THE PRESIDENTIAL COMMISSION on the HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

HEARING ON Research

February 18, 19, 20, 1988

August 24, 1988

TO OUR READERS:

The Presidential Commission on the HIV Epidemic held over 45 days of hearings and site visits in preparation for our final report to the President submitted on June 27, 1988. On behalf of the Commission, we hope you will find the contents of this document as helpful in your endeavors as we found it valuable in ours. We wish to thank the hundreds of witnesses and special friends of the Commission who helped us successfully complete these hearings. Many people generously devoted their volunteer time in these efforts, particularly in setting up our site visits, and we want to fully acknowledge their work.

The staff of the Presidential Commission worked around the clock, seven days a week to prepare and coordinate the hearings and finally to edit the transcripts, all the while keeping up with our demanding schedule as well as their other work. In that regard, for this Hearing on Research, we would like to acknowledge the special work of Peggy Dufour, along with Jane West, Christopher Hanus, Amanda Benedict, John Sonnega, Ken South, and Barry Gaspard, in putting together the hearing, and Peggy Dufour in editing the transcript so it is readable.

For the really devoted reader, further background information on these hearings is available in the Commission files, as well as the briefing books given to all Commissioners before each hearing. These can be obtained from the National Archives and Records Administration, Washington, D.C. 20408.

One last note--We were only able to print these hearings due to the gracious and tremendous courtesies extended by Secretary Bowen's Executive Office, especially Dolores Klopfer and her staff, Reginald Andrews, Sandra Eubanks and Phyllis Noble.

Sincerely,

Polly L. Gault
Executive Director

Gloria B. Smith
Administrative Officer

PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

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PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

RESEARCH HEARINGS
BASIC RESEARCH AND VACCINE DEVELOPMENT

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

Thursday, February 18, 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.
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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 Hearing
February 18, 1988

I - N - D - E - X

Research Hearing
February 18, 1988
(continued)

P R O C E E D I N G S

February 18, 1988 [9:07 a.m.]

OPENING

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 open today.

Chairman Watkins?

OPENING REMARKS

CHAIRMAN WATKINS: 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 four areas we identified as topics to be addressed in our interim report to the President, which we will deliver to him 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 now no known cure.

Last November, two persons with AIDS appeared before our Commission in Florida to talk about the need for further research and drug development. Unfortunately, those two persons with AIDS, James Sammone and Patrick Haney, have since died of AIDS. I talked with the fathers of these two young men, and they in turn have dedicated their lives to furthering AIDS research on behalf of their sons.

So it is on behalf of the persons like James Sammone and Patrick Haney and their families 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 also 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 the 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 effort 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.

This morning I have the honor of handing the gavel over to Dr. Frank Lilly, who will chair these particular 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.

Dr. Lilly?

[The prepared statement of Admiral Watkins is included in the Appendix.]

DR. LILLY: Thank you, Chairman Watkins.

Some very brief remarks. AIDS is a new disease. Although many of the individual symptoms, complicating factors, and opportunistic infections that are seen in the course of AIDS have also been seen in other diseases, physicians agreed from very early in the epidemic that they had never seen this disease before.

The Administration was slow to encourage and sponsor research into causes and mechanisms of the disease, but there were a few biomedical scientists whose fascination and horror of AIDS goaded them into studying it using research funds earmarked for other, sometimes very important, purposes.

The fortunate result was that during the third year after the first published recognition of the disease, a new virus was discovered called human immunodeficiency virus or HIV that the vast majority of scientists and physicians agree is the fundamental cause -- the sine qua non -- of AIDS.

Other advances have been made in our understanding of the complex disease that is AIDS, but we are still far from our goal of controlling the disease by making vaccines to prevent it, drug therapies to cure it, and educational modalities that will

influence people to alter their behavior in ways that can enormously reduce their risk of contracting it.

These next three days of hearings will certainly reiterate some of the successes that have been achieved in the fight against AIDS, but what we now need more than that is an analysis of the areas in this epidemic where we have not yet succeeded. Thus we have tried to organize these hearings to bring out in as clear a way as we can what needs to be done and to reveal what may be the obstacles to getting them done.

Our first session this morning is essentially an introduction to the basic research in AIDS, and our first speaker is Dr. Jerome Groopman from Deaconess Hospital, in Boston. Dr. Groopman is a very distinguished physician, who has treated a large number of persons with HIV infection, and who has very much more experience with AIDS than he would like to have, I'm sure.

Basic Research and the HIV Epidemic

DR. GROOPMAN: What I would like to do and what I was asked to do by Dr. Lilly is to very briefly highlight some of the basic biology of the virus with an emphasis on the unanswered questions. And clearly in the fifteen minutes that I'd like to do this, one can't encompass the entire complexity of the biology of the virus or all of its clinical ramifications. What I thought I would do is highlight for the Commission what I see as some of the major unresolved issues in basic science.

[Slide.]

As you know, there are several human retroviruses which are associated with disease conditions. HIV-1 is the cause of AIDS in the United States and Western Europe. Recently a second human retrovirus which results in immunodeficiency has been identified in West Africa. Cases have been reported in Europe, and as I'm sure you're aware, the first case in the United States was reported from New Jersey of HIV-2. This virus is distinct from HIV-1, but many of the clinical ramifications are similar to infection with HIV-1.

The HTLV-1 virus is a virus which is distributed particularly in the southern islands of Japan, such as Kyushu, as well as throughout the Caribbean. This is associated with a T-cell leukemia and malignancy, and it is appearing, though, in the United States among certain populations which are also at high risk for the AIDS virus, for HIV-1, particularly among intravenous drug abusers and cases of infection with both HIV-1 and HTLV-1 have recently been reported.

HTLV-2 has been rarely identified, and it has been associated with a malignancy of T-cells similar to that of HTLV-1, but of a less aggressive form.

There is considerable search for other human retroviruses, other pathogens that belong to this family which might be associated with disease conditions, and two have been remarked upon. One is a possible association of retroviruses with multiple sclerosis. That is not conclusive, to say the least, and there are reports of pathogenic retroviruses in Amazonian Indians in Venezuela, although those have not been confirmed as well.

It is likely, though, that there will be other viruses belonging to the general family of retroviruses which may account for certain human disorders.

[Slide.]

Now this is simply a cartoon of the genetic structure of the virus. We don't have time to go into the detail, but simply to say that the entire virus is known in terms of its constituent bases or its components, and there are a number of genes that code not only for the structure of the virus -- that is, its core and its exterior envelope -- but there are genes that code for proteins that regulate virus function and probably cellular function. And one of the major issues in terms of understanding the biology of the virus is to understand in great detail how these functional genes called the tat gene or the trs/art or the 3-prime orf, the boxes that you see up there, how these gene products interact not only to regulate viral replication, but also how they interact with basic cellular processes to interfere with normal cell function. So to understand why lymphocytes or other important cells are impaired with patients infected with HIV, we need to understand how these gene products interfere with normal cell function.

[Slide.]

This is a cartoon to review the life cycle of the virus, and I think there are several important points that can be made in terms of the biology of HIV-1.

As you see, the virus is shown in the left upper part of the slide. It has an exterior envelope called gp120. That binds to a protein on the surface of the target cell called the CD-4 protein. You can see initially that a great deal is known about this virus compared to other viruses in terms of having identified the exterior of the virus and actually the portion of the virus that binds to a specific protein which is necessary for entry of the virus into the cell.

After the virus enters the cell, it is uncoated, and the RNA, the genetic information of the virus, is made into a DNA form. As you know, in all of us, genetic information flows in general as DNA to RNA to protein, and these reverse viruses or retroviruses change that flow of information and have an RNA base which goes to DNA, and then DNA integrates within the nucleus of the cell and is able to code for protein and viral RNA and make more viral particles.

Two important point in terms of this slide. One is the identification of the receptor or the binding protein on the surface of the cell, which appears to be a necessary component for infection of target cells. And as you may know, there are several groups that are attempting to exploit this observation in terms of a specific binding protein for the virus and to form through genetic engineering decoy forms of this protein which could inhibit and compete for the AIDS virus, stick to it if you will, and prevent it from binding to the CD-4 protein on the surface of the target sell -- that is, to use a decoy genetically engineered form.

Similarly the reverse transcriptase enzyme is a necessary enzyme in the life cycle of the virus for reproduction, and a number of drugs are designed as inhibitors of the reverse transcriptase, most prominent among them, AZT, the currently licensed drug for the treatment of AIDS.

You can also see that once someone has been infected with the AIDS virus, with HIV, that the genetic information in its DNA form integrates itself within the nucleus of the cell. This means, for all intents and purposes, that once a person has been infected by HIV, that person is permanently infected in that he or she carries genetic information of the virus integrated within his or her cells, and therefore potentially infectious to others. So this is important from a public health point of view, based on the biology of the retrovirus.

Now the target cells of the virus appear to be broader than originally thought. The initial observation of lack of T4 or helper lymphocytes in people with AIDS was followed by the laboratory study showing that HIV could infect the T4 lymphocyte. It is now known that the AIDS virus, HIV, can infect another important white cell form called the monocyte macrophage, and the biology and the characteristics of the virus appear to be somewhat different in the monocyte macrophage versus in the lymphocyte. It appears to be less toxic or cytopathic to the monocyte macrophage, and it may be that the monocyte macrophage, which circulates in the bloodstream and enters a variety of tissues, most particularly the brain, that this cell may be quite important in acting as a vehicle or a transport mechanism for dissemination throughout the body.

Similarly recent work initially from Mal Martin at NIAID and now from Jay Levy out in San Francisco indicates that colonic epithelium, the lining of the lower gut, expresses this T4 or CD-4 protein and may be infected by the AIDS virus. This could be important in terms of understanding the transmission of the virus particularly through sexual behavior such as receptive anal intercourse where one might be able to get direct infection of the lower bowel as opposed to requiring trauma to capillaries and blood contact.

There is considerable speculation, and it has not been definitively shown whether other target cells may be infected within the body. So this is one area of research which I think should be pursued, and people are particularly focused in terms of infection of neurons or brain cells as well as the lining cells of blood vessels, endothelium.

So I don't think we have fully defined yet the full spectrum of cell types that may be important with respect to HIV infection. This is terribly important, I think, because when one screens drugs or when one attempts to elicit an immune response for a vaccine, one wants to be sure that one is blocking the AIDS virus not only within the lymphocyte, but also within any other cell type that the virus could infect.

As I mentioned, the monocyte macrophage is a current area of research, and some data are available, but there's consideration given that the virus could potentially enter these cells, which are called phagocytes or gobbling type cells. They ingest particles and microbes. Perhaps the virus could enter not through this binding protein but through actual engulfment by the cell. That hasn't been shown, but it's an area of research.

There is debate whether a drug like AZT is as active within the white cell, within the monocyte macrophage, in terms of blocking HIV as it appears to be within the lymphocyte, and this is quite important, obviously, in understanding the benefits and limitations of a drug like AZT.

As I said, the AIDS virus, HIV, appears to be more latent within the monocyte macrophage than it may be within the lymphocyte, and understanding how the virus can remain in a latent or covert form is important. And finally to understand whether the bone marrow stem cells, the progenitors of the monocyte macrophage, are infected is quite important as well.

[Slide.]

I will say that I think basic science should be applied to better understanding of the transmission and susceptibility in that we don't understand in full terms yet whether there are individuals who are better transmitters of the

virus and others who may be more or less susceptible. We are involved in a very interesting study of the direct sexual partners of people with AIDS and ARC, and we find about a third of these partners are discordant -- that is, one is infected and the other is not, and this cannot be easily explained simply on the basis of behavior. There are individuals who have multiple receptive anal contacts whose partners are infected with the virus, and yet they have not become infected despite considerable exposure.

Are there factors related to the virus? Are there genetic factors in terms of susceptibility or transmission, or is there an immune response which is able in some way to limit transmission or to confer reduced susceptibility?

[Slide.]

And finally I think it's important to know how the AIDS virus, HIV, on a basic level inhibits lymphocyte function. I think it's important both in terms of designing strategies to block the virus and its deleterious effects on the immune system, and also because I think this is tragic opportunity to understand the basic physiology of the immune system and the basic physiology of lymphocyte function.

Thank you. I tried to be brief and focused, and I'd be glad to answer any questions.

DR. LILLY: Thank you very much. I think if you will permit us, we will go on and have Dr. Rauscher present his testimony, and then we'll have a question-and-answer period.

Our next speaker is Dr. Frank Rauscher, who is from the American Cancer Society. Dr. Rauscher has had an extremely successful career in direct biomedical research on retroviruses, and he has been administering research, and he has learned a great deal and probably knows more than anybody else I know about how to do that successfully.

So I would like to present Dr. Rauscher.

The Role or Research Planning

DR. RAUSCHER: Thank you, Mr. Chairman and distinguished members of the Commission.

My name is Frank Rauscher, and I presently serve as Senior Vice President for Research of the American Cancer Society. I believe you have my CV.

My background, in brief, is as follows:

I evolved primarily as a viral oncologist in retrovirology through 10 years of academia; 18 years with the National Cancer Institute at the NIH, and now 12 years with the American Cancer Society in the private or voluntary sector. During this time I have also served on a number of panels related to the subject of your hearing.

I have been asked by one of you, one of the most innovative scientists in this country, Dr. Lilly, a member of your Commission, to comment on the good or the not-so-good aspects, if you will, of the planning process; in particular, as the planning process relates and has related to two programs sponsored by the federal government which, in many respects, are similar to the charge that you have undertaken.

I will do this very briefly and then will, of course, be pleased to discuss any questions you may have.

In 1964, I was appointed head of what was called the Special Virus Leukemia Program, which I believe was the first major new program of the NIH that attempted to include planning as a major component of program implementation and evaluation.

At that time, during the middle of the budget year, interestingly enough, the National Cancer Institute received a supplemental appropriation of $10 million with a mandate from Congress to determine whether viruses were responsible for any human neoplasm, in particular leukemia and lymphoma, and to devise means for prevention.

That charge was not fully realized or fulfilled until Dr. Gallo and now others discovered the relationships of HTLV-1 and a form of adult leukemia in the early 1980s. The technology coming out of that program, I think it is fair to say, 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.

Now in terms of planning, a small number of staff, that is NCI staff together with advice from outside peer scientists, with approval and overview of the National Cancer Advisory Council at that time, attempted to do the following, and I find these are sort of golden threads through any planning process as regards medical research:

First, was to assess the history and state of the art as it existed at that time in viral oncology;

Second, was to determine what critical path might be followed to attain the objective quickly and with some economy;

Third, was to identify and solicit people and institutions to do the work -- that can be difficult, by the way;

Fourth, was to peer review, monitor and report on progress or the lack thereof in the program;

And then fifth, and I think as important as anything, we were charged with updating a rolling or a continuing five-year plan, if you will. It's terribly important because it helped to indicate, at least to the public, that we were not looking for an overnight kind of success in our attempts to prevent or to cure these particular forms of cancer.

These sub-objectives were accomplished at that time, 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 sort of conjured up the image of "Big Brother" telling scientists what to do and how and when. Also the program did not have direct budgetary staffing or reporting priority, as the National Cancer Program now does.

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 to '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 directly to the White House and to the appropriate committees of the Congress.

I was appointed the first director of that program. It came to be known as the National Cancer Program. In that short tenure, through 1976, we committed something like $3.5 billion in the quest for improved prevention, cure and rehabilitation as relates to cancer. I believe this was a relatively small sum, but I also believe it was well used.

At about the same time, beginning in 1970, over 1,000 American and international scientists were convened to plan this attack, a massive undertaking. This followed the so-called Yarborough Commission Report sponsored by then-Senator Ralph Yarborough of Texas, in which a panel of experts judged that there was sufficient available knowledge and technology which, if better and widely applied, would result in more meaningful benefit to people than was being realized at the time.

I believe it was true then, and I believe it is true today.

But in his State of the Union message and in comments made later, the President surmised that if this nation could hit the moon, we ought to be able to cure cancer. And there were comments made to the point of let's do it by our Bicentennial.

His conviction and goal, I think, were laudable, but it burdened the program with overpromise and overexpectancy. We didn't know where the moon was at that time, much less know how many moons there were.

So that I urge you to plan, but not to make that very 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 the Congress. It is an invaluable tool in reporting to OMB, the Office of Management and Budget, and to the Authorization and Appropriation Committees of Congress.

I believe firmly in the issues of relevancy, priority, need, who and how, as regards planning, and in my own mind this has come to mean this kind of thing: In regard to relevance, the project -- that is the grant or the procurement of work to be done -- must have a reasonable chance of helping to attain the overall program goal which you have set for AIDS.

The priority has to do with issues of merit and urgency. Money and talent are finite in any given program. No nation, as you know, can do everything.

Peer review is fallible, but must choose the best bets now. It is a difficult job, and this has to be re-evaluated every two years.

In regard to need, I think a very important point is that if it's 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 in this kind of science, there is any such thing as overduplication. It certainly is not a problem. The more minds brought to bear on a given problem, the better our chances of solving that problem.

And in terms of "who", you have got to get the very best people with the best track record and promise. Twist arms, if you have to, to get people coming into the program.

And finally, in regard to "how", for the most part, review, fund, and monitor investigator-initiated grants -- that is, throw it open to the scientific community and their imagination.

But there is another side to that coin, and I think it is a very important one, and this can be a bit tricky, and that is if you can get a group of peers, if this committee, based on peer advice, can agree on what has to be done, and what can be done now, then I would go out and solicit people to do exactly that.

So it's a two-pronged attack. You throw it open and let people run with their imagination as to what they think ought to be done. But if there are things that can be identified, then I would make them the number one priority. This could be not only basic research, but the development of drugs, the development of viral reagents, et cetera.

Mr. Chairman, this concludes my written statement, and I will be happy to answer any questions.

Thank you.

[Dr. Rauscher's prepared text is included in the Appendix.]

DR. LILLY: I would like to start the questioning to my right down here. Dr. Lee, would you like to?

DR. LEE: Dr. Rauscher, what kind of recommendations do you have for who should set these rules up, who is going to do the planning? Who or what are we going to suggest in the way of a committee, a group from the Institute of Medicine? What are your suggestions in that regard?

DR. RAUSCHER: Well, I think again there are some commonalities here, at least in my experience. Not only the programs I have mentioned, but also within the American Cancer Society. Now the buzz word is "strategic planning," and I find that people who have this capability are different from those of us who are trained in laboratory or at the bench or who work in hospitals. There are people who do this and they do it very well.

For the most part they don't understand or they don't know the science and they, I think, would be the first to admit this. So it is terribly important that you get the very best scientists in the country at the beginning to sit down with the people who know how to plan, who know how to develop rolling two to five-year updatable plans, if you will; who know what reporting requirements are going to be.

There's a report to OMB, there's a report to the scientific community, there are reports constantly to the public. They are all different. And they have to be handled differently. At least this is what I am continuing to find.

In our reporting, for instance, to the public on the need to have better early detection for colon and breast cancer in premenopausal women, as an example, that kind of planning is -- that is, for the science -- is much different than the kind of planning that goes into reports to the public that supports that research in the first place. So you have got to get a plan, and people who know how to plan.

DR. LEE: But who? We know the best scientists, but we don't know who is going to plan this research effort. Dr. Fauci doesn't want to run a one-man show, according to my recent conversations with him. Who is going to do this? Is there going to be a czar? Is there going to be a committee? Is it going to be the American Cancer Society?

DR. RAUSCHER: Well, you need a professional planner, and it would seem to me that you have to have a committee. You know, you are talking about two things, at least: prevention of the disease, as well as cure or treatment of the disease. You may wish to have two sub-panels that plan within those fairly limited umbrellas.

The planning process, for instance, at the Cancer Society. I am a member of the team. There are seven or eight other people that are scientist-physician members of that team, and then we have people who are trained in the planning process. Virtually every comprehensive cancer center in the country has an office of planning. They must do this in order to report well to their sponsors, the National Cancer Institute in this case.

It is a process whereby you meet as often as possible. Planning is nothing much more than a road map, the development of a road map, and as you solve some hurdles, you strike them from the plan, and as you recognize you weren't as smart as you thought you were in the beginning of the process, you change the plan. It's a guideline for scientists doing the work. It is invaluable in terms of committing finite resources. You can't do everything, and even though we may not be smart enough today to know everything that has to be done, choices have to be made. And in my judgment, the only way you can do this is by having a reasonably flexible plan.

DR. LILLY: Since we are running very late, I would hate to interrupt, but I would like to ask that we try to keep our questions brief.

Dr. SerVaas, questions?

DR. SERVAAS: I would like to ask, would you be able to provide to the Commission lists of other groups much smaller than the American Cancer Society, but in the private sector? Are they

a factor? The smaller groups who raise money as you do, and are doing research? Could you tell us if these groups are important in cancer and AIDS research now?

DR. RAUSCHER: There are something like 80 groups, believe it or not, in the country that raise funds for cancer research. There are a number of these that are very prominent. I'd like to think my organization is the best. There are others that are very good, however, but which are very much smaller. The Leukemia Society, for instance, is a very well known and very good organization, much smaller and more targeted. They, too, do planning. Dr. Gallo, as an example, has been a member of their panels, and so have I, from time to time.

So, yes, if you need a list of these kinds of organizations for the record, I can certainly provide that.

MR. CREEDON: Dr. Groopman, I wonder whether there is enough research now underway that in your judgment is specifically with respect to the AIDS problem. Are we currently doing enough? Are there enough people involved? Is there enough money involved? Is there enough activity underway, or are there some areas where we should be doing more?

DR. GROOPMAN: That is a complex question. What I would state is that the two areas of potential need currently are, to follow Dr. Rauscher's comment, to open up with a tremendous degree of flexibility, funding of investigator-initiated projects. I think there are excellent and well structured programs requesting grants and through contract mechanisms or cooperative agreements which obligate the scientists to work along a structured or set path. And those, I think, are in place and there are a number of initiatives from NIH and so on along those lines.

I don't know what the budgetary distribution is for AIDS research in that sphere versus investigator-initiated so called RO-1's.

The second area which I think is important, which you highlighted, is the idea of recruiting new scientists and new minds to work on the problem, and I think in order to do that, and in order to particularly train both young scientists and new generations of physicians to care for patients, as well as individuals, to do laboratory research. There have to be facilities to both handle the virus, which is a clear bio-hazard, and to be able to do both clinical research and laboratory research. The kinds of money for bricks and mortar which have to be obtained in order to do the research on a virus of this nature and see an increasing number of patients to my knowledge doesn't exist: there is no source for these funds at this point.

I think that facilities is one area which is limiting our ability to respond to research initiatives.

MR. CREEDON: How big a need is there? I mean do you have any idea of number of facilities that are needed? What kind of money are we talking about?

DR. GROOPMAN: I think the way that Cancer Centers were developed 20 to 30 years ago throughout the United States with the construction of facilities for basic research, as well as facilities for clinical care, it would be opportune at this time to consider establishing actual physical laboratory set-up as well as clinical liaisons.

I couldn't estimate, I am not knowledgeable enough about money to be able to say how much a cancer center would cost. Dr. Rauscher would probably be more expert in that area. But one could easily envision 10 to 15 institutes or centers like this which would allow for expansion of laboratory facilities and for clinical research.

DR. RAUSCHER: It is very difficult to give you a firm figure. Let me just say there are something like 70 cancer centers in this country, of which about 20 are so-called comprehensive centers. That means they do everything, from all kinds of research through patient care, through community service, public education and the like. It is not uncommon for their annual budgets to exceed something like $100 million, at that level of being comprehensive.

Fortunately, the physical plant attendant to those centers was in pretty good shape at the beginning of the program in 1971. On the other hand, some of the specialized facilities such as you will certainly need, and I agree with my colleague, in order to contain the infectious nature of AIDS, the hazard of HIV, this could well run into several hundred million dollars, if that is the way this nation is going to go, if we need those kinds of facilities.

That is by no means a lot of money or too much money. That's the ball park figure, anyway.

DR. LILLY: Thank you.

Dr. Conway-Welch, do you have a question?

DR. CONWAY-WELCH: A very short one. You mentioned investigator-initiated research projects. I think many of us are aware that the NIH research process certainly has its strong points in terms of quality control but also has its limitations in terms of length of the process and the expertise that you need to get into the process.

Do you have some recommendations you could give to the Commission in terms of particularly one or two areas that are under researched and that could benefit from a shortcut process of investigator-initiated research within the research community?

DR. GROOPMAN: I would say two areas that might be potentially shortcut and are complex would be, first, development of appropriate animal models, and second, some of the more basic studies on the function of the gene products. There are initiatives along those lines but I think they could be expedited. To be able to get particularly young or new investigators into the area, a grant review turn-around time of say three to four months as opposed to 8 to 12 might be beneficial.

DR. CONWAY-WELCH: Thank you. Dr. Rauscher?

DR. RAUSCHER: I think another part of your question has to do with funding mechanisms. It is one thing to be able to identify that which peer review says ought to be done, these are our best bets, and it is another thing to be able to get that money out very quickly.

When I left the National Cancer Institute in 1976, it was beginning to take something like the better part of two fiscal years. You received the application and if it had to do with a procurement contract-wise, there were all kinds of regulations that may have taken about 24 months before you got any money out of it.

That really is serious and has to be looked at. My own organization now, for instance, is able to award up to $75,000 within something like 45 to 60 days. We set up different mechanisms to do this.

As far as I know, not a single program like that exists or probably can exist in the Federal Government, because of procurement regulations. Somehow, you are going to have to cut through that time.

DR. CONWAY-WELCH: Thank you.

DR. LILLY: Dr. Walsh?

DR. WALSH: Two very brief questions. One, based upon the progress that has been made, if you were asked to grade where we are in these research efforts on the basis of an A to an F, what grade would you give it?

DR. GROOPMAN: I think when one gives grades, one usually creates a curve, a class. I think that is important because what we have is a perception and the reality of the

disease as a very terrible and major event in the United States. That is for real and I can speak to it on a personal basis having cared for literally hundreds of people with AIDS in the past six years.

On the other hand, when you put in context how much is known about this virus and how much progress has been made in terms of characterizing its genetic base, how it binds to cells, actually identifying the binding protein, beginning to do in depth studies on its genetic regulation and so on, I think we have a considerable knowledge base which has been accumulated in a relatively short period of time and one contrasts that with what the general state of knowledge is in a number of human diseases and in other viruses.

I would say B+/A-.

DR. WALSH: I think it is important that we recognize that we have done a remarkable job with all the difficulties that you have both pointed out. I think both the Federal and private sector has done a remarkable job.

My second question is was there any coordination or any reason for coordination between the designation of the so-called 19 research centers for AIDS and the existing cancer centers that were in place?

DR. RAUSCHER: Yes, I think to a large extent they are now, unlike what I think was going on in 1970/1971, having very good coordination among cancer centers. There is very good information exchange. There is so much information, it is almost too much. Nobody keeps their data locked up any more. It is characteristic of science to want to wave a flag and tell everybody what you have done. I think that kind of thing is very healthy, not only in this country, but the sharing of information among countries.

It seems to me that is beginning to happen with what you folks are trying to do.

DR. WALSH: I think that is very good. That is encouraging. I agree with you that if it is a B+, we should go for an A+, in anything as dangerous as this disease. I am very encouraged by what you have said.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: Dr. Groopman, could you explain to us more fully the role of macrophages in infection with AIDS as it is understood today?

DR. GROOPMAN: As I said, macrophages are a form of white cells which are quite important in body defense. They are one of the primary cells encountering microbes and they ingest these. They also present the protein of the antigen of an incoming microbe to important immune cells such as lymphocytes. It is clear they have this binding protein, the CD-4 protein, on their surface. That appears to be one way that the virus can enter the macrophage and as I said, it is not fear whether the virus could enter the macrophage through other routes rather than simply binding to that protein.

What is interesting about the virus is that it does not appear to be particularly cytopathic or destructive to the macrophage. It appears to live within it in a latent form without destroying it, which is different in some ways than its existence within the helper lymphocyte.

It also appears that one of the major cells within the brain that is infected is the macrophage. Clearly, the neurologic disease that is associated with HIV infection is very severe and very crippling. How the virus within the macrophage is either transmitted to other cells within the brain or whether products of the macrophage turned on in some way by the AIDS virus interfere with neurologic function is really not known.

I think we are just beginning to understand the biology of the virus within the macrophage, but it is clearly an area of research over the next two to five years, which should prove important. As I said also, there is controversy whether drugs like AZT or other agents are as active in the macrophage as they appear to be within the lymphocyte.

DR. LILLY: Dr. Watkins?

CHAIRMAN WATKINS: Thank you for calling "Dr. Watkins." Everybody calls me "General" and so forth.

[Laughter.]

I'd like to close out this particular group with this one observation and I was very much in synchronization with you, Dr. Rauscher, on strategy building and planning as an adjunct to the technical aspects of dealing with this disease.

In fact, the Commission is really being tasked to look at our charter very carefully to build a national strategy to deal with this infectious disease. That is what it is all about. We are trying to surround it now. We are picking out these four elements as almost partial modules to slip into a national strategy. We know we have to be relevant to what is going on in a nation that is concerned with AIDS, so we are trying to build

these modules incrementally and package them up in such a way that downstream, we can put it altogether in a national strategy.

This country tried to do something similar when we looked at computer microchip development. One of the things we had to do was try to put incentives into the system. To beat out the next generation of supercomputer microchips, we had to get the Congress together to say we are going to eliminate or exclude certain anti-trust rights, for example, and bring research groups together in a much more cooperative and collaborative way. We had to deal with such things as protecting intellectual property rights, to get over the business of vying for grants, awards, and international prizes, and try to pull a group of people together, the best in the business, in a collaborative way, to share in both the burdens and benefits of finding new answers to the questions.

It seems to me that if we are going to go into building facilities, we better be thinking in terms of the planning, and the strategy elements, and the information exchange, and the collaborative effort as the first order of business.

I am wondering if you have any ideas, either one of you, as to what we might recommend in a much more specific way, either changes in regulations that might be impeding or setting up obstacles to progress along these lines, or changes in the law, or just an announcement of a leadership role to pool these various entities together that now seem to be somewhat fragmented and disconnected.

We need your thoughts on information exchange, sharing views, where are you right now, and are there elements that can be centralized, not necessarily all research information, but enough of it to facilitate the kind of research that might be appropriate in the early stages of an infectious epidemic like this, that might be a template for the future. We need to set up a model for the nation for when the Secretary of Health and Human Services declares a national health emergency, so that we can push certain buttons and things would begin to move in a much more coordinated and integrated way.

Can either of you give us any ideas? We don't have a great deal of time left on this panel because of technical delays this morning. If you have already given thought to this in specific terms as to how we might set up a set of principles surrounding such a collaborative effort across the spectrum of issues I just raised, it would be very helpful to the Commission to know what that would be. We would appreciate hearing both from your point of view, Dr. Groopman, at the Deaconess Hospital in Boston, and your point of view, Dr. Rauscher, as Vice-President of the American Cancer Society.

DR. GROOPMAN: That is obviously not a short answer. Two things that immediately come to mind are to have longer term forms of support than are generally given. I think one has to take a long term perspective in terms of commitment of resources to research and following up on Dr. Walsh's question about whether we get an A, B or C and so on. A lot has been done rapidly but I think the reason people perceive or believe a lot has not been done or enough wasn't done is because of the severity of the disease. It is probably going to take a number of years, many years, perhaps a decade or more, to really arrive at therapies that lead to cure or vaccines and so on.

I would think initially one could consider developing funding mechanisms which are more long term than the standard three year forms of grants which are general Federal grants, occasionally five year grants. One finds scientists often spending 20 or 30 percent of their effort writing grants and applying for money and spending a good deal of time which could be spent in research along the lines of searching for grant renewals and refunding.

The other is possibly setting up collaborative working groups that work on a specific topic related to a grant initiative. There are a number of initiatives, and I think many of them are excellent in scope, that come out of the National Institutes of Health. One should study the function of the genes. One should study the interaction of the AIDS virus with the macrophage and so on. Once those initiatives are given out, it is not clear to me that the results of the work or the investigators are tied together in a collaborative way.

There are advantages obviously to competition. Competition is a stimulus and is important in productivity. At the same time, there should be a balance in terms of collaboration, and there may be mechanisms that could be set up whereby one is obligated upon receipt of the award to regularly interact, communicate on a six month basis or a yearly basis with the other individuals who had been recipients of that award either, in Bethesda or some other area that would be conducive to it.

Those are two things I think could allow for more effort to be put into research as well as more collaboration.

DR. RAUSCHER: Just to be very brief, I would agree with my colleague in everything he says about research. I think you will find there is so much competence in the country and enthusiasm that, naturally, people will begin to integrate and talk to one another perhaps more than they have.

I would repeat one other thing I said before and that is in some way, the funding agencies have got to let up on some of the restrictions that now apply to the granting or the

contracting process. When you are talking about a minimum of ten months before you can get money out to fund that bright, new and important idea, all the way to the two and a half years for competitive contract procurement, that is a major impediment to doing what you want to do.

One example of this has been mentioned already and that is you want to award grants for a period longer than three years.

One other example is the NIH has what is known as one year spending authority. That is, there is an appropriation every year and if they don't spend the money within that year, it goes back to the Treasury. What you always want to have is a program manager or leader with far more flexibility than that. The Department of Defense has "no year" authority. In other words, they get a $1 in this year and if they don't spend that dollar, ten years from now they still have the dollar. Atomic Energy used to have two year spending authority and NIH has one.

I think that is one thing to look into, reduce some of those restrictions on how money is spent. You can still maintain adequate peer review.

DR. LILLY: Thank you, and thank you both for an interesting presentation and discussion.

Dr. Anthony Fauci is our next speaker this morning. Dr. Fauci is the Director of the Institute of Allergy and Infectious Diseases; has been and continues to direct a research laboratory in his own right, even while bearing this very large administrative responsibility. He is going to talk to us today about the federal role in the support of biomedical research.

FEDERAL ROLE IN BASIC BIOMEDICAL RESEARCH

DR. FAUCI: Admiral Watkins, Dr. Lilly, Commissioners and guests, it is my distinct pleasure to be here with you this morning.

What I would like to do is address three general areas of the federal or specifically the NIH role in AIDS, and that is first the funding and funding mechanisms; second, the research itself; and then finally, the methods of coordination of the enormous biomedical research effort that is undertaken at the NIH and in the public health service in general.

If I could have the first slide, please.

[Slides.]

This is a breakdown of the budget vis-a-vis the United States Public Health Service. And I think it is important for me to just show this, because I know there is a good deal of confusion sometimes regarding the relationship between the different agencies of the Public Health Service.

As you can see, the budget for the 1988 fiscal year, which we are in, is just short of $1 billion, with the National Institutes of Health, whose efforts I will address specifically this morning, being $448 million. But if you add an extra $20 million to that for an infrastructure add-on, the NIH's appropriation is about $465 million for AIDS in 1988.

Again, another area of misperception and confusion is the difference between the different Institutes and how they fall under the general auspices of the NIH. When we speak of the NIH, we speak of all of the different Institutes -- the Cancer Institute, the Allergy and Infectious Disease Institute, Heart Institute, et cetera, et cetera. They all fall under the National Institutes of Health.

Because of the original mission of different Institutes, certain institutes, such as the Institute that I direct, the National Institute of Allergy and Infectious Diseases, play a more prominent role in AIDS research for the NIH because of the fact that AIDS is an infectious disease of the immune system, and, thus, one of the major areas of interest of our Institute.

The same holds true for the Cancer Institute, because of their original interest in viral-induced tumors, retroviruses and Kaposi's sarcoma.

Nonetheless, they all fall under the general auspices of the National Institutes of Health.

The budget itself, as you can see here, looking from the beginning in 1982, in which it was $3 million, has grown in a somewhat exponential manner, such that now the 1988 estimate is just short of a half of a billion dollars. As I mentioned, with the add-on, the budget is about $468 million for 1988.

When one breaks down the budget, in order to understand the general directions and the different weights that are given to these directions, we often use what we call a functional category of the budget. This merely designates the kinds of research activities for which the different amounts of money have been appropriated.

For example, if one looks at the 1988 budget, and one thinks in terms of pathogenesis and clinical manifestations,

including immunological studies, virology, you have here $139 million, up from $99 million in 1987.

Therapeutics, as you can see, has a major chunk of the action with regard to the budget being $162 million in '88, up from $122 million in 1987.

The same holds true for the accelerated effort in vaccine development, from $26 million in 1987 up to $53.4 million in 1988.

Then there are other areas in which the NIH has some activities, but they do not receive predominant emphasis. For example, things like Public Health control measures, information and education, which generally falls under the domain of the Centers for Disease Control. If you would look at their budget breakdown, you would see the predominant amount of money falling under this category.

In any event, for the NIH, this amount is $17.5 million, up from $12 million. Because NIH is predominantly a research agency, the patient care and health care needs are primarily addressed by other Public Health Service agencies, giving you here the total, as I mentioned, approximately of half a billion dollars for 1988.

It is important to understand that although we started off with basically two Institutes back in 1982 involved in AIDS research -- NIAID and the NCI -- for the reasons that I alluded to just a moment ago -- over the past couple of years, virtually every Institute has now gotten involved in some aspect of AIDS research.

The breakdown in the 1988 budget, as you can see, is that 50 percent of all of the NIH's AIDS appropriation is in the Allergy and Infectious Disease Institute, reflecting the fact that this is an infectious disease of the immune disease. Twenty percent of the funding goes to the Cancer Institute, and variable amounts, obviously much less, go to the other Institutes. When one thinks in terms of the relative commitment to AIDS, this is a slide which has some interesting data on it, that I would like to spend a moment on.

If you concentrate, for example, here in the National Institute of Allergy and Infectious Diseases, which is responsible for all of immunology, all infectious diseases, all the vaccine programs, organ transplantation, asthma, hypersensitivity, tropical medicine and sexually-transmitted diseases in addition to AIDS, 35 percent, or greater than one-third of the entire budget of that Institute is devoted to AIDS research, despite the fact that there are other areas that are of importance. Nonetheless, we feel that the importance of the

problem of AIDS at the present time warrants that at least one third of the entire budget of the Institute be designated for AIDS research.

Now you heard some of the previous speakers, Dr. Rauscher and Dr. Groopman, discuss the importance of basic biomedical research. I can only underscore this even more emphatically as I move on to the second area of the discussion, namely basic and clinical research at the NIH.

If one looks at the yields vis-a-vis AIDS, they almost all can be traced back directly or indirectly to basic biomedical research, much of which was undifferentiated. And as mentioned, I can only underscore that if you look at the specific designated areas from cancer research to vaccine development to transplantation to recombinant DNA technology, autoimmune diseases, et cetera, they all have their initial basis in the fundamental research, predominantly investigator-initiated research, supported by the NIH and other research-supported agencies.

This will hold true also in AIDS. It is very important to keep sight of the fact that although we need to direct research, we must never, ever let go of the basic fundamental research effort. Basic research will have yields not only specifically for AIDS, but also for other diseases as spin-offs of the work that is going on in AIDS research.

We can conveniently break down the NIH's AIDS effort into research into five empiric categories. I will very briefly touch on each of these, some of which have already been discussed: epidemiology and natural history; etiology; pathogenesis; anti-retroviral and immunological reconstitution; and vaccine development and evaluation.

First with regard to epidemiology and natural history, this is predominantly the mandate of the Centers for Disease Control, as I mentioned. Sometimes there is misperception of why the NIH is also involved in epidemiology and natural history, and concern that this may constitute unnecessary overlap.

As a matter of fact, as you have heard from Dr. Rauscher, overlap does not necessarily have to be nonproductive, but can be complementary and reinforcing.

For example, epidemiological studies and natural history studies are the source from which a variety of studies on pathogenesis and etiology spring. This is a very familiar slide to you, representing the breakdown of the cases of AIDS. As of February 1st, 1988, there have been over 51,000 cases in adults and adolescents.

The tracking of the natural history along the different groups, be they male homosexuals, IV drug abusers, heterosexual contact, transfusion recipients, or what-have-you, has served as prospective elements in studies to do the type of pathogenesis and etiological studies that have been done.

Here again is another slide I am sure that you have seen before, depicting the iceberg of HIV infection. The 51,000 reported cases represent the tip of the iceberg; then, about 150,000 or more individuals who have symptoms -- so-called "Aids-Related Complex" -- but who don't have the criteria fulfilled for full-blown AIDS; and finally, the greater than one million, probably a million to a million and a half, who are infected with the virus, but are completely asymptomatic.

Determining the mechanisms that lead to conversion of an individual who currently is asymptomatic to an individual who will either be symptomatic without disease or develop full-blown AIDS is the basis for the extraordinary effort on pathogenesis currently being undertaken at the NIH and at NIH-supported institutions.

Let me just show you this next slide, which essentially frames the question that investigators are asking. If one looks at the percent of individuals who developed AIDS and the years after infection, the closed circles are the actual data that we are sure of; namely approximately 30 percent of individuals within five years will develop full-blown AIDS.

The question remains: at 10, 20, 30 and 40 years, et cetera, will this be a linear function, so that 80 percent or more will have the disease if there is no effective therapeutic intervention? Or will the curve plateau? And what are the mechanisms that has a person go from an asymptomatic case to a case of immunological suppression and full-blown disease?

When I get into pathogenesis, I will very briefly describe why this is such a very important area of AIDS research. It is only through understanding of the epidemiology and natural history that one can do these types of studies.

The next area concerns the etiological agent. You have heard about that in some detail from Dr. Groopman, so I won't spend much time, except to say that the etiological agent of AIDS, the human immunodeficiency virus, has now been very well established. The evidence of HIV as the etiological agent is overwhelming in the eyes of virtually all scientists involved in the study of this disease.

This is a scanning electronmicrograph showing the virus budding off a target cell. As Dr. Groopman alluded to, it is important to understand the life cycle of the retrovirus. The

reason why this is important is that each of the steps in the life cycle serves as a potential target for what we call targeted anti-retroviral therapy, which I will mention in a moment. You will hear more about this later on from Dr. Daniel Hoth from our Institute.

The virus initially attaches itself to the cell and gains entry. A specific enzyme enables it to reverse transcribe to DNA and become integrated as a provirus. Later, it can be transcribed back to RNA, with the production of a mature virus. Understanding this process is critical to understanding how the virus destroys the body's immune system, and how you can interrupt that process.

Getting back to the theme alluded to earlier, the study of the life cycle of retroviruses long antedated AIDS itself. It was the work of basic scientists involved in retrovirology long before we ever heard of AIDS, that brought us to the point of being able to make the kinds of observations and advances that have been made in AIDS research. This is another very strong and compelling argument for the support of basic biomedical research; not only for AIDS now, but for what we will face with other diseases in the future.

The same holds true for an understanding of the functions of the various genes of the AIDS virus. This is a complicated slide. I will not go through it with you except to point out that the various genes, the structural genes as well as the regulatory genes of HIV, have been delineated with regard to their functional capabilities.

Again, this is critical in designing treatment and vaccine strategies. When you understand the genetic makeup of the virus, you can then begin to plan how you can interfere with certain critical functions of the virus itself.

Insight into pathogenesis stems directly from an understanding of the etiological agent. By pathogenesis, we simply mean how this virus exerts its destructive effect on the immune system. It is extraordinary, the amount of knowledge that has been gained over the past few years on this particular virus. We certainly have a long way to go to understanding each and every bit of the pathogenic mechanisms, but scientists have been able to determine that a very small stretch of the building block of the outer coating of this virus selectively binds to the major target cell on the immune cell, what we call the T4 lymphocyte.

In fact, it is the very molecule that makes this T4 lymphocyte a T4 lymphocyte, mainly the CD-4 molecule that serves as the specific and highly avid binding site for the virus itself.

Again, understanding this will help scientists be able to design targeted antiviral therapy.

Another important component of understanding pathogenesis is the realization that the virus can live both in a latent form, as Dr. Groopman alluded to, as well as in a form in which there is active replication, cell death, and immunosuppression. It is the constant and relentless conversion of this latent form into an active form that leads to the ultimate progressive immunosuppression that leaves the body defenseless against opportunistic infections such as pneumocystis carinii pneumonia, and the development of certain neoplasms such as Kaposi's sarcoma.

Moving on to antiretroviral therapy and immunological reconstitution, the details of the drug development and the drug evaluation programs at the NIH will be given to you by Dr. Hoth at a later session of this hearing.

What I would like to do right now is just very briefly again return to this model of the life cycle and show you what we mean when we speak about targeted antiviral therapy. Wherever you see an arrow is a potential spot in which you can direct an antiviral approach. You can block the virus' binding. You can interfere with reverse transcriptase which, in fact, is the mechanism whereby AZT or azidothymidine blocks replication of the virus. Nucleocyte analogs interfere with transcription here, and alpha interferon, which I will mention in a moment, is important in blocking the assembly of viruses before they leave the cell and bud off the cell.

Now I show you this slide, which really is a simple slide although it may appear confusing, because it illustrates an important point. A question that I get asked perhaps more often than any other, is are we ever going to have a cure for AIDS. If you define cure as eliminating each and every virus from the body, that is probably not an attainable goal in the reasonable future.

If by cure you mean to suppress the virus enough such that the body's immune system can recover and an individual can lead a healthy life, then that is attainable.

Now let me tell you why I make this distinction. As you see here on the left-hand side of the slide, when the virus is actively replicating in what we call a productive infection, there are multiple vulnerable spots which I alluded to just a short while ago. Drugs and immunological responses can attack those areas.

When the virus is existing in a latent form, it leaves us no vulnerable target. So drugs and immunological surveillance

would most likely -- I'm not saying it's impossible -- but would most likely not eliminate each and every one of these infected cells.

So the realistic goal would be to develop a drug that is safe and can be administered chronically to suppress the replication phase of the virus. Hopefully, then, the body's immune system can then ultimately control whatever latent infections remain.

When one speaks of drug development, again you should understand there are two major components. One is the screening of already existing compounds. That's how scientists found AZT, through the screening of compounds produced for other reasons. AZT was originally meant to be an anticancer drug. It was screened because of its projected anti-reverse transcriptase activity.

What we are concentrating on very much now is targeted development. That is something that does not occur overnight. That is understanding the structural components of the virus and the function of the virus, so that you can actually direct your antiviral therapeutic approach to a particular point in the virus' function.

At the same time that we are continuing to screen, what we are doing is having a major effort in targeted development, which you will hear about in more detail.

With regard to the current status of drug testing, I will only very briefly mention there are now 35 sites in the program that are participating. There are 25 active protocols. Four have already accessed the number of patients needed for the protocol. Twenty-one are still entering patients. There are 18 agents under study, nine antiretroviral, four biological response modifiers, five for opportunistic infection, and as of yesterday, there were 3056 patients that were in the studies.

This slide lists some of the drugs. Now we do not have the time to go through each and every one of them. Some of them are anti-HIV therapies. You have heard of AZT, di-deoxycytidine, acyclovir, AL-721, Foscarnet, desiclovir, alpha-interferon, et cetera.

Of interest is the fact that this group consists of more than just anti-HIV therapies. There are also biological response modifiers. We will soon be testing Ampligen and Ribavirin, because the protocols are going through final development and approval.

Other therapies include those for opportunistic infections ranging from aerosol pentamidine to DHPG, and therapy for AIDS-associated malignancy.

One of the things that is interesting about the AIDS epidemic, because of its charged nature, is that what gets into the press or what gets around anecdotally is considered very often to be the most effective therapy.

I will show you an interesting example of a therapy that has not gotten a lot of press, but has been evaluated in a careful study. This therapy, called alpha-interferon, is for individuals with Kaposi's sarcoma. A study that was just completed at the NIH is in the process of being put together for reporting, in which alpha-interferon was given to individuals with Kaposi's sarcoma, leading to a considerable number of complete and partial remissions, and also leading to suppression of the virus itself.

Now this slide provides an example of the kinds of responses one can see with alpha-interferon. There is an individual on the left-hand side with serious Kaposi's sarcoma lesions of the face, ear and the nose and the eyelid. Thirty-five weeks after alpha-interferon therapy, he demonstrates essentially complete clearing of the Kaposi's sarcoma lesions.

Perhaps more important than the clearing of those lesions was the fact that the virus was effectively suppressed. This finding now serves as the scientific basis for using alpha-interferon in asymptomatic carriers of the virus in a control study to determine if in fact you can suppress the virus and prevent the onset of severe symptoms such as full-blown AIDS.

Moving on briefly to vaccine development and evaluation, there are a number of potential vaccines being developed for AIDS, deriving either from the whole killed virus through purified natural products or synthetic products. As you may have read in the newspapers, a recombinant DNA vaccine product is presently being tested at the NIH, and will be tested shortly at our vaccine evaluation units. Another recombinant product is being tested in Seattle, Washington.

The vaccine candidate that is being tested in the Phase I studies in Bethesda, Maryland is what we call a recombinant product, in which DNA technology is used to splice out the gene for the outer coating of the virus, the envelope. You can do that by using cleaving enzymes. You can then take that gene and insert it into another virus, an virus called a baculo virus, which infects insects. Then you can produce unlimited quantities of purified envelope protein. And as I mentioned, this vaccine trial is in effect right now, and other vaccine trials are in preparation.

I must caution you that this is just a Phase I trial. Even if we are fortunate -- and there is no guarantee that we will be -- to develop a safe and effective vaccine, it almost certainly will not be until well into the 1990s before it is available for widespread use.

If and when that occurs, what we will have is testing of the vaccine in the vaccine evaluation units, which are already in place waiting for vaccine candidates.

Finally, I would like to close by just mentioning briefly certain mechanisms of coordination in AIDS research, from interagency coordination to advisory groups, intramural, international, and industrial and academic coordination.

First with regard to interagency coordination, the United States Public Health Service has an AIDS Executive Task Force on AIDS with representatives and representation from all of the Public Health Service agencies, depending upon the particular mandate of that agency.

For example, vaccine research and development falls under the auspices of the NIH, as does therapeutic intervention. Information, education and risk reduction, the CDC, blood and blood products, the FDA. We meet very regularly at the Public Health Service Office of the Assistant Secretary in Washington, and we coordinate the efforts of the various agencies.

At the NIH itself, we have an NIH Aids Executive Committee, whose predominant function is policy development, coordination and information exchange, the avoidance of unnecessary overlap, filling of gaps, resource allocation, and our liaison with the Public Health Service Committee.

The question was asked of one of the previous witnesses regarding the concept of planning and advising. This AIDS Executive Committee -- which includes all of the different NIH institutes that meet regularly to do what was shown on the previous slide -- is co-chaired by Dr. Wyngaarden, the Director of NIH, and myself. We also will have input from a newly-formed NIH AIDS Program Advisory Committee, the initial meeting of which will be February 26, 1988.

Already, we have had the advice and counsel of the individual advisory committees of the various institutes.

The advisory groups that we use are many. Let me give you one example of a very important function that was served by an advisory group in the summer of 1986. We called together some of the leaders in the area of virology, epidemiology, immunology to come together in Bethesda to examine the programs and to make

some recommendations regarding future directions in AIDS research.

This is just one of the examples of how we use outside consultants, and I think it should be underscored. Sometimes there is the misperception that the NIH or any other Public Health Service agency is working and making major decisions in a vacuum. In fact, there is extensive and very important interaction with outside consultants from academia, industry, et cetera.

This particular advisory group produced a document which I show here on this slide, "Future Directions for AIDS Research." If one peruses it, it can be seen that many of the planning suggestions made in 1985 and '86 have come to fruition in 1987 and now early 1988.

We have a significant intramural scientific coordination. There is a significant intramural AIDS effort on campus at the NIH and in the NIAID Rocky Mountain laboratories. This is an outline of a number of the committees which are involved in intramural research cooperation, from the executive committee to the vaccine and antiviral development programs, the decision network about what drugs to test, the clinical drug development committee, and the Bimonthly Aids Science Report.

International cooperation and coordination is extremely important because, as you know, AIDS is a global problem. We are in continual contact with our international colleagues by interaction with the World Health Organization, the Pan American Health Organization, the Carribean Epidemiology Center. These two have given us an extraordinary amount of information about the natural history of HIV infection in the Carribean and in South America.

Interestingly enough, in many respects the natural history of HIV infection mimics the kind of thing one sees in Central Africa with heterosexual transmissibility in certain Carribean countries, such as Haiti, becoming very important.

There are international cooperative and collaborative research projects. The Fogarty International Center at the NIH coordinates many of these international activities.

Finally, coordination programs have been established in which we encourage and foster collabaoration between industry, government, and academia. You will hear about these consortia in more detail from Dr. Hoth, but some examples include the National Cooperative Drug Discovery Groups I mentioned earlier, to design targeted antiviral therapy; the AIDS Treatment Evaluation Units and clinical study groups which are now forming one group of a

network of clinical trial groups; and the individual collaborative agreements with industry.

So in summary, then, the areas of collaboration are several and as we and others would admit, there is always room for even better collaboration and coordination, and that in effect is what we are striving for.

So in summary, then, we have discussed the budgetary component of the NIH and government research effort. I have given you a very brief outline of some of the research endeavors and finally have closed with an outline of the coordinating elements that are now undertaken.

Obviously, as mentioned by others, a lot has been done, but I certainly am the first to admit that there certainly is a lot more that needs to be done.

So I will close with that and be happy to answer any questions.

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

DR. LILLY: Thank you, Dr. Fauci, for a very clear presentation. I would like to take the opportunity to start with a very simple question.

You talked a great deal about how the research is being planned and coordinated. Has the increasing support that has been earmarked for AIDS research impinged upon basic research? You emphasized the importance of basic research. Is basic research in any danger from earmarked AIDS research?

DR. FAUCI: If you look upon the total research effort of the NIH as a pie, then there are slices of that pie. If you have research that is designated for one area and you don't make the pie bigger, then what is going to happen is you are going to infringe upon basic research in other areas.

Over the past few years, the AIDS money that has been designated for AIDS has been new money. I'm pleased with that. Early on, there was reprogramming.

My concern is that we need to do even more on basic research. Rather than say we are taking away from basic research, I think AIDS is a classic example of why basic research should be supported. If we didn't have basic research, I do not think we would have any idea of what was going on with AIDS right now. Although we are in a lot of trouble because we are in the

midst of an extraordinary and terrible epidemic, we would be much worse off if we did not have basic research.

DR. LILLY: Thank you. I acknowledge the arrival of Ms. Pullen and ask if she has any questions.

MS. PULLEN: Good morning, Dr. Fauci. Could you please indicate how a research study can be designed to test the effectiveness of vaccines in human beings after all the other tests have been completed?

DR. FAUCI: How a vaccine study can be designed?

MS. PULLEN: Yes.

DR. FAUCI: The vaccine studies go in three phases. The first phase, you take a product such as this glycoprotein 160 or 120, which shows an indication of being immunogenic in an animal and safe in an animal. You do a Phase I study. Phase I asks merely the question, "Is it safe to give and will it elicit immune response?"

If in fact you show in a limited number of individuals that it is safe and immunogenic, then you move onto what is called Phase II. These studies ask, "What the proper dose to get the maximum immune response." If the Phase II study shows that you have a dose that is safe and will give you a maximum immune response, only then do you go into what is called a Phase III or efficacy study. A Phase III efficacy study is going to be a significant problem in the United States. The reason for that is although the epidemic of disease is still not peaked, the epidemic of infection among individuals that you would classically consider practicing high risk behavior is in fact going way down.

You have an interesting situation where the only way you can prove the efficacy of a vaccine is if people keep getting infected. Meanwhile, you have an obvious ethical obligation to instruct people how to avoid infection.

If you have a very, very low infection rate, for example, in San Francisco -- where the rate was 12 to 15 percent per year, but is now down to less than one percent per year in infection -- it would require eight years or longer to do an efficacy trial there and would require thousands and thousands of individuals. This is the reason why we seriously consider now in our collaborations with the World Health Organization, that if we get to a Phase III trial -- if we ever get there -- to do it in areas such as Central Africa, where the infection rate is still very high. Otherwise, you would never be able to prove it was effective.

DR. LILLY: Dr. Primm?

DR. PRIMM: Dr. Fauci, recent reports have indicated varying degrees of susceptibility to the HIV and that there are certain factors that influence that susceptibility. For example, I recently read that birth control pills may make women more susceptible because of the endometrium being less resistant to the virus itself.

The cells in the intestines, I recently read, are now target cells for the virus, which previously was not known.

Can you comment on some of these co-factors?

Uncircumcised males, many black and Hispanic males are uncircumcised, that possibly there is something with balanitis or the lack of circumcision that may cause a person to be more susceptible to the virus.

DR. FAUCI: Certainly, there are co-factors that would give you a greater susceptibility if exposed, Dr. Primm. Probably the one that is best documented is a disruption of the genital epithelium, namely if you have genital ulcerations usually associated with other sexually transmitted disease, be it a cervical ulceration, a vaginal ulceration or a penile ulceration. That gets into the circumcised versus non-circumcised because of the fact there is a greater incidence of excoriation of the glans penis in someone who is uncircumcised.

The idea about the birth control pills is not really yet fully delineated. If you look at individuals in the study that was reported who were on birth control pills, there was a grayer "susceptibility" to infection but it is not sure if that is due to the birth control pill itself or the fact that if you do birth control pills, you don't necessarily have a condom or other barrier contraceptive.

It may not necessarily be physiologically due to the birth control pill itself but the fact that if you have birth control pills, you would be much less likely to use other forms of birth control.

Your initial question is quite correct. The thing that is clear through a number of epidemiological studies is that genital ulcerations or other sexually transmitted diseases that would disrupt endothelium or epithelium clearly give you a greater susceptibility to infection.

DR. PRIMM: I also mentioned the intestinal.

DR. FAUCI: You are talking about a colonic epithelium. As Dr. Groopman mentioned, a study was done originally by Malcolm

Martin at the NIH in which he showed that the intestinal epithelium had messenger RNA for CD-4 and in fact potentially could be infected. Certain colonic cell lines were infected. There was a recent paper in Lancet from San Francisco that showed that cells that might be expressing virus were epithelia cells. I think that needs to be verified by a number of other studies.

If it is true, it would mean that in fact one of the portals of entry, namely the rectal mucosa via anal intercourse, might explain how one can get infected because the very epithelia cells themselves could bind the virus.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: Assuming there were no other obstacles to vaccine research in AIDS, as you mentioned before, which there obviously are, in the best possible case, how many years would it take before one could conclude that a vaccine was effective, going through stages one, two and three?

DR. FAUCI: It is very hard to give a hard number but if one tries to project how long and how many people you would need to prove safety and efficacy, I would say I would be very surprised if that occurred before 1995. I think 1995 at best, if we are lucky. I always have to keep saying "if," because otherwise I get quoted saying that in 1995, we will have a vaccine. I do not know if we are going to have one, but if we do, it probably will not be before 1995.

DR. CRENSHAW: Seven or eight years minimum. Secondly, most vaccines work by precipitating in abundance the mobilizing antibodies prior to the actual infection occurring. With the AIDS virus, the mortality rate is as high as it is because we don't make effective antibodies. How is that being approached?

DR. FAUCI: We don't know right now what constitutes effective immunity. It very well may be that if protective antibodies were present prior to the exposure to the virus, that might block the initial taking off of the virus. Clearly, the presence of antibodies in someone who is infected is not protective, because people relentlessly go on to develop disease despite antibodies. That could be due to a number of things.

It could be due to the possibility that cell mediated immunity is even more important than neutralizing anybody, since the virus can be spread not only by cell free virus, but by cell to cell contact. You would need an effective cell mediated immune response, which is one of the reasons why investigators are concentrating very heavily now on looking not only at antibody responses but also at cell mediated responses. It does not appear that antibody alone is going to be effective.

DR. LILLY: Dr. Walsh?

DR. WALSH: Dr. Fauci, I am happy but concerned by your statement of the incidence of new disease, your utilization of say the San Francisco area as an example, when we have heard so much about the increased incidents in the IV drug population and the minority populations.

In concert with that, I am also wondering whether there is more consideration being given to recognize that the definition of what we call AIDS is not ready for another revision. Why do we persist in saying that ARC diseases are not AIDS? In other words, why aren't we talking about an "HIV-related disease?" Wouldn't that give us a more accurate picture of just what we are facing in the next ten years?

DR. FAUCI: The answer to that is yes. The definition of AIDS was revised just recently. It added about 3,500 cases to the original tally of the CDC by including two groups. One was neurological complications without immunosuppression and the other was constitutional disease of the type in which you had a ten percent of your body loss, body weight loss and 30 days of persistent or intermittent diarrhea and/or fevers.

This now includes some of the formerly ARC cases, that latter category. But I think there are enough people who are suffering significant consequences of HIV infection without falling into even the revised category, that it would be appropriate to re-examine that to see if we can get a broader inclusion of serious involvement with HIV infection. This has very important consequences for the patients.

DR. WALSH: It creates a problem for us in the recommendations that we are going to be called upon to make.

Dr. Rauscher and Dr. Groopman raised the question of two problems with Federal grant making. One, that you are limited to one year business and secondly, the long time that it takes from application to receiving a grant.

It seems to me that I have heard that you have taken steps to correct that; is that true?

DR. FAUCI: Yes. We have instituted a policy now of examining the feasibility of cutting the time from receipt of the grant to the actual awarding of the grant down to a maximum of six months, which I think would be a very important advance.

One of the problems with that is that is going to require significantly greater numbers of individuals to review the grants. I think if a recommendation for expedited grant review and processing is made, it should not go in a vacuum,

completely disassociated from the fact that you need bodies to implement it. You cannot just "do things quicker."

The other thing is, I agree completely with the concept of two-year, or even better, "no year" money. That would be very important in planning, particularly for example in areas of drug development and evaluation. You may have a few drugs in Phase I trial that you are not sure will show enough promise to go on to Phase II or Phase III. Nevertheless, in your planning process, you must specify that you need this amount of money. If you know you have to spend that amount of money in one year, you obviously need to be balancing your projections.

On the other hand, if you know that ultimately you are going to have four drugs that are going to be in Phase III trial, you say, "This is the amount of money we need," and you do not have to worry that if you do not spend it now, before the end of the fiscal year, you will lose it.

I agree with the idea of two-year or "no year" money.

DR. WALSH: I would think it would be valuable for other things besides AIDS. I think that has been handicapped, too.

DR. FAUCI: No question about it.

DR. WALSH: Thank you.

DR. LILLY: Dr. Conway-Welch?

DR. CONWAY-WELCH: Dr. Fauci, you mentioned that the level of heterosexual transmission in some of the African countries and some of the Caribbean countries was much higher than it supposedly is in this country. Could you help us phrase a recommendation that might cause research attention to be brought to this issue, particularly in terms of the impact this obviously has on women?

DR. FAUCI: I think that an area that requires immediate attention is the IV drug abusing population and particularly the minorities, blacks and Hispanics. Those are the individuals who are going to suffer most from the "heterosexual transmissibility," and are also the pool from which you are going to get women infected and ultimately children infected. Not all, but a significant amount of the heterosexual transmissibility in this country is centered around cases of IV drug abusers and their heterosexual partners. They are women also and obviously they have children. That is how you get your pediatric cases.

My recommendation to you as a Commission would be to put a very strong emphasis on whatever it takes to get to that IV

drug abusing population; drug treatment programs, educational campaigns, a real intensive approach towards that group.

DR. CONWAY-WELCH: The transmission in Africa, in some parts of Africa and in some parts of the Caribbean, it is not clear that the heterosexual transmission is related to IV drug abusers.

DR. FAUCI: It certainly is not. I can tell you what it is related to, and it is a question of a snowballing effect. We have a group that is now studying, in collaboration with CDC, the epidemiology of AIDS in in Kinshassa, Zaire. The amount of information we have gotten about heterosexual transmissibility by that group is extraordinary. I can tell you in 20 seconds what it is.

If you look at the general population -- forgetting IV drug abusers, anyone with high risk/low risk habits -- about 10 percent or more of the general population is infected with the virus. This means that the chance of coming into contact with anyone of any given sexual encounter who is infected is extraordinary. You add that to the fact that you have a high incidence of sexually transmitted diseases. It is sociologically quite acceptable for a married man or what have you to have any of a number of sexual partners; that is accepted by society. Under those circumstances, when you have a sexually transmitted disease, you have propagation of infection.

Lastly, you have a number of co-factors and those are the co-factors that Dr. Primm just asked about, namely other sexually transmitted diseases.

What happened is the horse is out of the barn there already because there is such a prevalence of infection.

At the point in our society where there still is a low broad incidence and prevalence, then I think that is the time you need to stop it in its tracks heterosexually.

DR. CONWAY-WELCH: The key is the incidence and prevalence in our society getting a handle on that?

DR. FAUCI: Yes.

DR. LILLY: Mr. Creedon?

MR. CREEDON: I hope I am not anticipating our Chairman, but I would like to personally thank Dr. Fauci for again coming before us and being so articulate and patient and illuminating.

I have two rather brief questions. In your slides, you indicate there was a report in 1986 which apparently was based on recommendations of a number of scientists from around the country. Is that an ongoing activity? Is it time for a new such effort?

DR. FAUCI: That activity will be taken up by the group that I alluded to, the NIH Advisory Program Committee, which will be meeting with the Director and the Institute Directors periodically to make these kinds of recommendations. It is going to be an ongoing activity, not a one shot deal.

MR. CREEDON: Good. The other point Dr. Groopman made and I had a visit a couple months ago from Dr. Baltimore and he made the same point, and that is the need for facilities, bricks and mortar, for research on the virus itself because of its contagious nature.

What Dr. Baltimore said when he visited was that there is money perhaps available from the Federal Government but it takes forever to get it and that the need for the research is now.

I wonder if you will comment on whether there is money available and how many facilities are out there and how many more do we need and what is the process, et cetera?

DR. FAUCI: Dr. Baltimore makes a very important point. I have discussed this in some detail with him on several occasions.

We call that infrastructure in facilities, namely, how do you get investigators who are qualified investigators and outside institutions to get involved in AIDS research when they do not have a laboratory that can handle the virus, when they do not have the kinds of facilities they need, when they either have to renovate or have to construct.

This is an important problem. It was addressed this year in the 1988 budget with approximately $20 million that went into infrastructure through the Division of Research Resources at NIH. I think that is a start. I certainly think we need to continue to seriously address the very important need for infrastructure, both within the NIH and in the universities. That is a very good point. I would again submit to you that you should consider that strongly in your recommendations.

MR. CREEDON: Thank you.

DR. LILLY: Dr. SerVaas?

DR. SERVAAS: Dr. Fauci, on the slide it indicated that the virus in active disease -- you had the word "transmissible," and then that wasn't indicated on the latent virus. And my question is, how much less infectious to others are the carriers, the HIV antibody positive individuals, than the people who have active disease? And does your alpha-interferon make the HIV antibody positive individuals less infectious to others.

DR. FAUCI: Well, the answer to your first question is that it is not as cut and dried as latency versus activity. In any given individual, there will be cells that are expressing virus and are what we call replicating, and in that same individual there may be cells in which the virus is latent.

So it is really too simplistic to say that one person is walking around and only has latent virus, and the other person only has expressed virus. There are varying degrees of infectivity. In fact, by following people closely over periods of months to years, we have been able to show that as people get into the later phases of disease, they have greater bursts of expression of virus. This would lead one to conclude, not necessarily totally accurately but at least with reasonable supposition, that when you're in that burst phase of expressing virus, you are more infective than when you're not very actively making virus.

So therefore one would think that if someone is in the later phase, they would be more infectious than someone who's not. But when you say that, you've got to be careful, because sometimes people get the misinterpretation that if they're feeling well, then they're not infectious. That is totally incorrect. Someone can be feeling quite well and still have a considerable amount of actively expressed virus in them, even though they feel well.

DR. SERVAAS: The alpha one --

DR. FAUCI: Yes, the alpha-interferon, anything that suppresses virus in a body might ultimately be used to suppress or at least lessen the possibility of transmission. The difficulty again is that you can transmit a cell that has latent infection. That cell is not going to get killed, as I showed on that slide, because a cell is only affected of it's actively producing. Once that latently infected cell is transmitted in semen or other fluids, it can still become active in the recipient.

DR. LILLY: Dr. Lee?

DR. LEE: Dr. Fauci, I'm going to submit my questions to you in writing. They have to do with your recommendations regarding organization, of the NIH and the PHS in particular,

facilitation of the AIDS effort, and funding, and I hope that you can respond in writing to our Commission, because it will be very helpful.

DR. FAUCI: I'd be happy to.

DR. LILLY: Admiral Watkins?

CHAIRMAN WATKINS: Dr. Fauci, on basic research, the relationship generally between the Defense budget and research is about 10 percent, all aspects of research. Under that, there is an element of basic research, and the pleas to maintain that level funding profile over a period of time are always very loud and strong, and generally they have been able to maintain that level.

What is your basic scientific research trend line? How does it relate to the NIH budget. How is it constrained? Why can't you just establish the basic research that you need and pound the table for the dollars and get it within your total budget?

Is there a complaint that you're not getting enough basic research dollars? Are there bureaucratic hurdles to your applying the dollars to basic research on a level funding basis so you can make some projections, you can build your facilities over the long haul? So what is the real issue?

DR. FAUCI: The issue, Admiral, is that first of all when you talk about basic research, much of what NIH does is basic research. It would probably be clearer to say investigator-initiated basic research, which is what we call the research project grants, as opposed to training centers, career, and things like that.

The difficulty is again the pie concept. We're constantly in a difficulty that if you put more money in investigator-initiated research project grants, you have to take it away from something else. If the pie stays the same size, then you're going to have to move things around.

One of the problems we face is something that was alluded to by Drs. Groopman and Rauscher, and that is the whole idea of training new investigators. When I sit down and make up the budget, I'm constantly torn between putting money into training, since I know we need to train more individuals, and taking it away from research where we already have a very difficult time funding all of the good proposals out there.

So I think the answer to the question is, the pie has to get bigger. We have already squeezed out as much as we can by cutting the pie in different ways.

CHAIRMAN WATKINS: But you went with a budget in the Administration, and the Congress doubled it.

DR. FAUCI: Right.

CHAIRMAN WATKINS: Why can't you take some money out and make a new pie?

DR. FAUCI: I'm not sure I know what you mean by "a new pie."

CHAIRMAN WATKINS: Well, if they doubled the budget that you didn't plan on, and all of a sudden you have dollars, why don't you make your pie larger on your own, or are you constrained by certain allocations within the budget process that preclude you from doing that?

DR. FAUCI: Right. As a matter of fact, there are a number of mechanisms and associated logistical difficulties. For example, there is a certain amount of money that one can spend on research projects, a certain number of grants that can be funded. Under certain circumstances, there is a reluctance to increase the numbers of grants because if you do, then you have a commitment for X number of years down the pike to fund that grant. So it isn't as if you're given a certain amount of money, and you can all of a sudden fund a certain number of grants.

As an Institute Director, I'm given a certain number of grants that I can fund, and that's it. So even though more money might come in and get distributed around, still in this particular Institute, that's the only number of grants that we can fund.

The amount of new money that comes in is almost always in areas that can be applied. For example, if you look at the slide, the big increase is in drug development and drug evaluation, vaccine development and vaccine evaluation. It was not an infusion into the basic research pool, which is the investigator-initiated pool that I was alluding to.

CHAIRMAN WATKINS: Would you be willing to respond to a letter from me that asks you specifically what the obstacles are that you face in ramping up to the proper basic research that you call investigator-initiated research, as opposed to the others, and give us some data of what you're spending now, what your constraints are, and what you would recommend in the future to stabilize the fundamental research work that you find so important, because I think that this panel will be receptive to that kind of approach?

We've heard it from many others besides you, and I know Dr. Lilly himself has talked about this at some length. I think this is important.

DR. FAUCI: I would appreciate the opportunity to respond to such a letter.

CHAIRMAN WATKINS: Another point. I notice in your collaborative effort up there, it all sounds very good, but we've heard witness after witness come before us from other vantage points that look into the NIH collaborative process and find that it's difficult to access. The information flow isn't quite as smooth as they'd like to see it, the linkage with academia, perhaps other groups that are studying redundantly.

We heard about redundancy is important in many ways, but by the same token, you'd like to know that it's controlled redundancy, that we want to have a certain amount, but we want to know what it is. I've gotten a call recently from General Abramson, who said he has $15 million a year under the Strategic Defense Initiative Office that is earmarked for basic medical research, such as free electron lasers that can get down to the cellular and molecular levels and do some amazing things.

The Department of Energy and the Department of Defense have extensive computer networks and bases that may have capacity that you could utilize.

How well is all of this interagency effort coordinated, so that we make sure we're taking advantage of the other spinoffs from technological explosions that are taking place around the various governmental departments?

DR. FAUCI: I think, Admiral, certainly, that area can be improved, and I certainly would be the last person to say that we cannot make major improvements in that.

The attempts of getting, for example, the Defense Department's research availability and facility made known to the AIDS effort is with the Governmental Coordinating Committee, the Federal Coordinating Committee, which includes representation from the Department of Defense. Whether or not the specific --

CHAIRMAN WATKINS: Well, how often do you meet? Every five years whether you need to or not?

DR. FAUCI: No, actually not. I am not on that committee. The Assistant Secretary represents the Public Health Service, and they meet approximately every three weeks to a month.

CHAIRMAN WATKINS: Are you aware that there is $15 million a year put into spinoffs from technology just in that one program alone, into medical research?

DR. FAUCI: Yes, I am.

CHAIRMAN WATKINS: I think it would be important for us, since we're going to hear from many witnesses today, and I'm not sure they're going to share your view of the effectiveness of the collaborative effort, if we're talking across all the spectrum of society including academia and so forth and the flow of information that's necessary out of that.

Maybe everybody will say it's there. You've even said you know you can improve it.

Have you got some specific recommendations that might enhance that collaborative effort on a more aggressive basis at the outset of this specific infectious disease that might be a pattern for the future in dealing with a medical crisis of this nature?

DR. FAUCI: Admiral, I think there are a number of things that can be done. I think one of the important things to do is to undertake better information exchange about what is going on. That is something that as biomedical scientists prior to the AIDS epidemic, we didn't have to spend much attention to, saying we're doing this, or we're doing that.

I think that there are some well-founded concerns -- previously more so than now -- about coordination and collaboration. But I also think that there has been a very significant lack of awareness of what is going on.

A very good example of that is the reason the reason I showed the slide of the Carpenter Report document, Admiral. When I was presenting a similar forum before the Institute of Medicine last year, one of my own colleagues in biomedical science got up and said, "Why don't you put together a committee of outside people? All you do is do things in a vacuum. What we need is a committee of outside people to come and make recommendations."

This was a very well-meaning person, who is actually a good friend. He didn't even realize that we had the committee, the committee had a report, and the report had been published.

That is the reason I showed that slide, because I think there's a lot going on that people don't realize, and besides improving what's going on, I think what we need to do is be much more vocal and much more expressive in what is going on, so people know about it.

CHAIRMAN WATKINS: But what is the institutional process to permit that? The CDC Clearinghouse that's beginning to get off the starting blocks now or --

DR. FAUCI: It's more than that. What it is is individual agencies getting the authority to do the kinds of things like those booklets. That's something that has been a problem in the past, getting things cleared through multiple layers of the Department about putting a booklet out.

CHAIRMAN WATKINS: That's the second question in the letter I'm going to send you.

DR. FAUCI: Please do. I'd be happy to answer.

CHAIRMAN WATKINS: And I'd like to have you come back, because it is important, and I think that you're absolutely right. Every time we go to a meeting, we find things that we haven't heard of before, and yet the problem been there for some time, because the pros that are working the problems on a day-to-day basis in many cases know it, but many others who have to tap into the system don't. I think that's why collaboration is getting more of an image perspective than, I think, a substantive perspective.

DR. FAUCI: I agree.

CHAIRMAN WATKINS: Because we're just unable to get the information flow going, and I think it's important that you let us know how we can enhance that and make some recommendations.**DR. FAUCI:** I will.

CHAIRMAN WATKINS: Thank you, Dr. Fauci.

DR. LILLY: Thank you very much, Dr. Fauci, for an enlightening session. We will now take a brief break, hopefully not more than two or three minutes, in order to fix the electronic system for better functioning.

[Brief recess.]

PUBLIC INTEREST GROUP SPOKESPERSONS

DR. LILLY: I would like to resume our hearing this morning. The next group of three speakers represent public interest groups. The first speaker of that group will be Dr. Murry Cohen from the Physicians Committee for Responsible Medicine. I'm sorry, the next speaker will not be Dr. Cohen, of the Physicians for Responsible Medicine. He had requested to testify, but has not arrived.

The next speaker will be Mr. Bruce Decker who is the President of the Health Policy Research Foundation.

Mr. Decker?

MR. DECKER: Thank you, Dr. Lilly, and particularly, thank you, Admiral Watkins, for your courage in having this hearing and the fine work of the Commission.

As America embarks upon its eighth year of AIDS, it is clear that our federal response is accurately viewed as both an incredible accomplishment and a colossal failure. Our failure is best exemplified by what I call the AIDS double standard.

On the one hand we are told by the bureaucrats and scientists that we are in a crisis, while simultaneously on the other hand being told we must do business as usual.

I have the advantage of not being a doctor, lawyer or bureaucrat, so I don't fall victim to the temptation to smugly congratulate myself and my colleagues for our incredible accomplishments. I am out there on the front line of the war and must on a daily basis witness the vivid results of our colossal failure.

Behind the statistics and the scientific mumbo jumbo, supposed facts created to obscure the terrible human toll of AIDS, is concealed a message. Quite simply that message is that we must get beyond the business as usual attitude.

Admiral, as a fellow Californian, you will be proud to know that we are expressing our frustration with these obstructive bureaucrats and scientists as the way we Americans have traditionally responded to tyranny, and that is through revolution.

Last year we created our own FDA. This year through our AIDS research tax credit initiative, we will create our own NIH and some say next year we may well succeed.

You don't have to be a rocket scientist. It just takes a little common sense to understand that our highest priority as it relates to AIDS must be intervening with those most imminently at risk, those million to million and a half Americans currently infected with the AIDS virus, as to preclude the progression from asymptomatic infection to serious illness.

Knowing that the natural history of this disease indicates that with each passing day, the likelihood of progression increases, why are we allowing petulant bureaucrats and squabbling scientists to get in our way?

It is unfortunate that the Ribavirin story will not be told here today or at this hearing. I believe that history will show that it is a textbook example of the AIDS double standard.

We are in an emergency and traditionally in an emergency we identify a vehicle, equip it with the appropriate safety devices, give it lights and a siren, and then get everybody out of its way so it can get to its destination, whether that be a hospital or a fire, as quickly as possible.

I believe that vehicle exists and we can with resolve break the AIDS gridlock. The most expeditious vehicle that is available to us today is the "treatment use IND." Through it, we can expeditiously make agents and therapies available to doctors so as to intervene with this infection through what I refer to as prudent risk management.

Under the June IND re-write, it clearly states that a non-approved drug may be made available under controlled circumstances if "premature death is likely without early treatment." Few if any in this room or in this nation, I believe, would quarrel with the fact that even asymptomatic HIV infection qualifies under that proviso.

After all, prudent risk management is what life is all about. We know all about that in Southern California. Daily, we risk breathing in toxic substances with air. When you consider the alternative, the certain prospect of suffocating if we stop breathing, the risk seems prudent.

I need not point out the obvious parallels. With AIDS, it is just a matter of time, time before infection becomes disease and eventually death. Time before we find the means by which to intervene.

How can we shorten the time it takes to identify effective interventions? Offering the best known fighting chance to those whose conditions begins to deteriorate, the treatment use IND.

Yesterday, I discussed at some length with Dr. Frank Young, some specific, measurable recommended action steps. They are as follows:

-- First, that in order to create a partnership rather than an adversarial relationship, the Commissioner meet with, within the next 30 days, representatives of community and patient groups to get our input in identifying prospective subjects for AIDS treatment INDs.

-- Second, that the Commissioner appoint a high ranking executive at the Food and Drug Administration to pro-actively

solicit and process on a priority basis AIDS treatment INDs. All those subjects for which there is safety data and some indication of efficacy, recognizing that through education and informed consent, patients be allowed the opportunity to determine and participate in prudent risk management.

-- Third, that the Commissioner seriously consider AIDS treatment INDs from community based organizations, individual doctors and other non-traditional applicants, to demonstrate his commitment to action, not just to high standing words.

I ask that this Commission request that the FDA report back to you within 90 days on their progress in the area of these recommendations.

We Americans are blessed to live in the richest, most technically advanced nation in the world. We have an awesome responsibility. Some medical futurists are telling us that AIDS may be the first in a series of mutating viruses. The next could be just as lethal as AIDS and as casually transmittable as the common cold.

We dare not hesitate. We must learn how to intervene. If not just for the sake of millions of Americans at risk of imminent death or the tens of millions of Africans, Asians, Europeans and others, then for the sake of an unborn generation who if we hesitate or fail, will never know the joy of life.

Thank you.

DR. LILLY: Thank you, Mr. Decker. We will have a presentation now from Mr. Vic Basile, Executive Director of the Human Rights Campaign Fund. After his presentation, we will have a question and discussion session.

Mr. Basile?

MR. BASILE: Thank you, Mr. Chairman, and thank you, 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 lesbian and gay citizens.

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.

The HIV epidemic is a crisis and the only appropriate response to a crisis is a crash program. There are two basic reasons for a crash program in medical research. First, most of the 1.5 million infected Americans with HIV probably face

premature death, unless new treatments become available. Thus, these people are utterly dependent upon medical research for their survival.

Second, there is good reason to believe that an intensive effort will produce useful life saving therapies in the near future. In the next two days, you will hear from other witnesses who will inform you of the widespread alternative therapies for AIDS, ARC and HIV infection.

I have here two models of medicine cabinets.

[Holding up display.]

One is full of bottles to represent the myriad of drugs under investigation as therapies in HIV infection, which have not been licensed by the FDA. Many of them are in widespread unapproved use in the community. In the other, is one bottle, one bottle representing AZT, the one drug licensed by the FDA for the treatment of HIV infection. This single drug still represents the great majority of the AIDS clinical trial work being performed by the NIH.

The contrast represents the tragic chasm between hope and reality for 1.5 million Americans infected with HIV.

I speak to you 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 from Los Angeles and Dan Bradley, former President of the Legal Services Corporation of America. It was painful to lose them as it was painful to lose many friends before them, more now than I care to count. That pain is magnified many, 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 more.

In these circumstances, there is no excuse for business as usual. There is no excuse for anything less than a crash program.

Toward this end, the political establishment and this Commission could be most useful in improving the management of the Federal research effort, so that increased resources can be translated as quickly and as efficiently as possible into greater and more productive scientific efforts.

A model for such efforts is the Accelerated Solicitation to Award Process, or ASAP, plan prepared recently by the NIH, that provides for fast track review of grant applications. This type of plan needs to be developed on a

coordinated basis in all the Federal agencies, not just the NIH and the Public Health Service, involved in any way with AIDS research. The Executive Branch should establish an interagency task force to audit all of these agencies in order to locate impediments to the efficient expenditure of funds previously appropriated and to document future needs.

There is clearly an immediate need for greater resources, particularly for space and personnel. Federal personnel policies must be revised to attract and retain scientific and medical professionals. Institutions involved in AIDS research should be exempt from personnel ceilings. The Executive Branch should conduct an inventory of physical facilities and develop a plan to meet those needs.

The largest gap in the national AIDS effort may be the lack of collaboration with private industry. Several mechanisms for closing that gap could be found in the Federal Technology Transfer Act of 1980 amended in 1986. NIH and its member institutes have just begun to use this law to develop and take advantage of cooperative agreements with industry and has not yet promulgated implementing regulations.

The Federal research efforts must also 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. These same mechanisms can be used to disseminate the results of research rapidly to them.

Legislation is currently pending in both Houses of Congress that address in a comprehensive fashion most of the concerns we have raised here. These bills, S. 1220 in the Senate and H.R. 3825 in the House, should be passed and signed into law as soon as possible. It is important to note, however, that all these measures could be implemented through administrative actions. We need not wait for Congress.

All that is lacking is the will to act and the will 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 demand instant attention and support. This Commission can present this critical opportunity to the President and we can together embark on this course today.

Thank you very much.

[The prepared statement of Vic Basile is included in the Appendix.]

DR. LILLY: Thank you, Mr. Basile. I would like to ask a brief question. How would we test the drugs?

MR. DECKER: By monitoring those individuals and seeing to it that any individual that is on a drug is being monitored and that the results are being reported. Today, we have a host of people as Vic has said, who are taking drugs in an unmonitored and unapproved format and will never know the results from that. The larger of the sample --

DR. LILLY: You haven't told me how we are going to acquire an experimental group.

MR. DECKER: It is my understanding that if you have a large number of subjects taking a specific drug and have the results reported back, that may supplant in the future the need for placebo controlled drugs.

DR. LILLY: I am not convinced yet.

Dr. Crenshaw?

DR. CRENSHAW: How many of the drugs that you have in your compendium have already been approved by the FDA for other indications, such as Antabuse, and a number of the other drugs that could be more easily and rapidly evaluated and studied if funding and acceleration processes were done? Are there just a couple of them, more? What can you do to get those into circulation? It seems they are the least problematic potentially if they show any efficacy.

MR. DECKER: You are absolutely right. I would suggest you might want to ask Dr. Young that question tomorrow afternoon when he is here for his two hours and fifteen minutes to discuss the subject.

DR. CRENSHAW: Thank you. Approximately how many are there in that category; do you know?

MR. DECKER: We estimate there are about 12 drugs that could be made available if we were operating on a "sliding efficacy scale." At this point, in order to get a treatment IND, you have to be able to demonstrate safety, which is exceedingly prudent, and you have to be able to demonstrate some degree of efficacy. It is, according to the June re-write of the IND rules, entirely at the discretion of the Commissioner to determine efficacy.

Ribavirin is a classic example. We have demonstrated safety. It is being pumped into the lungs of babies in its purest aerosol form. Why is it that Ribavirin has not been made available through a treatment IND? Quite simply because the

Commissioner has said that the studies that have been submitted do not demonstrate efficacy, but in California, we have hundreds, perhaps thousands, who knows, people going to Mexico and buying the drug for themselves, bringing it back and taking it in unmonitored circumstances. In the absence of a treatment IND, we won't know for three or four years the answers to questions that we could answer in six months.

DR. CRENSHAW: Thank you.

DR. LILLY: Dr. Walsh?

DR. WALSH: I wish, Mr. Decker, that your conclusions had some scientific validity. I am like Dr. Lilly, I am not convinced.

I wonder if in the anxiety we all feel for helping those patients that are seropositive as well as those who are sick, that we may have lost sight of not only safety values in the use of drugs, but also the things that it can lead to and the implications of asking the FDA to go any farther than it has already gone.

After all, we have millions of people dying each year from heart disease, yet new drugs for the treatment of heart disease admittedly, and the pharmaceutical companies I am sure would agree, have a much too long period before they get approval. Yet, millions die each year because of the lack of those drugs.

There is a valid scientific basis in most instances for controlled studies. The implication to me of changing the ground rules is it is very dangerous. If we do it for HIV patients, the pressures will mount to actually destroy the entire system of the FDA which was set up to protect the public, not to penalize the public.

I wondered if the implications of this have been fully considered. I think you have obviously given this a lot of thought. The point that was made repeatedly this morning of the shortage of scientists, remember, one of the great delays in the FDA approval system is the absolute shortage they have also of reviewers and of the very monitors you are talking about. They just aren't there.

I am curious to know, who would you have as monitors? Where would you get the scientists that the FDA and the universities can't get to solve your problem?

MR. DECKER: I am not advocating the dismantling of FDA or the absolute gutting of the process. What I am talking about is recognizing the extraordinary nature of an infectious epidemic

that has no treatment, no cure and no vaccine, that has infected 1.5 million Americans that we know of, and perhaps more. There is the ongoing comparison between AIDS and cancer and heart disease and other very important diseases that I must point out in my opinion is a comparison of apples and oranges.

I would suggest to you there are tens of millions conceivably, given the shell game that most bureaucrats are good at playing, and perhaps hundreds of millions of dollars that are currently allocated to AIDS research and specifically to the testing of AIDS drugs that were not spent from previous years' budgets.

As Dr. Fauci has pointed out, we are seeing a geometrically increasing number of dollars available to the Federal Government, the Federal scientists, on a yearly basis, through the wisdom of the Congress and most recently through the wisdom of the Administration, that could be allocated toward the high priority which we believe to be the intervention among those people who are infected so as to preclude the progression to disease and death.

DR. WALSH: Unfortunately, dollars don't bring us trained evaluators and scientists immediately. We need them. I would agree that I think significantly more of those dollars could well be appropriated for scientist training. I think it would be very important for the type of thing you want to have appropriate monitors and the like.

I share a lack of conviction for the position that you take in that there is a potential of a greater degree of harm than there is of benefit. I keep an open mind on it but I remain unconvinced.

MR. DECKER: Keeping an open mind is all we can ask.

I will say, Dr. Walsh, that we as a community created AIDS organizations out of whole cloth when Government was unwilling to respond early on. We in the last year have created organizations in this country to conduct clinical research. You will hear from the Community Research Initiative here in New York, and you will also have the opportunity to hear about a network of physicians, a network of private community and non-governmental AIDS researchers who are ready, willing and able to get involved in this struggle, but have not been given the opportunity to do so by the NIH in the past.

DR. WALSH: As Dr. Fauci pointed out this morning, I think what has been achieved with behavioral modification alone by organizations which were community formed before the Federal Government or anyone else got in it, have been among the most

impressive private efforts I have ever seen. I would like to see those continue.

MR. DECKER: We will.

DR. LILLY: Dr. Conway-Welch?

DR. CONWAY-WELCH: I am not sure if this is a question or a naive statement. Almost since we began hearings, I have heard from various community groups that large samples of people are available and willing to voluntarily participate in various drug studies and this would obviate the need for control groups and some of the more traditional scientific rigors.

I wonder if there is ever a way we can answer that very basic question? We seem to go back and forth all the time and never resolve whether or not in fact a very large sample could, if it were collected, be able to stand the test of scientific validity.

MR. DECKER: I can only suggest that we try it.

DR. CONWAY-WELCH: Is there a way that we could frame some kind of recommendation or a statement that would put this thing to rest once and for all?

DR. LILLY: I have a feeling we have a witness coming up that is very well qualified to resolve this question a little bit later on.

DR. CONWAY-WELCH: Thank you.

DR. LILLY: Dr. SerVaas?

DR. SERVAAS: I agree with you that we should be spending a lot of efforts on the AIDS antibody positive individuals to keep them from becoming ARC and AIDS patients. You said you could get a large number. How many AIDS antibody positive persons could you get for such a test? Do you have files? Are these people really available to you?

MR. DECKER: In the two efforts that are ongoing now, one here in New York with CRI, who you will hear from tomorrow, and one that we are launching very shortly in San Francisco, we believe that if we can offer to individuals confidentiality and if we can offer to them the opportunity to participate in their own treatment, i.e., to learn the spectrum of interventions that are available and to discuss with knowledgeable physicians, that they will come forward in significant numbers, whether you want 1,000 tomorrow or 5,000 next month.

We believe the awareness that you are antibody positive, you should be in a monitoring program, and if you are in a monitoring program and you see some deterioration in your immune system, that the very great motivation is there to educate yourself, to learn about the risks that you take, if you choose to go into a specific therapy, and then to decide whether to do it or not.

The alternative of breathing air in Southern California is suffocating. The alternative to many people who are HIV positive, who begin to see their system deteriorating is death.

What we are saying to them is that all of those drugs that are potentially efficacious are unavailable to them unless they wish to become criminals, and they are in significant numbers becoming criminals.

DR. SERVAAS: Thank you.

DR. LILLY: I would like to ask a question of Mr. Basile.

In the brief outline of your presentation that you gave, you summarized the role of the Commission with three paragraphs, each of which talks about management of research.

Now we've heard a good bit about management of research already this morning, and I think we all agree that there's a good bit of value in there being management of research, and yet I think many of us feel that among the best advances in imaginative ways in research, that tends not out of managed research but out of individual research.

Furthermore, a great deal of what we need to know is going to come out not of research that was entitled AIDS research, but research that was entitled basic immunology, basic virology, and so forth.

So I'm a bit worried about what seems, at least from just this little bit of paper, to be what I would consider your overemphasis on managed research.

MR. BASILE: Dr. Lilly, what I refer to is, I think, the inertia of bureaucracy frequently -- that is, that when the National Institute for Allergy and Infectious Diseases has the money for and requests additional lab space, they have to do it through the General Services Administration, and the General Services Administration has not responded to the request. They haven't said yes; they haven't said no. I think that's a management problem at the highest level of government.

If problems like that are holding up research, if the Office of Management and Budget says you can only have so many FTEs, and yet the job calls for many more -- that is, getting grant applications approved and out requires additional personnel to review them, so that many of the tasks can be done more quickly -- there need to be more scientists -- you can't have other branches of government restricting this research effort.

If the Office of Personnel Management will not authorize additional incentives for scientists to work within government, so that they can do research, rather than being drawn off for much higher salaries, I think the research effort is crippled, and it's that kind of management to which I'm referring.

DR. LILLY: Well, I would certainly agree with you that the area of additional facilities that are needed certainly corresponds to what you've been talking about, and there are undoubtedly others as well.

Admiral Watkins?

CHAIRMAN WATKINS: One of the approaches we're taking in our intended reports to the President is to identify the obstacles that you've just referred to to some degree, bureaucratic obstacles, management obstacles, that clearly need not be there. It is very difficult in a set of hearings where people are very conscious about putting their own bosses on report, to get all the information we need. Sometimes we have to shake it out; but it comes out eventually.

You have made some very interesting recommendations, many of which we have heard before and many of which we have already included in our thinking and in drafting some of our preparation for the Chairman's recommendation to the Commissioners that will be coming out next week on our four initial issues, one of which, of course, is in drug research.

So I think that this will be very important. I know that we've been working with your group, Mr. Basile, on a number of things to prepare for other hearings downstream. But it will be very important for us to have perhaps a further expansion on your formal statement that would talk about some of the things you just mentioned, because those are the kinds of things we can do something about in recommendations to the President.

In addition, we are very conscious of the need for more women and more HIV-positive asymptomatic people in the clinical trials, and so again there is a wave of presentations to us that talk about these kinds of things. So many of the things you've said today are in synchronism with what we have heard from

a variety of other sources, and therefore tend to reinforce that testimony.

So this has been valuable. It is always valuable to listen to interest groups, and it's always important that when we make an accusation about the lack of openness with your thinking and with your group that you come up with some positive recommendations about that.

What does it mean we can do? How should you factor into the collaborative effort that we saw presented in a diagrammatic form by Dr. Fauci this morning? How can that be done in an orderly, proper fashion where views can be clearly aired in a cooperative, collaborative way, not in a confrontational way in the normal scheme of doing things, particularly at this stage, early stage of this infectious disease?

Maybe this is one of the techniques that we should adopt and a lesson learned out of this disease process so far, that there might be a better way to engage many more groups, but in some orderly, unchaotic way that is in the process, to enhance the process when we push the health crisis button.

So if you have further thoughts along those lines, either one of you, we would like to have those submitted to us in writing, because I think it's very important that we hear the specifics and hear it in a constructive, all right now that you've made the comment, how would you do it. Then we'll take a look and see in our integrating process going on within the Commission on a day-to-day basis how we might be able to support some of the thinking along those lines that would be in concert really with what we've heard from a lot of people like Dr. Young himself in FDA.

So I don't think that you and Dr. Young and Dr. Fauci are that far off, and I think we can be more understanding of each other and more constructive in the way we put this together by that kind of a positive recommendation on what we might do in the future.

So I would ask you both for that. Feel free to come back, if it's not already well-documented in your formal statements, which I have not had a chance to read yet.

MR. BASILE: Admiral Watkins, I'm delighted to hear you say that. We have been looking at those bureaucratic problems for some time, and I would be happy to provide you and the Commission with many more details on those problems.

CHAIRMAN WATKINS: We need it fairly soon, Mr. Basile, if we're going to try and include that. So we need it like right

away. If you can take until tomorrow, something like that, that would be very, very helpful. We'll allow you even until Saturday.

[Laughter.]

MR. BASILE: It's in the mail.

MR. DECKER: Admiral Watkins, I would note that in my discussions with Dr. Young yesterday, he agreed that each of the three recommendations could be implemented immediately, and they were entirely within existing statute and at his discretion.

DR. LILLY: Thank you, gentlemen, for your presentations.

We will now have a slight change in the order of business. Dr. William Haseltine, who was scheduled to present at 1:00 o'clock, will be presenting now because of a scheduling conflict.

I should also announce that there will be no formal lunch break. The Commissioners will be taking turns to take lunch, so that we can try to get through our very heavy schedule today.

Dr. Haseltine will address us now. He is from the Dana-Farber Cancer Institute in Boston, a man who has been doing retrovirus research for many years.

Dr. Haseltine?

Medical Control of the HIV Epidemic

DR. HASELTINE: Good afternoon. The topic that I shall address today is the prospect of medical control of the AIDS epidemic. There are three tools that medical science holds for the epidemic control.

First is diagnosis -- that is, the ability to detect those who are infected; the second is treatment, the ability to provide medical care for those infected; and the third is prophylaxis, the ability to prevent the infection upon exposure to the AIDS virus.

The prospects for the development of these three fundamental tools for the control of the AIDS epidemic are bright. They are within our current technical ability, not necessarily in the precise form that we may wish, but they are available nonetheless. I will discuss the three separately.

Diagnosis. The discovery of the etiological agent of AIDS, a retrovirus now known 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 is 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 an 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 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 educational control programs is unmeasured. We have been, and to a large extent still are, flying blind with respect to our knowledge of the dynamics of the AIDS epidemic in our country. 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: first of all, treatment of those with advanced illness; secondly, treatment of those with detectable symptoms but not severe disease; and finally treatment of the infected HIV seropositive people who have no serious symptoms of infection.

Towards a curative therapy. Until recently, attention has been focused upon the treatment of those with serious disease. Progress in extending the life expectancy of some people has already been made. Such progress is all the more remarkable, as it is likely that the person with serious disease will ultimately prove to be the most difficult person 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 within 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 from ever occurring in the first place.

I look forward to the day when a diagnosis of infection with HIV is similar to a diagnosis of diabetes. With proper and continual medical care, those infected can someday look forward to a normal, full-term life.

I believe that such treatments are within our ability to achieve given our current biomedical skills. Systematic, intense, coordinated application of existing scientific and medical resources is very likely to be up to this task. Given appropriate resources and commitment of government, industry, and academic institutions, this is a problem that can be solved.

I base this optimism on close observation of the disease organism itself. My specialty is molecular biology, the taking apart of the virus bit by bit and its reassembly to see how it works. The more we study this 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 factors, interleukins, and cytokines, have been shown already to interfere with virus growth.

At latest count, there are more than 14 individual targets that this virus presents for attack. Additionally, there are multiple ways to mount each attack.

Enlightened drug screening. How can new drugs that act against the 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 now be vastly speeded up. Screening programs for each component part of the virus are being developed. It is expected that by the end of this year, 20,000 compounds will be examined. Next year, it is expected that more than 40,000 new compounds will be examined.

Rational design. The tools of modern molecular biology, biochemistry, and medical pharmacology 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 the AIDS virus proteins. The position of each atom in space relative to one another can be determined by X-ray crystallography and two-dimensional nuclear magnetic resonance. The interaction of each molecule with know drugs can be studied.

Predictions for the design of new drugs can be made. Such new drugs can be chemically synthesized and tested.

This is no pipe dream. Already three components of the AIDS virus have been produced in abundance and have been crystallized. The complete structure of these proteins should be available by the end of this year or at the latest the middle of the next year. The structure of other viral proteins will be available shortly thereafter.

With modern technology, the availability of new antiviral compounds is limited only by resources, i.e. money, and the interest and imagination of the scientific and medical communities. Within a year or two, our problem will not be what drugs to introduce, but how to select amongst a wide variety of potential drugs.

We are witness to the birth of a large, active, imaginative, coordinated drug discovery program. Over the past two years, via a variety of independent funding mechanisms, the National Institutes of Health have forged an alliance between industrial, academic, and government laboratories to foster preclinical drug development.

I think this is one aspect of the government program which hasn't been properly appreciated. This program is a model of its kind and has already engaged some of the best scientists of our time. The program is currently being expanded. In my opinion, this program should expand still further over the next few years.

The pace of development of new therapies. It is the pace of the progression of AIDS as a disease itself, rather than the pace of drug discovery, that will ultimately determine how rapidly curative therapy will be achieved. The time between infection and first serious symptom is typically no shorter than two years and very often five years or more. This lag period means that evaluation of the efficacy of treatments designed to extend the latent period will require at last two and possibly more years.

There is a way to speed this process up; that is, to plan much larger trials, but it can only be speeded up a certain extent.

The shape of things to come. It is likely that the best treatment will involve combinations of two or more drugs. Combinations of drugs are useful for reducing toxic side effects. Drugs can act in concert against the virus, multiplying their efficacy, without affecting normal cell function.

Combinations of drugs can help prevent the development of drug-resistant strains, a potential problem in chronic treatment for AIDS-infected persons. Combinations of drugs may

also prevent disease progression, as well as transmission from an infected to an uninfected person.

Prophylaxis, prevention. To think of prevention is to think of a vaccine, a medication that enables the immune system to protect us from acquisition of disease when exposed. Vaccines are ideal as a public health measure. Entire populations can be protected by either a once in a lifetime or perhaps a once a year 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 that it is impossible to make such a vaccine. Only it is to say that we are not certain of success. I remain cautiously optimistic that given a sufficient effort by virologists and immunologists, a vaccine for this disease can be developed. Indeed, I am very actively engaged in vaccine development; however, it is certain that we face significant problems in our efforts to create an AIDS vaccine.

The extent of the problems for AIDS vaccine development was highlighted by the failure of the initial vaccine trials in animals. Chimpanzees immunized with vaccine candidates were not found to be protected from AIDS virus infection. Monkeys treated with vaccine candidates for the Simian AIDS virus, a close analog of the human AIDS virus, were also found not to be protected.

Failure of the first vaccine trials does not mean that 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 understanding as to why vaccinations may be difficult. The fundamental reason, in my opinion, for such difficulties is that the AIDS virus appears to have evolved to cohabit with the human body in spite of an immune response. It is one of a number of viral and other types of parasites that have been designed by nature to establish long-term residence in our bodies.

Specific mechanisms for evasion of the immune response that the AIDS virus uses are of two general types. First, the structure of the surface of the virus is designed to evade the immune response. Secondly, the life cycle of the virus is also designed to evade the immune response.

The virus surface. The surface of the virus is comprised of a protein that binds to the surface of an uninfected cell via a specific cellular structure, the CD-4 molecule. Interference with the binding of the virus' surface protein, this

protein called CD-4, prevents infection. People infected with the AIDS virus usually make antibodies to that surface protein; however, these antibodies do not prevent growth of the virus and disease.

We understand the features of the surface which give this virus this property. First, the surface of the AIDS virus is coated heavily with sugars. The sugars serve to protect these proteins from recognition by antibodies that are made in infected people.

Secondly, the region of attachment of the virus to the cell is very likely to be very deeply recessed in the surface of the protein. Antibodies generally cannot reach into deep recesses of proteins, and the AIDS virus seems to be no exception.

Third, most of the functional working parts of the virus are tucked away either under the sugar coat or under other protein, hidden from our antibodies.

The life cycle of the virus also contributes to its ability to evade the immune response. The virus can infect a cell and then lie dormant, giving no sign of its presence. Indeed, dormant infections of cells are more the rule in AIDS virus infected people than they are the exception.

Infection of some cells also results in formation of viruses that are contained entirely within the cell. If the virus is not present on the outside of the cell, the immune system may not see it at all. The virus may circulate in a Trojan horse like state, invisible to the immune system.

These are all formidable obstacles to overcome. What is required is a large-scale, coordinated program to address these problems. Fortunately, such a program has been developed by the National Institutes of Health. This effort is a national coordinated or national cooperative vaccine development program. It's a program which is now being expanded.

Of significant help in our efforts to design an AIDS vaccine is the discovery of the model system of the Simian immunodeficiency virus that will be a great help.

I would like to end this presentation with some thoughts on chemical prevention. This is an ending on what I hope will be a positive note.

When we consider prophylaxis, we must keep sight of our goal. Our goal is not to create a vaccine. Vaccines are a means to an end. The goal is the prevention of infection upon exposure. It will soon be technically possible -- I emphasize

"technically" -- possible to prevent infection using antiviral drugs, in many cases using the same drugs that are used to treat those that are already infected.

The concept of chemoprevention is the treatment of uninfected, healthy people with antiviral drugs to prevent infection. The feasibility of prevention of infection by administration of antiviral drugs has already been demonstrated in two retrovirus animal models. The concept of chemoprevention may be applicable in several different settings.

-- First, 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 -- that is, short treatments with drugs -- following known exposure to the virus may be protective.

-- Second, treatment of newborns of seropositive mothers. The risk of infection of infants born to HIV-infected mothers is high. About half of the babies born to infected mothers become infected, and of these, many develop serious disease within a year or two. It is not known at present what fraction of these infants are infected before birth or at delivery. It is possible that limited duration treatments -- that is, treatments for a short period slightly before and after birth with antiviral drugs -- could substantially reduce the number of children that are infected.

-- Third, 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. I this context, chemoprevention means long-term, chronic administration of antiviral drugs for the uninfected healthy partner.

-- Fourth, high-risk populations. Chemoprevention on a population-wide 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 this year 5 percent annually of the sexually active population. Infection rates of this magnitude cannot long be sustained without endangering the entire population. Under these circumstances, in the absence of an effective vaccine, chemoprevention may be one of the only effective means of disease control.

The requirements for chemoprevention are strict. The toxic side effects must be minimal, as those treated will be healthy. Chronic as well as acute toxicity must be evaluated, The means of delivery must be simple, oral or slow release drugs

are preferable. The cost must be affordable not only to individuals but to nations.

There is a sense of urgency in the matter of chemoprevention. At present, there is no effective means to prevent infection of the newborn, our next generation. AIDS virus infection continues to spread rapidly and unchecked in large populations in some parts of the world.

Drugs such as AZT, and alpha interferon, that have already been approved for human use may be useful in this context. Results of chemoprevention trials could be obtained within one year of initiating the studies.

We are not helpless in face of the AIDS epidemic. Indeed, many of the essential tools for the medical control of the AIDS epidemic have already been forged. Means for the accurate diagnosis of infection are at hand, and improved diagnostic tests will be available soon.

The outline 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 that adequate resources are marshalled.

It is likely that the means to prevent infection can be developed in the near future in the form of chemoprevention. To be sure, chemoprevention 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, make chemoprevention imperative.

Thank you.

[The prepared statement of Dr. Haseltine follows in the Appendix.]

DR. LILLY: Thank you. Dr. SerVaas?

DR. SERVAAS: Could you tell us or send to the Commission in addition to chemotherapy and what drugs you think are going to be the way to prevent well people from becoming infected, could you tell us all the things that you believe the AIDS positive, AIDS antibody positive individuals could do to prevent, once they are infected, to prevent going on to get ill?

DR. HASELTINE: I think one of the saddest things that has emerged from the studies of the progression of the disease is first of all that most if not all people eventually progress if given time. A second, and very startling, observation is that contrary to what most people believe, there have emerged no clear co-factors for progression.

Jim Curran of CDC summed it up a year ago with a simple statement that the only known co-factor is time. It doesn't matter whether people take vitamins, are young, old, healthy, et cetera. It seems that the only significant and known co-factor is the amount of time that has elapsed since infection.

To the first approximation, there are no known co-factors for progression. At this point, the only thing that I'm aware of that could prevent progression is medical intervention in the asymptomatic state.

DR. SERVAAS: Pregnancy, it is believed by some to be a immunosuppressive, is that something that you are studying?

DR. HASELTINE: I haven't seen the studies. I am not aware of the data that has come from those studies.

DR. SERVAAS: Thank you.

DR. LILLY: Dr. Conway-Welch?

DR. CONWAY-WELCH: You mentioned a program, a cooperative program among private, academic and government sources. Could you tell us who is running that and where it is located?

DR. HASELTINE: That seems to be one of the dark secrets of the AIDS business, and that is how well the Government has organized pre-clinical drug discovery. Starting two years ago, the NIH began to organize what are called the National Cooperative Drug Development Groups. I would suggest you discuss this program with Dr. Dan Hoth when he gives his presentation.

I am the principal investigator of one of those programs. I can tell you I find it to be a magnificent program. It is a program where the Government offers money to groups that work together, that is academic groups with Government participation and with the participation of industry. Not only are there groups that get together -- I think there may be 15, initially there were seven or eight. The NIH is expanding these programs.

All program participants meet at least once a year. I have never participated in groups that have such energy and that involve the very active participation of many major pharmaceutical firms. There are representatives at those meetings of most of the drug companies and they talk about data well before it is published. I think they probably surprise themselves.

Recently, a series of proposals were just funded to do very similar things for vaccine development. That is put

together consortiums. I think it is really a highlight of the Government programs and I have been surprised it hasn't received more attention.

DR. CONWAY-WELCH: Who is coordinating that consortium?

DR. HASELTINE: Dr. Fauci himself. Dan Hoth has a major coordinating role. Dr. John McGowan is the next one down the line who is actually running around the country doing the administrative work. I think it is one of the most imaginative programs that I have ever seen Government involved in. It is very encouraging.

DR. CONWAY-WELCH: Thank you.

DR. HASELTINE: It is a pleasure to participate.

Let me give you an example. We found a drug, an obscure drug that grows in a chestnut tree in Australia. It was brought to my attention by somebody in Seattle. We tested it. It has some anti-AIDS activity. I made that known before publication to this group and within a matter of weeks, we got calls from three different drug companies, two of which weren't even participants in this program saying, look, we have analogs of these compounds that Dr. McGowan has brought to our attention, would you like to test them. Some of those look very promising, better than the original lead compound.

It is a program that is active and working. Another program I think people aren't aware of is the x-ray crystallography program. The NIH has coordinated a major program to determine the three dimensional structure of every AIDS virus protein. They have assembled probably the world's best group of crystallographers not only in this country but elsewhere, in industry, in universities and in Government. We all meet together and, again, in an unprecedented way, share preliminary results.

DR. CONWAY-WELCH: Thank you.

DR. LILLY: I am afraid we are going to have to cut off this very interesting discussion. Some of the other Commission members do probably have questions but we are running way behind. We appreciate very much your remarkably optimistic presentation, Dr. Haseltine, which is in stark contrast to others we have heard.

Immunology and Immunotherapy for HIV Infection

DR. LILLY: The next panel is comprised of people who are going to discuss immunological factors for us. Our first speaker is Dr. Jeffrey Laurence, a New Yorker, an immunologist at Cornell Medical Center, who has had a great deal of experience on both the clinical and research levels, who is going to talk to us about the immunological aspects of AIDS and research into those aspects.

Dr. Laurence?

DR. LAURENCE: I have been asked to talk about briefly what we don't know about the immunology of AIDS and I have divided it into five different topics that I will present briefly.

Some of this, you have already heard. I will start with the entry of a virus into a cell. When people start talking about transmission concerns, when you start talking about how you would develop a vaccine, and certainly when you start talking about how you develop a molecule to block viral entry, you need to know how that virus gets in.

As Dr. Fauci mentioned, the high affinity receptor is the CD-4 molecule. It is found on the surface of helper T-cells, macrophages, some B cells, some glial cells in the central nervous system, and perhaps on other cells. The problem is there are other cells lacking CD-4 that this virus appears to be able to enter. A number of these cells, you have already heard mention of intestinal epithelia cells, may not have CD-4 on their surface. They all have messages for CD-4, that is, messenger RNAs, but may not actually express the protein in any way we can detect.

There is also some evidence that this virus can enter endothelial cells that lack the CD-4 molecule. The mechanism by which the virus enters these cells is unclear. There are certain theories. One of them points to a molecule known as the Fc receptor, which is present on endothelial cells as well asmacrophages. As Dr. Groopman mentioned, another theory is perhaps a macrophage just goes ahead and engulfs a virally infected cell or the virus itself, setting up either an active or latent infection.

Other people have preliminary evidence that some molecules related to the way an immune cell recognizes a virus may even be a point of entry for that virus. Those are molecules known as MHC Class II products.

Besides the obvious problem of designing a vaccine strategy based on knowledge of these receptors and our need for

more knowledge in terms of which receptors are used and what are the low affinity receptors, it also points to the fact that when we use drugs to treat an infection and when we create artificial systems in the test tube to look at these drugs, we are really only examining what that drug does in a particular cell that we have tested.

As Dr. Groopman mentioned, there is at least one study now using a human macrophage line, known as U937, and this was published about two months ago. You can add all the AZT you want onto this macrophage and yet you will still not prevent the active replication of this virus in that cell.

It is not yet known what AZT would do in other immortalized macrophage lines from humans and it is not yet known what AZT will do in a normal human macrophage put into culture. Obviously, those experiments are ongoing and need to be done and we need to think more about those, not only in terms of AZT and why or why not it may work in a particular individual but how and how not it may work in a particular cell.

There is a lot of evidence now that AZT needs to be chemically modified, that is phosphorylated, when it gets into a cell before it has its anti-viral action. It is known that human T-cells can do that. It is known that this human macrophage line can't. We need to know more about other kinds of cells. That's the first point.

The second point is as you heard from Dr. Fauci and others, HIV kills cells. It particularly kills T-cells and in the test tube, it does it very rapidly. Yet, as you heard from Dr. Haseltine and others, this is really a relentless but a relatively controlled progression of infection. That is there is a long lag, there is a latency period from the time someone is infected to the time that individual develops AIDS. Right now, the data are that about 30 to 50 percent of infected individuals will develop clinical AIDS within a period of three to five years and no one has any idea after that.

The question is can we set up test tube models to help us distinguish or help us predict are there co-factors involved in this progresseion. As Dr. Haseltine mentioned, most studies coming from the CDC say that the easily looked at co-factors appear not to be involved in the development of AIDS. There was a paper published this week in the Journal of the American Medical Association, with CDC representatives, saying that CMV, cytomegalovirus, is not a co-factor for the progression of AIDS. EBV, Epstein-Barr virus, a very common infection among many of the risk groups, is not a co-factor for the progression of AIDS. Herpes simplex type 1 virus is not a co-factor for the progression of AIDS in this study, but Herpes simplex type 2 virus was in the epidemiologic studies that were done.

Do we have test tube models that will help us answer the question, how do you go from a latent state, from a relatively dormant virus, a virus that is not making a lot of viral specific nucleic acids, a cell that is not making a lot of viral specific proteins, a cell that may escape all the immune recognition and the vaccines and the killer T-cells and whatever else you want to dump on top of the cell, and how do we look at that?

You probably will hear more about this from Dr. Martin. Models are now beginning to be set up in which you can show that the HIV virus can come into a cell, it can set up a latent infection and you can throw activators into the test tube and convert that latent infection into active viral replication, killing a lot of T-cells. We could work on ways to block those "co-factors" in the test tube.

We need more information about other kinds of co-factors that may be operative. On the good news for co-factors, there was a recent report in the Lancet from the Caribbean. In Trinidad, a population of 100 gay men, either infected with the HIV virus alone or infected with both HIV and another human retrovirus, HTLV-1, these people at time zero, all were asymptomatic, and this group of investigators followed these people for four years. They asked the question, you started out at time zero and you looked healthy, you had one virus or two viruses, what happened to you at the end of four years.

There was a significant difference in the progression to clinical AIDS in the individuals that had the two viruses versus the one. If you had HIV virus alone, your chances of developing AIDS on that island in Trinidad was 8.8 percent. If you had HIV virus plus HTLV-1 virus, it was 50 percent. If you had HTLV-1 virus alone, the virus that has been associated with human T-cell leukemia and lymphomas, the chance that you would develop any disease in the four year period was zero.

There are ways that we have of looking at these co-factors. Dr. Haseltine is in the forefront of some of this work. It known that some of the regulatory factors responsible for increasing the replication of this virus in the test tube, are also regions where the proteins that some of these co-factors elicit in the test tube bind to.

For example, you can get a lot more virus out of a T-cell if you put in an artificial plant stimulant known as PHA. PHA induces the production of protein also induced by PMA, a chemical. Both bind to a region of consensus between the LTR, one of these regulatory regions of the HIV virus. When such proteins bind to that region, presumably it might up regulate the replication of this virus.

These experiments have now been done directly in the test tube in which you can take some of these chemical activators, throw it into a test tube and up-regulate the replication of this virus. That needs to be looked at more closely.

Another thing is, when we talk about treatment strategies, everyone loves the idea of immunotherapy. One of the most reasonable molecules to use in immunotherapy would be T-cell growth factor, interleukin 2. It was shown in some T-cell models that if you take an infected T-cell and plop in interleukin 2, you correct some of these deficiencies. The NIH initiated a study of this. It was recently reported in the January issue of The Annals of Internal Medicine that, rather than decreasing the amount of virus in the individuals who got the interleukin 2 therapy, there appeared to be either no change in the virus or a very large and unexpected increase in infectious complications in the individuals treated by what supposedly was an immune modulator.

Based on the test tube models, we know that if you put interleukin 2 in some of these cells that are latently infected, you do increase the amount of virus. We now have models that might be able to predict what is a good immune modulator and what isn't.

In addition, one of the problems and one of the apparent discrepancies between looking for viruses in the body and the way this virus might affect the immune system is if you use our best available techniques, in situ hybridization, and ask the question, how many cells in the body are infected with the virus, you come up with a very low number. I think the number is about 1 in 10,000 target cells. That didn't make a lot of sense in terms of the profound immune deficiency that you can find in infected individuals even very early on in this infection.

The idea now is that there probably are many more cells that are infected but contain latent virus below our levels of detection. You might be able to combine some of these immune activators with newer techniques in molecular biology to be better able to detect virally infected cells. I think this is one of the ways that I would call for programs that would combine the expertise of immunologists with molecular biologists and molecular virologists.

To finish up, against these odds, one might think that the host immune system were totally effete but this isn't the case. There are cellular immune responses that are directed against HIV and its products, their relative efficacy and how they might be amplified are important unknowns. Serologic responses to HIV envelope and structural components have been extensively charted but the relevance of certain patterns which

appear to distinguish the asymptomatic carrier state from AIDS remains controversial. In terms of serologic information, useful for vaccine development, it is unclear whether the consensus sequences of the viral envelope, the gp120, gp160 we have heard about, recognized by immunoglobulins from most infected individuals have any relevance for fighting the infection in the body.

Most neutralization assays that we use in the test tube correlate very poorly with the clinical situation. Until more appropriate knowledge of neutralizing epitopes in the virus are defined, vaccine strategies may not be very much more than hit or miss struggles. More attention also needs to be paid to killer T-cells in this entire process. There are T-cells that you can identify, that are activated, that recognize cells infected with the virus, present at a very low level, yet their efficacy appears to be very low, and a lot more attention needs to be directed at this as well.

To sum up, I have mentioned five target areas of research, of unknowns in immunology. As you can see from what I've said, a lot of what we don't know in immunology can be helped extraordinarily by what we do know in models in virology, not only with HIV but leads that have come from murine leukemia virus and feline leukemia virus and in other models as well.

A lot of this work is going to require that kind of coordinated effort. A lot of the immunologists, myself in particular, don't have the kinds of facilities we need to pursue the growth of the large amounts of virus required for experiments. We are building these facilities, but we are building them with private support.

I think the Government could be a lot more helpful in identifying these areas and getting the bricks and mortar money required to form these kinds of collaborations.

Finally, the idea of peer review was mentioned. If we are going to fund a lot more projects, if we are going to start building buildings, if you are going to start forming these collaborative efforts, and you want to do this quicker, you don't want to wait the nine to twelve months, but you want to do it in three to six months, who is going to review that?

Right now, the way study sections are set up, there are three special study sections to review AIDS proposals. I think a proposal for a regular study section that would incorporate people as in every other branch of the NIH to look at some of these issues might be something that the Commission might consider.

I will stop there.

[The prepared statement of Dr. Laurence follows in the Appendix.]

DR. LILLY: Thank you, Dr. Laurence.

Our next speaker is Dr. Klaus Dierig from Augsburg, West Germany, who is going to talk to us about his ideas about the involvement of syphilis in the AIDS syndrome.

DR. DIERIG: Mr. Chairman, members of the Commission, my name is Dr. Dierig from Augsburg. I want to introduce my partner, Dr. Waldthaler, who will present our testimony to you.

DR. WALDTHALER: I hope you won't mind if my English is not as good, and I will progress a little more slowly.

We are anesthesiologists with an office in Augsberg, Germany, and both of us spent years working in an intensive care unit. 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-3 became available in early in 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 condition. 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 the immunosuppression 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;

-- T-4 (helper/inducer) cells: In three cases, an increase was seen, for example, from 93 to 383 per microliter and from 205 tp 774 per microliter; in other cases, an initial decrease and an increase after two months;

-- T-8 (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 improvement, for example, the resolution of lymphadenopathy, skin problems, and herpes zoster, suggest that the increase in T-8 numbers may be due to an increase in cytotoxic cell numbers.

-- Lymphocyte mitogenesis assays with PHA, Con A, and PWM all improved in the 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 immune competent 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 analysis of CICs revealed the presence of treponemal antigens, the CICs dropped significantly.

-- Lysozyme: Increases were note in all cases where it was measured. In one case, the increase was over 200-fold.

-- Beta-2-microglobulin, which is a loosely bound part of the major part of the major histocompatibilitiy complex 1 in our patients remained above the normal range. The variable region of gp 120 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 mechanisms is responsible for the increased level of Beta-2-microglobulin in HIV-positive patients.

-- Vitamin B-12 and folate were measured because of anemia with high MCV, hypersensitivity to TMP/SMX, and an increase of T-4 and B cells after administration of potassium iodide. Vitamin B-12 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 sulfonilamides 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 1:5120. In the second case, it dropped from 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.

Syphilis may be a potential cofactor for acquired immunodeficiency. We conclude that in the HIV-positive patient:

-- first, a positive VDRL means active syphilitic infection;

-- second, a negative VDRL with a positive treponemal test means the presence of treponemal antigen;

-- third, a negative VDRL and negative treponemal test do not exclude treponemal infection because specific antibodies may be hidden within CICs, and antibody specificity is lost over time;

-- fourth, monoclonal antibodies may prove more helpful to diagnose syphilis;

-- fifth, 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 will contribute to the better understanding of some aspects of the HIV epidemic.

[The prepared statement of Drs. Dierig and Waldthaler is included in the Appendix.]

DR. LILLY: Thank you, sir.

Our next speaker is Dr. Arthur Gottlieb from the Tulane Medical Center, who has had a great deal of experience also with AIDS on both clinical and research levels.

DR. GOTTLIEB: Admiral Watkins, Dr. Lilly, ladies and gentlemen of the Commission, I am Dr. Arthur Gottlieb, and I'm Professor and Chairman of the Department of Microbiology and Immunology and Professor of Medicine at the Tulane University School of Medicine in New Orleans, as well as Chief Executive Officer of IMREG, Incorporated, 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 infections. My comments reflect my perspective and experience at the academic/industrial interface and as the inventor and developer of IMREG-1, an immunosupportive biologic, which is now near completion in Phase III trials in AIDS and ARC.

I have presented my CV to you. I might say that I have been a biomedical investigator for some 25 years from my initial training at NYU, the National Institutes of Health, and at Harvard. I have held faculty positions at Harvard Medical School, Rutgers University, and Tulane Medical School. I have been associated with the latter institution for over twelve years in my present position.

I have presented previously to you a position paper by myself and Dr. Robert F. Gary, my colleague who is with me today. He is the red-headed chap in the front row and is also Associate Professor of Microbiology and Immunology at Tulane.

Because time is short, I will simply highlight some of the points that I have made in that position paper. I might say that Dr. Gary's expertise, and it is considerable, is in virology and that he and I were responsible for the 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 United States.

The principal message that I would leave with you today is that the national effort directed to treatment of AIDS and ARC needs to place greater emphasis on ways and means to correct the state of immune deficiency seen in patients with these disease states. I believe that there is a need to pursue this objective with at least the same commitment as is being directed quite properly to the antiviral drugs.

It appears that some interest is developing in this area, but to date, the development of immunosupportive drugs has clearly had a lower profile and seemingly a lower priority.

It should be noted -- and you've had adequate evidence to that this morning -- 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 this virus on the immune system at both a cellular and molecular level, as well as a clear understanding of the regulatory abnormalities that result from HIV infection.

For example, we have very little information about the cells that are needed to trigger immunity against this virus. We remain puzzled as to why initial infection leads to circulating antibody which is not protective.

We submit that while extensive efforts have been undertaken in the area of the development of antiviral 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 the development of useful vaccines.

Moreover, in our judgment, there has been a lack of appropriate emphasis on the development of drugs and biologics which can repair or modify the state of immune deficiency. The drug development programs currently underway are, in our judgment, weighted too heavily in the direction of antiviral 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, in particular, has been unclear.

The specific rationale for an immunosupportive or biologic in HIV-associated disease is as follows:

-- One, a principal feature of this disease is clearly an immune deficiency;

-- Two, although it is possible, as Dr. Haseltine described, to design a program for the development of antiviral drugs for widescale application to all HIV-infected individuals, such drugs are not presently available. The anticipated timetable for such drugs is a minimum of five years with timeframes ranging out to fifteen years;

-- Three, 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 antiviral would eliminate the necessity for an immunosupportive drug, since the immune system would regenerate on its own, it is,

in my judgment, quite important to point out that the ability and/or the period of time required for appropriate lymphocyte cell populations 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, in fact, enhance immune reactivity against strains of HIV virus which infect particular patients. That is, this might provide a means for enhancing the ability of a patient's own immune system to react against the particular viral strains which have infected that patient. This concept of post-infection vaccination, which is possible owing to the long latency period seen in this disease, has been advanced by several researchers and is an initiative that should be vigorously addressed since:

-- one, it might provide a means for possible protection of patients who have already been infected with HIV;

-- two, it would be an extremely useful ancillary to a vaccine if a vaccine were developed;

-- and three, it would reduce the need to come up with effective vaccines against multiple viral strains.

I would like now to briefly describe a case in point concerning development of an immunosupportive biologic, because I think that in this brief history a number of points are made which the Commission needs to consider.

The particular 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 human immunity, in particular substances that could strengthen the body's response against foreign substances such as tetanus toxoid (or tetanus 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 now been shown to bear a chemical relationship to the enkephalins, a group of important neuroregulatory 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 immunoregulatory substances 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 known to affect cell mediated immunity, and therefore it is 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 properly 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 placebo controls, as we were looking for some effect on immunity and the need to assess toxicity. We did see evidence of improved immune function, as well as clinically beneficial effects without observable toxicity, and we have seen, by the way, no enhancement of viral production.

On the basis of these earlier studies, the company has invested time, effort, and funds in a multicenter placebo control trial of IMREG-1 in AIDS/ARC which could not wait for application to, and negotiations with NIH for support of such a trial, although I might say that an offer of cooperation from NIH, had it come forward then or if it were to come forward now, would not be declined.

Such a trial has been undertaken and has essentially been completed. 150 patients who were judged to have a high risk of developing AIDS in a six-month period have been enrolled and randomized in a 2-to-1 fashion. We expect to have the results of this trial in hand and a judgment of the efficacy of IMREG-1 in AIDS/ARC made by an independent scientific review group by the end of March.

I might say that these developments have been undertaken completely on our own resources, involving some $10 million over the last six years, and in particular, not a single penny of federal support has been used.

I would also emphasize that 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, with knowledge of the FDA, providing IMREG-1 for six months to any patient who completed the trial or reached an endpoint.

That concludes my prepared remarks, and I shall, of course, be pleased to respond to your questions.

[The prepared statement of Dr. Gottlieb follows in the Appendix.]

DR. LILLY: Thank you, Dr. Gottlieb.

Dr. Primm, would you like to begin the questioning?

DR. PRIMM: First, I'd like to compliment Dr. Laurence on such a well-written paper and one that's comprehensible not only, I feel, by physicians but by people who are not so aware of some of the many, many difficult terms that are used to describe this very difficult subject of human immunodeficiency virus infection.

I was very much interested in your co-factor study of other viruses and their impact on going on to develop full-blown AIDS. That was a study done in New Orleans at one of the drug treatment programs there, the Desire project, where almost 50 percent of the population tested were not positive -- drug-abusing population tested in a methadone treatment program -- were not positive for HIV-1 but were positive for HTLV-1.

What is the significance of that? Why do you feel drug abusers or intravenous drug users have a seropositivity of HTLV-1, and what does that portend for my population that I treat on a daily basis?

DR. LAURENCE: Well, first of all, HTLV-1 is a very much more important problem in the United States, particularly among drug abusers, than in the small study that I mentioned that came out of Trinidad. In Trinidad, approximately 6 percent of the population that they studied was positive for HTLV-1. In one borough of New York City, Queens, 27 percent of all intravenous drug abusers screened at HTLV-1 and HIV. In one city in New Jersey, Newark, 18 percent of all intravenous drug abusers screened that were HIV-1 positive also had HTLV-1.

The reason why there's such a high incidence of HTLV- 1 is probably because of the way it's spread. It's spread primarily through blood and sexual intercourse, the same way HIV is. It is known through at least laboratory experiments that HTLV-1 requires, probably almost certainly requires, cell-to-cell transmission, as opposed to HIV which can be transmitted as a free circulating virion.

Presumably this virus gets into a population like drug abusers and is transmitted through needles and shared through blood drawn up in a needle and remains in that population. I shouldn't say that this is limited to the drug abuse population. Six percent of all gay men screened in New York City that had HIV-1 also had HTLV-1 in a similar study.

Now in terms of co-factors, we have this one small study that came out of Trinidad. It was easier to do in Trinidad, because people argue that if you did it among drug abusers in the United States, especially in urban centers, their access to the same medical therapy perhaps as a gay man or someone in a higher socioeconomic level might be different, and that might be biasing it. But it said that it seems to be important.

We take that back to the laboratory, and in the laboratory we know that if you take this controlling region of HIV-1, known as the LTR, and you hook it up in a system that has an easily demonstrable readout -- we look at the ability to turn on another gene -- we know that if you put in an HIV-1 gene, tat-III, it will turn this gene on. If we put in one of these controlling regions known as tat 1 from the HTLV-1 virus, it will turn it on. If we put in T-cell activators, it will turn it on. It presumably also will turn on increased replication of the HIV-1 virus itself.

So the concern is that by getting two viruses, particularly HTLV-1 but maybe also HSV-2 and a couple of other viruses that have been shown to do what we call up-regulation or transactivation in the test tube, it might be an important cofactor for developing the disease in the body.

We just need larger studies, and those studies are being done. You know, I'm projecting from small studies. This Trinidad study was 100 people.

DR. PRIMM: Well, I wanted to just ask you one more question, and that concerns the narcotic implements used by addicts when they're shooting up. As you know, they use a needle and a syringe, and they also use a cooker, and they also use a small piece of cotton to filter the drug once they draw it up in the syringe.

What do you think the presence of -- or do you feel that there might be some inoculum or virions contained in the cooker itself or in that cotton ball?

We often see a seeding of the lungs on X-ray, and you probably have seen that, I'm sure, at Cornell in narcotic addicts who have shot up over a period of years.

What do you think the chances are, and I'm trying to relate that to the needle exchange program that's been mentioned here in New York City?

DR. LAURENCE: Well, I think if a cooker is used in a way that I imagine it's supposed to be used, and that is you actually, over an alcohol lamp or a flame, boil a concoction of

drug, then you are probably going to inactivate this virus. It's known that heating a viral preparation at 56 degrees Centigrade for a certain period of time is sufficient to destroy the activity of that virus.

In terms of something that may be resting on the cotton, we don't know, and that's a potential other vector.

DR. PRIMM: Thank you.

DR. LILLY: Dr. Walsh?

DR. WALSH: I would be curious to know what you think, Dr. Laurence or Dr. Gottlieb, any of you, as a matter of fact, Dr. Dierig, from listening to Dr. Haseltine. I got the impression of considerably more optimism in the area of chemo prevention than we have received from anyone else that has appeared before this Commission, within the bounds of your profession.

Do you share that optimism?

DR. LAURENCE: I share the potential for that optimism based on the two studies that Dr. Haseltine was talking about. One of them was done at Cornell-Ithica, and that was if you take a cat and you infect it with the feline leukemia virus, and you give it AZT, you can prevent that cat from getting infected. If you give cats feline leukemia virus and then you withhold AZT for upwards of 48 hours, you can absolutely prevent many cats from being infected, so you can withhold therapy for 48 hours and that cat will not acquire circulating virus, will not have latent virus and so forth. They use very high doses of AZT. They use the kinds of doses we are using in man. They had some anemia but they were able to prevent infection.

Dr. Haseltine's colleagues at Harvard did a similar experiment, but they used murine leukemia virus, another retrovirus, and they showed that if you put lower doses of AZT along with alpha-Interferon into this mouse, you can delay the -- I forget exactly what the period was -- you could prevent the infection of that mouse. And that is terrific news.

Now the bad news is feline leukemia virus and murine leukemia virus are not AIDS viruses. They lack the important regulatory element that so many people here have talked about. They lack these transacting factors.

So that it is truly unknown. These studies need to be done in a human population and, in fact, they are. There is a study, a non-controlled study that I have been informed is going on in Miami, in which surgeons that have had significant needle cuts or significant knife cuts with someone who is known to be

positive for HIV, would be given AZT, and they would be given it at the standard dose for 12 weeks.

Now the chance that you are going to get the HIV virus anyway from that contact is statistically only about three percent, so they are going to have to get a lot of people treated before they see some scientific data, but it is being done.

So I share Dr. Haseltine's optimism based on animal models, but my caveat is feline leukemia and murine leukemia are poor models for aids.

DR. WALSH: Dr. Gottlieb?

DR. GOTTLIEB: It is an interesting concept in principle. I think one would have to be rather cautious in its application, particularly with antiviral drugs that may have suppressive effects on bone marrow, immune cell progenitors or immune effector cells. I think a great deal of thought would have to go into that, but we shouldn't, by any means, exclude that sort of initiative. It is interesting in concept.

DR. WALSH: That was my prime question.

CHAIRMAN WATKINS: Dr. Lee?

DR. LEE: One quick one for you. It is interesting that so few HTVL-1 positive people have advanced disease. The fact is that everybody seems to get the disease from HTLV-3, and yet there are obviously a lot of asymptomatic carriers with HTLV-1. Do any of you have any gut feeling about how many carriers we are going to end up with HTLV-3?

DR. GOTTLIEB: I think it would be difficult to know. The epidemiologic studies are presently ongoing, and certainly there is concern about HTLV-1, as I understand it, in areas of the country that are close to the Gulf of Mexico and the Carribean where the virus is more endemic. But I don't have any good figures to share with you.

CHAIRMAN WATKINS: Dr. SerVaas?

DR. SERVAAS: We met with Dr. Resnick who has a paper about acyclovir and hairy cell leukoplakia. Do you consider that an antiviral -- is that interesting to you, and what do you think about herpes as a possible co-factor? Do you think it is?

DR. LAURENCE: In the test tube, herpes simplex virus will activate the same region of the HIV virus that is supposedly responsive to the HIV transacting element. So in the test tube it is certainly a co-factor. But in humans, you heard Dr.

Haseltine say that the CDC feels there are no clear co-factors, and there is a paper that just came out in which some of the authors were CDC members, looking at Epstein-Barr, CMV and the herpes simplex viruses, and the only virus that fell out of that as a potential co-factor was herpes simplex virus type 2, and not type 1. So these are very preliminary data. They need to be looked at more. There is certainly a test tube model for it.

In terms of acyclovir for hairy leukoplakia: Hairy leukoplakia is a whitish lesion on the inside of the mouth and in the gums, and is associated with AIDS and HIV infection. Some people feel it is an early manifestation that people that get it much more rapidly go on to develop clinical AIDS than if you are asymptomatic and you didn't have it, and a lot of that work comes out of NYU.

The virus -- what causes hairy leukoplakia is thought to be both Epstein-Barr virus and a papilloma virus, and acycylovir apparently has some sort of effect -- has an effect on herpes simplex viruses, has an effect on Epstein-Barr viruses, probably doesn't have an effect on papilloma virus, but depending on the direct viral cause, it will help one and not help the other.

Whether or not that would ever prevent anyone from going on to develop full-blown clinical AIDS hasn't been looked at. I doubt it. I figure they're probably too far along at that point.

DR. SERVAAS: Thank you.

DR. LILLY: Dr. Conway-Welch?

DR. CONWAY-WELCH: A couple of quick questions. Dr. Gottlieb, in your summary, you indicated difficulties with folks accessing funding through some of the more traditional channels. We have heard previous testimony about the need for investigator-initiated awards and mechanisms. Would you be able to share in writing with the Commission some very specific recommendations regarding investigator-initiated awards or that genre?

DR. GOTTLIEB: Yes, I certainly would, if I could make just a brief point. I was quite interested in the discussion this morning, because I fully support that. I think we need much more basic science, and that's what has gotten us to the understanding we have. But I do think you need to recognize that when people work in medical schools around the country, they are generally dealing with grants on the order of $50,000 to $100,000, and that doesn't buy very much. It certainly doesn't place you in the same position as the larger laboratories at the NIH which may have multi-million dollar funding budgets.

So I will be happy to address that quite specifically.

DR. CONWAY-WELCH: Thank you. That would be helpful.

Dr. Laurence, you mentioned that some surgeons in Miami, once they cut themselves or had multiple needle pricks, would immediately start AZT therapy. We have had previous testimony from the emergency room physicians that alluded to the fact that that might be a therapy they would initiate on themselves. Also several other scientists suggested that.

Do you think that we should frame a recommendation having to do with protocols for needle sticks for health care personnel that are as aggressive as what you seem to be suggesting?

DR. LAURENCE: I would think not, at least for the ordinary single pinprick through a glove that most health care workers are exposed to. But maybe for the significant needle sticks, when you are talking about a surgeon exposed to a significant risk from a scalpel cut or a needle puncture in which you can statistically tell what the risk is to that surgeon. It's 3 percent. The numbers are approximately .08 percent of all those people that have significant stick. The statisticians tell us that based on the null hypothesis, that probably represents a real number of three out of 100. That's a big number to me, and I think that population should be studied. So I am not recommending AZT for the nurse who may or may not have a little scrape with a needle, the kinds that I see all the time.

And I think what the proposal should be put out for is perhaps not doing something as drastic as I understand they are doing in Miami, and that is giving full dose AZT for a prolonged period of time, 12 weeks; but more towards the animal models, and that is perhaps lower dose AZT in combination with alpha-interferon, which seems to work very well in animals.

DR. CONWAY-WELCH: Could you frame something along those lines for us and send that to us?

DR. LAURENCE: I'd be happy to.

DR. CONWAY-WELCH: And my last is for Dr. Dierig. I understand you have not included any women in your studies.

DR. DIERIG: No.

DR. CONWAY-WELCH: Do you have plans to, and do you have any notions that there may be any different response?

DR. DIERIG: Between --

DR. CONWAY-WELCH: Men and women.

DR. DIERIG: No. No. Not at all.

DR. CONWAY-WELCH: Do you plan to go on and include women?

DR. DIERIG: We tried, if we have a possibility, we want to try.

DR. CONWAY-WELCH: Thank you.

DR. LILLY: I would like to ask a couple of brief questions of Dr. Dierig, and then another one of Dr. Gottlieb.

Dr. Dierig, how many patients have you studied so far?

DR. DIERIG: Six.

DR. LILLY: Six patients you have studied so far. From your studies, what fraction of HIV positive people do you think might be benefited by anti-syphillitic therapy?

DR. DIERIG: I don't understand you.

DR. LILLY: What percentage of HIV-infected people do you think might benefit from syphillitic treatment?

DR. DIERIG: I have no idea, to take a percentage out of this.

DR. LILLY: Do you think it is a significant fraction?

DR. DIERIG: I think it is a significant fraction, because it is in the same risk group.

DR. LILLY: How do you identify those people, those people who might benefit from anti-syphillitic treatment?

DR. DIERIG: This was maybe by using monoclonal antibodies, because they found that serology is not reliable on those patients. The antibody specifically is lost, and to use monoclonal antibodies, we have those antibodies, and if someone has symptoms like our patients have, lymphodenopathy, and so I first would treat, because in all patients lymphodenopathy was attributed to the -- of course, he has to have lymphodenopathy because he is infected with the HIV virus. In all patients lymphodenopathy disappeared. So it is not possible that this lymphodenopathy was a virus lymphodenopathy.

DR. LILLY: Okay. Thank you very much.

Dr. Gottlieb, we have had a very interesting presentation today about rational drug development. It seems to

me that it is relatively easy to see how, by studying the viral life cycle, one might identify points in that cycle where one could conceivably attack by chemotherapy in some manner.

Is that, to any extent, true with immunotherapy as well? Could we apply rational drug development in that sense, or in any other sense?

DR. GOTTLIEB: I think it is a very interesting question, Dr. Lilly, and my general response would be yes, but we are certainly not as advanced in respect of that initiative as we would be in the antiviral area, because we know much more about the virus.

I think there is a body of fundamental information about immunology which allows us to take certain approaches. I must candidly tell you that the approach we took was not taken by that means. We were much more empirical. Nevertheless, I think it certainly would be possible, for example, with the molecules we have, to make analogs, derivatives, and/or better forms, and so on.

So I think there is a need for that. I would like to emphasize, however, that there is a perception that I gleaned from the discussion this morning, and elsewhere, that if you have something that is immuno-enhancing, you are necessarily going to enhance production of the virus. That doesn't necessarily occur. It does occur with PHA and/or IL-2, and you have to look for that. You can do that in your pre-clinical screens, and you must do that. But once you pass that barrier, it seems to me that you should go on and develop these drugs. These are very important initiatives that we are not, in my judgment, emphasizing sufficiently.

DR. LILLY: Thank you, sir.

Admiral Watkins?

CHAIRMAN WATKINS: Dr. Dierig, what approaches have you made to the special task force under the World Health Organization about your theory about possibly expanding studies, about possibly working with the World Health Organization in your effort?

DR. DIERIG: We sent last year a preliminary report about some patients, but we didn't get an answer.

CHAIRMAN WATKINS: What has been the reaction within the Federal Republic of Germany on the issue? What has been the national response? Are there more studies planned? How have your theories been received by your own government?

DR. DIERIG: We did all those studies, all those treatments, without any support, with no support from the state, no support from any commission. We even paid for the laboratory data from on own.

CHAIRMAN WATKINS: You have no scientific support coming from the government itself?

DR. DIERIG: Until now, we have no support.

CHAIRMAN WATKINS: Dr. Gottlieb, we have heard some of the concerns you expressed today about perhaps the heavy focus in antivirus as opposed to immune-modulating drugs. Could you give us a little more specific recommendation, perhaps, of how you might see a better balance in resources dedicated to the two options?

You kind of implied that we may be building a Maginot Line on one side, and we are confining ourselves a bit, and we should be expanding our vision about the possible intervention in the work of the virus.

DR. GOTTLIEB: I think the answer to that question really is twofold, and I perhaps need to reflect on it a bit and give you a more detailed written answer. But one point is that there is a perception in the scientific community, particularly among the people in the more virologically-oriented disciplines, that the way to deal with this disease is to develop antivirals, and I totally agree. You have a virus, you would like to get rid of the virus. At the same time it is very difficult to develop antiviral drugs, and these patients have an immune-deficiency, there is no argument about that.

If in fact there are agents, and we may have one, but even if ours is not perhaps the best to come along, I still believe in the principle -- if there are agents that are nontoxic or have low toxicity that can treat the patient's immune deficiency, that is a desirable objective. And I don't sense in the discussions, particularly from the government sources and the NIH, that this has a very high priority. There are initiatives in the interferons, there are initiatives in the interleukins and so on, but if you look at that list similar to the one that was published in The New York Times earlier this week, you will see that by and large these things have low to medium, if any, priority. And I think we need a better balance in that regard.

I just don't sense that the commitment to drug development under the Government aegis is as strong in the area of immuno-modifiers, and what I call immuno-supportive agents, as opposed to immuno-stimulants -- to draw the distinction with agents that may stimulate production of virus. We need to do much more in these areas.

CHAIRMAN WATKINS: Would you give a little more thought to that and if you can, in the very near time frame?

DR. GOTTLIEB: Absolutely.

CHAIRMAN WATKINS: Would you discuss it with either myself or our staff representative? We have heard this before, I would like to get a little more steam in that engine, because I think you are making a good point. We need to know a lot more about it, and to see if there is some influence that we can bring to bear, particularly if we are going to be able to put more resources into the search to highlight this area.

And I would like to have whatever supporting documentation from your colleagues that might feel the same way. Is this a general concern? Or is this just a concern coming in from the special interest side of it? Or is it a general medical concern?

DR. GOTTLIEB: I think it is a general concern with many of the colleagues I talked with. I can't represent the entire medical community. But I will be happy to address that for you.

I might say this, Admiral, as a practical matter, if the timeframe for developing antivirals is as long as it appears, we'd like to do something for these patients in the interim. If there is a way of doing that I think we should do it.

CHAIRMAN WATKINS: Well, I certainly think we all would agree with that. The question is what can we do as the Commission to bring special focus to your point.

Would you just tell us briefly, did the IMREG trials include women?

DR. GOTTLIEB: Yes, there are some women, but it's predominantly a male population. They are IV drug users. We are at eight centers nationwide, three in New York, one in Boston, Cleveland, New Orleans, California.

CHAIRMAN WATKINS: Do you have any early indication of how they might react differently to immune modulators?

DR. GOTTLIEB: No. The data are still blinded. We will know fairly shortly, and I think it would be premature for me to comment on any information we might have from the earlier trials.

CHAIRMAN WATKINS: We would be very anxious to be an early recipient of your end-of-March report, and any advance information you could provide the Commission would be very helpful.

DR. GOTTLIEB: Certainly. Fine.

DR. LILLY: The hearing will now stand adjourned for a very small number of minutes: five to seven minutes.

[Recess.]

A F T E R N O O N S E S S I O N

[1:15 p.m.]

DR. LILLY: If we can come back to order, please.

Our first speaker of the afternoon is Dr. Malcolm Martin, who is the Director of the Laboratory of Molecular Microbiology at the National Institutes of Health, and a researcher who has for many years been working with retroviruses both in animal models and in humans.

Virology and Retrovirology

DR. MARTIN: Thank you, Frank.

I should perhaps introduce myself. I am a government employee. In my capacity as an NIH Laboratory Chief, I direct a group of about 40 individuals who conduct research in various areas of virology. Most of the staff in my department work with retroviruses, and about half of them investigate HIV. So what you are going to hear are the thoughts of an investigator who concentrates on the biology of HIV.

Dr. Lilly asked me to give the Commission my perspective of where we stand today regarding the biology of HIV. I thought in the few minutes allotted to me I would put what we know about HIV in a conceptual framework and indicate points of vulnerability during HIV infection for which the development of antivirals might be considered.

Could I have the first slide, please.

I am going to show slides, so you are probably going to have to turn around, and we are going to need the lights off in the front.

Some of this material has already been presented today. It is more than four years now that a virus has been identified with people infected with what we now call the human immunodeficiency virus. We have learned a lot about this virus during this period of time. However, I should point out that, despite the explosion of information about HIV, we are talking about a system with no animal model. Furthermore, virtually everything we know about HIV comes from experiments done in the laboratory using human T-cell lymphocyte tissue cultures.

Next slide, please.

Now this is a slide given to me by Dr. Koch from Sweden. It is an idealized version of the human immunodeficiency virus particle, constructed from EM photographs. Those green tree-like structures around the outside are components of the viral envelope, the gp120 you have heard about. The ball of that green structure is the part of gp120 which interacts with the receptor on T4 lymphocytes, macrophages, and other human cells. This portion of gp120 permits the virus to attach, and subsequently enter target cells.

Inside the virus you see a core-like structure. This core is encoded by the HIV gag genes; deep within the core is the genetic material of the AIDS virus, the two RNA molecules shown in yellow. Those little orange structures in the center of the slide represent the enzyme you have heard a lot about: the reverse transcriptase. Molecules of reverse transcriptase are attached to the RNA, primed to do their "dirty work", that is to make a DNA copy of the viral genetic material (RNA), which then become inserted into the chromosome of the infected cell.

A question frequently asked of me is, "Why is it so difficult to deal with the AIDS virus? Why is it so difficult to deal with retroviral infections?"

I have listed on this slide a series of RNA viruses that we know about: polio, measles, and HIV. As can be seen, when polio and measles infect cells, those little orange circles, representing virus particles, attach to cells. They are binding to those structures sticking out from the circle, the so-called virus receptor.

After a period of time usually measured in hours, both measles and polio viruses make RNA copies of their genetic material, produce viral proteins, and these proteins are then assembled into progeny particles indicated by those yellow dots in the third and fourth panels.

At a point later in infection, the cells infected with measles or polio virus burst, and die. Subsequent to cell killing, the immune system comes into play, antibodies are elicited and, in most cases, the infection is controlled. Infected individuals, after developing symptoms characteristic of these two types of viral infections, recover.

In contrast, HIV, like other retroviruses, although containing an RNA genome, does not produce progeny RNA molecules directly. Instead, a DNA copy of the viral RNA genetic information is made, using reverse transcriptase. However, this DNA copy of HIV is not capable of programming new viral proteins or new viral particles. Instead, what happens is that the DNA

copy enters the nucleus of the infected cell, and a copy of the HIV DNA becomes permanently inserted in to the chromosomes of the infected cell.

There are two possible outcomes of having this piece of HIV inserted into the chromosomes of infected cells. If you follow the right path of the slide, one can see that the copy of HIV, which is now part of the cellular chromosome, can direct the synthesis of viral proteins and viral particles resulting finally in the release of progeny virions from the cell.

On the other hand, as shown on the left-hand portion of the slide, the HIV genetic information, may just remain dormant, situated on the chromosome to which it was originally attached. When this cell divides, you are going to have two copies of HIV DNA. In the next cell division, there would be four, then eight, 16, et cetera, et cetera, copies accumulating in tissue cultures or infected cells.

The point here is that the genetic information for the retrovirus is permanently part of the genetic apparatus, the DNA, of the infected individual.

Another frequently asked question is, "Where did the AIDS virus come from?" This slide indicates that on the basis of molecular biologic analyses, it is clear that HIV is a member of the retrovirus group. You can see, however, that in comparison to prototype retroviruses, such as the murine leukemia virus or Rous sarcoma virus, which only have three major genes--the gag or core gene, the polymerase gene, and the envelope gene--the AIDS virus has several additional coding sequences and is therefore more complex. Some of these sequences, such as <u>tat</u>, <u>art</u>, or "B", encode proteins that regulate HIV replication in T-lymphocytes.

Another question that has come up is what is the relationship of a virus that you will hear about from the next speaker, a simian immunodeficiency virus or SIV, to HIV-1 and HIV-2? This slide indicates that there are many branches of the retrovirus family, most of which are associated with or cause neoplastic diseases. One branch represents the lentivirus family, of which HIV is a member. The several arms of the lentivirus family tree include viruses affecting horses, goats, cats. and also, of course, primates. On this slide, I have only illustrated three limbs of the primate lentivirus tree, and, based on what we know from detailed analysis of the structure of the SIV, HIV-2, and HIV-1 genomes, we can say that SIV and HIV-2 are very closely related to one another. At the DNA level, SIV and HIV-2 are different primate lentivuruses and are clearly more related to one another than either is to HIV-1.

The next slides indicates that when you do a detailed analysis of the RNA present in different isolates of HIV-1 -- isolates from New York, San Francisco, Alabama, and Zaire -- the conclusion is that no two isolates are the same. The differences that we see in the genetic structure of the viruses actually predominate in the envelope region. However, all of the other genes are also divergent but not to the extent seen in the HIV-1 envelope. The significance of this difference and the role of the immune system in producing this diverse group of viruses is unclear. Furthermore, the effect of this diversity on our ability to produce effective and protective vaccines is not presently understood.

As Bill Haseltine indicated this morning, many labs have studied the structure and function of the different HIV genes and the proteins they encode. An approach that many labs have followed, including ours, has been to produce defined mutations in different HIV genes, and then analyze the effect of the mutations when they are introduced back into the HIV genome.

These kinds of experiments can be done on several different levels. You can take an individual gene, for example, the HIV polymerase gene, shown at the bottom of the slide, and introduce it into a system that produces the enzyme reverse transcriptase and no other protein. You can then ask questions about the structure of reverse transcriptase and its function. It would also be possible to produce a lot of reverse transcriptase by this method and ask what potential drugs can be developed to interfere with its action.

One approach that we have used is to actually produce a mutation in a particular gene and then reintroduce it back into an infectious molecular clone of HIV and ask what happens to virus production in infected T-cells. Because of time limitations, I will just mention two experiments of this type that we have carried out involving the envelope gene and the HIV gene that is designated "A" on the slide.

This next slide shows that a portion of the viral envelope called gp120 interacts with a protein receptor on the surface of human T-cells called the CD-4 molecule. This process is called adsorption and represents the phase of infection when the virus particle attaches itself to the cell. As the slide indicates, following the attachment step, the outer coat of HIV fuses with the cell membrane and the virus particle enters the cell.

All of the steps occurring during the early phases of infection are amenable to attack of we are clever enough to identify drugs that could block any one of them. For example, if we understand what portion of the envelope is involved in adsorption or penetration, and know the biochemistry of these

various reactions, we could design specific inhibitors of infection to stop HIV at the "portal of entry." I will discuss one type of study involving the HIV envelope and these early steps of infection carried out at least in three different laboratories.

The next slide depicts the coding sequence for gp120 in a cartoon form. The black and white rectangles indicate that portions of the HIV gp120 are divergent or highly conserved, respectively. We collaborated with scientists at Genentech and inserted an envelope mutation they had made, which affected binding to the CD-4 receptor, into our infectious clone of HIV.

In every case examined, individual amino acid substitutions affecting the segment of gp120 shown on this slide, resulted in a virus that was unable to bind to the CD-4 receptor and were therefore defective.

This particular discovery now will enable us to focus in on this specific portion of gp120, and possibly generate a form of HIV that is incapable of binding to its natural receptor, and might be, for example, an attenuated vaccine candidate.

This next slide summarizes work from many different labs across the country and indicates the functional domains of the HIV envelope.

You know, of course, there are two envelope proteins, the so-called gp120 and the gp41, and as illustrated on this slide, there are different functional roles. There is a portion of gp41 that's involved in fusing the membranes and allowing the particle to get into cells. There's a part of the gp120 that I just talked about that's involved in binding to the receptors. There's another part of the gp120 that's involved in getting the particles actually to penetrate and get into the cells, and we feel, and many other labs feel, by understanding in detail the processes involved in the early stage of viral infection, we will then better be able to design drugs and attack this very crucial phase of infection.

This next slide illustrates on the intrinsic problems facing investigators in this field -- the mutability of the HIV genome. This is an experiment showing the replicative cycle of wild type and mutant HIV. The black spots are the reverse transcriptase activity representing new virus particles which appear during infection. As you can see, the black spots peak around day 12 to 14; that is what you would expect to see with fully-infectious HIV.

In contrast, the HIV mutant containing a defective envelope gene, was completely dead and producing no reverse transcriptase, even for periods up to 60 days.

At the bottom of the slide is an example of what happened to this mutant in three experiments out of thirty. Beginning on day 22, we started seeing the appearance of reverse transcriptase in cells infected with the "non-infectious" HIV mutant.

What was happening? Well, we actually cloned this mutant out and found out that this mutant had been repaired in tissue culture. That is to say the envelope gene was so "plastic" and so able to change that, despite the fact we started out with a defective mutant, a change occurred right under our eyes, permitting now this mutant of HIV to replicate and regain infectivity for human T-cells. This may be akin to what is going on in infected people who harbor heterogeneous collections of HIV. It could explain the variation observed from isolate to isolate.

One other experiment I would like to show today involves the sor or "A" gene of HIV. As you can see from the diagram, the "A" gene is unique to HIV. What does it do? That's shown on the next slide. In contrast to the normal, fully infectious HIV, which efficiently grows in human T-cells, sor or "A" mutant virus particles are not infectious as free virions. However, as shown in the upper part of the slide, the sor mutants can spread "cell-to-cell." So the sor or "A" gene of HIV is vital for particle-mediated infection. This experiment also impels that fully infectious HIV has the capacity to spread "cell-to-cell" as well as free particles. This is exceedingly important in considering the development of drugs and vaccines, since it means that infected cells as well as virus particles must be evaluated in such tests.

The next slide indicates that there are many other HIV genes, including a gene called tat, a gene called art, and a gene called B or 3'ORF. These three genes, in contrast to the others I have talked about, are "non-structural" genes; they code o they don't code for structural proteins, they code for regulatory proteins that regulate the synthesis of HIV RNA and proteins. In contrast, viral structural proteins in general are components of mature virus particles. Regulatory proteins govern the efficiency, or the rate of viral RNA or protein production.

This next slide illustrates the retrovirus life cycle. Initially, virus particles attach to and then enter cells. This is followed by a phase where particles then use their reverse transcriptase to make viral DNA. The viral DNA is then inserted into the chromosome, as I mentioned earlier, and finally, the viral DNA, located in the chromosome of the infected cell, is used for the production of viral messenger RNA, viral proteins, and particles. These particles are then exported from the infected cell

The next slide shows that the regulatory proteins, the tat, art and B proteins, act, as the five, six and seven in the life cycle of HIV, that is to say they regulate how much messenger RNA is made, they regulate how efficiently this messenger RNA is used to make proteins, and how these proteins then are processed to their mature forms. These regulatory proteins are never components of virus particles. Many people think that by understanding how these proteins work, one can devise drugs that would interfere with the efficiency of the whole process.

Information is now accumulating which suggests that none of the HIV regulatory proteins -- that is tat, art, or B -- act directly to regulate viral gene activity. What seems to happen is that these viral regulatory proteins interact with or stimulate cellular proteins and, together, the combination modulates the amount of virus particles that are produced. Inhibitors of the HIV regulatory proteins could also interfere with normal cellular processes, an outcome that could be deleterious to an infected individual.

This next slide brings into focus one of the major dilemmas of HIV infection in man: the great difficulty in demonstrating virus-producing cells in clinical specimens obtained from infected individuals. Thus far, everything I've said in terms of HIV virology has dealt with infected T-lymphocytes in culture.

As shown on this slide, the technique of in situ hybridization can be used to identify HIV infected cells. This cell, containing the black grains, represents one of the two cells out of a million that we examined from this particular patient which actively produced viral RNA. In fact, our examination of a series of patients would suggest that approximately one cell in 50,000 to one cell in 100,000 is actually making viral RNA and producing virus. One might ask, and several people have, how can AIDS patients be so sick yet harbor so few virus-producing T4 lymphocytes?

The next slide shows the use of in situ hybridization on a sample of brain tissue from an individual with HIV encephalopathy. Although it's not as clear as I'd like, this multi-nucleated giant cell, which clearly has black grains over it, represents a cell of macrophage lineage frequently seen in the brains of infected individuals. These large macrophages actively produce virus, and, of course, HIV RNA, which is detected by this technique. But here again, too, there is not an overwhelming abundance of particles.

So how can one explain a clinical picture associated with AIDS in the absence of significant viremia or evidence of virus producing cells?

Well, this is one possible explanation. In fact, I'm going to show you in a very dramatic form an experiment to go along with it. The big question is: "How does HIV kill lymphocytes?"

In the upper left-hand portion, yellow is a virus particle attaching to a cell. It then gets into the cell. The cell then starts producing particles. When such a cell meets up with a normal T4 lymphocyte, even in the absence of producing particles, the virus-producing cell is able to attach to the uninfected cells and actually produce a structure which is called a syncytium, and I think you can barely see it here. This is an example of a cell that actually represents the fusion of about 15 or 16 nuclei and these little dark objects represent the nuclei. The red area is the result of our using an HIV gag antibody in this experiment, and indicates that the syncytium is producing virus proteins.

In the laboratory, when you actually look directly into a microscope at infected cells, this big-balloon like structure represents the cytoplasm of a large syncytium, as seen by light microscopy of live cells. This syncytium may contain 20 to 25 nuclei. The formation of giant syncytia could represent a mechanism whereby one cell out of 100,000, that is producing or budding virus, can kill a large number of T4 lymphocytes.

This is just like the diagram I showed in a previous slide. We tested such a model experimentally by using a cell line that persistently produces defective virus particles. The chronic synthesis of virus particles obviously means that the surface of these cells is studded with the HIV envelope protein, gp120.

As the next slide shows, these cells were incubated with 10, 100, 1000, or 10,000 normal T4 lymphocytes. We simply asked how many viable T4 cells remained at various times following the mixing of the virus producing and the uninfected lymphocytes? As you can see, even when a 10,000-fold excess of normal lymphocytes was present, by 13 days, less than five percent were still alive. The experiment shown on this slide clearly indicates that a few virus-producing cells have the capacity to kill a large excess of T4 lymphocytes. Maybe this is one explanation for the paradox I mentioned a few minutes ago.

On this slide, we again see the life cycle of a typical retrovirus. While there has been a literal explosion of new information regarding the structure and function of HIV genes, most of our information comes from tissue culture systems. There are a lot of questions that we have absolutely no answers for that concern this "retrovirus life cycle" in an infected person. For example, how is HIV transmitted to an uninfected person?

A few minutes a go, I showed a slide which illustrated free virus particles infecting cells. That's certainly how we study HIV in the laboratory. However, there is very good evidences to suggest that the initial inoculum may very well be infected cells rather than free particles.

The implications of this on vaccine or antiviral strategies could be profound. How sensitive, for example, to antibodies raised against a vaccine would an infected virus-producing cell be, compared to a free particle? We don't know the answer to that.

If we are talking about the initial inoculum being an infected cell rather than a particle there are certain steps we don't have to worry about. For example, we probably don't need reverse transcriptase to get things started. A propos of some of the other data and information I presented showing the fusion of cells on a few slides ago, it is perfectly conceivable to think of moving nuclei from an infected cell to a recipient cell carrying along with in the process the already integrated copy of viral DNA. So this raises the possibility that some of the inhibitors for example have reverse transcriptase, may not necessarily be effective to combat this type of inoculum.

Another big question is, "What is the initial target cell for HIV infection in vivo?" In the laboratory, we commonly study the infection of T4 lymphocytes since this is the most efficient and reproducible system for the propagation of HIV. However, it is more than likely that the initial target of infection in an infected individual may be monocytes or macrophages rather than T4 lymphocytes. Furthermore, if lymphocytes are indeed the initial target, in vivo, most lymphocytes circulating in our blood are refractory to infection because they are not "activated." They are not dividing.

As the slide shows, unactivated lymphocytes may take up HIV but virus fail to replicated. The virus particles remain in a quiescent phase as indicated by arrow number 3, and sit around for several weeks until the cell is activated. We have recently carried out experiments indicating that this actually happens with human peripheral blood lymphocytes. Finally, as you heard earlier today from work that was originally carried out in our laboratory, the cells of the rectum and the colon represent a possible target and portal of entry for HIV. In the laboratory we have been able to infect cells of the lower GI tract.

The next slide shows that in the brain, the target for HIV is the macrophage rather than the lymphocyte. In the central nervous system, the majority of the cells, that is, greater than 95 percent of the cells producing virus, are not lymphocytes.

We know very little about the replicative cycle of HIV in macrophages. We don't know how effective some of the therapies that are being worked out will be, for example, inhibiting reverse transcriptase or protease, in cells other than T4 lymphocytes. However, a few groups including our own have been propagating and infecting human macrophages in culture. The next slide shows an infected macrophage. As was the case with lymphocytes, we observed cells containing many nuclei, representing the fusion of many, many cells. This may represent the initial phase of cell killing. Thus, like lymphocytes, macrophages may undergo fusion upon exposure to HIV and die as a result.

Another important question is "How does the virus spread in an infected individual?" We commonly think of it spreading as free particles. In fact that is the way we do experiments in the laboratory. But on the basis of what I showed you with the "A" or sor gene mutant, it is very likely that the virus has the capacity to spread from cell to cell via transmembrane "tunnels" without going through a free particle phase. This has implications again in terms of developing drugs to combat infection in an individual who is already infected.

Finally, a topic that you heard mentioned many, many times today, the issue of viral latency, if the viral genome is present in a cell in an integrated form, and is for example either methylated or exposed to certain proteins that are present in normal cells, no viral RNA, no viral protein will be made, no particles will be produced and we can go for long periods of time without any evidence of active infection.

On the other hand, this cell will divide, as I indicated earlier, and has the potential to represent a reservoir of many, many copies of the HIV genome.

This next slide is an example of another type of latency that I think was alluded to today. This is what happens in macrophages where virus particles are actually encapsulated inside vacuoles inside cells. There is virtually no budding of particles on the cell surface. The macrophages containing these vacuolated forms of the virus represent another potential reservoir for HIV.

So I think you can see that it is somewhat naive to think of a very simple model that we think about in the tissue culture system in the laboratory of just simply infecting cells with particles. Much more work needs to be done with virus in infected individuals. Certainly an animal model that involves the complete life cycle of the virus would provide answers to these questions.

I want to close by discussing the pressing issue of safety in the laboratory. As many of you know, during the past year, two laboratory workers have been infected with HIV. IN one case, the virus isolated had the same genetic structure, that restriction map, as the virus the infected worker was using. Many people think that a P3 laboratory is a panacea for HIV studies. However, aficionados of the containment business know that the main thing a P3 laboratory does that a P2 facility does not, is to protect an individual walking down the hall from being exposed to a human pathogen when the laboratory door is opened. This is because P3 laboratories are under negative air pressure.

The two individuals who were infected with HIV both worked in a P3 facility. Clearly, physical containment is not the answer. But we do need more contained labs. More important, perhaps, is the need for a national training program for people handling or propagating HIV.

In my travels around the country, I have encountered numerous scientists who are reluctant to work with the virus. Most indicate that they have no room or facility -- even at the P2 level -- to work with live HIV. What is also sorely needed is a good program to train people in the handling of human pathogens. How many have been trained to work with pathogenic organisms? I am concerned that other laboratory-acquired infections will occur. I am afraid that when this happens, it will be impossible to carry out basic virology on HIV.

As a result, I have discussed the idea of licensing investigators to work with HIV. We certainly license investigators in the proper use of radioisotopes. Although I don't want to rigidly control things in a way that would stifle research, licensure may be important from both safety and policy perspectives.

Finally I should point out that we might want to think about re-evaluating standards that we currently think about or use in terms of working with the virus.

Presently the Public Health Service has issued recommendations that fall out in terms of the quantity of virus that people work with. I might point out that the individuals who were infected worked in a laboratory setting where industrial levels -- 70 to 100 liters are produced a week. I serious question whether that quantity of virus has to be made.

I think we ought to be looking into the reasons for large-scale virus production. I understand that most of it is going into the present ELISA test to screen blood. There are certainly more modern ways to make proteins. By using more modern techniques, recombinant DNA biotechnology, to make large quantities of envelope and core proteins, for example. I think we

ought to urge the FDA to consider rapidly consider some of these second generation test kits for screening blood. That way the need for large scale virus production would be significantly curtailed.

Thank you.

DR. LILLY: Thank you, Dr. Martin.

I should comment that the Commission has an upcoming hearing on "AIDS in the Workplace," which will include not just any office but indeed will include the HIV study in laboratory. So that issue will come up. It would be very helpful if we could have in writing your recommendations for how to handle the problem, what your recommendations are for containment of HIV in the research laboratory.

Vaccine Development: The Institute of Medicine Conference

DR. LILLY: Our next speaker this morning before we go into questions is Mary Jane Potash, from the Institute of Medicine, who will report on the vaccine conference that the Institute of Medicine sponsored concerning the development of a vaccine for HIV.

DR. POTASH: Thank you. I have reversed protocol a little bit here and I brought my boss with me. This is Dr. Robin Weiss, who is the Director of AIDS Activities for the Institute of Medicine and also runs the AIDS Oversight Committee for the Institute of Medicine and the National Academy of Sciences.

I will make a brief statement concerning our vaccine conference and both Dr. Weiss and I will be glad to answer some questions.

Our vaccine conference arose from recommendations that were contained in the report, Confronting Aids, which was published about a year and a half ago.

At that point it wa suggested that we needed a forum to bring together government, industry and academic scientists to discuss both drug development and vaccine development for AIDS. I believe in your background papers you had the report of the first conference on drug development, which we held early in the Fall. The vaccine conference was held mid-December and we will have a report available for you probably in about a month.

I would like to really highlight three points from the conference.

First of all, what we might consider to be hopeful about vaccine development, what we think precludes vaccine development and then the issue that concerned the most controversy, being the entry into clinical trials.

I should say at the outset the sense of most of the conferees was pessimistic. That is, no one looked forward to rapid development of a safe and effective vaccine for HIV.

However there are a lot of experimental data which speak to what we have learned, and I will hit those as fast as I can.

We do know -- and Dr. Martin illustrated very clearly -- that there are specific regions of the outside surface of the virus which are necessary for the virus to infect cells. What we also know is that using those particular regions as antigens, they can be injected into experimental animals and these very regions elicit antibodies which block infection in culture. These are what we call neutralizing antibodies and it is an important term because once again what we know about infection is from tissue culture results.

We also know that cells which can kill virus-infected cells can be elicited by immunization with certain constructs of the virus.

We know quite a bit about the way to elicit avid immune responses: that is, how to construct a very good preparation which will make a large amount of antibodies or a large amount of cells which kill infected cells.

We have a good animal model in the parallel simian immunodeficiency virus infection in macaques.

I think that there are certainly results in human beings in both the generation of neutralizing antibodies and the generation of killer cells, which indicate that we do promote -- we do have -- some immune responses to HIV. In fact we of course detect infection via our immune responses to HIV.

The question is what relevance these immune responses have to the course of disease progression and the answer, as far we call tell, is none. So we need to re-examine the utility of immune responses and re-examine establishing immune responses prior to any infection.

I would like to talk a little bit about what specific problems there are in the existing vaccines that are being thought of -- the existing candidates.

For instance, once again we would like to focus on the gp120, gp160, gp41 envelope proteins which form the outer service of the virus, because we know that some interference with that can inhibit infection in vitro.

What we don't know, unfortunately, is if this is the major mode of infection in vivo. In fact, we can imagine a number of situations where infection occurs via other sorts of receptors. I will get to that in a minute -- well, let me say it now. One can imagine that a virus with accessible gp120 has elicited a response making anti-gp120 antibodies and is now decorated with these antibodies. These very antibodies can promote the uptake of virus into macrophages -- the phagocytic cells we discussed before -- both by specific interactions and by nonspecific interactions.

We know that this is true in some other slow viral diseases. The question therefore is, "Do antibodies enhance the transmission of the virus?" and "Do we want a vaccine at all?"

Another question about the utility of vaccines is "Will an antibody in fact help?" We introduce a vaccine into a person and he generates antibodies. Will the antibody cover important sites on the virus that would be recognized by other parts of the immune system and therefore prevent what could be a protective immune response?

We can again imagine this, as this blocking antibody has been described in certain cancers.

We would like to know in the development of any particular kind of vaccine what kind of immunity we would need and that is important because again we don't know that the initial events in transmissions is -- what they are.

For instance, if the initial events in transmission happened via these colonic epithelial cells, we may need a particular kind of immunity -- mucosal immunity -- which we don't necessary generate with some conventional vaccines. Vaccine design is going to have to take that into account.

Then there is an existing fear that any particular immune responses are going to have to be accessible to virus which is present in the central nervous system and is in general not purely accessible to the immune system, although we do know there is antibody synthesis in the CNS in infected people.

I am going to leave much about what we know about HIV infection in chimpanzees to Dr. Fultz, who knows it much better than I do. But I would like to may two points about how it leads us to be a bit pessimistic about vaccines.

Because we know human sera contain some neutralizing antibodies which block infection in culture, some human sera were used to transfer into chimpanzees and the question was raised, "Do these human sera protect against infection in the chimps?" Although questions have been raised about whether sufficient antibody was transferred, these chimps became infected. So even this prior exposure to antibody did not protect against initial infection, at least in a few cases. I think I will leave this superinfection experiment to you.

Returning to the question of clinical trials, in terms of our vaccine conference, that was really the question that elicited the most kind of controversy. As you know, there are two vaccines which are presently being introduced into people -- well, subjects have been recruited in one case, and are being recruited in a second.

These vaccines have been approved by our standard methods by the Food & Drug Administration. The difficulty or the question that was raised about these vaccines at our conference was what is the evidence from animal studies that these vaccines have a possibility of providing protection for any humans who would ultimately be exposed to HIV.

To say this quite clearly, previously any vaccine which has been introduced into humans has shown some evidence of protective efficacy in animal trials. At the time that the first vaccine was approved for clinical trial, it had not been tested to see if it prevented infection in the chimpanzee model.

Upon subsequent tests, it was proven not to change the course of infection in chimps. So what we have is a vaccine which is being tested now purely for safety which we have no reason to believe would be effective against HIV infection.

We discussed in great detail whether this precedent-setting move was warranted or not, precedent-setting in that vaccines are being tested without the traditional proof of efficacy.

And we had really very clearly two different opinions:

The first opinion essentially revolved around the fact that because the chimpanzee is not a perfect model of HIV infection in man -- that is, it does not contract AIDS, it contracts a much milder disease -- we need to validate the chimpanzee's immune response to HIV as paralleling the human response. The only way to validate the chimpanzee's response as a parallel is to look at the human response to a vaccine.

It was hoped that by learning what the human response is -- that is the human antibody production and so on -- we would be able to make further judgments about the utility of chimps.

It is clear that because we have, as was described earlier, vaccines derived from genetic engineering, they are a bit different in some cases from some we have a lot of experience in, and there are reasonable questions of safety which, once again, could be answered for this initial vaccine and perhaps could be generalized in future vaccines. And then there is the question of what kinds of antigens are these envelope glycoproteins, do humans make good responses to them outside of any HIV infection.

So that those were offered to us as some of the rationale for beginning these clinical trials.

The other opinion concerning these clinical trials was that the scientific justification was weak; that the utility of animals is to approximate the human being and not vice versa; that the volunteers who are exposing themselves to these vaccines may, first of all, experience some particular toxicity; we don't know what the side effects of an envelope glycoprotein which does interact with T-cells may have in human beings; but in particular these people would be ineligible for any future vaccines which might have a better chance of protecting them against HIV.

We are somewhat limited in terms of the pool of suitable volunteers, and these people would be ineligible, and to some degree, it calls into question the very basis of trust between the scientific community and people at risk, or infected people.

The analogy was raised to our experience with the early trials of AZT. As you recall, it was insisted that we conduct placebo-controlled trials, because that was going to be the only way we would really validate the utility of the drug.

The trials were curtailed because the evidence was so overwhelming, because it was felt that it was because we scientists operated in their standard mode that we could see the results quite so clearly.

I should say that both opinions were represented at the conference, and I can't speak as to the ultimate conclusions we will draw.

One particular other issue which was relevant to us, but I don't think we have time to go into, was some of the liability questions which would be associated with any vaccine, were it developed.

We need to protect any particular pharmaceutical house so that their liability questions would not be so overwhelming, their damages would not be so overwhelming that they would find it unprofitable to market a vaccine, and there are some standard formula that have been developed, and I can send you that in writing.

I think I would like to close just asking the question about what our future standards for entering clinical trials will be, because we understand from the Food & Drug Administration that each vaccine will be evaluated on a case-by-case basis, and that it's hoped that what we have learned from these initial vaccines will inform future decisions.

We would like to see -- the conferees are unanimous and I think everyone here who has testified would say that we need animal models which reproduce the entire natural history of the disease, in particular for vaccine development, because it's only in that case that we can determine what protective efficacy would be.

Thank you.

DR. LILLY: Thank you, Dr. Potash.

Animal Models for AIDS Research

DR. LILLY: Our next speaker is Dr. Fultz, who comes to us from the Yerkes Regional Primate Center, in Emory University, in Atlanta. She is going to talk to us about this problem that has been referred to by so many speakers today of the really severe lack that we feel of a good primate model for AIDS, and how hampering that is.

DR. FULTZ: I want to contradict what everyone has said today. I think we have some excellent animal models for AIDS, but one of the problems is that they are in non-human primates, to which most researchers do not have access.

Can I have the first slide?

What I want to do today is to mention first some of the problems that are associated with work with non-human primates, to talk to you about the animal models that are available for AIDS, primarily HIV infection of chimpanzees and SIV infection of macaques, and then to mention some of the needs in this area.

I think, as has been mentioned before, animal models are extremely useful and valuable in the study of diseases; primarily, they are used to study the pathogenesis of infection, to define immune responses to pathogens, to determine mechanisms

of susceptibility and resistance to pathogens, to test drugs for therapeutic efficacy, and to test the protective effects of potential vaccines.

As I said before, one of the problems with animal models for AIDS is that the animal models that best resemble human infection with HIV occur in non-human primates.

Research on animal models for AIDS has been centered in the Regional Primate Research Centers. There are seven Regional Primate Research Centers in the United States, which are associated with universities. These centers receive a base grant of funding from the NIH, and just last year there was a competitive supplement to that base grant which was generated from money from NIH through DRR (The Division of Research Resources), in conjunction with the U.S. Army Medical Research and Development Command. Four of the Regional Primate Research Centers were given substantial funds for the development of primate models for AIDS.

The NIH also is involved in research on animal models for AIDS, and this includes work not only with the simian model, but also with HIV infection in chimpanzees. USAMRDC is also involved in some research on animal models, as well as the private research institutes such as Southwest Foundation for Biomedical Research in San Antonio, and some universities, to a smaller extent.

I must also emphasize that although the Primate Centers do have substantial numbers of macaques available at their centers -- at Yerkes, we have over 1200 macaques -- there is also ongoing research in other areas that were heavily involved in the use of these primates prior to the onset of AIDS, and many of our animals, in fact the majority, are committed to these other studies which include behavioral, neurobiology and vision, pathology and immunology, reproductive biology and conservation, and veterinary medicine. So, despite the fact that we do have large numbers of macaques at the center, only a very small number of these are available for AIDS research.

This leads to another problem: insufficient numbers of macaques, and because primates do not breed as rapidly as mice, we can not have a new generation of animals within a couple of months. A large portion of the funds that were provided in the supplemental grants last year to the four centers most heavily involved in animal model research for AIDS, was for increasing their breeding capabilities. The increased breeding capabilities leads in turn to a need for compounds and facilities in which to place both the animals to be bred, and their resulting progeny. In addition, to set up the breeding groups, animals may have to be taken from other programs, to generate offspring for future work.

As I mentioned before, the animal models for AIDS involve primarily HIV-1 infection of chimpanzees, SIV infection of macaques and, also, work now in progress to develop HIV-2 infection of macaques. HIV-2, as you heard earlier, is a human virus, which is clearly associated with and does cause AIDS in humans, primarily in West Africa. This virus is 75 percent homologous to SIV at the nucleotide level, whereas both of these viruses are only 40 percent homologous to HIV-1.

We have had some success in infecting macaques with HIV-2, and I know that the French have also had some success, and preliminary indications that HIV-2 may cause disease in macaques. I might mention at this point parenthetically, that I did submit a grant to NIH to develop this model further. It was not awarded because the reviewers felt there was no indication I would be successful. We hear more and more, from Commissions and advisory groups on AIDS that we need more and better animal models. Here we had a chance to develop a human virus-macaque model, which would be much better than using chimpanzees, and yet NIH did not provide the opportunity to see if it would be successful, even though we did already have infection in some animals. Some macaques have been infected with HIV-2 for more than a year now, and we can still recover virus from them.

With respect to the chimpanzee-HIV model, many people say that it does not reproduce human infection, that the animals do not develop AIDS. My personal bias is, as was said earlier today, that the major cofactor in development of AIDS in people is time. I feel like that is probably true also of HIV infection of chimpanzees. The longest time that a chimpanzee has been infected with HIV is now about four and a half years. We have three animals whose immune responses to HIV are slowly changing to mirror those of humans. Loss of antibodies to the gag proteins, which often precedes development of viremia late in infection, has occurred in two of our animals. We have one animal that, over the past few months, has become very lymphopenic, and, two weeks ago, and at the last bleeding, the animal had only 134 T4+ cells, which is down from a normal of about 1500.

So, I think the argument that HIV infection in chimpanzees may not be a good reflection of human disease is premature and based on limited data, and that not enough time has passed since these animals were infected.

Currently, we are continuing to study the chimpanzees that are infected with HIV to define the pathogenesis of HIV and to analyze immune responses to the virus, and how they develop over time.

The chimpanzees that are now infected with HIV were used initially in experiments designed to show that the

chimpanzee could become infected with HIV by various routes, to determine the number of virus particles needed to establish infection -- so that we could select a reasonable dose of virus for use in challenge trials, and, also in vaccine trials, to test for protection from infection.

I think chimpanzees are extremely valuable for use in testing whether vaccines can protect against infection because an animal can be inoculated with as few as ten TCID50s of the virus, and will reliably become infected. I believe that if it can be shown that a vaccine can protect a chimp from becoming infected I would be very confident that it would protect people also.

Some of the animals currently infected with HIV are now available for drug trials, in which we would test to see whether a drug might eliminate infection.

The majority of those animals, as I said, are analogous to seropositive, asymptomatic, healthy people, so they would be valuable in looking at the effect of drugs on that type of infected person.

We are also using some of our animals to look at disease progression, and the influence that HIV infection has on secondary infections. These animals are also being used to look for potential co-factors in the development of ARC or AIDS.

And I might also mention as far as drug trials, we are also doing some experiments to look at therapeutic vaccination or immunization, which again was mentioned earlier today as maybe a valuable means of intervening in progression of disease.

The chimpanzee model, as I said, is extremely valuable, I feel, because it is reliable as an indicator of an infection with some strains of HIV. Not all strains apparently have the same pathogenicity in chimpanzees, just as we see in people. Chimpanzees are the closest evolutionary relatives to man, and their immune systems are very similar to ours. What we know about infection to date closely resembles what you see in people.

A negative factor in the use of HIV infection of chimpanzees as a model for AIDS -- and this is an old slide -- was that there had been no documented disease, other than lymphadenopathy. However, I think this may change very soon, if you consider what I told you just a minute ago about changes we are seeing in immune parameters in some of the infected animals.

A definite negative for using chimpanzees is that they are extremely expensive and there are limited numbers available. Currently there are approximately 210 chimpanzees that are allocated or set aside for AIDS research that are supported by

government funds, and in addition to that, there may be another 500 or so in the United States, that in an emergency could be used for AIDS research. These include primarily about 350 animals that were used in hepatitis experiments, or are currently being used in hepatitis experiments.

Since there is a lot of concern about using all of the chimpanzees that are available, potentially using them all for AIDS and eliminating their availability for use in other research -- for example, hepatitis -- measures have been instituted to try to conserve the use of chimpanzees in AIDS research. One of these is formation of the PHS AIDS Animal Model Committee, which does oversee the use of chimpanzees in AIDS research, by ensuring that there is no duplication of experiments and unnecessary use. But this committee only can control the use of those animals that are supported by government funds. It has no control over other chimpanzees, of which there are a substantial number, that are owned and supported by private groups or universities.

A second measure is that a national chimpanzee breeding program was instituted last year with five centers receiving awards. The centers hope to generate at least 35 new chimps every year, half of which will go into AIDS research and half will be maintained in the breeding population. Last, a "flag" will be put on all grant proposals that come into NIH for use of chimpanzees in research.

The other animal model for AIDS that I mentioned -- and at the present time this is probably the most important -- is the infection of macaque monkeys with various isolates of the simian immunodeficiency virus. Currently, studies that are in progress using this model are transmission studies, to assess the effect of route of infection, and to determine the dose required to establish infection. Also, studies are being initiated to assess maternal-fetal transfer of SIV, which is an area that we haven't been able to investigate with the chimpanzee model system.

Additional studies involve pathogenesis, to determine mechanisms of persistence, and to determine the immune responses to the virus. These animals infected with SIV are also being used in drug development quite extensively. As was mentioned earlier, the National Cooperative Drug Discovery Group for Treatments of AIDS that are funded through NIH. Many of these groups do utilize the SIV macaque model for testing drugs.

Currently at Yerkes, we are involved in two of those. We have just submitted two more grant applications which, if funded, would commit us to work with two additional groups. We, and several of the other primate centers, are using SIV as a model for vaccine development, because this system has the

advantage of having so many more animals available for testing a wider range of candidate vaccines.

Also, with SIV, you can test not only for protection against cell-free virus, which is what all the challenges to date in chimpanzees have done, but you can also test for protection against cell-associated virus, and you can test for protection against challenge by various routes.

We are also doing studies with therapeutic intervention in disease, and more recently, we have isolated at Yerkes a variant of SIV which kills animals within a two-week time period. This isolate, we feel, will prove extremely valuable in screening new drugs for efficacy against lentivirus infections by providing a rapid assay system.

Generally, with the macaque model, you do see disease in these animals much sooner than you do in chimpanzees. You can see evidence of immunodeficiency, diarrhea, lymphadenopathy, thrombocytopenia within three months after infection, and deaths can occur anywhere from six months to three years after infection.

What makes the macaque SIV model valuable is that you see the entire spectrum of infection that you see in humans. You see animals that are persistently infected, that stay apparently asymptomatic and healthy for many, many months. You have others that are chronically ill, that have periodic bouts of disease and then recover. And then you have others that develop disease more slowly with time.

You also see in these animals the loss of gag antibodies and increase in viremia prior to infection. You see loss of T4+ cells. The pathology in animals that die very closely parallels what you see in people who die of HIV infection.

One of the major things that we hope to obtain from the pathogenesis studies with the SIV model is to identify the primary and secondary sites of virus replication, to determine the route and the time of entry of the virus into the CNS, to identify different cell types that may be infected by the virus, and also to try to correlate specific disease manifestations with viral determinants. And we can do this by using molecular recombinants of the viruses.

So, in general, there are really no negatives against using the SIV macaque model, except that you only find macaques in very limited places. So many investigators who want to do these studies generally have to contact one of the primate centers, and you can imagine with all the drugs and the centers and the universities trying to develop drugs, that there is a

very great demand for the use of macaques and involvement of primates and personnel at the different primate centers.

As far as current needs, the primate centers definitely need facilities for breeding more animals, for, as I said, many of the macaques now at the centers are committed to other studies unrelated to AIDS. We need facilities for housing our HIV- and SIV-infected animals. All of these animals, once infected, are kept in isolation away from the general colony. By isolation, we do not mean each animal is enclosed and set off by itself and cannot see any of the other animals. We keep all of the infected animals in large rooms that can accommodate many animals in cages. With the chimps, we try to keep two animals per cage. None of the animals is really in isolation, deprived of contact with others of their species, they are merely isolated from the rest of the colony.

Of course, if you want to breed more animals and house infected animals, you need the personnel to execute the experiments and take care of those animals. We need not only the scientific staff to oversee the research, but we also need the research technicians, we need veterinarians, and animal caretakers themselves. Macaques and chimps require much more care than do mice and rabbits, and we need a larger number of veterinarians per number of animals.

And then also, because of the expanding demand for the SIV-macaque model, and also for chimpanzees, everything increases exponentially. We need then more laboratory equipment and more space, and one of the problems with NIH funding is that in general they do not provide funds for construction. In the past, we have had to get around that by erecting temporary or relocatable structures, which can be listed as "equipment." So, if there could be some mechanism whereby funds could be allocated for actual construction of facilities to house animals, and facilities to provide laboratory space, that would be a great improvement over the present system.

Thank you.

DR. LILLY: Thank you, Dr. Fultz.

I would like to open the session now for questions.

Ms. Pullen, would you like to start the questioning?

MS. PULLEN: I don't really have any questions. It sounds fascinating, but I have no question.

DR. LILLY: Then Dr. Primm?

DR. PRIMM: I would like to ask Dr. Fultz a question particularly about the breeding program of chimpanzees. There was a national breeding program that you spoke about? If these animals are bred before natural breeding time, aren't they subject to a number of stressful conditions if bred before the normal breeding cycle? And I have been told that as they procreate that the offsprings are often taken from them almost immediately after birth and that stress that they undergo during those periods of time certainly influences their susceptibility to disease probably. It becomes a variant or variable.

DR. FULTZ: The national breeding program was set up to ensure that we don't deplete the chimpanzee as a resource. We do not accelerate their breeding -- I mean, you cannot force chimps to breed; they breed when they want to. What the breeding program does is to support a certain number of males and females, proven male and female breeders, out of the general pool, and to place them in compounds together. Yerkes is part of that breeding program and, in general, has been very successful in breeding chimpanzees. I might also say that of the seven Regional Primate Centers, we are the only one that does have chimpanzees. The rest have primarily monkeys.

We do not take baby chimps from their mothers unless the mothers will not take care of them. Those are the only animals that are taken away during the first one to two years after the animal is born. The others are kept with their mothers in the breeding groups.

DR. PRIMM: Do you artificially inseminate the chimps?

DR. FULTZ: No.

DR. PRIMM: There is no artificial insemination?

DR. FULTZ: No. These are natural pregnancies; the chimpanzees are put together and they breed at will.

DR. PRIMM: In other words, every five years -- they breed every five years?

DR. FULTZ: No. Chimps are very much like humans. They have an eight month gestation period. They do not mature sexually until about eight or nine years of age, so we don't even have the ability to use these chimps as breeders until they are 9, 10, 11, 12 years old. They can live to be 50 years old in captivity -- which is another problem associated with AIDS research in chimpanzees. We will not sacrifice these animals; but, we have to take care of them now for the next 40 years.

DR. PRIMM: Do you think, Dr. Fultz, that stress plays any role in susceptibility in your animal population?

DR. FULTZ: It has been shown that stress can influence the immune system. If you would consider that stress would play a role and affect the immune system, generally it is detrimental to the animal.

From the evidence we have with our HIV infected chimps, stress -- they do not apparently appear to be under stress and certainly stress has certainly not accelerated their susceptibility to disease from HIV.

DR. PRIMM: But you haven't measured that?

DR. FULTZ: No. We haven't measured stress.

DR. LILLY: Dr. Walsh?

DR. WALSH: Dr. Potash, you have I think very rightly expressed pessimism about the future development of a vaccine, but let us assume that we get something. You brought up also, I think, the medical-legal problems with which we are faced, particularly in this country and that the best way to test the vaccine's efficacy is to go to a high-risk population that is uninfected and ask them to take it and continue to be exposed to infection, with the assumption that they will continue their bad behavioral habits rather than improve them. This of course led us to the likelihood, and I think you did suggest that it was discussed, that the best opportunity we would have might be in central Africa, and so on.

At your conference -- I unfortunately was out of the country when that conference was held and missed it -- but at that conference was there anything brought up at all about the resistance or reluctance that the central African population would have being used in this fashion. Because we certainly have seen that with unapproved drugs and the like and many of these countries even have statutes that prevent use of unapproved drugs. I wondered if this came up at your conference -- that they would be resistant to the testing of the vaccine?

Secondly, do you know what kind of resistance the French researchers may have had when they were trying to test the vaccine they did in central Africa?

DR. POTASH: First of all, from what we can gather from various health officials of some of the countries most at risk, a vaccine is what they pray for.

They have -- as you well know, vaccines are among our most cost-effective kinds of medical intervention and with such a large number of people at risk and no good therapeutic save extraordinarily expensive AZT, they would dearly love to have a safe and effective vaccine.

What is happening now is the World Health Organization is evolving a series of stipulations -- statutes to describe the kinds of collaborations that should go on between, let us say, a developed country and a developing country, to use volunteers at high risk.

In particular, one of the questions what was raised was that the subject country, the country with the population at high risk should initiate the inquiry into the trials, should initiate the collaboration so that they will be very definitely involved in the design and evaluation of trials.

I am not sure whether our representative from NIH is still here. Maybe you can tell us, Dr. Martin. I know, for instance, that the NIAID is also part of participating in these collaborations or at least the scheduled collaborations.

In terms of the French experience, and I am sorry this is only hearsay, as I recall, the French experience was at the level of collaboration between individuals -- that is, the scientists involved and the particular health officials in the localities enlisted volunteers, so that there was not reluctance. On the other hand, I am not sure that it was evaluated at a very high level.

DR. WALSH: You know, the point is that it would certainly seem a logical place to do it because the chances of behavioral modification are very limited in those populations because of the inability to reach them with education. But I just wondered whether the same resistance is potential because of the high degree of resistance they expressed when it was so identified as an African disease and they wanted to be sure that it wasn't labeled as starting in Africa from the green money and that sort of thing, whether you had in your work come into any of this. I think there is nowhere else to test it at this time, nowhere else that has the volume. And I was hoping you would give us the kind of answer you did, because that is at least hopeful if we ever get it. Thank you.

DR. LILLY: Thank you, Dr. Walsh.

Dr. Welch, would you like to ask a question? We are running out of time at this point, but perhaps we could go just a little bit further.

DR. CONWAY-WELCH: One quick question. I am still trying to think of how one encourages the cats to breed.

The issue of vaccine testing, Dr. Potash, I know that six or seven medical centers around the country have come together to begin vaccine testing and that there is a major -- at

least has been a major concern in terms of liability of the institution.

Could you comment briefly on whether or not there has continued to be a problem, and if it has continued, perhaps you could share recommendations in writing with the commission as to how we might assist in that problem.

DR. POTASH: Certainly I should say that this is a question that people want to ask before it becomes a problem. That is, the trials are yet to begin, but because the institutions involved want to be sure there are no surprises down the line, they are reconsidering their coverage.

I should say that traditionally experimental vaccines are not -- let me put it positively: Damages which may be associated with the test of an experimental vaccine are seldom awarded in our judicial system. People's medical benefits, as I understand it, are certainly paid but the volunteer are certainly very well informed and grant informed consent.

So the question that is raised is: Will an HIV vaccine be unique in that a volunteer who might suffer an injury seek particular kinds of damages.

DR. CONWAY-WELCH: Has that been resolved or answered or is that under discussion?

DR. POTASH: It is very actively under discussion.

DR. CONWAY-WELCH: But there has been no resolution?

DR. POTASH: Not so far as I know.

DR. CONWAY-WELCH: Is there anything the commission can do to facilitate that resolution?

DR. POTASH: Yes. There are, for instance, compensation schemes that recently been evolved and approved to compensate people who were injured receiving childhood vaccines and that legislation exists. I can also send you the recommendations for the kinds of compensation schemes that the Institute of Medicine has evolved in other vaccine evaluations. But yes, I believe the commission could be --

DR. CONWAY-WELCH: If you could share those with us along with your personal suggestions as to how we might move in the most efficient manner possible, I think that we would at least appreciate reviewing those.

DR. POTASH: Certainly. I should say that were the Commission able to move quickly, it would be quite useful since the trials are about to begin.

DR. CONWAY-WELCH: Thank you.

DR. LILLY: I would like to ask one quick question of Dr. Martin before we have to move on to another panel.

This is a very quick question. Since there has been a couple of indications that the colon epithelium is susceptible to infection, is there any indication that other epithelia might also be susceptible, such as either the vaginal, the urethral or the oral epithelium?

DR. MARTIN: To give you a quick answer, the answer is "no" --

DR. LILLY: No, they are not susceptible or no, we don't know?

DR. MARTIN: So far where people have looked and purposely tried to infect those types of tissue, the answer is "no." We should really look at the fresh clinical material by <u>in situ</u> hybridization or immunohistochemistry to get a more definite answer.

DR. LILLY: Okay, thank you.

Dr. SerVaas has a quick question.

DR. SERVAAS: It is just a quick question to Dr. Fultz.

I saw a lot of large primates being used for research in the laboratory. Near Johannesburg, where encephalitis -- the equine encephalitis breakthrough was made, and they just have cages full of these animals. Is there any possibility we could work with scientists in South Africa, where the chimpanzees are prevalent?

DR. FULTZ: Since chimpanzees are an endangered species, there is a ban on importing them, unless something has changed by the FDA or whoever controls that.

DR. SERVAAS: But as far as doing the research there? I meant leaving the animals there and collaborating with their scientists. They have some very good research going on there in Johannesburg.

DR. FULTZ: I am sure that any group here who is interested in testing, say, an HIV vaccine in chimpanzees, if animals are not readily available I'm sure that they would be

amenable to talking with those scientists and seeing if it were possible to test in South Africa.

DR. SerVAAS; Thank you.

DR. LILLY: Yes, Dr. Martin?

DR. MARTIN: Perhaps I could tell you that NIAID has been contacted by a group in Zaire who happens to have a very large group of chimps. They are interested in collaborating. They are actively trying to arrange a working arrangement with NIH.

DR. LILLY: I would like to thank the panel members very much for their presentations and their answers to our questions. I have had to cut short the questioning. You may possibly receive some questions in writing. If so, we would appreciate it very much getting a relatively rapid response to those. Also, if you have any new thoughts in the near future about the matters that we have been discussing, we would very much appreciate hearing from you about them.

Basic Research: Obstacles to Progress

DR. LILLY: The next panel will include Drs. Richard Ross, Mathilde Krim and Lewis Thomas.

We now have the pleasure of hearing from institutions who are involved in basic science research on different levels and have been asked to give us their thoughts on how we can remove whatever obstacles they see to progress in basic research.

Our first speaker will be Dr. Ross.

DR. ROSS: Admiral Watkins, Dr. Lilly, and members of the Commission, it is a great pleasure to be here. I will start by telling you who I am and what my background is. I am the Dean of the Johns Hopkins Medical School, but my professional background is as an internist and cardiologist. More especially, I am not a virologist; however, I have a keen interest in this problem and have locally, at least, demonstrated that interest by spending several millions of scarce institutional funds to turn a bookstore into a P3 laboratory for the study of the viral diseases in animals.

I think I can save you some time because my message is short and simple.

I believe that the medical schools recognize the HIV epidemic as the major medical problem of our time and feel an obligation to contribute to its solution. I believe that the medical schools and the universities are ideally suited to become

the focus of major comprehensive programs directed at the control of the HIV virus epidemic. These programs should include public health and prevention and hence universities which are fortunate enough to have both medical schools and schools of public health have special strengths.

Clinical investigation to include the evaluation of therapeutic agents is another area in which the medical schools and teaching hospitals have unique expertise. Basic retroviral research, which has been mentioned today, must also be a fundamental part of any effort.

The medical schools have the people with the necessary skills and interest in these areas, and more importantly, they can attract and train others, and produce succeeding generations of investigators. But the limiting factor -- and this is my message -- is lack of space. I don't know of any top academic medical centers that can allocate available in the quantity necessary to mount a comprehensive program at the present time.

New space of a very special sort, such as the containment facilities that Dr. Martin and others have mentioned, must be provided if the pace of research, education, and patient care for AIDS is to accelerate. I see that so clearly at my own institution. People come to me with ideas; they come with plans; they come with the hope of recruiting a virologist with an interest in retroviral problems. But I am not able to provide them with space. And as I've told you, we have had to convert a bookstore into a P3 laboratory, but that sort of thing is only piecemeal. This problem requires major new space.

I suggest that the space problem be addressed in two ways. One way would be to look at the comprehensive cancer center program of the early '70s and take that as a model for an HIV centers program and create four or five HIV centers in conjunction with major academic medical centers. Each of these would have programs in prevention, education, clinical care, clinical investigation, and basic retroviral research. Such centers could provide a critical mass of experts in these various areas, and the interaction between the various groups would be extremely productive.

I think "interaction" is the important word. It is necessary to have the people who are engaged in prevention, and those engaged in community programs, meeting on a regular basis with people doing the clinical trials and the people doing the basic viral research. Problems arising in patients can be taken to the laboratory for solution, ideas developed in the laboratory can be brought to rapid testing in the clinic.

Furthermore, I would suggest that these centers be bound together by a coordinating mechanism, so that concentrated

action could be directed at specific problems. For example, a new drug which emerged could be subjected to trial using the same protocol in all four or five centers, and therefore more patients could be observed during a shorter period of time and questions of efficacy answered more rapidly.

As you know, numbers are terribly important in statistics, and a network of centers would be a way of getting a multiplier effect.

The comprehensive centers are one approach, but I would not spend all your money that way. I would suggest that an approximately equal amount of money should be made available for allocation to institutions proposing quality research programs in one or more, but not all, of the areas of the comprehensive centers. In other words, one medical center might be especially strong in basic virology, another in clinical investigation, and they should not be excluded from participation, but a mechanism should be available for funding them as well.

For example, it should be possible to provide funds for the creation of a new laboratory or to encourage an established virologist to enter HIV research, by recruiting an associate who would do this.

So in summary, my message is very simple. We have the people; we have the interest; we have the commitment, but we do not have the space, and we need your help in getting the space.

I have been sent a list of questions which I have looked at and would be happy to attempt to address, if you wish to take them up later.

Thank you very much.

[The prepared statement of Dr. Ross follows:]

DR. LILLY: Your message was very clear, Dr. Ross. Thank you very much.

Our next speaker is Dr. Mathilde Krim. Dr. Krim represents the AmFAR, the American Foundation for AIDS Research, of which she is the founding chairperson.

Dr. Krim?

DR. KRIM: Admiral Watkins, Dr. Lilly, and distinguished members of the Commission, I want to thank you for inviting me to present my personal ideas, and I want to say from the outset that most of what I will say reflects my personal thinking, because I want to be able to speak to you very candidly, and I couldn't check every idea or every suggestion with the Foundation.

I want to start, and just let me say this, I am speaking on behalf of AmFAR, the American Foundation for AIDS Research, that we have been extremely grateful for your preliminary report. We found it all -- the people connected with the Foundation read it and found it very comprehensive, very reasonable, very balanced, and very compassionate, and I assure you that the compassion part of it was extremely appreciated.

Now I would like to, since we're talking about research, to go a little beyond the biomedical research and beyond basic research.

In the area of basic research, as you know -- and I'm not teaching you anything new here -- there has been very little federal funding up to the end of 1984. From the standpoint of an investigator working in AIDS research in the early '80s, I have not felt the presence of federal dollars around me in my lab or that of my colleagues until the end of '84. It has been very little and very late.

Specifically, as Dr. Ross mentioned, there was no money for construction, for the renovation and equipment of labs in which HIV could be handled, and there is not, not even to this day I think, there was no money for the training of young scientists who wanted to acquire expertise in the field of HIV research, and there was no long-term funding, not longer than three years, so studies, follow-up studies on patients were difficult to do and uncertain, because nobody knew whether their funding could be renewed.

Specifically there was -- in an epidemic that clearly had from the very beginning very important social implications -- no research money in the social sciences to study its ethical, legal, economic, and other humanistic aspects, psychosocial aspects.

My recommendations regarding biomedical research, basic biomedical research, are that we need much expanded and broad effort in basic biological research on retroviruses, on antiviral substances, in microbiology in general. Let's not forget that opportunistic infections are also diseases for which there is very rarely good diagnostic methods or good treatment methods, and there is need for basic research in immunology, of course.

In addition, there is need for support of social sciences and humanistic research.

We need training grants to attract young people to research, either psychosocial or biomedical. We need money for the construction or the renovation or the re-equipment of laboratories. In New York City, are there, to my knowledge, only

two P3 facilities in which HIV can be handled on a large scale in a concentrated form, and those two facilities were built with private sector money, one at Cornell Medical School and the other one at St. Luke's-Roosevelt. There was no federal money for the construction of these labs.

And finally we need an accelerated process of review. The "business as usual" review of applications as done at the NIH takes up to 18 months. In an epidemic that doubles in size within 12 to 14 months, this is hardly tolerable. I would say it is intolerable, and I cannot believe that the process cannot be accelerated and cut down to six or eight months.

Let's talk about clinical research. That started in the summer of 1985 when it became obvious that what was needed was a method of suppressing the multiplication of the HIV virus, and this research could obviously not start before we knew that there was an HIV virus involved in the causation of AIDS.

Towards the end of that year, NIAID was put in charge of clinical research in AIDS, although the original basic investigations were done at the National Cancer Institute -- and I must say that we should be forever grateful to Dr. Gallo and Dr. Broder for their contributions to the field.

Dr. Broder has done something that has changed the history of AIDS research, insisting in a very stubborn way that there should be a way of treating this disease. Remember that in 1985, we had given up on treating AIDS. He developed, first of all, a system in his lab in which he could demonstrate and measure the cytopathic effect caused by HIV and therefore also measure the protective effect of certain drugs against the cytopathic effect.

He studied first Suramin that ended up being a drug that was too toxic to be useful in the clinic, but soon enough, he studied AZT and demonstrated its activity.

At that time, it was decided at the NIH to hand the whole AIDS clinical research package to the NIAID because it was a viral disease. The NIAID is a meritorious institute with a distinguished, competent director, but it had no experience in the organization of large-scale, collaborative clinical trials across the country, unlike the NCI, and I think the NIAID took on more than it could chew at that time.

It organized a Drug Selection Committee to evaluate the promise of drugs coming out of Dr. Broder's lab, and it decided to organize clinical trials, to sponsor those trials, to fund them, and to decide what drugs were going to be tried and following what protocol, and it decided also to write the protocols.

By June 1986, NIAID has selected 15 AIDS Treatment Evaluation Units, clinical centers with which it wanted to work. It started the first trial -- these ATEUs started enrolling patients in an AZT Phase II trial. The Phase I trial was done at the NCI by Dr. Broder. They started enrolling them in February '86. They finished the enrollment in June '86, and that was the controlled trial that led to the use of AZT on a compassionate basis and then the marketing of the drug in early 1987.

This was good work. Unfortunately it is my personal opinion that the design of the protocol was faulty, that AZT should not have been studied in a controlled fashion in people with AIDS, that this was unethical, that it was a dangerous thing to do, because unless the drug was extremely effective, it is difficult to expect a drug to show clinical effect in people with advanced disease such as AIDS. It would have been better tested in a controlled fashion in people with ARC. It would have been ethically acceptable and a situation where results would have been more easily observed.

But we were lucky. AZT was effective enough to show an antiviral effect even in people with AIDS, and the trial could be stopped early.

It was my observation that in the design of this trial, there was very little discussion. There was very little involvement from anybody else outside the NIH scientific community, and those fewer who complained about the design of the trial and the unethical nature, in our opinion, were not paid much attention.

We were told at that time that -- well, some of us also at the time, perhaps particularly me, asked that AZT be given immediately to patients on a compassionate basis, and I personally supported that this be done immediately after the Phase I trial, because it seemed to me there was enough promise in the results of that trial, having absolutely nothing else to give, to do this.

I was told at that time that this was an unscientific approach, but I shouldn't worry, because within a couple of months upon stopping the AZT trial, the Phase II trial, there would be 2000 patients enrolled and receiving AZT on a compassionate basis. This was obviously a very overly optimistic promise. It didn't happen, and NIH fell far short of reaching that goal. In fact, NIAID could never catch up with the epidemic. As of today, there are 2700 or 2800 or 2900, depending who answers the question, patients enrolled in clinical trials, and we have at least 30,000 patients with AIDS and a couple of hundred thousand patients with ARC out there.

In general, there are two few drugs in clinical trials. The trials are at very early stages, if they've started at all. There are virtually no trials of combination therapies, except one or two for AZT, and much too few patients enrolled.

We have had drugs around for several years, such as HPA-23, Ribavirin, Foscarnet, AL-721, not to mention the interferons, which have been on the market for several years, for which trials have hardly begun.

The trouble is that people take these drugs. I know people who take fifty pills a day, a combination of all those I just mention, and this is very dangerous to them. So we have been very slow and very prudent and very concerned about placebo-controlled trials for the sake of the patients, but at the same time, we have tolerated a situation where thousands of people take unapproved, unknown drugs in combination and may be killing themselves in the process.

There are now 34 or so clinical groups committed to working with the NIH in clinical trials. The NIH has assured itself a kind of monopoly with a number of clinical centers who have the appropriate staff, facilities, and sufficient numbers of patients to work with. At the same time, it has not delivered protocols fast enough, so that we have had a number of groups, very competent groups, capable groups, embargoed so to speak, whose services had been preempted as far as the industry is concerned.

Well, in this country, the traditional way of developing drugs and studying them is via the pharmaceutical industry. The industry buys patents or the rights to develop drugs from academia or discovers its own drugs and pays for the toxicity studies and clinical studies.

In the case of AIDS research, it is this fantastic capability and experience that we have suppressed, so to speak, and we have tried to reinvent something which has taken us too long to do.

I hear recently that the NIAID has decided to encourage collaboration between itself and its staff and industry and academia, that academic and industrial scientists will be brought into discussion and planning. But we haven't seen this happen on any important level yet.

There is a terrible sense of frustration and despair in the public because of the developments I've just described. Physicians, in fact, have come to cooperate with their patients in the use of unapproved drugs, because they sympathize with the despair of their patients, and even State Health Departments in

at least two states I know of have set up their own regulatory agencies to go around federal agencies.

I'm not blaming any one person -- I want to make that very clear -- at NIH or NIAID. I think the leadership of NIAID is composed of honorable and competent scientists. They are just not captains of industry. It is their managerial skills and their abilities to solve logistical problems that have not been up to the challenge. There is a certain amount of naivety among them when it comes to organizational matters.

In addition, there has been a factor that has made even what they could do more difficult, and this is -- it is my feeling -- that the leadership of NIAID and other agencies, by the way, that are involved in this situation, such as the FDA, have not been given the support at the highest level they needed. These men needed not only money, but they needed authority. They needed freedom to hire people, and they need the freedom to adjust, and to adapt the facilities they had to work with in order to deal with AIDS.

Construction money, permission to build, permission to renovate and to equip, permission to hire was not given to them, and therefore even money was not very useful, and the agencies that have constrained are, in my opinion, mainly OMB and GSA.

Now the public that does not understand the process of drug development has complained a lot about the Food and Drug Administration, and I think this was not justified. The Food and Drug Administration has existed since 1906 to protect the safety of the American public, and since 1962, it was added to its mandate that it was to ensure that drugs released on the market were not only safe, but also efficacious for certain indications.

The system developed by the Food and Drug Administration for the approval of drugs has been slow and cumbersome, we all agree with that, but it's one that has worked very well in protecting the public health. It falls short, I think, only the case of very serious, life-threatening conditions where patients have a very short life expectation and situations in which there is no available drugs.

To compensate for this shortcoming, there is the Orphan Drug legislation passed in 1983 that gives tax breaks to companies that have drugs that have promise for rare diseases, and there is also a practice, which is not a regulation at the FDA yet, but a practice that has been used for many years called "compassionate use IND" that allows the release of investigational drugs to patients whose lives are in danger and who have no other treatment available.

These two, the Orphan Drug legislation and the use of compassionate IND, are useful in the case of AIDS seen as a terminal disease, but not useful enough, because the numbers we're talking about are very different. We are not talking about a dozen patients with cancer for whom individual physicians can ask for individual compassionate IND and a situation in which the sponsoring pharmaceutical company is willing to give the drug, because, in fact, what's required is very little, so they can make a good gesture at little cost.

In the case of AIDS, we're talking about thousands of people, in the future perhaps hundreds of thousands of people, drugs that are probably going to be expensive, and industry is not willing to give them -- make them available for free, even if sponsoring companies can get tax abatement through the Orphan Drug Act.

Largely because of this, I think, the FDA has recently published new regulations, and these were discussed at the meeting during the last two days, Monday and Tuesday of this week. The FDA held this meeting because it was surprised that there were very few applications for the treatment IND. There was, in fact, only one that applies to AIDS, and this is the distribution of trimetrexate for the treatment of PCP pneumonia.

The new regulations take the principle of compassionate IND and make it a regulation. They now call it a "Treatment IND." And, they have decided that the release of experimental drugs, instead of being done on a case-to-case basis, will be done for groups of patients. These regulations were discussed, at this meeting.

In the case of trimetrexate, the sponsoring company is willing to give the drug, and it will be distributed to approximately 300 patients as of today, which is not a very large number. But I am sure, I am personally convinced, that the fact that the new regulation has restrictions. In the past, the drugs had to be given away. In the new regulation, they can be sold, but it is specified that they must be sold "at cost." And I think industry is very worried by these words, "at cost," because the FDA has not specified how it is going to verify that it is at cost, or what enforcement mechanisms will be in place. I'm sure the pharmaceutical industry hates the idea that the Feds are going to come in and look at their books and make them disclose the procedures used in the preparation of their drugs. Some of this information is, of course, of high commercial value.

At the meeting, it became clear that there is in the public great confusion about what an IND is to start with, the investigational new drug procedure, that nobody understands the criteria for eligibility for any IND, but specifically not for the new treatment IND, that physicians don't understand what

being qualified means, that nobody knows what drugs are or will be out there available for distribution under treatment IND, that there has been no serious study of the implication of selling investigational drugs under the conditions, you know, of "at cost" particularly that I mentioned, and that nobody in particular -- and this is maybe the most important and serious aspect -- that nobody has really given a thought of who will pay for these investigational drugs when they are going to cost something.

The companies won't. The are going to sell them; they are not going to give them away. The patients, as we know, particularly people with AIDS, exhaust their own economic resources very quickly. Most of them are uninsured.

Does it mean that we are willing as a society having nobody pay? Will people live or die on the basis of their personal economic resources, or are we introducing in a surreptitious way the notion of a system of national health insurance, where the Government will pay for certain drugs for the treatment of certain people?

I am not making any recommendation one way or another. I think we just should think of this thing. And I was very surprised that the FDA went into this public discussion without having a position or a recommendation or any thinking of its own on these different matters.

I was originally very well disposed to the institution of a treatment IND, because I felt that this was one way of getting drugs to people who are very sick and for the industry to cooperate, because they're going to be able to sell these investigational drugs. But I left the meeting with a feeling of unease, because I had the impression that perhaps somebody in government had gotten the bright idea that one could deregulate the pharmaceutical industry or start doing so with this new measure and at the same time get off their back patients with AIDS and their advocates who complain on the unavailability of investigational drugs, avoid giving additional funding to the FDA and increasing its staff, which it clearly needs, and at the same time please the industry, because they're going to be able from now on to sell investigational drugs.

In fact, one of them, one of their representatives openly said, "Why don't we decide, instead of calling this a treatment IND, why don't we call it licensing?"

So I mention this because I think this Commission should pay serious attention to these developments that are very new.

I would like to make now some recommendations regarding clinical research on AIDS. I think the NIH should restore the role of industry and of individual clinical researchers in the early trials of any drug for the treatment of AIDS. I think NIH and the FDA should conduct clinical controlled trials -- I should say the NIH first; FDA does not conduct trials -- the NIH should conduct controlled trials in patients with ARC or with asymptomatic infection, that all people with AIDS should be given drugs on a compassionate or treatment IND basis.

If this is done, there will be no more reason to fear that treatment IND or the much more extensive use of compassionate IND will interfere with controlled clinical trials, which has been a legitimate worry.

Clinical research needs to be much accelerated with an infusion of dollars for the NIH and the FDA and in particular also additional authority to hire and expend facilities. The net must be much broadened; the catchment net for patients must be broadened. To have designated a few clinical research centers is not enough. We must reach as many patients as possible in Phase III trials for which there are hundreds of opportunities.

Dr. Young, the Director of the FDA, has mentioned himself that there are maybe 60 drugs worth trying. Each of them has to be tried at different stages of the disease, at different doses, and in combination with others.

Thirty four clinical centers cannot do all this work, and broadening the net would mean collaborating with perhaps all the hospitals in this country that have patients with HIV infection and also with community research initiative groups. I refer, under community research initiative, to physicians in the community who have organized themselves as groups and are a not-for-profit legal entity to collaborate and conduct clinical research in patients in their own practices. There have been several initiatives already across this country, and there is every reason to believe that they are very viable and are going to be very useful in the evaluation of drugs for the treatment of AIDS, particularly in the Phase III, the later trials.

In fact, the pharmaceutical industry is already convinced of that, because it has come already directly under agreement to conduct clinical trials sponsored by the industry.

The OMB and the GSA must be told to help, not impede the work of the NIH and the FDA. There is also great need for other agencies -- and I don't want to go into that in detail -- in the planning of new diversified systems for the delivery of medical care.

And finally, the FDA must do its homework concerning the treatment IND. It must publish clarifications on what it means by IND and by treatment IND. It must produce a list of drugs that would be distributed under the treatment IND. It must clarify who will do the paperwork related to treatment IND. It must clarify the question of sale and cost of experimental drugs.

And we as a society have once and for all to agree whether there is a right or not to life-saving medication and how we intend to pay for it.

We must also be very concerned, I think, to preserving the Food and Drug Administration in its role of protector of the American public and preserve the procedures that are time-tried, that have protected the public from dangerous drugs and delivered efficacious drugs.

The OMB and the GSA and other federal agencies have to be told that all government agencies have to operate on the basis of a single set of priorities, once we have decided what our priorities are. Is it to cut costs for the Government or to save lives?

And this brings me back to an issue I raised several months ago with the Commission, which is that of leadership. It's essentially that. Federal agencies must know what their goals are, what the goals of this nation are as expressed by our top leader, and then work in concert and not in impeding each other.

Thank you very much.

[Applause.]

DR. LILLY: Thank you very much, Dr. Krim, for that analysis.

Dr. Lewis Thomas will now talk to us.

DR. THOMAS: Thank you very much, Dr. Lilly, Admiral Watkins, and colleagues. I am acutely aware of the passage of time. I do have formal prepared remarks, which I will turn over to the Commission, and just lift from them at this point. There are several matters that I would like particularly to emphasize.

I begin with the assertion already made or implied by others who have testified before the Commission that the problem of AIDS is first of all almost but not quite exclusively a problem which will only be solved by basic science. It is not a political problem, or it shouldn't be, and it ought to be kept as far away from politics as possible, nor can it be viewed in any

real sense any longer or dismissed as a moral or behavioral problem. It is a lethal infectious disease, and its cause is now at large.

Moreover, it is beyond argument, but most important, an urgent problem confronting today's biomedical science, the most in need of intensive study by the best of our basic researchers in many different but interrelated fields of science. It is also a problem abundantly filled with promising openings, some of which you've heard about in earlier testimony today, a good collection of solid facts already at hand, some feasible technologies available for much deeper exploration, and ultimately, one hopes, for the uncovering of crucial details which underlie the deep mechanisms of this disease.

In short, it is, in my view, an eminently approachable and eventually solvable problem, but one that cannot possibly be got at without the best of all possible basic research. The urgency and the magnitude of the problem are, of course, beyond dispute. Not only are hundreds of thousands of young lives worldwide at stake, with more to come in just the several years ahead.

For the longer term, with or without the explosive epidemics that have affected high-risk segments of the population now infected by the virus, society at large faces the certain prospect of a new endemic venereal disease unlike any of its predecessors, because of its appalling lethality, which is already firmly established and simply bound to spread, in my view, perhaps slowly and gradually, but sooner or later into the population at large.

It is true that education and energetic public health measures were useful in modulating the spread of syphilis, especially when applied in the armed forces during the two World Wars of this century, but these measures were at their best only marginally effective against endemic syphilis in the civilian population. The great hazards to life in the case of syphilis remained those of tertiary syphilis, principally the brain and the spinal cord and the vascular lesions which turned up ten years or more after the initial infection, and these did not vanish from medicine until the disease finally became curable by penicillin.

We may be in for something like this history for AIDS in the years ahead, not one explosion of disease after another, but the gradual spread of infection into the general population. Indeed, as a matter of prudence, I would take it for granted that this is going to happen unless and until we learn enough about the underlying mechanisms of the disease to be able to cure it outright at its onset or to prevent its occurrence by a vaccine or, I would be more optimistic about the possibility of

preventing it by other immunologic methods. Neither approach is a possibility at this stage of comprehension.

And I can see no way of accomplishing these things except by reaching an understanding of AIDS in all its most reductionist biological details, hence the requirement for a lot more basic research.

As you have already heard, the efforts and achievements already on the record of basic science in this case are not just encouraging and promising; they are nothing short of astonishing. Within just a few years after the recognition of this as a venereal disease, the HIV retroviruses had been isolated, identified, and revealed in much essential molecular detail. And already just a few years after the recognition of AIDS, we probably know as much about the intimate details of this agent as we do about any other virus on Earth, and maybe more.

But there is a great deal more to be learned, as you've been hearing, especially from Dr. Martin, and without that information, we are going to be stuck with great gaps in our understanding and still without effective methods to deal with it.

We have to find somehow an effective class of drugs with the capacity to interfere with the process of invasion or replication of the HIV virus at an early enough stage of the infection before a critical mass of T-4 lymphocytes has been invaded and destroyed, and we do not possess any such drugs today.

I don't believe that this level of sophisticated pharmacology can be reached by simply screening all the chemical candidates that are now on shelves. I may be wrong, and we might be very lucky, but I am skeptical about the effectiveness of blind screening. I am entirely confident that drugs can be designed, once we know what we should be designing them to do, but I do not believe that they are simply going to fall off the shelves into our laps.

We ought to be looking hard for new ways of restoring an incapacitated immunologic cell system, and a great deal of good work along these lines is going on in immunology laboratories all across the country and indeed around the world.

We need a lot more information than we have now about the receptors for HIV viruses at the surface of target cells, but as you have already been hearing, much good work is going on.

We need maybe most of all at the moment new information about the constituent molecules of HIV viruses that are primarily responsible for the virulence and invasiveness, and we need as

well to learn whether other virus molecules provide misleading antigenic signals leading to irrelevant or blocking immune responses. Are there, for instance, polypeptide antigens that elicit neutralizing antibody and polysaccharide antigens that evoke non-protective or interfering antibody. The suggestion has been made, and it needs a lot more work.

We are badly in need of a set of more feasible animal models, better ones than we have now, in which not only can HIV infection be produced, but the whole disease itself reproduced. There are, as you have already heard, several primate models available for study in retroviral infection in a variety of other species in which other types of retroviruses can be looked at closely, but there really aren't any satisfactory models in small animals, common laboratory animals, for studying AIDS, and we need some.

The HIV retrovirus, as you've been hearing, is an exceedingly strange creature, behaving almost like a tiny and malignant intelligence. In the course of its devastating effects, it seems to me little expenditure of its own energy. It capitalizes on each of the orderly, but complex defense of the host in which it lodges. All it needs is the opportunity to invade the target lymphocyte and convert itself to its DNA counterpart, and once that is done, everything that follows is a free ride and dependent on the work of the host.

The foreign DNA is integrated into nuclear DNA, and whenever mitosis occurs, that DNA is multiplied in the case of latent infections, and mitosis is the natural response to the presentation of any antigen to which that T4 lymphocyte is already sensitized.

Leon Cooper has hypothesized that if intense reactions to other irrelevant viruses or other parasite, including perhaps Treponema pallidum, begin to occur in a patient with latent infection, any T4 lymphocyte that is now mobilized in recognition of the new invader, will begin to multiply with the production of more and more infected T4 cells. And Cooper has proposed that the same cycle might be launched by new exposures to HIV itself, and here the antigenic dosage of HIV in successive infections may be enough to determine the course of the illness.

I could go on, and will not, with a long and increasing formidable list of possible questions, some of them possibly evocative questions. They do keep springing up in random conversations with people now engaged in research on other aspects of immunobiology or molecular virology or pharmacology. And as I listen in on such conversations, I have the strong impression that the AIDS problem is surely one of the widest open and most approachable of all the deep puzzles in today's biology

and that it covers a broad sweep of interrelated biological and biomedical disciplines.

But at the same time, I am even more impressed and dismayed by how relatively few laboratories there are in this country and overseas, especially in the largest cities like New York where the disease is now almost rampant, which are committed to basic research on AIDS. Considering the magnitude and urgency of the problem itself, we have what really amounts to only a handful of excellent laboratories working on the problem, a lot of them represented in today's hearing, and I would suggest to the Commission that this is a matter of highest priority, and there ought to be more such laboratories.

Perhaps I should say a word about the possibilities for spin-off in fundamental research. Briefly, they are endless. The immunological defect produced by the HIV virus brings about, for example, an increased vulnerability to Kaposi's sarcoma, and that same class of immune cells may play an important role in the defense of humans against other and perhaps all types of cancer.

The dementias that occur in terminal AIDS infection are a little bit like other types of human dementia, and any new information about the former may shed light on the latter.

If we can learn how to block the HIV virus without killing the cells in which it is lodged, we will find ourselves armed with a new and more general class of antiviral drugs of very general usefulness.

I don't for a minute believe there is any shortage of investigators among the brightest and youngest now on the scene, nor do I believe there is any reluctance to work on this problem.

To the contrary, I am quite confident that there are a lot of researchers, good ones, and especially young ones, who would like nothing better than to go to work full time on AIDS. But there are some formidable roadblocks in the way at the present time.

One of these, mentioned by my colleagues, perhaps the most bothersome, is the requirement as perceived within the scientific community, anyway, that physical facilities that are doing the work must include very sophisticated and very expensive installations for biological containment.

It would be very difficult to enlist new laboratory groups without the provision of adequate funds to construct new laboratories with P3 standards of safety.

The perception of high risk is there, and it will not go away, even though the incidence of accidental laboratory

infection that is on the record is extraordinarily low. And the cost of such installations is going to be very high, but they are essential if the research, the basic research effort, is to be expanded.

There is also a need for a new kind of stability and predictability in the federal funding for AIDS research. This is not going to be a quick scientific fix. It will require a long-term commitment on the part of the laboratories and their scientific personnel who want to get into it, and it cannot be launched on the basis of a two-year or three-year grant to be turned off at the next budget crisis.

I would recommend the setting up of much longer term grants than has become the fashion in the recent years at NIH. Laboratory support and research fellowships for at least seven-year terms, with review and renewal commitments scheduled no sooner than at the end of five years.

It is likely that the need for new containment facilities within the academic and industrial communities working on AIDS will be somewhat ameliorated by the setting up of regional laboratories where the most hazardous part of the research, the preparation and processing of concentrated purified virus in bulk, can be undertaken.

One model that I would like to see put in place already exists potentially in institutions like the Public Health Research Institute of the City of New York, which is closely connected to the Bureau of Laboratories within the same building.

Units like this could become indispensable for research in both academic and industrial research laboratories in the same region, particularly for the distribution of cloned virus and selected fragments of virus.

Also, in view of the likelihood that monoclonal antibodies are going to become increasingly useful for deeper studies of these viruses, the regional centers could be equipped for this, and should be equipped for this technology on a large scale.

Incidentally, I can see no reason why the private sector, represented by highly competent and sophisticated pharmaceutical research laboratories, should not be included in NIH grant and fellowship programs.

There has emerged just in the last few years a much closer collegial relationship between the academic and industrial scientific communities, and biomedical science in general, and the new kind of research talent, plus a new level of technology

not available in most universities now exists within American industry.

I would favor whatever inducements that are needed to bring more of the industrial research laboratories into the basic science approach to AIDS.

And finally, at the end, I recommend that the federal budget allocation for basic biomedical research on AIDS, whatever its size, be kept separate from other necessities. I would hate to see competition and wrangling with the educational enterprise or with behavioral research, and I am fearful of the outcome if AIDS research becomes entangled in the politics of AIDS.

I hope that the work of this commission will lead to a public consensus that the AIDS problem can be solved, but can only be solved by the most skilled and imaginative science that the country can muster to the effort, and as quickly as possible.

Thank you.

[Applause.]

DR. LILLY: Thank you, Dr. Thomas.

I will open the session now for questions. Since we are running late, I would hope that the commissioners would keep their questions brief.

Dr. Lee?

DR. LEE: This panel was another wonderful panel.

We take your three major recommendations: that from Dr. Ross for space and facilities; and from Dr. Thomas for broad basic research, both in the private scale and academic institutions and in the government; and from Dr. Krim for broadening the base, broadening the base of the doctors doing this research, and broadening the base of the patients that can go into this research.

I hope that all of these will be part of our Interim Report, and eventually our Final Report.

I would like to ask one additional thing from you three. I have submitted some written questions. What I want to know is, what is going to be the mechanism? Do we buttress the present bureaucracy? Do we strengthen it? Do we short-cut it? Do you see ways of improving it? Who else should be in on the input side of it?

If we could get some answers, even quirky or off-beat answers, that might help us come to some innovative solutions for these problems, because we need to make improvement. We from our panels of their constant problems in dealing with the establishment, and I am sure there are improvements that can be made. If we can get those from you early, we can incorporate them into our Interim Report to the President.

Thank you.

CHAIRMAN WATKINS: Dr. SerVaas?

DR. SERVAAS: No questions.

CHAIRMAN WATKINS: Mr. Creedon?

MR. CREEDON: Well, I think my question would be related to the one that Dr. Lee just raised, and that is, it has been suggested in the past on some occasions that perhaps what is necessary within the federal establishment is some kind of a super agency that could bring all the activities that are going on in the different places together, and give it some direction, that is coordinated direction. And I wonder whether each of you has any reaction to that.

Of course, you know, the people in the agencies, if we asked the government people, they say, well, that's not necessary. And maybe it isn't necessary. But you do have the feeling that each one is doing its own things without any real coordination from a national standpoint. And I wonder if you feel that yourselves, and whether you have any suggestions with respect to that.

Yes, Dr. Thomas?

DR. THOMAS: I'll try a quick answer. Before Mathilde proves me wrong. I am devoted to the NIH. It is in my view maybe the only example in the 20th Century of something done by government that really works and works well, and I wouldn't want to meddle with it.

My concern is how much Congress will really commit to the basic research enterprise relating to AIDS, and to what extent will they try to micromanage the funds. But if all goes well and if the appropriation is of the size that I have been hearing recently, and if the NIH is allowed freedom to organize itself, to expend that money, I would be quite content and happy.

MR. CREEDON: Dr. Krim?

DR. KRIM: I am devoted to the NIH, too. I think, in fact, what I tried to say is that in many instances the people at

the NIH did not have the support and the help and the assistance from other federal agencies to do their work at the level at which it needed to be done.

I am leery about an additional or new agency because, remember, 15 years ago with the National Cancer Program, we attempted to do that, and it was in a way misunderstood. The leaders there felt that they had to design and direct something, and that misfired. The National Cancer Program, however, was extremely useful in supporting broad basic research, because it brought in a big infusion of funds in biomedical research. So that part was excellent, but to the extent it was a directed effort, it was not so good. And I am afraid of this happening with AIDS, too.

I think there are certain segments of AIDS research that could, to a certain extent, be managed now, but not all of it. A lot of it is still from the mental work, and I think we are better off trying to encourage collaboration, collaborative efforts between industry, government and academia, and leave a measure of freedom, of action.

I come back to my leadership point. I think what is needed, nevertheless, is for the President to say do it, you know, I want it to be done, do it. And then it will be done.

DR. ROSS: I basically agree with that. I think the NIH has a great record and knows how to do things like this, but they need to be given a mandate to take this money and spend it on AIDS research, and then there needs to be some oversight mechanism to be sure that this is done.

But to try to recreate another review and funding mechanism, I think would be a mistake and a waste of time. Waste of money.

CHAIRMAN WATKINS: Ms. Pullen?

MS. PULLEN: No.

CHAIRMAN WATKINS: Dr. Primm?

DR. PRIMM: One of the most important and, I think, most underutilized areas in our country for space and for research are our community mental health centers and our health centers where caregivers on that level often are not associated with industry nor government nor academia, though I know Johns Hopkins indeed does sponsor some health centers in Baltimore. But the relationship is not what it ought to be. And I know we are talking about research that eventually filters down and is able to be utilized by people working in those areas.

I'm wondering, haven't you thought of utilizing some of those areas, both for your space and to bring together those areas into that consortium that we speak of so reverently, industry, government and academia, so that we can involve more physicians who have more than a prurient interest in this field and are in it for the reason and not just for the season.

DR. ROSS: I would think that the community health centers and the networks that are related to the academic centers would be useful in the trial of drugs and the organization of studies of epidemiology. But when I am talking about facilities, I am talking about high tech research facilities which that's not the place for those. Those need to be within the centers.

DR. KRIM: Dr. Ross is right, that these community centers could be part of a wide network of facilities used in clinical research.

DR. PRIMM: My point is that they are not thought of and they are not used as they could be now. Many, many studies, seroprevalence studies are done there, but many other things could be done. They are not high tech research; we know that. But I think you understand what I am talking about, too. I think they lack funding, I think you are losing their interest by ignoring them and not reaching out to them. I think when you get grants at a major center, for example, to teach minority communities about education and prevention, and then have to reach out to that community and bring in people to do the very teaching that you are funded to do should tell you or telegraph to you indeed that you need to include those people beforehand. That's the point I am trying to make.

There is no way that esoteric and all the kinds of research issues that have been explained here today could be done in a health center. I think one of the most significant studies of late that was done in terms of seroprevalence studies were done in an STD clinic associated with Hopkins in Baltimore. So that's the kind of thing that I'd like to see done and improved upon, and funded by AmFAR, for example, also.

DR. KRIM: I wish we could.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: No questions.

DR. LILLY: Dr. Walsh?

DR. WALSH: I was glad to see that you had unanimous agreement that there should be no new super agency. I feel very strongly about that myself.

The comment and question I have is really that, you know, in the '89 budget, for example, that there has been $1.4 billion, I think now, into the budget. My concern is part of the concern really that each of you have brought up: I am not aware of any serious modification of priorities in that budget. And I wonder if -- of course, this commission has been given a charge, but I think a magnificent opportunity that you can help us with, because the way in which that money is used is still, I think, up for grabs, as it were. We can modify it, perhaps, by the proper recommendations.

What we need you -- and we need you not to be reactive to certain errors that have been made or slowness or errors in judgment and so on, but I think that taking into consideration that the Federal Government has done really quite a good job through NIH, as you have all pointed out, in the last couple of years, since we have isolated the virus, that they really need almost militant guidance in order to achieve what each of you have talked about.

I think NIH wants to do the right thing. They would like to get rid of the one year limiting authority and go to seven years, as Dr. Thomas has said, if they could. No one recognizes more than NIH the limitations on building and laboratory space that they themselves have. And I think if you could help us -- like, Dr. Ross, I am sure you have thought through and know from experience, or you have people who do, the cost of five centers. What is it going to be, $100 million, $200 million? If you adopt that and then the philosophy that Dr. Thomas has advocated of trying to tie in or have this commission sold on the fact that we go to a seven-year concept, so that the Congress and the Administration, whichever Administration may be in, can see the sustainability of the building once it's built. Because that's the first thing that OMB and GSA and everybody starts to say, well, once we build those facilities, then we've got to keep them going. And I think your philosophy basically gives them part of an answer.

But if you could give us, not today, but if you could give us quickly, as I'm sure the Admiral will tell you, some specifics on cost, so that maybe we could move in on that '89 budget and get a -- chop a little bit at it, that's what is left in '88, and go to the people in NIH that we know share your beliefs and share your philosophy and are fully aware, but whose hands are really tied by regulation and policy, I think you could do us a great service, and we in turn, I think, could do not only you but the American people a great service in getting this stuff off on the right foot. Because the best thing that I heard from that table was Dr. Thomas' comment that there "ain't no quick fix." And there isn't any. And we have to look five years, six years, seven years ahead. And if we are lucky enough to find an answer sooner than that, that's great.

But you are the people in the front line, and we have heard so much about care and treatment, and these are very important and very compassionate, and I agree with you, Dr. Krim, on that -- but we are not going to find the answer if we don't have more emphasis on basic research. There just is no answer unless we solve those problems. And you are the people who know how to solve them. We don't. But you've got to give us the tools to make those recommendations.

DR. LILLY: Dr. Krim, I'd like to ask you a question that I asked already this morning of someone else, and didn't get a very clear answer.

If experimental drugs are to be made available, a particular experimental drug is to be made available on a compassionate or treatment IND to anyone who wants it, how are we going to get the drug tested?

DR. KRIM: I thought I addressed that earlier.

DR. LILLY: Well, you did, but I'm still unclear on the issue.

DR. KRIM: I think it's very simple. You test the drug on people with early disease, and there you can use placebo, you can use all sorts of different controls, and do the test under ideal conditions, scientifically speaking. And you reserve the compassionate IND or treatment IND for people with very advanced disease. By definition, perhaps all people with AIDS should be given --

DR. LILLY: I'm sorry, I didn't grasp that.

DR. KRIM: And therefore, then the two procedures don't interfere with each other. You can do the trials and you can give drugs on a compassionate basis to the others.

DR. LILLY: Thank you.

Dr. Watkins, or, Admiral Watkins?

[Laughter.]

DR. LILLY: I insist on conferring a doctorate on you.

CHAIRMAN WATKINS: Thank you, General Lilly.

[Laughter.]

CHAIRMAN WATKINS: Dr. Ross, in follow-up to two Commissioners' statements, from Dr. Lee and Dr. Walsh, it sounds as though Johns Hopkins has done some work specifically on facilities development to do exactly what you want to do. It would be very helpful if you could work with our staff, or designate people to work with us, to show us a generic model of what you are talking about in specific terms so we could begin to look at that, perhaps, in our downstream work on the fiscal side of our charter, which is going to try to put this all in perspective.

And it's not just facilities and research that we have been hounded about; it's drug treatment facilities, it's a lot of brick and mortar that normally is disallowed in much of the funding, as you know. So I think we need to get very specific here. And it might be that you and Dr. Thomas would have similar concerns, might get together on this, so that we could see perhaps a couple of options of facilities we might see moving into a five to seven center national program concept.

This is going to take some time, but it would be very useful to get much more specific about what we are talking about.

Maybe Dr. Krim would like to join in. Since the three of you are here today, and this issue has come up -- and it has come up before, this isn't the first time. We have received many letters about this. We are very concerned about the long range for the country and having inadequate facility, and we see it in many other ways. FDA is a classic example of inadequate facilities to do the job that they know they are going to have to do. We don't see the dollars there, we don't see any plan moving into that. So we need to see a plan so that we can begin to build in our minds an approach to this and put it into perspective in the budget aspects of what we are talking about in the context that we have to look at a range of budget issues surrounding this disease, which could be overwhelmed unless we know exactly what we are talking about in dollars.

So I would ask maybe you to trigger off that, Dr. Ross, and maybe send your draft concept to the other two and let them comment, and let's let you three make an input to the Commission about what you think we are really talking about here in the proper research facility, proper containment. What does it really mean? How many do we need in the nation? What would that cost stream would look like?

Dr. Krim?

DR. KRIM: Yes. I would appreciate participating in this process, because the American Foundation for AIDS Research has actually done this. We have set up a lab, including a P3

facility, in our case -- at St. Luke's. It was built here in New York. The cost was $1.5 million the first year, including construction, equipment and staffing.

Now I'm sure there can be more ambitious labs than that, but basically that lab has all the facilities needed.

CHAIRMAN WATKINS: Well, that would be an excellent prototype and concept, where you have actually information that has been costed-out, which gives more credibility to the cost projects.

DR. KRIM: That's right.

CHAIRMAN WATKINS: So that would be very helpful, I think.

I would like to ask Dr. Ross, because this was your single recommendation, to take the lead on that and work with the other two panelists and try to do that as soon as you can, only because it will give us a lead-in when we get into our budget hearings as to what we might be talking about here, to balance it off against the other fiscal demands against the account.

Dr. Krim, you triggered off a thought in my mind on the definition of basic research. It came up this morning with Dr. Fauci, and I was talking about basic research, that is the topic of our discussion today, and I find that basic research may have a "business is before" ring to it, and we may find that his term of investigator-initiated research, as opposed to applied research, which many people pick up as basic research, may be part of our problem when we're dealing with the early stages of a killer disease like this that has all of a sudden come on the country.

Perhaps in your broader definition of research, there is a way to look at this as a possible model for the future as well, where again when we have a crisis come on us like this, do we stick to the normal institutional process that has been dealing on a day-to-day basis with things over time, or is there an enhanced mechanism that can be put into place that would deal with facilities, moving quickly to move into that field, training of young scientists, putting incentives to pull people in right away? You know you are going to need those resources, the planning function, which we heard earlier today is not very well done by the excellent and wonderful scientists we have, because that's not their normal bag. We need to have them helped by programmers and people who can take concepts and move them into the bureaucracy that has to deal with these things and actually appropriate dollars, and then the research on the broader aspect of ethical, legal, financial, the whole public policy issue, if we don't parallel our technical work with the potential obstacles

we are going to have to put this into effect, whether it's testing in this case or confidentiality or all the other issues.

It seems to me we are wasting time in not doing that in a more formal way, and those are the kinds of concepts that I think you referred to as doing some research in a lot of areas that need to parallel technical research. Is that correct?

DR. KRIM: Yes, that is correct.

CHAIRMAN WATKINS: So it seems to me that you have almost defined a new approach to dealing with research in a broader sense that isn't quite there, and maybe you could give us a recommendation that we might put into our Final Report on 24 June. But we need to have it earlier than that, in a couple of months, if we could, a concept that says this is what research means when you are trying to solve the very front end of a confusing new disease. It requires you to move in a variety of directions, not just scientific-technical alone.

DR. KRIM: That's right.

CHAIRMAN WATKINS: That's extremely vital, we know that, and that's where the dollars have to go. But we have equally important other areas that we are floundering about in the country right now; simple issues like legal issues, and attitudinal issues in the nation, and educational issues. Those are the kinds of things that also need, it seems to me, a spurt of coordinated effort at the outset, which we knew we would run into and in fact we have just run into a lot of blind alleys, stumbled, come back and regrouped, and now I think we are beginning to put a handle on the strategy that will deal with this.

But it's come up before, and I think it is confusing, as to what research really is in the broader context that we just talked about.

DR. KRIM: I would be very happy to try to do this with the advice of my colleagues.

CHAIRMAN WATKINS: And then the last thing I think we need to know is how do we make the chart that Dr. Fauci put up about the very, very thorough collaborative effort going on, on the hand, which is the image of real effectiveness as opposed to what you're saying is we have a little bit more image than we do effectiveness, and how do we make it effective? This is the most difficult thing in any field, whether it's education or whether it's new technology development and research, where proprietary rights are concerned. Collaboration is a wonderful word, but how do we bring what you'd like to see, the collaborative involvement of the variety of people that have the influence, how do we bring

that to fruition? And what is that collaborative network that makes sense?

DR. KRIM: This might sound a little excessive, but I think how it is done for the President to call in one room the people that he wants there; the captains of industry, the heads of academia, the investigators and knock heads, just speaking bluntly telling them that he wants them to do a job.

They should get together and cooperate. The industry should be a little less jealous of some of its proprietary information and be more willing to share and lend a hand from the organizational standpoint to the academics and get things rolling this way.

And then I think he should something else. For example, Dr. Fauci has been designated the AIDS Coordinator for NIH. He is the Director of the Institute in charge of the bulk of AIDS research. Somebody, hopefully the President or somebody at the very high level has to say, "This is my man and now you are going to cooperate with him and I don't want any nonsense at the OMB dragging feet on delivering money that he is entitled to, any nonsense at the GSA forbidding him to buy desks for personnel." These things have happened, I understand.

Or any nonsense anywhere else. The same for the FDA. Dr. Young should do his job. If he says that he needs 50 more investigators or monitors he should get them and there should be no question. This is how things get done. When you are military man, you know that is the way that they are done in the military. There is authority and there is respect for authority and obedience.

We unfortunately, everybody is doing their best but it is a confused effort to say the least.

CHAIRMAN WATKINS: Have you identified the entities in academia industry and government in other entities that work in this field. Have you identified the kind of generic leadership that should be involved in that, and where does that stand? Have you got something like that, that you have proposed in the past?

DR. KRIM: I could easily give you names of the large companies that are involved already or would like to be or should be involved.

CHAIRMAN WATKINS: Do you see this as some kind of leadership coalition?

DR. KRIM: Yes.

CHAIRMAN WATKINS: Can it be made up of a manageable group so that it not overwhelming and really can do work?

DR. KRIM: Yes, the very top people.

CHAIRMAN WATKINS: Would you give us your thoughts on that in writing because I think there again as we get downstream on this, we are going to wanting to be making recommendations on what kinds of things we might either have to put into statute or that we might want to recommend for continuation of bodies that have been borne out of lessons learned on this infectious disease and not lose the opportunity to take advantage of these while the iron is hot.

And while many of you have made these same kinds of recommendations in general terms, now we can get quite specific as we approach our Final Report on what might be done to enhance the effectiveness of the Federal Government leadership and all other levels of leadership dealing with an emergency of this type.

DR. PRIMM: I just wonder where in the consortium that you suggest which is fantastic, where would the minority representation come from? That's why I said what I did before. I think that we need to look at that very closely with the number of persons of minorities that are represented in this disease entity and certainly that are infected.

When we talk about history and government and academia, we are excluding that.

DR. KRIM: You are right in a way. I was really thinking of people that have power in this society, people who can call the shots and can give orders, not about the consumer side.

DR. PRIMM: I understand. But what I am saying is that there are people in this country who need to be represented in that power consortium so that when decisions are made it is not after the fact, it is not post-factum that they have to accept those decisions but be part of the making of those decisions.

I think that is why I am here and I think that is what we need in this country, a representation of all people if possible. Of course you have been a champion of that thing and that's why I surreptitiously started to talk about at the expense of being embarrassed, talk about the mental health centers and community health centers to try to get you all to see what I was talking about. Do you follow my rationale there? I have to shut up now, the Chairman is on my back.

[Laughter.]

DR. LILLY: I have a minority that I am very interested in too, Dr. Primm.

[Laughter.]

I will pass on that for the moment. I would like to thank the present panel members and go on to the last session, which I am looking forward to very much.

We have had a very complex day. We have been talked to about some extremely complex matters. Not all of us have understood everything that has been presented to us by any means.

We have asked Dr. Irving Weissman, who is one of the finest immunologists in the country and who has a good bit of experience at this type of wrap up overview of a problem, having sat through today, that hopefully he is going to clarify things and simplify them for us to some extent.

Dr. Weissman.

Hearing Summary

DR. WEISSMAN: I have been rapidly taking notes all day so that I could summarize it for you. Of course, you can't do that sort of thing on the spot, so I am going to let you know that I did send you a document prepared for the National Academy of Science IOM Task Force confronting AIDS, and you should receive in your files today a couple of documents that I prepared for the Waxman Congressional Oversight Committee.

They contain most of my suggestions and comments. Of course, Lewis Thomas has already told you almost everything, and better than I ever will. But let me make a few points.

First, you have heard at least two very bright spokesmen state:

--First, that our knowledge base, at least about the virus, is sufficient to carry out applied research to find cures; and,

--Second, that the funding of AIDS research through NIH is now via add-on money, that is, NIH is capable of funding AIDS research not at the expense of basic research.

In my view, both of these assertions are wrong.

I think we are in a very difficult and paradoxical situation. First, if you were to list five years ago the 20 top retrovirologists in the country, and the 20 top T-cell

immunologists in the country -- that is those people who would best study the AIDS virus or the cells which are affected by the virus -- and now ask yourself five years later what percentage of those people are doing AIDS research in more than a very small, minor fashion, the answer is: very few.

That is not to say that the people that have been doing NIH molecular virology, AIDS immunology, the clinical work on AIDS patients, and the remarkable accomplishments in epidemiology are not very good; but only that AIDS research has been limited to the few. That is a very serious situation.

There are five main areas of fundamental research that are essential to give us a knowledge base so that we can begin to understand what is going on with this infection and how we can begin to interdict it: these are, virology, immunology, developmental biology, lymphocyte biology and neurobiology.

Paradoxically, in each of the past six years, the people doing that kind of research, at least under NIAID funding, have had reductions every year in their budget. They have not had an add-on. And this year, even though we just heard that now AIDS research is an add-on, research carried out by those people who are not doing what is designated as AIDS research by NIAID have another nine percent cut: not the inflation that they need, but a nine percent cut.

So now we have a situation where we need desperately to develop several infrastructures -- a scientific infrastructure, a training infrastructure, a facilities infrastructure -- we have instead followed the mandate of Congress to redirect funds away from the development of these infrastructures and focussed only on the immediate problem. I think that is a quick fix; it is not going to work.

What we need most is to bring in the best minds, and we need to do it in a way that it is not forcing them, that is not directing them, but is asking them what ideas they have and how can they carry out those ideas for the betterment of society in this particular case.

You have asked me to consider the major obstacles to the development of effective scientific strategies to combat AIDS. There are several obstacles, and I will go as fast as I can through them. The first one -- one that has been stated by virtually every speaker -- is the obstacle of facilities. Let me give you an example. I went to my dean and said I wanted to do research on HIV and I need to do it in a high containment facility because it is not safe to do it in the workplace; and that I wanted to try to develop an animal model that can be infected with the AIDS virus. The dean said, sure, if you can find the space and the money because I can't.

We need a change in funding for bricks and mortar. You have heard a very important plea from Dr. Ross that one way to do it is to designate five, six or seven centers, which would be comprehensive AIDS centers. I understand that from a dean's point of view that you want to bring together basic science, clinical medicine and clinical care and so on.

But if there is a limitation on funds, the worst thing that you can do is to isolate researchers from the fundamental basis of their research. I think it is far better to spend money to develop safe facilities with minor building funds at maybe 50 centers around the country, so that the best people who are in those areas of retrovirology and lymphocyte biology will find that there is no barrier for them to expand into AIDS research.

Otherwise you are only going to end up with people at five institutions who will be placed in isolation with megastructures. I am not against megastructures; I think the Cancer virus program worked beautifully. If you have tons of money that you are going to be able to get out of this Administration or the next Administration, go for it. But don't leave science behind.

We need containment facilities, and we need them not only for handling the virus but handling animals that we be infected with the virus. I will go a little later on into obstacles about getting a real animal model that will work. I think, by the way, that there are very good chances down the line but we have obstacles that go beyond NIH funding you are gong to have to look at.

There are other kinds of hi-tech facilities that are necessary, even though Bill Haseltine says that there is a functioning group of x-ray crystallographers who now have all of the facilities that they need to study the virus. In fact, we need at least five new structure, that is x-ray crystallography and other hi-tech equipment that goes along with it to begin to study; one, structure of the virus as it is; two, the virus as it attaches to and infects the cells; three, most important and this I think is the key for vaccine trials, to begin to understand what footprints of the virus are left on the surface or put on the surface of an infected cell.

All of the vaccine work you heard about today and virtually all of the industry initiatives have been aimed at the virus itself as intact particle making an antibody to the envelope to neutralize that virus particle from infecting a cell.

We heard from many people that the real problem is that neutralizing antibodies don't stop the infection, that it is a

cell to cell communication where virus somehow passes from one cell to the next.

The part of immunology that deals with how you get rid of or wall off infected cells is T-cell immunity. And the rules for T-cell immunity are entirely different than for this neutralizing antibody. For each virus that has been studied, and so far HIV as far as I know has not been studied systematically, influenza is the best studied virus for this aspect.

You need to find what little part of a viral protein gets put on the surface of the cell in the context of what is called the self-MHC marker. That is a scientific term but it will get into the report somehow.

That is that T-cells see. If you are going to kill off the infected cell and thereby stop the infection from spreading, you are going to have to think about strategies, vaccines, drugs and structure facilities that will begin to define which viral gene product is being tracked and which is left on the surface of the cells and which the immune system can detect.

There are lots of other high cost equipment that is $10, $50 to $80,000.00 equipment that none of us have been able to get on our NIH grants for the last 15 or 20 years. That's because cost cutters cut that out first. There is an enormous renewal of resources needed in laboratories around the country for those kinds of facilities and there are very few ways that you can get it expect private sources.

I am going to move onto the funding focus fairly rapidly, at least that I see the funding focus. As I have told you, there must be a redirection of funding still going on because funding in basic research in those areas that I have described is still being cut this very year.

If you look at the charts and figures prepared by Dr. Richard Krause, former head of NIAID, for the Institute of Medicine report, the proportion of NIAID funding that is investigator-initiated versus funding given through contracts, or used by the director within the NIAID campus as intermural funds, it has gone from a majority of about 70 percent investigator-initiated in 1982, to less than 30 percent now.

If you want to bring the best minds into a field, you don't direct them what to do, e.g., contracts; you put out the opportunity for them to sample their ideas in the marketplace via peer review. You can make peer review faster, and I hope you do. You can make it more efficient. Most of the peer review that I was involved in contained a massive amount of paperwork that was a waste of time for both the grant writer and the grant reviewer. You need very little.

Most grant request are from established investigators. The most important information is in the CV, that is, the published work this person did in the last five years. You need a simple statement of what they are doing and what they hope to do, and not all that garbage about experimental details which must be put into the grants that everybody wastes their time reading. Very few investigators do, or should, adhere to a finely mapped set of experimental techniques -- the field moves too fast for that. One only needs that kind of detail from young, inexperienced investigators, so that one can be sure they are up to date at the time of grant submission.

We must have a reclassification of what is AIDS research and what is not. It must include those fundamental disciplines that underpin the development of a knowledge base so that we can begin to understand what is going on in AIDS patients. We know very little about the actual events that happen from the time of contact of the patient with the AIDS virus until the patient dies. We don't know the pathways of spread of the virus through the body, that is, the cells which become infected early, mid-, and late in the infection. We don't know the parts of the immune system that could be, should be, and aren't responding. We just have the basic framework of knowledge of the basic biology of the cells which can become infected and diseased. The study of the normal and pathological function of the cells, tissue, and organs, directly affected by the AIDS virus, are in the disciplines I described: basic biology, neurobiology, developmental biology, virology, and so on.

How do you bring new minds in? You do it through training grants. What group of people are you aiming at? Undergraduates, graduates and post-doctoral fellows. Have we brought them in? No. In fact, over the past five years there has been a cutback on training grants from the National Institutes of Health for both graduate and post-graduate fellows.

I think we need, just to give you some real numbers, on the order of 200 to 400 new Ph.D. post-doctoral fellowships a year, in these five areas of research that I just described.

I think we need 50 to 150 additional M.D./Ph.D. fellows per year because these people are the ones who can learn in the medical schools what the problems are, learn in the clinics what is happening and then take these problems back to the laboratory bench. It is especially important, I think, to focus on this group of people.

We need to have post-doctoral fellowships for M.D.'s who wish to get a full research training. There should be a special category of bringing M.D.'s into research, maybe for the first time; for that category, there would have to be

post-doctoral fellowships that are competitive in salary with what they would make in their beginning years, at least in academia. I know we can't match private practice levels. I would say you need on the order of 50 to 150 of M.D. post-doctoral fellows per year.

Finally, I think we need somehow to try to get to people who are at the decision points in their lives about whether they are going to enter the biological and biomedical sciences. That is at the undergraduate level. I know I started at the high school level, and most of the people I know who I think are very prominent in biomedical science, had opportunities very early in their life, in high school or college, and were brought into it.

If we could respond to Sputnik by changing our education in science for the country, why can't we respond to AIDS, a much more dangerous and present crisis, by at least finding a way to attract people, simply by providing research funds and fellowships to work in laboratories that are doing fundamental research.

Let me talk for a little bit about animal models and why they are important. First, as I said, we know very little about what happens in patients from the point of contact to the point of death. There is only one way we are going to be able to investigate this disease in detail and that is to have HIV in an animal model in which it causes the disease. The best animal would be plentiful, not expensive, and genetically manipulatable, so that you can have whole cadres of animals which are genetically identical.

We might then be able to do a simple experiment that has never been done. Let's say an animal becomes infected with the virus or injected with a potential vaccine. Five, seven, ten days later, you want to know which elements of the immune system can you transfer from one animal to another that will protect that second animal from an infection. That has been done time after time with all the other viruses that can infect animals, bacteria, even in cancer research. We haven't been able to do it in an animal model and we must be able to do it. It is unethical to do it in humans. We cannot approach the question of which organs would harbor these immune cells without taking samples that would require very major surgical interventions.

We need to find out a lot more about whether the virus is eliminating CD-4 (T4) lymphocytes only as they are out in the circulation or does it get them where they are being developed. If we do get a drug that can hold back the onslaught of the infection, are we going to have to replace the bone marrow stem cells and the thymus and all the peripheral organs that promote the development and function of these cells, or are we just

looking at the peripheral lymphocytes? We don't know that and we need an animal model to test it.

I already talked to you about cell immunity and the necessity that we can now take apart each of the different viral genes and test each of them as a potential for a vaccine to induce killer and inflammatory T-cells.

Of course, an animal model will allow us to have the only pre-clinical vaccine and drug testing model around. We aren't going to be able to do 200 or 500 or 1,500 chimpanzees and we certainly aren't going to be able to do it if we have to send our ideas to South Africa.

We need to have that in laboratories and we need it now. There are many obstacles. Let me just list a few of the obstacles that you can help overcome.

First, there are plentiful objections to the use of animals in research, just the use of animals in research. You may not feel it here in this room but I can promise you at Sanford University, we feel it every day. We have a blockade in development of research. We have two research buildings and an academic building that can't go up because of local objections to animal research, to infectious agents in animals, to the potential of recombinant DNA materials being used in animals. These are real social, ethical, and political problems that we cannot avoid. I think we have to face them head on.

If we are going to develop an animal model that is relevant, we may have to be able to put human tissues in an animal. That means, as far as I'm concerned, that one may have to use fetal tissues for research. This is another issue that has tremendous ethical, moral, and even religious problems surrounding it -- but we have to face that issue.

We are going to have to face those issues. I am asking you to face those issues, because they are not simple issues.

As I told you, there is not only a lack of government-supplied capital funds for research but also for adequate new facilities to house mice, or rats, or monkeys. I think we need to look carefully at ways of funding animal facilities at universities and research institutions, and ways of maintaining the cost of those buildings. NIH simply does not increase funding at the inflation rate for animal care, and if we have to build first rate animal centers, it is going to be even more expensive.

Finally, there is the issue of liability. Let us say we actually can develop an animal model that is a relevant animal model for AIDS. We infect the animal. It is in some kind of a

containment facility which should prevent the infection from spreading from that animal to the researchers and caretakers that handle those animals. But what if one of these people seroconvert to AIDS antibody positive? I have been informed by my Dean, for example, that Stanford University no longer has liability protection for any HIV related accident that could lead to personnel becoming injected or infected. That is a serious issue that has to be faced head on.

DR. LILLY: Why don't they?

DR. WEISSMAN: Whoever was providing that insurance no longer provides it. It probably sounded like a high risk.

My recommendations are:

--First, I want a clear statement, I hope, from the Commission and the President, that the use of animals and human fetal tissues in research is essential, and that one should not construct barriers to their ethical and humane use for research;

--Second, there should be construction funds and maintenance funds for appropriate animal facilities from NIH budgets;

--Third, there should be investigator-initiated grants for the development of new animal models; nobody knows ahead of time which one is going to be the relevant one but since we are in it for the long term, we better do something about it and soon.

--Fourth, I think we need not amplify the bureaucracies that oversee the use of animals in research because right now, it is a very difficult and time consuming delay for anybody who wants to write a grant. For example, it is not uncommon to write a grant, it is about to be sent off, and it gets sent back to you, we can't send it off because the animal committee hasn't met yet and they meet once a month, and they are good and honest people but what has happened is at the behest of the NIH and local communities to do something about the use of animals in research, we have ended up delaying research in these very critical areas.

--Finally, I hope that you can develop some method in the Commission to protect academic and research institutions against the kind of liability problem I just raised.

I could talk about vaccines but I think Dr. Potash gave an exemplary talk about it. I could talk about how to make grants go faster, and I will probably write you about it. I do agree with all of the people that you questioned, that I don't yet see the need for a "Manhattan Project" to oversee this kind

of research. I do think you have to keep in mind clearly that we want to have investigator-initiated research. We want to bring the very best minds into this field. We want to continue to do it by attracting them early in their education, and then fund them adequately to allow them to bring their own ideas and initiative to bear on the AIDS crisis.

I thank you very much.

DR. LILLY: Dr. Lee, do you have any questions?

DR. LEE: I have no questions but I just want to tell you how much I agree with you when you say you want to cut down on those aspects of the peer review process which are so onerous to people in the field, and I congratulate you. I hope you send that to us in writing.

DR. WEISSMAN: Yes, I will. I want us to have peer review. I believe in peer review but it is such a heavy job that anybody who is a serious scientist can't do it for long. It is a heavy job for many useless reasons.

DR. LILLY: Dr. Walsh?

DR. WALSH: Only that I appreciate your urging us once again to prioritize what we do within the limits of how we can do it.

DR. LILLY: As far as I'm concerned, any question I would ask would only be a request for further amplification of what you have said on the various topics. I can't think of a sentence that you said that I don't fully agree with. I think I will pass for that reason.

I will turn the meeting back over to Admiral Watkins.

CHAIRMAN WATKINS: Dr. Weissman, I think it would be important to the Commission, having had you sit through this complex set of hearings with many of us today, to take, if you could, a day or two and put your thoughts down in writing to us. It would be very important for us to have that summary if we can within the next few days as we wrap up our hearing. You have given us new insights and to strengthen what others have said is also important to us. We asked you to give this summary wrap up today. We would like to have it if possible in writing when you have been able to sit back a little bit and absorb some of your own thoughts about the testimony today.

Would that be something you could provide us?

DR. WEISSMAN: I would be happy to.

CHAIRMAN WATKINS: Thank you very much.

Before we close out the hearings and adjourn until tomorrow morning at 9:00, I see Dr. Krim still in the room, I would like to express my thanks to Dr. Krim.

She came to us in December publicly to give the first sign of support to a stumbling Commission that had come back to life. Since that time, she has certainly been a personal inspiration to me. I think she has been an inspiration to all on the Commission, and to our staff. She has been extremely positive and constructive in her recommendations to us.

We have asked her to come back today for this complex hearing on research. She has done equally well there. Because you passed us a nice compliment on several occasions, you have helped a great deal to give the feeling that this Commission is serious about its mission, does have a plan of action, is trying to put its arms around this problem, has pulled together probably the finest set of witnesses that the nation has ever seen on a health issue in my opinion, and I think we are going to come out as a result with some very substantive and constructive recommendations, both in the near term and the longer term.

I want to thank you publicly, Dr. Krim, for your early support in what was a questionable outcome on the part of the Commission because we simply were not getting any support for the effort that we had put in. You gave us a little bit of a push which made a big difference because of the respect that you have nationally and your stature in this very complicated field of AIDS.

I wanted to say that tonight while you were still here. I meant to say it earlier, when you testified. I'm glad you came back so that I could give you my thanks publicly.

DR. KRIM: Thank you.

CHAIRMAN WATKINS: The Commission stands adjourned until tomorrow morning at 9:00 a.m.

[Whereupon, at 5:32 p.m., the Commission adjourned, to reconvene the following day, Friday, February 19, 1988, at 9:00 a.m.]