisexual men are being supported.

[3] The Armed Forces reported in July that 0.15% (1.5 in 1000) of individuals presenting for recruitment were positive for antibodies to HIV. The ratio of Blacks to Whites was 2.5 to 1. In five localities (New York, New Jersey, District of Columbia, San Francisco) the prevalence was 1 in 100 or 1%.

In addition, programs of research can be focussed on specific methods for reaching various populations including,

- health care providers and health care delivery institutions
- media
- school-based programs
- clinic-based programs.

I propose that programs of research be developed in each of these areas. In each area, a minimum of 5 to 7 studies should be funded to reflect national distribution. The investigators should be encouraged to request funding for at least five years, and the best methods of science should be employed to plan the studies and to evaluate outcomes. The studies should be designed to shed light on basic behavioral processes as well as to develop disseminable programs. The investigators should be brought together semi-annually to plan their studies and share their results. The best place to accomplish this research is within the NIMH, hopefully within the AIDS Branch to be established there.

Costs

The costs for this program of research are estimated to be around $100 million over a 7 to 10 year period of time. This is a small amount of money in comparison to what it will cost if we continue to go on with business as usual.

A Final Note

We all recognize that we are working in a delicate arena. We are not dealing with smoking or exercise, or weight reduction where individuals can agree on what kinds of changes can occur. We are working in the area of sexuality, and we as a society have deep feelings about sexuality. It is important to discuss sexuality with all of its moral, philosophical, psychological, and societal implications. But we cannot afford to let this discussion get in the way of preventing spread of infection. Part of the research agenda must be methods of resolving these differences so that important work can go forward.

The AIDS epidemic is not the first epidemic of sexually transmitted diseases in the past two decades. Herpes, chlamydia, and unwanted pregnancies are serious national problems. Efforts to take care of this problem have been hampered by a variety of issues, not the least of which is our reluctance to solve our philosphical differences and our squeamishness

to discuss things sexual in public. I am glad that we have the opportunity to do this. The program of research we have identified will be important in dealing with the whole range of sexual issues in our society. Hopefully, we can put in place an effective program so that we are never again caught off guard.

STATEMENT FOR

THE PRESIDENT'S COMMISSION ON AIDS

SEX RESEARCH AND THE AIDS CRISIS

by

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In spite of increasing public acceptance of the significance of various aspects of intimate behavior for normal adult human functioning, relatively sparse funding for research into this fundamental dimension of human existence has been available during the last 50 years. As a consequence, there exists only a limited body of scientific data upon which to base sound public health, social, religious, and legal policy decisions. In spite of their obvious limitations, the existing data sets when used appropriately, can provide initial guidance in our efforts to control the progression of the AIDS epidemic in the United States and around the world.

The AIDS crisis poignantly demonstrates the limitations of our current knowledge in this area, and underlines the urgency of our need to expand the body of reliable information crucial to the establishment of effective and efficient national policy. It is vital that we develop dependable, current data regarding the sexual practices and attitudes of various segments of our society linked to accurate estimates of the size and demographic composition of these diverse communities. Makeshift studies, crudely formulated and conducted interviews, and popular magazine surveys provide rough sketches of what people may be doing and feeling, but such efforts are simply inadequate to the task of providing the type of information upon which meaningful predictions, interventions and solutions can be based. The techniques to derive and carry out research commensurate with our critical needs have been developed during the last several decades -- we are lacking only the will and the means necessary to underwrite such a crucial program.

Establishment of an adequate data base requires the funding and conduct of sophisticated, broad spectrum, in-depth, multidisciplinary research conducted with individual subjects. In essence, appropriate research must:

a) be designed with the assistance of representatives from the diverse age, racial, ethnicity, and socioeconomic groups within our society;

b) be based on proper sampling techniques of the nation as a whole, including sufficient sampling of minority populations;

c) be culturally sensitive; and,

d) involve highly trained and experienced interviewers, themselves drawn from diverse segments of our society and employing advanced interviewing techniques and methodology.

Modern research has made it clear that the medical, physiological and related biological aspects of sex are exquisitely interconnected with the behavioral expression of sexuality. The present data base, while providing tantalizing suggestions for the prediction of the spread of the AIDS virus and the potential control of its transmission throughout our population, is woefully inadequate in providing answers to many of the most basic questions concerning sexual, reproductive, and developmental physiology and their cellular and hormonal foundations. These must be addressed if effective action is to be undertaken.

Our lack of fundamental knowledge pervades the whole range of problems regarding the AIDS dilemma. At one end of the spectrum, we know very little indeed about the actual sexual practices of the American people; the factors that shape their expression in particular communities; and the forces which serve to block or facilitate change in attitudes and behavior. In another domain, while we recognize the urgency for increased condom use, even such simple questions as, "What are the pressures and frictional stresses to which condoms are subjected during intercourse?" remain to be answered. This latter issue leaves scientists evaluating the effectiveness of condoms as a barrier against infection, while lacking the most elementary laboratory standards with which to judge the protective capacity of the condom in practice. In fact, we do not even know what constituent(s) of semen is the infectious component(s). Is it free virus? Is it HIV-laden lymphocytes or macrophages? Is it virus-bound sperm? The answer is unknown!

Inasmuch as the viability of the AIDS virus is strongly pH dependent and inactivated at low pHs, we must ask whether acidically buffered vaginal creams, gels and spermicides could provide a hostile environment for HIV at pHs still tolerated by the vagina and penis? Also, we must ask whether the HIV in semen is localized on sperm or within white blood cells as noted above and, if so, whether vasectomy

would diminish infection of sero-negative women by HIV positive men. Hemophiliacs might provide a model test case, inasmuch as 90% of them are sero-positive and many are vasectomized. Numerous similar possibilities are evident to sex physiologists, but these possibilities go unnoticed or ignored by those at the helm in planning the course of AIDS research and education.

We recommend the establishment of a multicentered national program for the collection of the widest possible range of behavioral and biomedical profiles of our nation's population(s). In order to accomplish this goal in a manner which will permit development of a compelling national strategy, the research must include the full panoply of ethnic, racial, economic, religious, sociosexual, and age groups which comprise our society. These constituent groups must be included both in the design and conduct of the research as well as serving as the diverse foci of study. It is vital that this effort include face-to-face interviews of a large sample of Americans from teenagers to senior citizens, from rural towns to the urban inner cities. If one thing is clear from the currently available behavioral data, it is that no real boundaries exist among the diverse groups of our culture. The economic and social mobility of our population, of which we are justly proud as a nation, is equally relevant in the sexual sphere -- heterosexual and homosexual; asian, hispanic, black or white; old or young; rich or poor; east or west-- all are part of the overlapping communities which form our society. All must be studied and understood if our country and the rest of the world are to caste off this dread disease.

TESTIMONY TO THE PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

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I have spent a good part of my scientific life interested in the social and psychological dimensions of human sexuality --- that is, I have attempted to do research that would increase our understanding of the role that sexuality plays in both the lives of individuals and in the collective life of the society.

I do not think that I have to re-iterate the constraints under which such a research career has operated. One need only examine the recent publication of the Institute of Medicine, Confronting Aids, and examine the frequency with which the work of Alfred Kinsey and his colleagues is mentioned to get some flavor of the limited amount of information that we have about the sexual life of persons in this society. That we cite data gathered nearly half a century ago to suggest parameters for contemporary conduct is more than problematic. Who does not believe that the general patterns of sexual conduct have changed since the end of World War II and the end of the penultimate decade of the twentieth century? Yet who would argue conclusively that they know, except in the most gross terms, what has happened to sexual conduct inside of marriage, to sex among young people, to sex between men and men, to sex between women and women, to sex between married persons and persons who are not their spouses, to bisexuality, to sex between those who pay for sex and those who are paid for it?

This is not to say that no data on human sexuality have been gathered in those decades. Some limited data on heterosexuality among young people has been systematically gathered since the early part of the 1970s. Data on age at first coitus, estimates of coital frequency, a little data on sexual partners have been gathered primarily from young women and less often from young men in the context of studies of pre-marital fertility and contraception. I know of only one carefully conducted national study of the sexual conduct of young people which touched on a wide variety of sexual issues in this period. The work of the Jessors on young people in the early 1970s and the recent work of Richard Udry are signal and rare examples of sophisticated research in psychosexual development. We do have some information on the coital experience of married women, usually based on a few items. Again this data has been gathered in studies which have been primarily concerned with fertility behavior. A number of interview studies of convenience samples of gay men and lesbians were conducted in the late sixties and early seventies. These studies were conducted well before the current surge of AIDS related research on gay men which began in some cities in 1983. There is also one national sample survey study of attitudes toward homosexuality which also asked some sex behavior questions, conducted in 1970. In addition there have been a number of smaller and more focussed studies on sexual dysfunction in marriage, on sexual psychophysiology, on sexual functioning in the seriously ill, on psychological responses to erotica, and on

sexual violence and victimization, which have yielded some valuable insights. Indeed one can find other studies that reference the sexual, if they do not confront it directly. There are, for example, studies of cohabitation, that in a patchy way tell us something about contemporary sexual life.

Everyone concerned with the AIDS epidemic knows about the lack of easily available and relevant databases. However, there are other consequences of the lack of a systematic program of research on sexuality over the last forty years that may not be as apparent as a simple lack of data. We do not have at the present time an accumulated survey research tradition about how to ask questions about sexuality that will provide us with valid and reliable answers. A brief examination of the recent Handbook on Survey Research edited by Peter Rossi and others, and the two volume work on measuring sujective responses in surveys (edited by Charles Turner and Elizabeth Martin) will suggest how much instrument design rests on art and not on science. We still need to learn how to ask questions about sexuality in all its guises.

Unfortunately we don't have much accumulated wisdom and that which has been developed has largely been misplaced, if not lost. Asking questions about sex is not the same as asking questions about fertility, or contraception, or even abortion, or other "taboo topics". There is some knowledge about sexuality in terms of data sets and instruments, but it needs to be gathered together. I worry that in the press of wanting to get something done quickly we will re-invent a series of square wheels that are square in different ways, so that we will not be able to discover in what ways they are out-of-round. In my view it is easy to go wrong in this area and that more care needs to be taken in the design of studies from instrumentation to sampling to data analysis than is being currently invested.

The absence of a serious scientific research tradition in the area of sexuality does not mean that we have lacked "reports" on sexuality produced by all manner of "experts". Magazines of all sorts include questionnaires in their pages which they ask their readers to fill out. Persons with "credentials" hand out self administered questionnaires to receptive groups or they interview small numbers of volunteers. These are then packaged as "reports" on sex, love, intimacy, and desire. They are the fakelore that flourishes in the absence of carefully designed research and they compete with the findings from good research. Indeed I have seen data from these "fake" surveys used in serious scientific studies because of the demand for knowledge. How much will this fake-knowledge about sexuality interfere with learning about sexuality or AIDS or indeed interfere with behavior change that might be necessary? I don't know, but the illusion of knowledge may be worse than the knowledge that we are ignorant.

There is a dangerous belief that that anyone can do sex research simply by making up a questionnaire and asking questions. It is this that has resulted in a number of studies that are of high quality from the biological or medical side having weak social and behavioral science underpinnings. Samples are poorly selected, interview schedules inadequately designed,

and questions badly asked. Much of AIDS research is interdisciplinary research and the lack of a sex research tradition in the behavioral sciences means the lack of trained personnel who are experienced in the design of sex research for these studies. While a high level of general methodological skill is necessary, it is not sufficient to the task. Researchers need to have substantive knowledge about sex as it is exists in different cultures and social contexts. Sex is not just another commodity that a market research firm can ask a question about. It is not enough to be able to ask about soap today, cars tomorrow, sex the next day. Sex is not a topic that should be unthinkingly plugged into the standard interview format.

Perhaps what concerns me the most about the rising concern with sex is its association with disease. Most of the work that I (and some others) have tried to conduct has been linked to trying to understand the way sexual conduct was intertwined with the rest of social and psychological life. The key phrase is "to understand". The current interest in collecting data on sexuality is driven nearly entirely by the presence of the AIDS epidemic, much as our interest in adolescent sexuality is driven by a concern with adolescent pregnancy and sexually transmitted diseases. The sex questions that are selected to be asked (of all the questions that could be asked) are generated by a concern for disease transmission or some other sex-related social problem.

A weak consequence of this concern is that what is interesting about sex is what the disease makes interesting. A strong consequence is that concern may make us once again see sex as a disease producing or sin producing form of conduct. One can observe consequences of this movement in a variety of contexts: in the selection of interview items --- a question is asked about fisting or anal-oral sex as if they were part of the standard repetoire of sexual activity --- rather than conduct that is generated by context and script. In the discussion of how to manage the epidemic, sex has become a vehicle for disease transmission rather than a form of conduct that is complexly related to pleasure, sin, reproduction, getting old, growing up, and the like. This medical model tends to simplify and distort the role that sex plays in our lives.

It is not the the job of those who are interested specifically in controlling the epidemic to gather data with larger purposes of "understanding sexuality" in the sense that I mean it. AIDS must be managed and controlled and everyone applauds those goals. At the same time we need to think about the potential downside of our scientific and statistical interests. Research on sex that is driven entirely by a concern for the disease may provide us with a very different view of sexuality than one driven by a concern for the larger roles and purposes of sexuality in culture and society. As we all know, the visions that science provides of various forms of conduct is consequential for the culture and society. The information about sex that AIDS researchers create and publish will be widely consumed as evidence about sex. Yet after the AIDS epidemic is history, sexuality will continue to provide humanity with both pleasures and difficulties.

Finally a narrow view of the sexual may work in social bookkeeping and epidemiological modeling, but it may be inadequate as we think about the more complex task of behavior change. Here sexual conduct is embedded in culture and in social relations and as we think about this dimension of the epidemic we may need to know more than how old and how often and with whom --- we may need to know a good deal more about why. This detailed cultural knowledge about sex can only be gathered by an approach that seeks to understand the way in which sexuality is embedded in social and psychological life.

What are the practical consequences of these observations and what can the committee do to promote them:

1. Research quality control: A great deal of AIDS research is now going forward and more is coming on line which involves the gathering of sexual data. It is important that the very highest levels of research quality control be supported and this should involve peer review of projects both in the biological and behavioral sciences for the specific adequacy of their sex research components. This is not only in reference to surveys, but to the instrumentation of bio-behavioral studies as well. This is not a high cost item, but it requires systematic administrative attention across those agencies that are funding and doing AIDS research with a behavioral sexual component. It is particularly important to resist the "need to know yesterday syndrome". If this requires increasing intramural staffing and funds for research review, this should be done.

2. Research Coordination: With the growth of research there is also a proliferation of differing techniques used in various investigations. It would be valuable if an ongoing review of research initiatives involving sexuality across federal agencies could be instituted to increase the use of common techniques or at least the awareness of tested and useful approaches to gathering sexual information. No one wishes to constrain the imagination of independent researchers, but attention to what is already known is critical. A mechanism to increase awareness may be necessary .

3. Research in Methodology: It is absolutely critical to have some proportion of the funds given for AIDS research in the behavioral sciences (as well as the behavioral aspects of bio-behavioral studies) directed toward methodological research. In the haste to get data, careful methodological checks are not preformed and studies come to nothing or worse. There is a desperate need to do a number of methodological studies prior to the time that major research initiatives are taken or these studies need to be done while the initiative is going forward. The RFP for the new Household Seroprevalence Study takes some steps in that direction. Perhaps some percentage of funds given to agencies should be targeted for methodological research. I do not mean this to inhibit research by nitpicking, but to suggest that careful work on an accelerated schedule be undertaken.

4. Training: The lack of a research tradition means a lack of trained personnel. There are very few well trained sex

researchers in the United States. Often the very best have been self trained. Further the AIDS epidemic calls for the ability to do interdisciplinary work. The epidemic will be with us for at least another decade and its consequences perhaps longer. There is a desperate need to establish a number of innnovative interdisciplinary training programs at the pre-doctoral and post-doctoral levels. These need to include training for professionals from the less developed countries, particularly Africa.

5. Support for general sex research: It is important to start to support sex research which is more expansive in its interests than that which is driven by the AIDS epidemic itself. While the committee has not been given responsiblity for such issues it is clear that if we had a better general knowledge of sexuality and how it was changing in the society we would have been better able to respond to the AIDS epidemic.

6. Data Archiving and Data Sharing: While there is not a great deal of accumulated data on sexuality there is some which would be helpful in developing new instrumentation and offering evidence about rates of change. Data should be archived (in the same way we store blood) at a number of sites. Funds should be made available as part of the funding process for new research to carefuly archive data tapes as well as raw data if necessary. This simple act would increase data quality control. As a correlary to this it is imperative that data (including instruments and whatever other information required for understanding how a research project was conducted) be rapidly shared. This includes data gathered under contracts, grants, and cooperative agreements. Principle investigators (both extramural and intramural) should be given time to publish their own work, but this should limited so that other scientists can benefit from federally funded data gethering. Perhaps as part of the process of receiving funds from the federal government, researchers should agree to make data widely available, restricted only by limits of confidentiality.

Testimony on Research and Prevention Efforts about Intravenous Drug Users and their Sex Partners

by

Samuel R. Friedman
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I. Given the probability that we will not have either vaccine nor therapy for AIDS in the near future, prevention of HIV spread is crucial to prevent the spread of the epidemic. Unfortunately, we do not have adequate knowledge about the best ways to do this.

II. Thus, we need to learn how to affect risk and transmission behavior. This behavior is social behavior: transmission involves at the least an interaction between two or more persons, and the context that leads to contaminated syringes being shared can involve small group pressures as well as a wide range of broader social factors including race and the particular laws in a jurisdiction.

The complexity of these factors for IV drug users is shown by abundant evidence that in spite of their chemical dependency and, often, their lack of education and their alienation from social institutions, many IV drug users have taken actions to protect themselves and others (and thus that stereotypes are wrong), and that they did so even before any prevention efforts were aimed at them; and by the complexity of the factors that mean that gay men's organizations have been set up to deal with AIDS, but that drug users have been much less prone to do so (but, nonetheless, that the junkie unions in Holland have taken on AIDS).

The complexity of these issues poses difficult methodological and re-

search problems:

A. By and large, research has focused on what helps the individual to reduce his or her personal risk of becoming infected. This research has used the experimental model from psychology as a model, which means that it looks at individuals as the unit of change and that it assumes that history is irrelevant (i.e., that what works at one point and time during the epidemic will work at other times and places.) Research has to get beyond this in several ways:

   1. Focus also on reduction of behaviors that potentially transmit HIV to others. This is a different set of motivations than personal protection. Many IV drug users are more willing to listen to outreach workers when the issue is raised as how to protect loved ones rather than self-protection.
   2. Look at prevention efforts that take seriously the fact that risk behaviors -- both IV drug use and sex -- are social. We are beginning projects to change the values of IV drug users and their partners to reduce transmission and to help them develop ways to implement such protective ideas in practice One example is street user self-help groups to get peer support for risk and transmission reduction.

   3. Look at risk and transmission behaviors as historical events. At the beginning of the epidemic, few drug users believed in their own vulnerability to AIDS; since then, more acceptance has occurred, and considerable risk and transmission reduction; later on, we may encounter a sub-

culture of despair about AIDS. Each of these periods involves different contexts for the individual who is confronted with a given intervention, so we would expect reactions to differ in accordance with the history of the epidemic. The standard models of research, however, do not take this dynamic into account, nor the fact that the stage of the epidemic may differ in different cities.

4. Decisions about research into behavioral change and prevention programs are often taken by medically trained persons -- often, by superb medical scientists. They make these decisions -- about what programs should be set up for funding through an RFP mechanism, what specific proposals should be funded, and what articles should be accepted or rejected -- on the basis of their medical research training. Their input into these decisions is of course useful, but social scientists have necessary expertise and experience that also has to be included in decision-making. Medical training tends to be of only limited applicability to the social science research we need in order to figure out how to change the behaviors that spread this epidemic -- for example, it exalts the experimental method, ignores issues of historical change during phases of the epidemic, and simply assumes that the individual is the appropriate unit of analysis -- and thus produces requirements that hold back the development of innovative research. The fact that medically-trained researchers are often unaware of these issues simply aggravates the problem.

5. Here, the history of national research policy just prior to AIDS becoming a major recognized threat is a warning to us. Good social science in AIDS is rare -- as has been pointed out by both the National Academy of Sciences and the American Foundation for AIDS Research. This is due, in part, to the restriction in social science research funds in the early 1980's. Decisions such as that to have NIMH focus on the biological aspects of mental health, and to move away from funding social science research, meant that when AIDS hit we had had less research into drug use and its prevention, into sexual behavior, and into the methods for studying these topics; and that we also had a shortage of researchers with skills in these areas.
6. AIDS means we have to examine and test some ideas that are controversial in order to protect the public health. In Sweden and Germany, methadone treatment is itself controversial, but in Sweden they have doubled methadone treatment in response to AIDS (from 150 to 300 slots, which is 30% of their heroin users), and in Germany they have syringes sold over the counter and have made sure that pharmacists actually do sell them to addicts (and in Sweden they have an accepted unofficial syringe exchange). In the US, controversial issues include syringe exchanges and methadone without supportive counseling and vocational services.

   Here, it is important to understand that, although it is sometimes argued that there are contradictions among vari-

ous projects and goals -- eg, between methadone and becoming drug free, or safer injection programs and entering drug abuse treatment -- experience and research alike show that these programs support each other. Syringe exchanges in Europe do not reduce treatment admissions, and teaching New Jersey users about how to use bleach to clean syringes led to increased demand for treatment.

7. We absolutely have to be able to do research in these controversial areas if we are to learn how to prevent the spread of AIDS. Federal agencies, however, are inhibited on this. The CDC Innovative Research Projects have been hindered by requirements that local committees approve educational materials. Calls have been made for experimental tests of needle exchanges, but so far none have been funded.

   There is no apparent compelling logic behind why some approaches are accepted in one country and rejected in another; or why the particular ideas that are controversial in one country are nonetheless tested out, while in the US such research is stymied.

III. Specific suggestions about research management

   A. We are reaching a point where we cannot train medium level researchers at the rate we need through normal channels. We need a way to bring established researchers who have not been doing AIDS research into our on-going projects through a senior-level equivalent of a post-doctoral program; appropriate persons might be associate professors who want to change careers or who have

sabbaticals. Stipend levels would be in the order of $35-50,000. This would let us train needed project directors and senior analysts and methodologists without having to give them line authority in research grants while they are being trained. It might also help us reduce the serious paucity of minority researchers in this field (which is important in research about behaviors that lead to disproportionate infection of minorities.)

B. Expansions in research funding have not been matched by funding agency infrastructure expansion. This means that researchers have not had adequate support by staff of agencies such as NIDA due to the extreme overload of responsibility on Federal staff.

C. AIDS research moves fast, and often does not fit funding cycles well. Sometimes, grants are initially budgeted small, but it turns out that they need and deserve considerable expansion in mid-year. The mechanisms to do this are very awkward, and need stream-lining.

IV. Research that has been done suggests the following interventions to reduce AIDS among IV drug users and their partners:

A. Prevent initiation of IV drug use. Much research is needed on this.

B. Rapid and sizable expansion of drug abuse treatment. We have capacity for perhaps 10% of IV drug addicts, and considerable waiting time to get into treatment. We need improved levels of space, facilities, and staffing, since research shows that these affect the extent to which clients alter their behaviors.

C. Outreach to IV drug users and their partners has begun, but needs expansion and additional innovation. This should include individual educational outreach, efforts to promote safer injection, and

also efforts to mobilize the small groups and subculture for AIDS prevention.

D. Given the extent to which AIDS is impacting Blacks and Hispanics, special programming to involve minority community organizations and institutions.

Supporting Materials

I. Background -- Des Jarlais presented this in fuller form
   A. IV drug users have attempted to protect themselves and others
   B. Many have not been able to do this consistently
   C. Thus, prevention projects that work with users to make it easier to reduce transmission to them and from them are appropriate

II. Issues in an evaluation include:
   A. Who and how many take part?
      1. They do not flock to be tested
         a) Magura -- 10%
         b) Minneapolis -- almost all of an MMTP program got tested
         c) AOP
         d) Partners don't flock to Beth Israel couples study
      2. Drug treatment programs
         a) They are over-subscribed and have waiting lists
         b) Different modalities vary in popularity
         c) Need a vast expansion
      3. Outreach models
         a) AOP 3000 contacts per month
         b) vans for partners
   B. Does it work? This is complicated to figure out the appropriate measure for success. For immediate impact -- over a year period, or even more -- all we can measure is changes in risk behaviors and in related indicators such as knowledge and program attendance. Over longer time periods, we can try to measure infection. In all these evaluations, a critical issue is whether the evaluation focuses only on the individual being intervened with, or upon the totality of IV drug users/partners in a given area.
      1. We know some about impact on knowledge, self-reported behavior change, and treatment entry We know nil on impact on infection.
         a) Testing -- may work if excellent counseling, and voluntary. We suspect that the counseling is the key, not the testing.
            (1) Casadonte
            (2) Cox (Montefiore)
            (3) Marlink study of New Bedford IV drug users in methadone detoxification treatment

b) Outreach evaluations
    (1) San Francisco bleach
    (2) McAuliffe
    (3) New Jersey
c) Treatment evaluations
    (1) Long history of studies of treatment effectiveness
    (2) Studies specifically focussing on effects of treatment on risk behaviors in the AIDS era
        (a) Ball -- "Good" MMTP treatment is effective, but varies
        (b) Abdul-Quader et al.
d) **Key finding is that of non-contradiction between efforts aiming at "safer injection" and those aiming at ending drug use.**

III. Innovative program ideas

A. AIDS means we have to examine and test some ideas that are controversial in order to protect the public health. In Sweden and Germany, methadone treatment is itself controversial, but in Sweden they have doubled methadone treatment in response to AIDS (from 150 to 300 slots, which is 30% of their heroin users), and in Germany they have syringes sold over the counter and have made sure that pharmacists actually do sell them to addicts (and in Sweden they have an accepted guerrilla syringe exchange; methadone without supportive counseling and vocational services is controversial in US; needle exchange aproach is controversial.

B. We absolutely have to be able to do research in these controversial areas if we are to learn how to prevent the spread of AIDS. Federal agencies, however, are inhibited on this. The CDC Innovative Research Projects have been hindered by requirements that local committees approve educational materials. Calls have been made for experimental tests of needle exchanges, but so far none have been funded.

C. By and large, research has focused on what helps the individual to reduce risk of becoming infected. This research has used the experimental model from psychology as a model, which means that it looks at individuals as the unit of change and that it assumes that history is irrelevant (i.e., that what works at one point during the epidemic will work at other times.) Research has to get beyond this in several ways:

1. Focus also on reduction of behaviors that potentially transmit HIV to others. This is a different set of motivations than personal protection.
2. Look at risk behaviors -- both IV drug use and sex -- as social. We are beginning projects to change the subculture of IV drug users and their partners in some of the ways that gay men have changed their subcultures -- i.e., to incorporate risk and transmission reduction as important values within the subculture, and to help users and their partners develop ways to implement such protective ideas in practice. Here, street self-help groups among users to get peer support for risk and transmission reduction is one example.

3. Look at risk and transmission behaviors as historical events. At the beginning of the epidemic, few drug users believed in their own vulnerability to AIDS; since then, more acceptance has occurred, and considerable risk and transmission reduction; later on, we may encounter a subculture of despair about AIDS. Each of these periodsinvolves different contexts for the individual who is confronted with a given intervention, so we would expect reactions to differ in accordance with the history of the epidemic. The standard models of research, however, do not take this dynamic into account.
4. Decisions about research are often taken by medically trained persons -- often, by superb medical scientists. They make these decisions -- about what programs should be set up for funding through an RFP mechanism, what specific proposals should be ranked well or poor (and thus funded or not), and what articles should be accepted or rejected -- on the basis of their medical research training. This training tends to be of only limited applicability to the social science research we need in order to figure out how to change the behaviors that spread this epidemic -- for example, it exalts the experimental method, ignores issues of historical change during phases of the epidemic, and simply assumes that the individual is the appropriate unit of analysis -- and thus produces requirements that hold back the development of innovative research The fact that medically-trained researchers are often unaware of these issues

simply aggravates the problem.

5. The methodological issues I have alluded to are difficult ones. We need to find ways to lure creative methodologists to apply their skills to help work out better ways to approach research in these areas.

IV. Specific suggestions about research management

A. We are reaching a point where we cannot train medium level researchers at the rate we need through normal channels. What is needed is a way to bring established researchers who have not been doing AIDS research into our on-going projects through a senior-level equivalent of a post-doctoral program; appropriate persons might be associate professors ho want to change careers or who have sabbaticals. Stipend levels would be in the order of $35-50,000. This would let us train needed project directors and senior analysts and methodologists without having to give them line authority in research grants while they are being trained. It might also help us reduce the serious paucity of minority researchers in this field (which is important in research about behaviors that lead to disproportionate infection of minorities.)

B. Expansions in research funding have not been matched by funding agency infrastructure expansion. This means that researchers have not had adequate support by staff of agencies such as NIDA due to the extreme over-business of the Federal staff. At NIDA, for example, AIDS money has multiplied by 10 between FY 1986 and 1988, and more than doubled between FY87 and 88. Staff has increased only by a factor of 5, and in FY88 will increase only by 3 persons. Travel moneys have been insufficient to allow optimal management and assistance to the large demonstration grants and contracts, in spite of valiant efforts by staff. The staff shortage has meant that NIDA has been less able to attract people into submitting proposals for AIDS research. For those who do enter the field, NIDA would ideally be able to provide them with considerable mentoring and other guidance specific to AIDS research, but the large volume of research as compared to staff renders this all but impossible. The Community Demonstration Projects are NIDA's major expenditures on AIDS, and will involve 28 grants and 15 contracts by the end of FY88; the unit that oversees this has only 8 staff members, and many of them have only been work-

ing on AIDS for a year or two.

C. AIDS research moves fast, and often does not fit funding cycles well. Sometimes, grants are initially budgeted small, but it turns out that they need and deserve considerable expansion in mid-year. The mechanisms to do this are very awkward, and need stream-lining.

V. Suggestions for Interventions to reduce AIDS among IV drug users and their partners

A. Prevent initiation of IV drug use. Much research is needed on this.

B. Rapid and sizable expansion of drug abuse treatment, including improved levels of space, facilities, and staffing.

C. Outreach to IV drug users and their partners. This should include individual educational outreach, efforts to promote safer injection, and also efforts to mobilize the small groups and subculture for AIDS prevention.

D. Given the extent to which AIDS is impacting Blacks and Hispanics, special programming to involve minority community organizations and institutions.

Prepared for the President's Commission on the HIV Epidemic
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AIDS IN ADOLESCENCE: BEYOND EDUCATION

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INTRODUCTION

As we approach the end of the first decade of the AIDS epidemic, it is apparent that there are special considerations for the adolescent population. Both the epidemic of AIDS and "AFR-AIDS" have touched the lives of most adolescents.

Currently, there is a low cumulative prevalence of AIDS cases in the adolescent population under the age of 21 years compared to adults. While adolescent sexual behavior is a common and controversial concern, we are only beginning to recognize the AIDS risk associated with this behavior.

The premise of this report is that certain subgroups of adolescents form bridges from those adults currently infected to a larger group of adolescents. As the virus spreads from individuals initially infected to their partners and beyond, some teenagers are directly in the path of the epidemic. In this epidemic, geography can be destiny.

DIFFERENCES BETWEEN CHILDREN, ADOLESCENTS AND ADULTS

Although the Human Immunodeficiency Virus (HIV) does not select people by age, nonetheless, there are differences between children, adolescents and adults that have bearing on the AIDS epidemic. Some of these differences are biologic, others are behavioral or sociologic. Briefly stated, the differences between affected <u>children</u> and <u>adolescents</u> are the route of infection in young children is usually vertical from an infected mother, the shorter mean survival time in young children, and the need for day care and foster care for pre-school aged children.

Some of the differences between adolescents and adults are a higher percent of teenage cases acquired by heterosexual transmission, a higher percent of teenaged asymptomatic individuals (who will become symptomatic during adulthood), a higher percent of black and Hispanic cases, a special set of ethical and legal issues regarding testing and informing partners and parents for those adolescents below the age of majority, cognitive differences in processing information, the special medical, economic and social implications of teenaged mothers delivering HIV infected babies, emotional differences in coping styles, the lack of a unified community for support (as opposed to the homosexual adult population), differences in sexual behavior patterns (a higher percent of "sexual adventurers", less use and availability of contraceptives), and the lack of availability of services that are convenient, appropriate and attractive to youth.

ADOLESCENT DATA

Currently, the number of reported AIDS cases in adolescents is low (1% of all cases), but is doubling each year. Statistics for adolescents over the age of 13 years have only recently been reported separately from the adults. These data show that critical differences in sex ratio, ethnicity, and reported risk groups exist not only between adolescents and adults, but also among adolescents from different localities. Currently, 503 young people age 13-21 were reported to the CDC as of January

1988 (Personal Communication, H. Gayle, CDC, January 1988). The Centers for Disease Control reviewed AIDS cases aged 11-24 in a 1986 report.[1] Thirty-seven cases were 11-17 years of age versus 1122 between 18 and 24 years. Eighty percent of the younger males were transfusion recipients as compared to 4% of the older group. Homosexual or bisexual males comprised 18% of the younger group but 79% of the older group. Females in both age groups were mostly infected through sexual contact.

Analysis of cases of AIDS in adolescents in New York City is instructive for several reasons. New York accounts for roughly 1/3 of all AIDS cases in the US and also accounts for 20% of the reported cases in adolescents.[2]

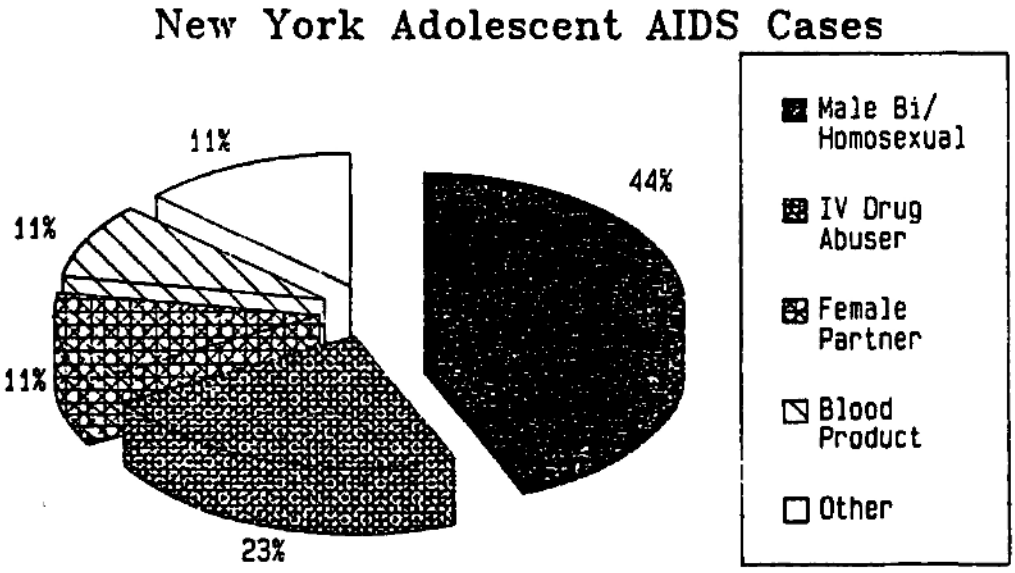

Figure 1

Analysis of 114 NYC adolescent cases 13-21 yrs revealed significant differences ($p<0.0001$) in the sex ratio (male:female) of 2.9:1 compared with NYC adults (7:1) and US adults (15:1).[2] Teenage cases increase with age ($p<0.0001$). In the US, 60% of cases were white, whereas minority groups predominated among both adolescent (58%) and adult (55%) cases in NYC.

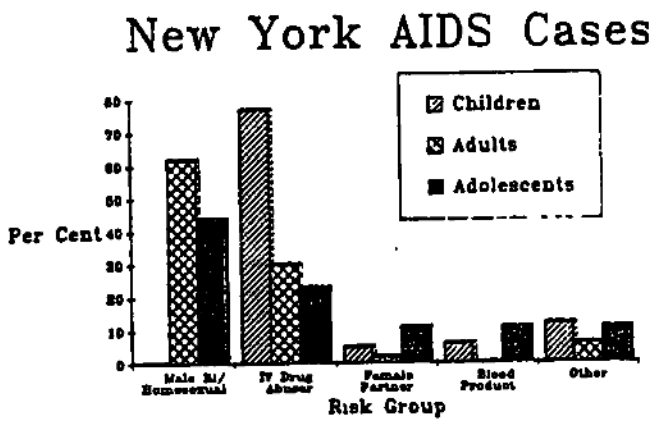

Figure 2

As in NYC adults, homo/bisexuality and intravenous drug abuse were the leading risk behavior categories in adolescents but the proportion of adolescent cases differed from adults (Figure 2). In adolescents, the percent of total cases was lower for homosexual/bisexual (44%) category and higher for intravenous drug abuser category (23%). However, female partners of high risk males were far more common among adolescents (11%) than adults (4%), representing 45% of all teenage female AIDS cases ($p< 0.01$). Nationwide, hemophilia is the leading risk factor for AIDS among young adolescent males (79%), but in NYC only 18% of male cases were transfusion related.

In summary, with scanty information about the prevalence of HIV infection among adolescents, analysis of AIDS cases in New York City points to groups of young people in inner city settings that are bridging groups to other adolescents. Previous data about rates of sexually transmitted disease and sexual and drug related behavior among some groups of adolescents provide a rationale for concern.[3] The rapid rise in the percent of cases in young adults 20-29 years (21%) probably includes many individuals infected during adolescence.

The long (but variable) latency period from viral infection to diagnosis of AIDS or death from AIDS is currently estimated to be 7 years on average. Therefore, persons infected during adolescence may well remain asymptomatic until young adulthood. Evidence for this phenomenon is the observation in 1987 that 10% of the mothers of AIDS babies in New York City were 21 years of age or less. Although many of these young women were well, they were identified by having an affected child. The risk of developing disease does not decrease over time and infected individuals transmit virus while remaining asymptomatic.

The concentration of adult cases in certain areas within the mid Atlantic states, West Coast and Florida has particular relevance for further spread to the adolescent population.

CONCEPTUAL FRAMEWORK

We must create meaningful categories of risk with in the teenage population in order to target specific recommendations for specific groups. The teenage population does not have a wall around it nor is the infected adult population quarantined.

Figure 3 provides a conceptual framework in which we might view adolescents.

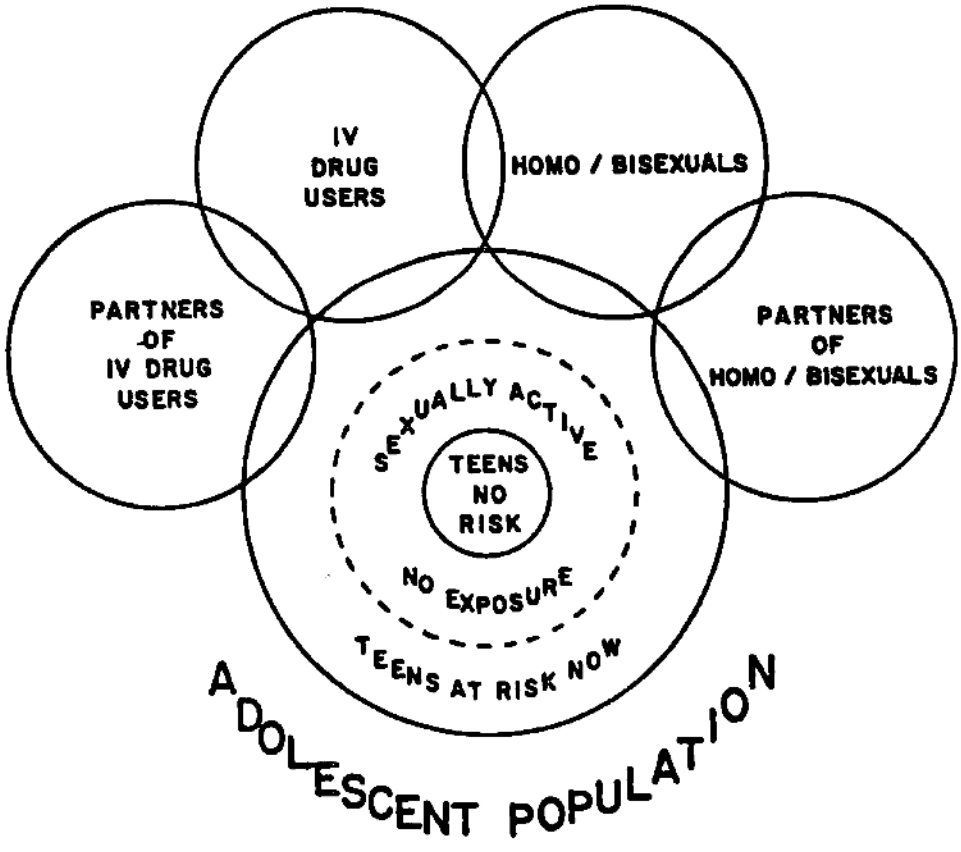

Figure 3

The inner circle: At the center is a group of adolescents who are currently not at risk for HIV infection by virtue of their current lifestyle or the absence of the virus within their sphere of activities. These are the very young, virginal, non-intravenous substance abusers who have not received transfusions. Although shown as the smallest circle in the diagram, they represent the largest group of adolescents at the moment. However, as the individuals in this group get older or move to a different location or engage in new and different behaviors, they may move into a different circle putting them into a higher risk category. Issues for them include:

- "worried well" (how to live in an atmosphere of concern and maintain an appropriate level of concern without undue anxiety)
- need for casual contact information (encouragement to engage in those activities that do not put them at risk)
- support for sexual decision making

In the second circle are sexually active teens who are not yet exposed. The boundary between them and the at risk teenager is fluid and easily crossed. As the virus becomes more prevalent, this group will shrink as the next outer circle enlarges correspondingly.

Issues for this group include:

- knowing (or not be able to "know") their partners
- reconsidering patterns of sexual behavior

use of contraceptives in general and condoms in particular

In the third circle are the at risk teenagers. This group is at risk of HIV acquisition because of exposure to infected individuals. The overlapping circles forming the outside of the model provide possible sources of exposure. Exposure can emanate from any or several of the four groups of adults or other teenagers shown including adult IV drug abusers, adult sexual partners of IV drug abusers, adult homosexuals or bisexuals, adult sex partners of homosexuals or bisexuals, teenage IV drug abusers, teenage sex partners of IV drug abusers, teenage homosexuals or bisexuals, and teenage sex partners of homosexuals or bisexuals.

It would appear from the reported cases of AIDS that many of these teenagers are most likely residing within inner city areas in the mid-Atlantic states (New York and New Jersey in particular) and on the West Coast. Currently minority group youths are disproportionately represented. Issues for these groups include:

- decisions about testing
- knowledge of serostatus of partner(s)
- need for barrier methods of contraception
- reconsideration of patterns of sexual behavior
- decisions about continuing pregnancy
- need for services geared to the adolescent age group for crisis intervention & follow-up of HIV infected

teenager & partners

These categories are not mutually exclusive. The more the overlap, the higher the risk.

This model has both heuristic and practical value in that it can form the basis for a research and action agenda. It is important to remember that although the inner circle currently probably contains the most adolescents, the dimensions of each circle are unknown and are changing continually. Regardless of the dimensions, the categories each represent real adolescents.

EXAMPLES OF RECENT RESPONSES TO THE CHALLENGE

Within the past year there is growing recognition of the special considerations for adolescents regarding the AIDS epidemic. Initially it was hoped that the activities could be concentrated in the area of prevention. However, it is now apparent that, although adolescents still only account for a small percent of total AIDS cases, some adolescents are already infected.[4] Therefore, a series of parallel activities must be launched to address the needs of a spectrum of adolescents from the uninformed to the "worried well" to the already infected or ill.

The following examples are listed to illustrate the range of responses in different parts of the country. Three operating assumptions underlie the development of interventions. 1) the heterogeneity among American adolescents; 2) timeliness of the AIDS problem and 3) limitations of past interventions for

changing behavior in relation to sexually transmitted diseases and drug use. We will need to go beyond traditional institutions for teenagers (schools and health care facilities) in order to reach many adolescents. Although most teenagers are in school, current controversy about the role of school based health clinics and limitations imposed by school and parental groups present obstacles that delay necessary rapid interventions that might curtail the spread of HIV infection. Therefore, in addition to working within the framework of schools and the health care system, we must go beyond to identify organizations, settings, programs and even individuals who can directly affect teenagers.

1. NETWORKS OF YOUTH SERVING AGENCIES CONCERNED ABOUT AIDS

A few examples of networks of youth serving agencies now exist. They facilitate the development and dissemination of educational materials, guidelines and information. Two "Task Forces on AIDS in Adolescents" have been organized. One on the west coast is based in San Francisco and sponsored by the Mayor's office (Richard Brown, MD, Coordinator). The other, on the east coast, is located in New York City and is currently administered through the New York AIDS Service and Delivery Consortium (Kathe Karlson, Coordinator). Each has participants from organizations in the educational, community-based direct service and health sectors. These groups have been used to facilitate referrals, share resources, develop policies, and identify problem areas (such as access, payment, confidentiality) for mutual discussion

and resolution. These initiatives have developed on a volunteer basis but their existence might enable innovative approaches to be developed with ongoing support in the future.

Many organizations previously involved with adolescent health, education or welfare have shifted to include new services related to AIDS. The first Adolescent AIDS Program in the nation exclusively dedicated to the issues raised by the epidemic for teenagers has been launched in 1987 in New York City at The Montefiore Medical Center affiliated with Albert Einstein College of Medicine.

2. ADOLESCENT RESOURCE GROUPS

Resource groups have been formed representing various subgroups of adolescents. Focus groups have served as advisors to screen films, educational materials, program outlines, advertising appeals, survey questionnaires and research protocols requiring adolescent cooperation. Specially trained peer counselors have helped in some supervised activities. A few examples are: 1) The New York City Department of Health has been using focus groups to test the appropriateness and appeal of their brochures and educational campaigns; 2) High school students in Bethseda formed an AIDS Hotline in 1986 using volunteer students specifically trained to answer questions and make referrals; 3) the American College Health Association formed an AIDS Task Force to help develop and oversee educational and

service activities on campus (including the use of peer counselors) for the college-age population.

3. DEVELOPMENT OF EDUCATIONAL MATERIALS

During the past year, visual, audio and printed educational materials being developed specifically for adolescents. Availability and cost are still obstacles. Attempts to evaluate their usefulness in changing behavior are only now being proposed. The film "Sex, Drugs, and AIDS", for example, was commissioned by the New York City Board of Education in 1985, completed April 1986, modified in 1987 and is only being shown to graduating Seniors in New York City schools. Both the original and the modified version of this film, however, are being used by community based programs and other school programs in other parts of the country. Training programs for teachers, counselors and other youth workers in the appropriate use of these educational adjuncts are now underway. Regional workshops have been organized by colleges particularly in the Mid-Atlantic states and California. AIDS related curriculum planning is being encouraged through CDC initiatives and The National School Board Association (NSBA) and other health and education sponsored workshops. There are plans to expand these activities in 1988.

There is currently no central clearing house for existing materials. Agencies with information to offer include not only educational institutions, but also umbrella organizations such as the American School Health Association (ASHA), National School

Board Association (NSBA), The Center for Population Options (CPO), Centers for Disease Control (CDC), and Sex Information and Education Council of the United States (S.I.E.C.U.S.). Other youth serving organizations such as the Gay Men's Health Crisis, the Institute for the Protection of Gay and Lesbian Youth (IPGLY), and many neighborhood associations are developing resources independently.

4. ANALYSIS OF AVAILABLE DATA

Available data are being analyzed with a focus on adolescents. Until 1987, data were generally collected, reported and analyzed in terms of children under 13 years of age and adults. The Centers for Disease Control and local health departments in areas of high viral prevalence like New York, are now disaggregating data and adapting existing protocols and software to enable those concerned about adolescents to separate teenagers from age groups bracketing adolescence. The age groupings used by various agencies differ. For example, the New York City Department of Health has been reporting adolescent AIDS cases ages 13-19 years since October 1987 in the monthly surveillance reports. The reports of The World Health Organization divide the age groups by 5 yearly intervals (e.g. 10-14, 15-19 etc). The earlier reports of the Centers for Disease Control used the division younger adolescents (11-17 years of age) versus older adolescents and young adults (18-24).

These divisions each may serve a particular purpose but do make comparisons difficult.

5. SURVEYS OF ATTITUDES, KNOWLEDGE AND BELIEFS AMONG ADOLESCENTS

Little is known about adolescents' views and beliefs about AIDS. In theory, this should be a first step before developing programs or materials in any local area. Adapting pilot questionnaires already in use has been extremely useful to professionals who work with youth in the area of AIDS prevention. The more localized the survey, the more useful the results. But local areas often do not have the time, resources or expertise to do survey analysis. A national survey is currently being designed for high school students by the Centers for Disease Control for distribution in 1988.

Four pilot questionnaires have been developed specifically for adolescents in Boston,[5] New York City,[6] San Francisco[7] and Los Angeles.[8] The questionnaires could be adapted for longitudinal use so that repeated periodic contact with different adolescent populations could be maintained. In this way, the spread of information, changes in attitudes, beliefs, knowledge and behavior could be followed prospectively over the next few years. Longitudinal surveys of drug use among adolescents have been successfully maintained over the past decade. A similar effort could now be launched for AIDS.

6. MORE WIDESPREAD CONDOM DISTRIBUTION

Condoms are being made more available by reducing cost and increasing distribution. Advertising has been one route to promote use as part of safer sex practices. Targeting mechanisms of distribution and barriers to teenager use is another strategy, albeit a controversial one. A mass condom distribution campaign was instituted in a family planning clinic serving young adults in Atlanta and an adolescent pregnancy program in New York City. A survey of the Atlanta recipients who could have up to 50 free condoms was conducted to discern the number of condoms accepted and their fate. The appearance of "safer sex kits" containing condoms and information relevant to AIDS on some college campuses and the increase in condom availability via installation of conveniently located vending machines or other modes of distribution are examples of recent attempts to slow the spread of HIV in the adolescent population.

7. STUDY OF THE INCIDENCE, PREVALENCE AND NATURAL HISTORY OF HIV INFECTION

Three types of studies could be supported, all of which are necessary for health professionals to understand the nature and spread of AIDS in the adolescent population: 1) incidence of HIV infection among adolescents; 2) prevalence of HIV infection in various subgroups; 3) natural history of HIV infection. Specifically these studies would help elucidate modes of transmission, geographic patterns of spread and progression of

disease from asymptomatic to symptomatic state in HIV infected teenagers. Basic information about age, race\ethnic distribution, means of acquisition, could be combined with a prospective study of the extent of spread to partners. The patho-physiologic features of HIV infections including immunologic changes, types of opportunistic infections and cancers, the role played by other co-factors (such as tuberculosis, the presence of other venereal diseases such as hepatitis B, gonorrhea, syphilis, etc.,) have not been studied in adolescents as yet.

8. NEW FUNDING INITIATIVES

Although a variety of federal, state, local, public and private agencies are now beginning to fund projects related to HIV infection, the mandates and categorical definition of the mission of each agency makes analysis of available resources for adolescents difficult. Some of the federal agencies that have included adolescents with other age groups in recent funding initiatives include (but are not limited to) the following: NICHD (National Institute of Child Health & Human Development), NIAID (National Institute of Allergy & Infectious Diseases), NIHM (National Institute of Mental Health), NIDA (National Institute on Drug Abuse), MCH (Division of Maternal and Child Health), CDC (Centers for Disease Control). One group of funding agencies, The New York Regional Association of Grantmakers, in their September 1987 meeting on "AIDS: An Update for Grantmakers"

highlighted adolescents in the selected AIDS issues update.[9] Thus far, few agencies have targeted funds specifically for adolescents.

9. ETHICAL AND LEGAL CONSIDERATIONS

Ethical and legal considerations related to testing, screening, informing partners and counselling are complex when dealing with adults. The principles and guidelines need modification when applied to minors. The impact of policy decisions about testing and exclusion of HIV positive adolescent military recruits and applicants to the Job Corps and Peace Corps and dependent minors of adult employees in certain federal agencies has not been systematically studied. Yet anecdotal reports indicate severe disruption in the lives of HIV positive adolescents and their families due to inadequate mechanisms for appropriate counselling and following up of high risk or HIV positive adolescents.

The HIV screening currently being conducted needs further debate and clarification of purpose. The implications for young people differ from adults. In particular, exclusion based upon positive test results is an issue of immediate concern. The young person must not only deal with the disappointment of rejection, but is not offered ongoing help in a time of personal crisis. In addition, the stipulation for parental notification of test results for persons under 18 years is contrary to guidelines for other sexually transmitted diseases.

CONCLUSION

Some of the events that have helped introduce and support the need to recognize the distinctive features of adolescents within the past few years include:

1986

The report of the Institute of Medicine, "Confronting AIDS"

1987

The Surgeon General's Workshop on AIDS in Children and Their Families

The conference on AIDS in Adolescence sponsored by The Center for Population Options

Hearings on AIDS in Children and Adolescents conducted by the House Select Committee on Children, Youth and Families

Report of the New York Regional Association of Grantmakers on AIDS: An Update for Grantmakers

1988

Testimony before Presidential AIDS Commission on AIDS in adolescence

Invitational Conference on AIDS in Adolescents: Exploring the Challenge co-sponsored by the Bureau of Maternal and Child Health, CDC, National Institutes of Health (NICHD, NIMH, NIDA), and the Society for Adolescent Medicine.

The basic message in this report is the need to recognize the special needs and opportunities related to AIDS in adolescence. Thoughtful but quick action is the goal. If we cannot determine and deter the AIDS risk for our adolescents now, we are likely to face massive morbidity and mortality among our young adults in the near future.

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