PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

RESEARCH HEARINGS
DRUG DEVELOPMEN AND EVALUATION

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the Metropolitan Life Building Auditorium
New York, New York

Friday, February 19, 1988

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Research Hearings
February 19, 1988

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P R O C E E D I N G S

February 19, 1988 [9:00 a.m.]

MS. GAULT: 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.

Chairman Watkins?

CHAIRMAN WATKINS: Good morning. Today marks our second day of hearings on research and drug development. Yesterday we heard from a number of expert witnesses who addressed issues of basic research and vaccine development.

The witnesses identified many obstacles to progress and outlined recommendations as to how we might move forward more expeditiously in drug development. The Commission will review these recommendations carefully for inclusion in our Interim Report to the President which we will issue in about two weeks.

Today we will focus exclusively on drug development, taking an indepth look at the process of approving new drug for distribution. We will hear from both those seeking access to new drug therapies and those involved in approving new drug therapies. We will also hear from the pharmaceutical industry which is a critical partner in the drug development process.

I would like to especially welcome and thank our first panel this morning, many of whom know first hand the frustrations of trying to find effective drug therapies.

I will now turn over the hearing to Dr. Frank Lilly, who will continue to chair these hearings for the next two days.

Dr. Lilly?

DR. LILLY: Thank you, Chairman Watkins. The subject today is one of extreme importance. Yesterday we talked about basic research very broadly. Today we are going to focus much more on a specific aspect of basic research as it works into clinical research, and that is the development of treatments for people with AIDS.

HIV Therapy: Problems of Access

DR. LILLY: To start off the panel this morning we have a group of three individuals who are going to relate not only their personal experiences, but also give us a start on the expertise that they have gained over the months and years with the problem of trying to obtain treatments for their disease.

The first speaker of the morning will be Barry Gingell, who is the Medical Information Director of the Gay Men's Health Crisis, an organization that has worked since the very earliest days of this epidemic for the benefit of people with AIDS. Dr. Gingell.

DR. GINGELL: Thank you Dr. Lilly, Admiral Watkins and members of the Commission for allowing me to speak and deliver testimony to you today.

I have been asked to discuss my personal involvement with AIDS drug development and access. I am a physician and I am currently the Director of Medical Information for Gay Men's Health Crisis, the nation's foremost private organization providing patient services, education and advocacy for people with and at risk for AIDS.

For several years, I was a primary care physician and have treated many patients with AIDS and ARC. Over three years ago, I myself was diagnosed with AIDS.

My diagnosis in January, 1985 was, of course, a great shock to me. But, being a physician, I felt that I had a better-than-average chance of beating AIDS. I thought I would be able to access clinical trials and experimental drugs easily. I knew that some progress was being made in the search for effective antiviral drugs.

But much to my dismay, I soon discovered that my search for experimental drugs would not be easy. I had waged a successful battle with PCP pneumonia, but the next hurdle, accessing antiviral and/or immune modulating therapies proved infinitely more difficult.

I discovered that there was no centralized registry of trials of AIDS drugs, and so my search for appropriate clinical trials took the form of an endless series of telephone inquiries to researchers across the country. I was promised that I would be first in line for two different trials, one with Ribavirin and one with Foscarnet, in the spring of 1985.

By September, neither of the trials materialized and I knew I was losing precious time. I learned that Ribavirin, a drug which was shown to have activity against HIV in vitro one

year earlier, was available essentially over the counter in Mexico. And so I joined the hundreds of patients in Tiajuana to smuggle in a drug that I hoped might stop the progressive damage that I knew was occurring in my immune system.

I was successfully maintained on Ribavirin for over 14 months without serious opportunistic infection. When AZT became available on a Treatment IND, I opted for it instead of Ribavirin, primarily because of the easy availability and apparent superior antiviral activity.

We now know that AZT exacts a very expensive price, both financially and in terms of toxicity. The magnitude of this toxicity is increasing with time. A recent study on the original cohort of AZT recipients who took the drug for one year provides us with the sobering figures: fully 40 percent of patients experience serious hematologic toxicity after one year, and 25 percent have to be discontinued entirely. That's one in four patients cannot tolerate AZT for more than one year.

The magic drug Retrovir which has been foisted on the public as a triumph against AIDS is actually turning out to be a cumulative poison. While it may prolong life in the short term, AZT creates its own set of hematologic problems which may in fact contribute to the disease rather than moderate it.

Yesterday none of the testimony focused on the serious limitations of AZT and I feel they need enumeration. First, as I have mentioned, AZT causes serious bone marrow suppression resulting in lowered red and white cells in the blood. AZT induced anemia is becoming quite commonplace, and some have expressed fears that the increasing numbers of transfusions associated with AZT may put a serious strain on the nation's blood supply. AZT induced neutropenia may be a contributing factor for the increasing numbers of bacterial infections now being seen in AIDS.

Second, AZT works at a stage of viral replication after biding of the virion to a susceptible lymphocyte. As mentioned in previous testimony, cell-to-cell transmission is an important way in which HIV is spread within the body. AZT has no effect on blocking cell-to-cell HIV infection.

Third, it has been recently demonstrated that AZT is not effective in the monocyte-macrophage because this type of cell lacks the types of enzymes necessary to activate the drug. Thus, the cell which is already thought to be a reservoir for virus in the body actually protects the virus within it from inhibition by AZT.

Because of these serious shortcomings of this drug, AZT should actually be considered only a prototype antiviral drug.

However, fully 80 percent of patients in NIH-sponsored clinical trials are taking AZT. At the same time, many drugs which have shown promise either in in in vitro studies or limited pilot studies elsewhere are less toxic than AZT are being ignored.

Ribavirin, the drug which I procured in Mexico in 1985, was shown to have in vitro anti-HIV activity in November, 1984. From preliminary studies, none conducted at NIH, Ribavirin seems to be less toxic than AZT. Why has it taken over three years to get a definitive study of this drug underway? What does this kind of delay say about the process by which we are evaluating potential AIDS therapies?

A similar in vitro observation was made for AL721 in October, 1985 by Dr. Gallo at the NIH. This anti-HIV activity has been since confirmed by Dr. Laurence, who delivered testimony during yesterday's session. AL721 actually a food substance, seems to have no toxicity whatsoever. Yet these and other promising drugs are being overlooked by NIH while they exhaustively study their crude first attempt, AZT.

These follow-up studies of AZT could be easily financed and conducted by Burroughs Wellcome which is making money hand over fist with the drug. Why are we devoting precious government resources on studying every conceivable aspect of AZT when we know its critical limitations. Why at the same time, are other drugs caught up in endless red tape or stymied by petty quarrels between pharmaceutical companies and government agencies?

As is typical for people taking AZT in the long term, I reached the end of the road with the drug less than one year after starting it. Eight months after beginning AZT my white cells progressively decreased to dangerously low levels despite dose reduction and culminated in a bacterial pneumonia which almost cost me my life.

Since there is no alternative antiviral available to me even through a clinical trial, I again have found myself in the situation I was in three years ago: searching for available, hopefully safe and possibly effective therapies. If I am to continue antiviral therapy I must again procure a substance which is illegal and for which very little is known. There is no excuse for this ignorance, given the long delays that these drugs have experienced in the testing process.

I would have hoped by this time at least pilot studies would have been done on AL721, Ampligen, Ribavirin, and dextran sulfate to assist me in my decision. They have not.

Based on my own experience and the experiences of other people with AIDS, I would therefore make the following recommendations to the Commission:

--One, it is imperative that a comprehensive, up-to-date registry of clinical studies of AIDS drugs be created in order that patients and physicians might find appropriate clinical studies. Locating clinical trials must not be a hit-or-miss endeavor. A similar system, PDQ, exists for cancer trials and must be created for AIDS trials.

--Two, the NIH must expand clinical trials and lower the threshold for testing potential AIDS therapies. Substances which have passed toxicity studies and which are in widespread use must be tested in small pilot studies to confirm or disprove anecdotal data.

--Three, community-based research groups should be given special consideration in designing clinical trials for AIDS therapies. These organizations represent large patient populations in all stages of HIV related disease who are generally eager to participate in clinical trials. By coordinating clinical trials with primary care, trials can be accelerated and patients' lives simplified.

--Four, physicians and patients must be made aware of drugs which have been made available through the FDA's new Treatment IND regulations. In addition, physicians must be trained on how to access these experimental drugs for their patients. At the recent conference in Washington sponsored by the FDA and the AMA, it was disconcerting that physicians left the conference as ignorant as they arrived as to the procedure for applying for drugs through Treatment INDs.

Thank you.

DR. LILLY: Thank you, Dr. Gingell. Our next speaker is Mr. Jay Lipner, a lawyer with a New York firm who has a great deal of experience in the area of attempting to locate the drugs and find them for his own use as well as that of other people. Mr. Lipner.

MR. LIPNER: Thank you, Dr. Lilly, Admiral Watkins and other members of the Commission. I have submitted written testimony but this morning I would like to summarize it. There are also additional materials which I have provided this morning. Therefore, instead of reading my testimony I am going to summarize it and point out to you that in my written testimony my credentials and recommendations are set forth in more length.

I am a lawyer in private practice and have been working as a lawyer in New York City since 1962. Before that, I was involved with Federal rulemaking, litigation and policymaking at the national level. I began in 1982 to work with the Gay Men's Health Crisis as a lawyer, providing assistance to people with AIDS.

I have probably seen well over 150 people with AIDS in my capacity as a lawyer. I have seen people in hospitals and in my office. I have seen people get sick and die, and I've watched over the last several years as the epidemic has increased and I thought I understood it.

Last March I, myself was diagnosed as having PCP. I then understood the extreme difficulty that people with AIDS have in coping with the disease and in particular obtaining drugs for their own use. I have set forth in my testimony one particular example.

I am on AZT. This was strongly recommended by my doctor. I am fully aware of the fact that AZT has toxic side effects. Indeed, in the time that I have been taking it, I have required two transfusions. I would prefer to be taking an antiviral drug that does not have toxic side effects, but of this point in time there is no way for me to lawfully get such a drug because of the restrictions that are built into the FDA process. I am going to elaborate on this.

To this point, there is no immunomodulator that is approved by the FDA for use. An immunomodulator is a drug designed to help reconstitute an immune system. Most doctors that treat AIDS patients agree that the best combination at present would be an antiviral and an immunomodulator.

Because of the structure of the present FDA process and the way that the drugs are tested in this country, it is not possible for a person to lawfully obtain an immunomodulator at all. AZT it the only drug that has been approved by the FDA.

I began to research this issue last summer, probably in the month of June. I began to look at what legal handles might be available to people with AIDS and ARC who wanted to obtain drugs for themselves. My attention was immediately drawn to a set of regulations that were issued on May 22, 1987 by the FDA.

These regulations are called Treatment IND regulations. They have been widely reported in the press as marking a major change in policy on the part of the FDA. The impression that the public has been given is that the Treatment IND regulations make it easier for people with AIDS and ARC to obtain experimental drugs. This is not the case.

I have over the last several months made valiant attempts to get clarification from Commissioner Young, and from members of his staff at the FDA. I have gone to a conference sponsored by the FDA and the Pharmaceutical Manufacturers Association in Washington, D. C., very similar to the one just held in Washington two days ago.

Every attempt to obtain clarification from the FDA about the exact meaning and procedure for the Treatment IND regulations has met with a stone wall. There has been a lot of press discussion about the use that will be made of Treatment INDs. But to date, nothing has really happened.

The bottom line is that eight months after the Treatment IND regulations appeared in the Federal Register, not a single person in the country has received a single AIDS drug as a result of the Treatment IND regulations.

AZT was made available before the publication of the Treatment IND regulations. The availability of AZT is not a result of the regulation change.

I have provided Commission members with a copy of the actual regulations. Since I have been given only five minutes to present testimony and Commissioner Young is going to follow me with two hours, some of the remarks that I am going to have to make this morning I am going to address to the Commission members and hope that you will be able to obtain clarification from Commissioner Young.

Let me just summarize for you briefly the requirements that are set forth in the FDA's own regulations for a Treatment IND. The basic idea behind a Treatment IND is that if you have a drug which is in clinical trials and if the drug is intended to treat a serious or life threatening illness; and if there is no comparable or satisfactory alternate drug currently available; and if the drug is under investigation pursuant to an IND; and if the sponsor of the drug is actively pursuing marketing, then in that event, the sponsor of the drug may apply for a Treatment IND and may sell the drug for treatment use.

In the case of persons with AIDS, that may occur as early as Phase II of clinical trials. In the case of people with ARC or with a serious illness, the regulations are unclear because it does not specify.

Dr. Young has provided a number of articles which clarify the Treatment IND process. I have given you one of them which you should have in front of you. There is a chart that has been devised by Dr. Young which actually shows how Treatment INDs are supposed to work and indicates that for a life threatening

illness, which AIDS certainly is, a Treatment IND drug would be appropriate as early as Phase II.

On Tuesday and Wednesday of this week there was a conference sponsored by the AMA and the FDA in Washington, D. C. The subject was Treatment INDs. The conference was opened by an announcement from the FDA that Treatment IND status had been given to Trimetrexate, a drug used to treat opportunistic infection for pneumocystis carinii pneumonia. This, although hopeful, is not a great breakthrough. The drug has been around and has been known about the last several months.

It is not an antiviral, and it is not an immunomodulator. Significantly, Dr. Young was quoted in the New York Times as saying there are no other AIDS related drugs currently under review at the Federal agency that have progressed far enough through testing to warrant consideration for wider distribution.

I have provided the Commission members with a copy of a January 1988 publication of the Pharmaceutical Manufacturers Association. There is a list in this publication of all the antiviral and all the immunomodulators presently under FDA trials.

There are seven antivirals not counting AZT presently in Phase II FDA trials. There are presently 11 immunomodulators under FDA trials. Under the FDA's own set of regulations, these would be likely candidates for Treatment INDs. People with full blown AIDS do not have the time to wait until clinical trials have been completed to find out whether drugs are fully effective. That is not the standard that should be used. If you use that standard the regulations are meaningless.

That is in fact why at this point, no drugs have been made available under a Treatment IND. Unless the FDA revises its regulations and makes specific changes which you will find in my testimony, the Treatment IND regulation is going to continue to be meaningless and it is going to serve what it has served so far, which is basically an opportunity for the FDA to get good press and create the impression that it is making progress in the battle against AIDS.

This is simply not the case.

DR. LILLY: Thank you, Mr. Lipner.

Our next speaker is Michael Callen, who is a founding member of the PWA Coalition, here in New York City, an organization that has provided outstanding service to PWA's.

Mr. Callen.

MR. CALLEN: What I am going to do is briefly read through my remarks, summarize occasionally, and end with some off-the-cuff remarks.

My name is Michael Callen and I am a gay man with AIDS. I was diagnosed with cryptosporidiosis in the summer of 1982 and have been hospitalized several times since then with various other opportunistic complications. I am one of the 15 percent or so long term survivors of AIDS recently reported in CDC researcher Dr. Rothenberg's long term survivor study.

At the risk of being glib, I attribute my survival in part to the fact that I have studiously avoided participating in federally designed treatment research trials. You could not, for example, pay me to take AZT, and I believe that my instincts in this regard have been proven correct.

I mention the fact of my long term survival to emphasize that I have been dealing with the epidemic a long time and I have seen a lot in the five and one-half years since I was diagnosed. I, too, have witnessed the desperate scramble for treatments, any treatment. And have seen friends fly around the world in search of a cure, frustrated by the sluggish treatment research response here in the United States.

Because my time is limited, I will focus on two points. One, and I shan't belabor this point, is that I do not believe that HIV has been proven by any respectable standards of classic scientific inquiry to be the cause of AIDS. To that extent I think this Commission is woefully misnamed. But I don't intend to take up that particular hot potato -- at least not directly. Therefore, my first point could be restated thus:

Since the cause or causes of AIDS remain(s) unknown, we are senselessly limiting our search for treatments to drugs which are anti-retroviral because we arrogantly assume that we know the cause of AIDS.

If I understand the recent New York Times series on AIDS, specifically Monday, February 15th's article entitled "Campaign to Find Drugs for Fighting AIDS is Intensified," we are limiting drug trials to substances which in the test tube show some anti-retroviral effect. That is a lot of eggs to be putting in the HIV basket since other viruses which don't happen to be retroviruses may well be more important than HIV in actually making people sick with what we call AIDS.

I, for example, think a CMV treatment would do far more good for people with AIDS than an anti-HIV treatment.

I recently asked FDA Commissioner Frank Young if anti-HIV activity was the litmus test used to prioritize substances to be tested, and he denied that this was so. But the Times article seems to suggest that my suspicion is correct. There are many substances which the people with AIDS community is clamoring for which aren't anti-retroviral, but which anecdotally at least, seem to be making people feel better. Isn't this, after all, what the goal of treatment research ought to be?

My main objection to what I call the "religion of HIV" is that it oversimplifies what is a very complex disease. T-cell problems are only one small part of AIDS. There are B-cell problems and autoimmune components. Indeed, just about everything that can go wrong with the immune system seems to be going wrong in AIDS, and it seems simplistic to attribute everything to HIV.

I fear that by limiting our search for treatment to anti-retrovirals we are only pursuing one small portion of what we might be doing.

Lipid research is a good example of this problem. Lipids may or may not be anti-retroviral but they seem to repair cell damage, something which is certainly happening in AIDS. Why have Dr. Fauci and the NIH only so begrudgingly begun trials? It's as if they don't want to believe that anything does damage other than the virus.

Another example is PCP prophylaxis. Preventing the number one killer of people with AIDS ought to have been the number one treatment research priority. Instead, it was the AIDS community which has brought it about largely through word of mouth. As a result, in nearly every AIDS practice in New York City, PCP prophylaxis is now standard procedure despite the lack of the kind of proof that the NIH seems to be demanding for all drugs.

I believe that PCP prophylaxis will, in a single stroke, save more lives than all the AZT in the world.

Before I end with my second and final point, let me acknowledge that I am unable to fulfill your request to recommend improvements in the Federal agencies or to suggest better working partnerships between the private sector and Federal, state and local public entitles. I am as much at a loss for solutions as the government seems to be.

Except for the Community Research Initiative, about which you will hear testimony tomorrow, I see no other creative solutions to the log jam of federal treatment research other than the creation of a Manhattan Project for treatments which would essentially pursue every reasonable lead with all due haste.

That said, my final point is this. One essential fact of human nature has been ignored in the design of Federal treatment trials. That is that desperate people, people who believe they are facing certain death, will lie and cheat, and generally do whatever they have to do to stay alive.

In a situation like AIDS where there are no proven treatments, getting into a treatment trial is viewed as the only chance one has of saving one's life. In other words, we are losing the important distinction between providing access to drugs and the proper conduct of treatment trials. They are not the same thing, but with AIDS they are.

Much of the treatment research done so far -- and in particular, I refer to the AZT trials -- isn't very good research because it has been designed in academic ivory towers, far from the real world.

Placebo double-blind trials may be the quickest, simplest and cleanest way to get good data, but they are not the only way; and given the reality of AIDS it is unreasonable to expect us to participate in placebo trials. As I said, there has been lying on the part of participants, some doctors have fudged lab tests to permit their patients to meet trial entry criteria, some people have had their pills analyzed to see who was on placebo and who was getting medication, and there has been just about every other kind of cheating that you could imagine.

But before you blame us, put yourself in our shoes. Wouldn't you do the same thing if you believed that your only hope was to get an experimental drug?

The central problem seems to me to be the placebo fixation of Federal treatment research design. People with AIDS should not be asked to die for the greater good of research. Death in a placebo group should not be the efficacy measure of a drug.

I will end with one suggestion which tries to connect the two points that I have just made. There exists in the world a veritable arsenal of substances which one could lay out on a spectrum from herbs and lipids through highly complex and toxic synthesized chemicals. I would suggest that one can construct two parallel lines and lay out each substance along those lines.

One line would represent each substance's toxicity -- at one end, substances like lipids and herbs which have no, or low, toxicity, and at the other end, substances like AZT which have staggering toxicity. Parallel to that toxicity spectrum would run a line along which one could estimate efficacy -- and hopefully not just efficacy as an anti-retroviral.

Rather, the question to be asked should be this: is there any theoretical reason to believe a particular substance will help any of the impairments found in AIDS?

Once one has laid out all substances along these two lines, it seems to me that the place to concentrate first is on substances with low or no toxicity which have some theoretical efficacy. Again, lipids provide a good example.

Instead of blasting people with AIDS with the most toxic stuff we've got, let's start at the other end of the spectrum. Or, if we must, let's do both kinds of treatment research simultaneously.

As others have said, and I's sure others will say, there ought to be many more clinical trials going on than there are. The time for excuses is long past.

I will make just two other quick comments. I am a founding member of the People with AIDS Health Group, which is a group of people with AIDS which have, by hook or by crook, tried to import into this country substances which are not, strictly speaking, legally available, or which are food substances.

Since we formed about six months ago, the People with AIDS Health Group has sold over 11 tons of egg lipids. This is the desperation and the kind of frantic search. This is in New York City alone.

In addition to the People with AIDS Health Group, there are lipid buyer clubs forming around the country. People fly in from Ohio, Canada, Brazil to get these substances which, as I mentioned, seem to be showing some efficacy. We don't know because there aren't any clinical trials that will tell us this, but have no toxicity.

Two other quick points. We keep hearing that there are all these problems in starting and designing clinical trials. We keep hearing this from Dr. Fauci. The Community Research Initiative, which was formed by the People with AIDS Coalition, is set up to sponsor clinical trials using the practices of private physicians.

In six months we have approved five trials, three of which are already enrolling patients. So, it can be done. We are doing it. What seems to be lacking is sufficient political will.

The last thing that I would say would be that the NIH is obsessed with the notion that only they know how to run proper clinical trials. I would suggest that if you look at how AZT is actually being used, most people are on half doses or they are on

for a week and off for a week, this is magic. This is as magic as lipids. We know a little bit about AZT taken at a certain dose over a certain period of time, but very few people are taking AZT that way because the doctors and people with AIDS know from their own experience that it can't be tolerated.

I would suggest to you that our knowledge about AZT is about equal to our knowledge about lipids, which is to say that we don't know very much. With that, I will end my remarks and welcome any questions from the panel.

DR. LILLY: Your remarks have been very striking. I wish that we had a lot more time to question you further about this. Unfortunately, we have to go on. We will take a small number of questions. Dr. Lee, Dr. SerVaas, do you have urgent questions that you would like to bring up?

DR. LEE: This was a very striking panel. You are all impressive individuals, and, I can assure you, you have left an impression on all of us this morning.

DR. LILLY: Mr. Creedon, Cardinal O'Connor?

CARDINAL O'CONNOR: Mr. Callen, I have felt from the beginning rightly or wrongly, that however effective the efforts of this Commission and other activities may be that ultimately a Manhattan Project is going to be needed.

Since you mentioned it, could you say a few words about your concept of such?

MR. CALLEN: Yes. I think there is at this point, we call it an "AIDS Mafia" actually, the people within the AIDS community. There seem to be a handful of individuals many of whom I hasten to add, I am sure are well intentioned and want AIDS to go away. But their grip on AIDS is so tight that they ruthlessly exclude any views which do not comport with the prevailing party line.

It is my understanding that the way science ought to work is that someone proposes a hypothesis and then others try to knock it down, try to find evidence which disproves it. If it cannot be disproved then it is probably correct.

Instead what has been happening with AIDS is that people make pronouncements such as that HIV is the cause or that AZT is a wonder drug, and no one seems to challenge it because there are reports -- at least in the PWA community -- that if you don't tow the party line then you can't get published and you get your research funding cut off and your institution won't be chosen to be an ATEU, et cetera.

I would like to see gathered those people who have demonstrated significant clinical experience. I made a point in my speech about research being designed from an ivory academic tower. Those physicians who are faced with the day-to-day management of patient care in my opinion know more about AIDS and could design better treatment trials than someone who is studying AIDS in the test tube.

They know what is going on in the street, they know what other substances their patients are on. That is actually the principle behind the Community Research Initiative. I would like to see someone empowered with the authority to say: "Lipids are an interesting substance. Let's do a trial of 100 people."

The Community Research Initiative has proven that such a trial can be gotten up and on its feet in six months. The excuses from the NIH that it takes years or that there are all these problems, we don't understand because I think we have proven that it can be done.

That is my concept of a Manhattan Project: to gather together a small group of people and give them tremendous power to pursue any and all reasonable interesting leads.

DR. LILLY: Dr. Walsh?

DR. WALSH: Dr. Gingell, as a physician yourself as well as a patient, do you share Mr. Callen's point of view that placebo trials on these drugs are unwise?

DR. GINGELL: For people with full-blown AIDS, I do believe that placebo control trials are unethical. For people in earlier stages of disease who have a longer expected life span, a case certainly can be made for placebo control trials because indeed they do shorten the amount of time and the number of subjects necessary to achieve statistically meaningful results.

However, with large population samples, placebo control trials are not necessary. In the case of when you are talking about someone with a life expectancy of six months or a year it is completely unconscionable that you ask them to take a sugar pill.

MR. CALLEN: I would like to clarify that there is a place for placebo controlled trials in people with lesser illness. But in terms of people with AIDS, I agree with Dr. Gingell that placebo control trials are completely unethical and would suggest to you that the history of placebo controlled trials isn't that noble and was never conceived for a disease with a mortality rate like AIDS.

MR. LIPNER: Let me point out to you that the FDA's own Treatment IND regulation specifically point the way for a mechanism in which drug trials to occur in the classical manner with placebos at the same time giving people for treatment use drugs that are not yet tested.

That is the whole point of a Treatment IND. When you look at someone who has a life threatening illness and you look at a drug that is promising, and when you say this drug may have promise, it has manageable side effects or it is not toxic at all and we know that people are probably going to die from the illness, you then in essence have a two track system.

On one track you have the drug going through the FDA approval process from Phase I to Phase II to Phase III. In those trials it is appropriate to have placebos. The Treatment IND regulation devised by the FDA also recognizes that for a certain class of people that you break off and you say for this group of people for whom the illness is already progressed you give them the drug for treatment use.

The FDA's own Treatment IND regulations recognize the concept of giving people treatment drugs even as the trials progress. It is a good idea. The problem is that the FDA has not implemented it. All we have gotten eight months afterwards is simply rhetoric.

My recommendation is that the Treatment IND regulations be made to work. And at the end of my testimony where I set specific recommendations for changes in the IND regulations which I think will make them more workable.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: In matters like this where survival itself is the issue it is easy to lose sight of the quality of life or the things that can be done to improve the quality of life for people living with AIDS.

I think it is even easier to lose sight of the fact that the emotional consequences can be fatal. People get depressed and feel like taking their own lives.

What do you feel can be done or should be done to give you better resources in emotional support systems, counseling and family counseling, how adequate is what is there and what do you think can be done to make more meaningful services available?

DR. GINGELL: I think that such counseling and such emotional and psychosocial support are woefully inadequate in the AIDS epidemic. Ranging from the healthy person who learns that he is seropositive over the telephone, is provided with no

pre-test and no post-test counseling, and then goes and takes his own life; to the person with full blown AIDS who is often rejected and neglected by family, by loved ones. These kinds of support for these people are woefully inadequate.

These few studies that are being done with pharmacologic intervention in HIV-related depression are all being done privately. The government has undertaken no such studies which is a very clear indication of the lack of breadth of treatment programs and research programs underway at the NIH.

DR. LILLY: I am extremely sorry to have to cut this session off. As you can see, we have a very charged schedule, and we hope that you will be able to hear at least some of it.

Your presentations have been very striking, and we thank you very much for them.

MR. CALLEN: I would like to make just one brief comment which is that I am actually impressed and thank you in particular, Dr. Lilly, for allowing us to speak not only as people with AIDS but people who have opinions. Usually we are dragged out in front of the media and they wait for us to cry or tell some story about how horrible it is to have AIDS.

But I think you can see, we are fighting for our own lives with all of the resources that we have. Jay is a lawyer, Barry is a doctor, and I am a founding member with the PWA Coalition. There is an entire network of the fight against AIDS which is being conducted by the people with the disease themselves.

I thank you for recognizing us not only as experts because we have the disease, but because we are involved up to our armpits in the fight against AIDS. So, I thank you for that.

DR. LILLY: You are examples for us of how this disease is wasting very valuable human lives. Thank you.

The Role of the National Cancer Institute in AIDS and Drug Development

DR. LILLY: Our next panel bring us members of the National Cancer Institute. The subject of the panel is The Role of The National Cancer Institute in AIDS and Drug Development.

To the extent that the federal health bureaucracy has been involved in drug development in the past, this has taken place in the National Cancer Institute. Our witnesses will outline to us the experiences of the National Cancer Institute in that area.

Our first speaker is Dr. Maryann Roper, who is Acting Deputy Director of the NCI.

DR. ROPER: Good morning Dr. Lilly, Admiral Watkins and members of the Commission. I appreciate the invitation and, on behalf of Dr. DeVita, would also like to express his thanks for your invitation for us to illustrate for the Commission this morning what the National Cancer Institute has done to date in AIDS research.

The National Cancer Institute is the largest of the NIH Institutes on campus in Bethesda, and has been involved in AIDS research since 1981. I have been asked to summarize this briefly and I would like to do that by going through first the history of what the National Cancer Institute has done in the past; next, its present scientific program, at least delineating the scope of that program. And finally, to speak a little bit about the budget in AIDS research, where it came from, where it is now, and what we intend to do with it in the future.

The NCI's interest in AIDS goes back to 1981 when the Cancer Institute sponsored a national meeting on the NIH campus to discuss the whole issue of AIDS with intrarmural and extramural scientists. Following this meeting, the Institute recognized that a more formal organization of AIDS activities would help scientists exchange ideas more freely.

Along these lines, AIDS was seen primarily as an immune deficiency disease at that time. Many of the problems that cancer patients faced were quite similar to those seen in patients who had immune deficiencies, particularly the problem of recurrent life threatening infections.

In fact, pneumocystis carinii pneumonia was first described in cancer patients. Given this, we felt it was inherently right and logical for the Institute to be involved at the forefront of AIDS work.

In response to this, an internal committee was formed called the Special Task Force on AIDS. Formed in 1982, its purpose was to discover the etiologic agent of AIDS and also to improve treatment for AIDS associated conditions including opportunistic infections and Kaposi's sarcoma.

We had at the NCI a number of people who were intimately familiar with retrovirology as well as virology in general and also people who had extreme amounts of expertise in basic immunology. This Committee was chaired by Dr. Peter Fischinger who is the Deputy Director for whom I am acting. He is now the PHS AIDS coordinator for the Public Health Service. Dr. Robert Gallo was the scientific director of this Committee, and Dr. Sam Broder was the clinical director.

Membership in that Committee included both intrarmural and extramural scientists with expertise and interest appropriate to the problem. This Committee was then dissolved in 1984 upon the discovery of HIV. Interestingly around this time, Mrs. Heckler who was then Secretary of Health and Human Services held a press conference to announce the co-discovery of the virus both by Dr. Gallo and the reports by Dr. Montagnier in Paris.

At that press conference, she mentioned that, scientists now having isolated several strains of the virus, she anticipated that there would be a test available in six months and a vaccine -- not ready to vaccinate -- but a vaccine available for testing within two years.

In fact, the test that was then hoped for took approximately nine months to develop and a vaccine preparation ready for testing was available pretty close to the two year outline that she had initially set.

The NCI then realized that scientists in many different parts of the Institute in different scientific divisions were interested and involved in AIDS research. So a second Committee was formed that would draw scientists from different aspects of the Institute together into an AIDS Vaccine and Intervention Strategies, or AVIS, subcommittee working group.

The purpose of this was to follow up on the work of the first Committee and identify gap areas of research, note the research that was already going on within the Institute and to identify gap areas where further research and study was strongly needed. The Committee members of this group consisted of Dr. Dani Bolognesi from Duke, Dr. Hilary Koprowski, as well as intramural scientists.

The major product of this Committee was to initiate the Frederick Cancer Research Facility contracting program which has

become a great resource in vaccine research and supply for a lot of materials for basic research.

Most recently, the coordination of AIDS research at the Institute is done at the Executive Committee level. The executive committee internally consists of the division directors of all of our scientific divisions, with advice given by the National Cancer Advisory Board whose members are appointed by the President.

Most recently, we have formed an advisory subcommittee of this board that is chaired by Dr. Howard Temin, the Nobel Laureate from the University of Wisconsin who dexcribed reverse transcriptase.

The charge of this subcommittee is to advise the National Cancer Institute on all aspects of its AIDS program; scientific aspects, budget aspects and policy aspects, and we intend to listen to their advice.

Next, to move on to a brief summary of the scope of basic research at the National Cancer Institute at the present time. The research is concentrated in four major areas. First, we have a strong commitment to basic research because we believe that it is out of basic research that clinical results and cures eventually follow. This includes research in retrovirology in AIDS and in other retro viruses and other viruses from which lessons can be learned for AIDS.

This includes genetics, the mechanisms of action of different viral genes and the immune response to the virus. We have a budget of approximately $28 million dedicated to this effort.

Next, the drug development effort. This occupies the major part of our AIDS budget of approximately $40 million. This includes basic research laboratory efforts to discover new drugs, as well as the development of drugs perhaps as a pharmaceutical company might, a large screening effort to look for known compounds and screen them for their anti-retroviral activity. In addition we have in-house an early clinical trials program, primarily in Phase I studies of new drugs that is directed by Dr. Broder.

The next effort in the NCI is the vaccine development effort. This occupies approximately $20 million of our fiscal 1988 budget. The vaccine approaches being studied are sub-units and T-cell epitopes. This is again, primarily a basic research effort not directed at clinical trials.

Finally, we have a fine, perhaps one of the finest, epidemiology units in the country if not in the world. It is out

of this epidemiology unit that a lot of the early work in AIDS the descriptions of the syndrome, being able to know how things might be for people who got early infections, what clinical symptoms they might develop down the line. Much of this work came out of this unit.

This unit is now directed at looking at studies to examine risk factors that will be important to the future spread of the infection in heterosexuals, in spouses of hemophiliacs and children, looking also at AIDS related malignancies and further studying the spread of the infection in intravenous drug abusers.

To briefly walk you through the budget, I think a comparison between 1982 and 1988 will perhaps speak for itself. In 1982, the AIDS budget at The National Cancer Institute was $2.4 million. In 1988, our AIDS budget is $89 million. In 1982, that $2.4 million represented 75 percent of the NIH effort and approximately 50 percent of the Public Health Service effort in AIDS. In 1988, the $89 million that we are spending is only 20 percent of the NIH budget and only 10 percent of the PHS budget for AIDS.

I would like to close by saying that I believe that the National Cancer Institute has been at the forefront of AIDS research since the initial recognition of the symptom complex in homosexual men in 1981. Because of the research programs in place at the Institute as well as the administrative mechanisms in place at the Institute that had been established through the authorization and funding provided by the National Cancer Act, our scientists were rapidly able to apply existing methods in drug screening as well as the latest advances in cancer virus research technology to study the AIDS problem.

This existing framework along with the rather hard work of a great number of dedicated individuals, permitted both the rapid discovery of the AIDS virus and the identification of anti-retroviral activity of the first drug AZT that was shown to have some reproducible effects in AIDS patients.

Because of the crisis nature of the AIDS epidemic, the National Cancer Institute feels committed and compelled to provide ongoing help where possible to solve the problem of AIDS.

Thank you very much.

DR. LILLY: Thank you, Dr. Roper. Our next speaker is Dr. Samuel Broder, who is an Associate Director of the Division of Cancer Treatment, Clinical Oncology Program.

DR. BRODER: Thank you, Mr. Chairman. It is my privilege to be here in front of this distinguished body. I will try to be brief and then be seated.

I speak here not necessarily as a representative of the National Cancer Institute per se, but as an individual clinical investigator in the intramural program of the National Cancer Institute. Before I start, I would like to take a more global view of what I think the Clinical Center of the National Institute (NIH) represents.

Approximately 50 years ago, Franklin Delano Roosevelt inaugurated the first building at the NIH campus which now exists in Bethesda, Maryland. In his inauguration speech he recognized that the foundation of the NIH was being undertaken as, in his words, a remedy for a stricken world. This was at a time when the world was at war. Basically, I believe that the scientific method and ability to harness science to benefit human beings who are suffering is at the core of what we are trying to do. Speaking for myself, this is the only reason why I remain an intramural scientist clinical investigator at the NIH.

Could I have the first slide, please?

[Slide.]

I would like to very quickly go through a few comments. I apologize if anything that I say here gives offense but these are my personal views of some of the issues that we hear.

First, there is the issue that clinical investigators who declare their patients incurable seldom contradict themselves. I want to stress this point for a moment. There was an enormous, and in my opinion defeatist, strategy of convincing ourselves that nothing could be done about retroviral infections. I believe that that mindset could have been very damaging to the development of therapies that can either, in the long run, cure patients or at least alleviate suffering where cure is not possible.

I believe it is very important for doctors to be very careful whenever they say that a disease is incurable. Skepticism is a tool of science, it is not a substitute for science. That is, skepticism is part of the scientific method by which a trained mind can evaluate data, make decisions, assess priorities and seek new truths. But skepticism per se is not a substitute for science. One does not have to be exceedingly bright to be consistently skeptical. Unwarranted skepticism was a barrier to much of the early work in trying to develop new treatments for AIDS and its related disorders.

Now, for one of my strongest points: Lack of toxicity does not prove efficacy. I think this is an extremely important point. The AIDS virus only respects one thing, and that is whether something works or not. We have to recognize that death

or suffering from AIDS is also a toxicity. The lack of toxicity by itself should not be a criterion for allowing a drug to be represented as having a role in patients.

Without a controlled trial, physicians will generally agree on the toxicity of a drug before they reach a consensus on its benefit. I would make an additional comment. If there is an agreement on the toxicity of a drug before there is a consensus on its benefit, it is my personal experience that this can be the death of the drug, that a drug will therefore be dismissed.

The next point I wish to stress is that the search for a perfect drug should not interfere with the finding of a good drug. Death is irreversible. In pursuing the goal which all of us seek, i.e., obtaining perfect therapy, by which I mean cures in the absence of toxicity, we should not throw away intermediary but useful drugs.

There is no substitute for a clinical result. Laboratory results are one thing, but it's a long road from the lab to the clinic and there may be a number of reasons why assumptions from a laboratory perspective may not be valid in human beings. Therefore, the clinical result has to be our goal.

And finally, getting a wrong answer in a study does not help anybody. In fact, it is my personal view that among the most unethical things -- not the only unethical thing -- but among the most unethical things a clinical investigator can do is to obtain the wrong answer. In that context, I mean dismissing a drug which may have value erroneously or accepting a drug which has no value erroneously. I think this, in the long run, does not help anybody.

I would like to list very briefly some research objectives; however, my talk is not primarily designed as a basic-scientific one. I would be very happy to go over any issues that people would like elaborated on, on perhaps a more scientific basis.

I have listed a few of the sites that can be used to attack the AIDS virus. We have a plethora of target sites by which we can attack what I believe to be the primary etiologic agent of AIDS and its related disorders. I believe there may be other factors indeed that are exceedingly important from both a laboratory and clinical point of view. But I believe that the process that we call AIDS is initiated by a pathogenic retrovirus which we can, for the purposes of our presentation here, call HIV.

This virus has shown us an enormous amount of complexity in terms of how it chooses to replicate and,

therefore, provides a number of targets of opportunity in our ability to defeat it. We can attack its binding to target cells, we can attack its fusion phenomenon by which it enters cells, we can attack its entry into target cells and uncoating of RNA, a process by which the virus must replicate. We can block its transcription from RNA to DNA by the special DNA polymerase, called reverse transcriptase. We can theoretically block the orderly degradation of RNA by an enzyme called RNase H, which is encoded by the virus.

We, theoretically, could attack the virus' ability to integrate into the DNA of a host genome. We could affect viral transcription and post-transcriptional events. We could affect viral RAN translation to proteins. We theoretically could attack a special process called Ribosomal frameshifting by which the virus needs to synthesize certain proteins. We may perturb its ability to make viral components and assemble them accurately. We could block viral budding. These are all target sites. I apologize if I have left off somebody's favorite target, but the list is, of course, longer than this.

Each one of these is a target of opportunity for us. I want to stress a few things. I am showing a small number of drugs here, but the list of promising agents is very long, indeed.

[Slide.]

I agree with the sentiment expressed by the earlier witnesses that we open up our minds and open up the format for studying many drugs. I want to focus on a few drugs, not necessarily because they are the best or will in the long run prevail, but because I believe they have settled the point, in my mind immutably, that the AIDS virus can be treated. It is my belief that before these drugs were made available for testing and, in one case for prescription drug status, that point was not established and there were many who subscribed to the opposite point of view.

The other point I want to stress is that it is our goal, at least my goal, and the goal of the many fine men and women who work at the Clinical Center not necessarily to study drugs but to get them into the hands of practicing doctors. We all want to get away from central governmental authority as soon as possible, and move drugs so that decisions can be made in an individual doctor's office with an individual patient. In order to do that, we have to have a knowledge base.

I am going to discuss certain nucleoside analogs which are modified versions of building blocks for part of what the virus needs to survive. These are all slightly chemically

modified from normal building blocks, and they are building blocks as the virus attempts to go from RNA to DNA.

I am going to pick one called AZT which is the azido version of dideoxythymidine. This is not a new drug. It was first synthesized by Jerome Horowitz in 1964 on an NCI grant. The drug's activity against retrovirus is not new. In 1974, Dr. Ostertag and his co-workers at the Max Planck Institute showed in vitro activity against Friend leukemia virus using AZT, azidothymidine. Thus, the drug's ability to block replication of a mouse retrovirus is also not new. Unfortunately, mouse retroviruses were among the only retroviruses available for study in 1974; there were no human retroviruses recognized at the time. And even though this work was published in a prestigious journal, I think it is fair to say that it languished in obscurity. I think this is a lesson for us that there is no escape from the importance of scholarship and accurate reading of what has been done.

[Slide.]

These are some data which I just want to stress very quickly. We now know a great deal now about AZT and other drugs. We know that there are certain enzymes in cells that activate them, and basically, we know certain dose response features. The development of AZT represented an emergency collaboration between the Wellcome Research Laboratories and the National Cancer Institute, in which a conscious decision was made to pull out all the stops and at least deliver one product to prove the point that the AIDS virus was treatable. I'm sorry to keep coming back to this point, but perhaps the ultimate value of AZT is not that it is a perfect drug, but that it points the way. It has toxicities, and it is a drug which perhaps we could abandon some day. But it has silenced, in my point of view, those people who said, "Retroviruses are inherently untreatable, so why bother?"

We know certain enzymes that can activate these drugs. Where the enzyme affinities are not good, congeners of AZT will not work. That is the only point that I wanted to make from this slide.

[Slide.]

Many of the drugs which we are developing including AZT, a cousin of AZT called dideoxycytidine, and yet another cousin called dideoxyadenosine, in addition to working against HIV-1, work against all retroviruses that we have tested in vitro. This includes HIV-2, shown here. You can see if you add HIV-2, you can destroy cultures that otherwise would have lived. By adding these drugs you can protect them.

There was a statement made by other witnesses earlier in the testimony which we disagree with. These drugs, all of the chain terming dideoxynucleosides that I am describing can in fact definitely block cell-to-cell retroviral transmission. The only variable that is relevant is that the recipient target cell have the relevant kinases (enzymes). We also disagree with the published literature that suggests that these dideoxynucleosides do not work in macrophages. We believe there are technical issues, but we have observed in elutriated macrophages or monocytes -- that is, cells that have not yet been cultured -- that these drugs do work.

So there are some technical issues. The point that I am raising is that even if we focus on the limited drugs that we have discussed, we have agents that have strong activity across the board. Although the emergence of drug resistance is always a concern, the primary determinant is not the retrovirus itself but appears to be the host cell and whether it can activate the drug, that is, whether it has the relevant kinases.

Basically all of these drugs work by being a false building block for the virus as it attempts to go from RNA to DNA. When a wrong insertion is made, pro-viral DNA cannot be made. For those of you that are scientists and have been scientists, you use these drugs in their triphosphate forms in the Sanger sequencing reaction. It is aesthetically very pleasing to me to think that we are Sanger sequencing, terminating, the AIDS virus in the cytoplasm of patient cells.

In addition, what we think happens here is that once one of these false building blocks is incorporated, the virus has not evolved a capacity to make a repair and that the RNase H and other mechanisms in effect make the virus molecularly dead once it has made this false insertion.

[Slide.]

I want to turn to other ways that we might use to help patients. These are not original data from my lab; these are confirmatory data. But basically a number of labs -- primarily I think through the intellectual driving force of Dr. Axel and his co-workers -- have in fact started to study the CD4 receptor, the actual binding receptor by which the virus gets into cells. It is possible to genetically engineer that receptor so that it can be used to block viral replication <u>in vitro</u>. Moreover, I personally believe it will be possible to develop chimeric molecules in which the CD4 is put at one end which is called an amino-terminal end of a protein, whereas human FC, a portion of human immunoglobulins, can be put on another end, called the carboxy terminal end. This is likely to yield a useful chimeric antibody, in my personal point of view, because CD4 belongs to the immunoglobulin supergene family. One can artificially

construct a neutralizing antibody in this way. This is a hypothesis. I do not know this to be the case, but I am outlining one of may future areas of research that we are doing in collaboration with several private sector technology firms.

[Slide.]

This is an experiment in which various concentrations of genetically engineered CD4 are able to block and protect cells from viral replication. So we might be able to use the evolutionary mechanism by which the virus has chosen to infect cells as a tool against the virus. And we hope that we will be able to do a clinical trial in the Clinical Center within the next year.

[Slide.]

Other compounds are being studied. We believe it is possible to make short stretches of DNA, especially synthetic DNA, in particular phosphrothioate analogs in which a sulfur is substituted for what would be an oxygen. One can make certain stretches of oligodeoxynucleotides with this sulfur, and block the expression of genes in infected cells, something which perhaps would have been previously concluded to be impossible. We think, at least on preliminary evidence, that it is possible to do so.

I can't go through all the details, but I will show you that a synthetic stretch of DNA which is about 20 nucleogide segments long, and is set in what is called an antisense configuration to what is called the art/trs gene, can block viral expression. In data which I will not show, viral RNA expression in cells that are already infected can be suppressed.

You will have to take my word for it that the relative controls are in here, because I don't want to take any more time. I believe it is possible to block expression or at least theoretically, even in the reservoir of a cell that is already infected.

[Slide.]

I want to turn now to our clinical results. I am not really a basic scientist. Some would say I'm not a clinician either! But basically, I think I am a hybrid. I feel that results are not meaningful in the combatting of AIDS unless we can get clinical results.

These are early studies done by Dr. Bob Yarchoan and others in our group, in which AZT was administered to human beings for the first time. Dr. Hiroaki Mitsuya in our group, in collaboration with the Wellcome Research Group was able to show

that AZT blocked replication of the AIDS virus in a test tube in February of 1985, and also accurately predicted the therapeutic target concentration as being between one and five micro molar.

On July 3, 1985, the drug was injected into the first human being at the NIH Clinical Center. The drug had never been given previously to human beings. I understand the concern of the earlier witnesses, and am deeply sympathetic to the concern of speed in drug development. But I don't believe it is possible to move that much faster than from February to July of the same year in taking a drug from a laboratory observation to the injection into the first human being.

Basically we did see in the Phase I study that the CD-4 population, here designated LEU3, rose in certain patients and certain immune functions were corrected. In addition, we clearly started seeing other evidence including the suppression of viral product in the bloodstream. and to us, very gratifyingly, reversals of dementia in certain patients.

The reversal of dementia is particularly noteworthy in children with AIDS. There may be significant toxicity in the bone marrow but nevertheless, there can be very dramatic reversals of the dementia that are very prominent in children who have AIDS, especially under the age of three.

[Slides.]

This is a so-called positive emission tomogram which is simply being used by way of illustration today. This is not the only database upon which I am making these conclusions about neurologic improvement.

This is a normal individual. Yellow and orange areas indicate that radioactive glucose is being taken up. This is a computer simulated picture through the patient's brain. This is a patient who is demented before receiving AZT. The blue areas, the "cold" areas, show hypoactivity in what is called the occipital, temporal and subthalamic regions.

Following clinical improvement on AZT, we did the study again and you can see clearly that there is a re-activation -- normalization -- of areas that had been hypoactive. I believe at least on our database, that it is possible to reverse some of the dementias. I will go further than that.

In some patients it seems that the reversal of dementia is more amenable to treatment than other manifestations of the disease. Once we learned that the AIDS virus could get into the brain there was an enormous surge of pessimism that nothing could be done about that. But, we have proof that something can be

done about it, and hopefully, other medications may do a better job.

[Slide.]

This is the double blind placebo controlled trial in patients with advanced disease in which patients were asked to volunteer and agreed to be randomized by computer to receive either placebo or drug. I know that this is a controversial area, and I agree with the sentiment that is now expressed today that placebo-controlled trials in advanced AIDS are unethical.

I completely accept that point of view.

However, when these studies were undertaken, I don't think facts were so clear. I believe that as I mentioned at the beginning, the issue of toxicity certainly would have overwhelmed the issue of efficacy. There is no question looking at the cumulative mortality rate, that AZT was able to prolong survival in patients who had AIDS.

I believe that this is an important first step. A great debt of gratitude is owned from society to the patients who agreed to volunteer for this study. In many ways they are a heroic group of individuals.

I urge that we use the model of airplanes for this discussion. When the Wright Brothers took off in their first airplane it probably would have been inappropriate to begin a discussion of airline safety. The question was, can we fly? Now we can go back and improve on what has been started.

There are other issues involved here. It is true we do not know the best way to use all of the drugs that may be available. But there is also an important choice here. Once a drug is shown to have meaningful, substantial, incontrovertible benefits to patients, although these benefits may not be durable, what does one do with that information? My position is that we should not simply continue to study the drug. We may have to deal in an imperfect world. We have to get drugs out to individual doctors who then can make their own decisions and who also may, under current drug regulation, even use what is called innovative therapy on their own to extend knowledge. This is my own personal view.

[Slide.]

I want to switch to another drug in finishing up, called dideoxycytidine which is being studied at the NIH. Basically this is a drug given in our Phase I study in which it was clearly possible to suppress the AIDS virus in patients. In addition, there were certain immune functions, <u>in vitro</u>

parameters such as the ability to kill influenza infected target cells, that got better.

So this agent was also accurately predicted on the basis of in vitro screening tests, to have an in vivo effect. This drug is 50 to 100 times more powerful than AZT. Potency by itself is probably neither here nor there. But the point that I want to stress is that it has a different profile of toxicity.

The dose limiting toxicity for this drug is a peripheral neuropathy, and at very high doses one can get bone marrow suppression. But for most patients it is a peripheral neuropathy. For most patients on AZT the dose limiting toxicity is bone marrow suppression. We could act on that kind of information.

We have combined a study in which patients receive AZT for one week and dideoxycytidine for another week, alternating back and forth. And we believe that we have significantly, not completely but significantly, reduced the toxicity of both agents.

Fifteen patients are currently in this study. None to date have received a blood transfusion as a result of drug induced toxicity. In addition, five patients are past the six month mark. None of those patients has developed peripheral neuropathy. I am not saying that all of the toxicity is gone, but I am saying that we can use scientific principles and what we learn from a clinical trial to expand and to bring new knowledge. Maybe this regimen will not be the final one, but again, it illustrates how we can apply new knowlege.

Here you can see that viral replication is dropping and remains down for over six months. In addition, the patient's T4/T8 ratio remains quite elevated. And I believe this is a significant difference from what would have happened with AZT alone, although it is possible to argue that AZT given every other week could have accounted for this. If so, so be it. Then we have learned another method for giving AZT. Further studies will address these points.

[Slide.]

I want to finish on what I think is perhaps the most important lesson of all. These are not my data. These are data of Dr. Ruth Ruprecht, which I have taken from the published literature.

It is very important that we come up with solutions for people with advanced AIDS. There is no doubt in my mind that that is an important societal goal. But like many other situations, preventing a problem may be in the long run be

infinitely more important than trying to correct it once it has occurred. And I submit that perhaps the model we should be looking it strokes and high blood pressure.

It is a good idea many times, to try to lower a patient's blood pressure once they have a stroke, I accept that point. But there is only so much repair and only so much that can be done at that point. Lowering blood pressure before a stroke is best. Perhaps what we should be looking for are methods of early intervention in which we prevent the devastation that we call AIDS from occurring in the first place, and that, in the long run, may be the best kind of use for anti-viral drugs.

I would give you the analogy of a burn as well. The same therapy that might save a patient's life when there is 30 percent full thickness burn may not be able to do anything when there is a 95 percent full thickness burn.

These are studies in which Dr. Ruprecht did an early intervention study against a mouse retrovirus, in which the mice were randomized to receive tap water or tap water than had AZT in it. All of the mice that did not get AZT died. All of the mice that got AZT lived.

So maybe we are on the threshold of early intervention type of studies, and maybe these are the kinds of areas where we can make a significant impact against AIDS and its related disorders.

I will finish with two slides and I will go over them very quickly.

[Slide.]

I personally believe that we should set achievable goals for ourselves and not be afraid if we don't meet the deadlines. It is better to state a goal, maybe even a slightly provocative goal and not meet it, than not to have a stated goal at all.

I believe that all of the goals I am now going to show you can be done and, in some cases, have been done. I think we can establish clinically predictive screening systems of anti-retroviral agents, that is, we will be able to predict drugs that will have value in patients. We can do comparative in vitro anti- viral efficacy profiles of drugs against both human and animal retroviruses. We know a lot about structural activity relationships for many drugs. We have anti-viral agents now that inhibit HIV binding to cells. We know a great deal about the biochemical pharmacology of anti-retroviral agents. We have developed anti-viral effects using synthetic stretches of DNA

that can be chemically modified in what is called an anti- sense configuration to block viral expression in cells already infected.

We can rapidly implement Phase I studies in both adults and children. We have initiated early-intervention studies. We can develop therapy directed against retroviral induced neurological diseases. We can develop principles of combination or alternating anti-retroviral therapy.

I, from the beginning, have been a cautious optimist. I would like to say that perhaps I could lose some of my sense of caution. I believe if we adhere to the scientific method and generate knowledge, we can defeat this virus.

Thank you very much.

DR. LILLY: Thank you, Dr. Broder. We are running overtime again. I am very sorry. Ms. Pullen, do you have any questions for the speakers?

MS. PULLEN: No.

DR. LILLY: Dr. Prinn, Dr. Walsh?

DR. WALSH: Dr. Broder gave us his usual, enthusiastic presentation, and which such enthusiasm I can't see how we can lose.

I wanted to ask a combined question; one question but it has two phases.

DR. BRODER: I hope I can remember both parts.

DR. WALSH: First of all, do you have a good spirit of cooperation at NIH and interchange between the various Institutes, like yours, Tony Fauci's and the rest of them, so that you are aware really aware of what one another are doing? That's part one.

Secondly, as the previous witnesses have testified there is tremendous anxiety about getting some of these things out for clinical trials. We have heard from previous witnesses that at NIH from time to time, a scientist falls in love with a particular drug and directs all of his interests toward that drug even on the grants available for clinical trials that this may be a cause for delay.

I wondered if you could answer both of those in just one question.

DR. BRODER: I can answer the first part very quickly with a yes. There is a high level of cooperation, both on a professional and personal level. Dr. Fauci and I go back -- it chagrins me to say at least 16 years. We are accustomed to seeing each other very late at night. We are the only ones around after 10:00 at night in the building and we work very closely on a number of projects.

As to your second point, I wanted to emphasize that I am here representing myself as an intramural scientist trying to develop what is my own personal goal, which is to cure AIDS. In that sense, I guess indirectly I am representing investigator initiated research.

I do not review extramural grants. I am not in that process, and therefore that particular question is a little bit beyond what my focus is. I believe that people do not solve problems unless they believe they can be solved, and unless they are given the format for solving them and doing the best they can. And if they fail, so be it.

But I don't believe a drug or an idea or concept can be developed to fruition by just saying we will test whatever comes along. I think in any project there has to be someone who takes the position: "I want to see this through." I think as many opportunities should be created for as many qualified clinical investigators to see their projects through.

So I guess what I'm saying is, I believe in the principle of investigator-initiated research.

DR. LILLY: Thank you. I will start at this end. Dr. Lee, do you want to ask a question?

DR. LEE: Yes. It is a pleasure to be with some real pros, and you people have demonstrated that today. I think it is also important for all of us who don't know, to realize how much of the very excellent foundation of basic research in AIDS was done at the NCI. You deserve credit for that.

I have submitted some written questions which I hope you can answer. One other nuts and bolts question: In your budget in the money here, is this all new money or has there been some fudging, by placing money from cancer treatment programs into AIDS research?

DR. ROPER: Does anyone have a Bible in the room for me to put my hand on? I think if you were looking at 1988 as an isolated slot, yes, 1988 is new money. I think if you went back to 1982, that $2.4 million is much in the range of a drop in a bucket. AIDS, at that time, piggybacked onto existing programs

within the National Cancer Institute, existing research laboratories and existing facilities.

Rather than spending $10 million to set up a new effort, AIDS kind of took the benefit of the $10 million that was already there and maybe only spent $1 million to benefit from the infrastructure that was existing.

I don't know how we could go back and put a price tag on that, but I am sure that AIDS has encroached on the cancer research budget most particularly in the earlier years of its existence.

DR. LEE: Thank you. I may get some better figures from you or documentation at a later date.

DR. LILLY: Dr. SerVaas?

DR. SERVAAS: Thank you. I have no questions.

DR. LILLY: Mr. Creedon?

MR. CREEDON: You may have partly answered this question already, Dr. Roper. Both this morning from Dr. Gingell and Mr. Lipner and Mr. Callen and on prior occasions of meetings of this Commission, we have heard very understandable frustrations about the fact that the Federal government just doesn't seem to be doing enough about experimentation with drugs other than AZT or if it is, it doesn't seem very visible.

If you were we -- is that correct grammatically? If you were we, how would you react? How would you react to the criticisms that are being made here?

DR. BRODER: I believe that all of us should be criticized as long as one patient who has AIDS dies. I think that unless there is a cure for the disease, I think criticism is to be expected.

MR. CREEDON: But how do we respond to the criticism? What needs to be done so that people who are affected feel that as much is being done as can reasonably be done?

DR. BRODER: I think we have a duality here. I don't want to take a lot of time, but I think we have certain ethical issues about what one does or how one acts or what one does with knowledge that is very new.

Whenever one deals with a true Phase I drug, that is a drug that has never been given to human beings before, one is in an unknown world in which technically the patient may be subjected to more harm than good. That is true with any new drug

application in human beings. When that happens we have to get informed consents from patients and do the best that we can.

The problem that we face is that once a drug is shown to work, and particularly when there are short term gains in a sub-set of patients, how does one deal with that? If a boat is sinking and there were 10 people on it and we can save four people, six will die. But if we can save those four, what do we do? That is still better than losing 10.

If something is working, should we spend all of our effort, or a high percentage of our effort, in trying to refine and get out what is known to as many people as possible, and to learn as much as we can about something that is starting to work -- or should we do other experiments with restricted drug access?

I think that is a complicated issue. I think that we need to keep a balance. But, to be candid with you, this is sometimes almost an issue for bioethisists and not scientists.

MR. CREEDON: But if these drugs are available in Mexico and France or wherever, couldn't there be some kind of international cooperation that could help this situation?

DR. BRODER: If I might interject, I would have to take exception with one point. With respect to the problem of slow drug development -- I am exceedingly sympathetic and, since I was and still am a cancer doctor, I am very familiar with the concept of a chronic and lethal disorder.

We are very familiar with it. Women who have metastatic breast cancer, individuals with metastatic colorectal cancer. There are a lot of people who have diseases which are both chronic yet lethal. We need to get therapies out, best case therapies, to patients as best we can.

We also have to worry about not only the patients that are here now, but we have to be smarter doctors a year from now. There will be more patients in our clinics a year from now than there are now. The only thing that can permit us to stay in the business of experimental drugs psychologically, is that we can assure ourselves that we will be smarter doctors a year from now, we will be able to help more people in a year than we can now.

That requires a scientific method. If one simply approaches the problem of drug development of giving any drug in any concentration in any unorganized way that one may want, I think that progress will suffer.

MR. CREEDON: I do not think that anybody would suggest that.

DR. BRODER: Let me give you two examples. I believe that without controlled trials, AZT certainly would have been dismissed because it came very close to dismissal. Because the only thing that was recognizable from AZT was the bone marrow suppression. In the double blind placebo controlled trials, none of the investigators realized that the death rate was phenomenally higher in the placebo arm than in the drug arm until the code was broken. All they recognized was that there was toxicity going on with what they thought was AZT.

The second point is that from a drug like dideoxycytidine, we have encountered a situation where we have developed a new anti-retroviral drug -- but we can cause a peripheral neuropathy with that drug. We think we have learned a way to get around that by building in organized rest periods.

I believe that knowledge would have been very difficult to get without controlled trials, and to be as candid as I can, I think that drug might have been dismissed. Although I do not know if it will ultimately have merit, I think it is still an interesting drug. That drug might have been dismissed as being too toxic to peripheral nerves to be used without systematic studies.

Therefore, there is a balance between how to study a drug, how to fine tune it and how to capture the best parts of it. That is a balance. And I'm not sure that the most efficient way to develop a drug is simply to release it at an exceedingly early phase. I think the drug may end up dead. We need systematic research if for no other reason than a good drug may be buried otherwise. Even drugs that are available now would not necessarily work if we had to develop them from scratch and had no idea of dose, no idea of schedule.

We could end up declaring digitalis to be an exceedingly toxic drug if we were developing it for the first time and allowed every doctor to simply use it for any patient who had cardiac disease.

So there is a principle that we need to develop. My personal view is that no patient who has a terminal illness should be denied something that might work. I take that as a given. But general on-demand release of drugs is not without drawbacks.

MR. CREEDON: But then, how do we get that operative? How do you get it operative because it isn't operative now? I mean, you refer to AZT as being released in five months I guess, but as you indicated AZT has been known, it's been around and studies have been conducted with it for six or seven years.

DR. BRODER: No. Not for six or seven years. The drug was known to inhibit animal retroviruses in a test tube since 1974. The first human use was begun at the NCI on July 3, 1985.

MR. CREEDON: How long?

DR. BRODER: AZT was first shown to have activity against the AIDS virus -- reduced to practice is the term that lawyers would use -- in February, 1985.

MR. CREEDON: But AZT had been experimented with in other connections.

DR. BRODER: Never in human beings. Never for a human retrovirus or a human virus. With AZT, it wasn't at all clear that it would work. Drugs that work in animal systems frequently work differently or not at all in humans and vice versa. You can't extrapolate. Basically, AZT was started in February of 1985 by Dr. Hiroaki Mitsuya in my lab. We crash-rushed it though in collaboration with a private sector company so the first human being got it on July 3, 1985, about five months later.

The Phase I study was finished by the end of 1985 at the Clinical Center in collaboration with Duke University. The drug was basically on IND status nine months later. The reason it was released was because it was shown to prolong survival in a way that convinced the medical community.

My concern, my firm belief, is that AZT would have been dismissed and worse -- I am sorry to speak with such apparent animus but I have been through this and I guess I'm getting burned a little bit -- that AZT would have been dismissed as an example yet again, of the folly of trying to treat human retroviruses. Many prominent intellects told me that retroviruses were inherently untreatable; moreover, that the drugs we planned to use by definition could not work. Basically a failure of AZT, I think would have been exceedingly damaging for the field and might have, in fact, swayed people in a very durable and harmful way to not keep the fight going.

MR. CREEDON: I think we are very grateful to you for that, Dr. Broder. I wish you would think a little more about this question of how do we react to the concerns and frustrations that not only the people affected, but we all feel, we feel it on this Commission, what do we do, what do we recommend? What log jams are there that have to be broken down for us to be more effective in this area?

Do you have any comment, Dr. Roper, on this?

DR. ROPER: No, sir.

DR. LILLY: Cardinal O'Connor, would you care to comment on this?

CARDINAL O'CONNOR: Dr. Roper, you were speaking in part of basic research. Is there a mechanism for rapid feed from basic research to applied research, particularly in regard to AIDS? There is a contingency finding; is this rapidly fed into the applied research?

DR. ROPER: There is a mechanism particularly in the drug research area, that once an investigator would discover a drug that seems to have value as an anti-retroviral agent that he can make use of the system that is existing at the National Cancer Institute. I would imagine there are probably mechanisms in many of the private sector pharmaceutical firms as well, that then all the t's that need to be crossed and i's that need to be dotted with respect to the safety of administering that drug to human beings, that is all the lengthy studies can be quickly undertaken and that new drug be put into the pipeline for further development.

CARDINAL O'CONNOR: Thank you.

DR. LILLY: I have been told that Dr. Roper must leave now so there is no further time for that. Admiral Watkins has a question for Dr. Broder. Thank you very much for your participation, Dr. Roper.

DR. ROPER: Thank you, sir.

CHAIRMAN WATKINS: Dr. Broder, we heard yesterday testimony from Dr. Gottlieb and we heard some more testimony today and we have heard it in the past, the perception that there seems to be a possible research bias for anti-virals as opposed to say immunomodulation as a technique.

The question is, do you sense that there is biased research focused in certain directions within your own broader organizational relationships, and is the balance correct? Do we have a free flowing, more open exchange of approaches to this disease than just focusing solely on anti-viral?

We have heard that on a number of occasions, that there may be other kinds of research that is not getting the kind of resource attention and dedication perhaps, because of leadership focused too much in one general area.

DR. BRODER: With no disrespect intended, I think if we were doing biological response modifiers, then we would be criticized for not doing anti-virals. So I feel that there are two imperatives here. There is an imperative to get something practical out quickly to show that something can be done. There

are significant societal and scientific issues that are tied in with the successful development of something that can prolong survival in AIDS.

So one has to make a value judgment of what is the most efficient way of doing it. Biological response modifiers, immunomodulators, provide an exceedingly interesting goal to pursue. Many laboratories do so. There are studies involving interferon, there are studies involving interleuken II, there are studies involving a series of things. Ampligen, which I think is an exceedingly interesting biological response modifier, is now in a randomized trial.

I think these are interesting ideas. But I guess there is a philosophical issue, and I will speak now only for myself. There are very few precedents in infectious diseases in which one can make an impact against an infectious disease by trying to deal with a sequelae of the pathogenic agent as opposed to attacking the pathogenic agent itself.

For example, in rheumatic heart disease we know that much of the damage in the heart, in effect, can be viewed as an autoimmune phenomenon due to the patient's body making a response against cardiac valve tissues and so on. Yet, demonstrable gains against rheumatic heart disease were made by antibiotic treatment of the streptococchis that starts the process going to begin with, not attempting to solve the problem by relying on anti-inflammatory agents or steroids or other things to pick up the damage that has already been done.

In tuberculosis and in leprosy there are a number of host reactive changes, immune perturbations that may occur. In other diseases there may be similar events. Bacterial infections may lead to disseminated intravascular coagulation and other problems which may be addressed.

But in almost all cases that I am familiar with, it is always better from an overall impact point of view to try to attack what is starting the problem. That is why in my own personal laboratory we focus so much on anti-retrovirals, because we believe that this is the most direct approach, and we believe the clinical data now support the principle that they can play a major role.

Now I take your point that we should keep an open mind, and I believe that many investigators are pursuing other options. So I think from my point of view, again it gets back to the issue that we should sponsor, encourage investigator initiated research and allow individual clinical investigators to pursue their ideas. If Dr. Gottlieb and others have a different point of view, and if Dr. Carter wants to pursue Ampligen and so on, these

are good ideas. They should be pursued, they should have the mechanism of doing it.

As individual investigators, they should be able to pursue them and get answers.

CHAIRMAN WATKINS: I take it from your comment you see no bias; you think it is free floating and is finding its own level in the proper fashion?

DR. BRODER: I think that what we want to encourage is a competition of ideas and ideas that work should be pursued. Ideas that don't work should be abandoned. I think that's the bottom line. That's why I think clinical results are so critical.

If an idea is working then we should pursue it. I think that if biological response modifiers are shown to have a role by studies that have been launched, they can be expanded and they can be encouraged and other appropriate analogs can be made and so on.

But there are two sides to this story. Activating T-cells from a certain number of experiments might be expected to lead to more viral replication. The virus seems to have evolved the capacity to use T-cell activation signals as a signal that it should start replicating.

So I don't think that we should always say that biologicals and immune stimulants are somehow inherently safer or more logical. There can be two sides to it. We need to keep an open mind and let individual investigators pursue their ideas. I do not personally see a bias that should impede investigators from pursuing the ideas that they think are important.

DR. LILLY: Thank you for your participation today and for your very illustrative presentation and also very much for the work that you have done and will continue to do.

DR. BRODER: Dr. Lilly, in view of your record in retroviruses, it is my esteemed privilege to be here. Thank you.

DR. LILLY: We hope that if you have further comments and further thoughts in the area, that you will come back to us with them.

The History of U.S. Drug Development and Regulation

DR. LILLY: The next presenter this morning is Mr. Peter Barton Hutt, of Covington & Burling. Mr. Hutt is former Chief Counsel to the FDA and is going to briefly survey for us the history of drug development and regulation in the United States.

MR. HUTT: Thank you very much.

For roughly the past 30 years, I have been involved one way or another with FDA regulation of new drugs. I have been invited to present the results of that experience to you. During 1971 to 1975, I was privileged to serve as Chief Counsel to the Food and Drug Administration. I have spent a great deal of time studying the drug approval process. I believe a few of my articles on this subject have been presented to you.

I will not attempt to get into the details of present day regulation, particularly with respect to drugs for the treatment of AIDS, because I am quite well aware that the Commissioner of Food and Drugs is following me.

I do want, however, to place these regulatory issues of today in historical context. I think it is important for this Commission and others to understand how the system works.

First, I must emphasize that I will be talking about regulation of research, not about research itself. It is FDA's role to regulate research but not to conduct the research that it regulates. This differentiation of functions is important to understand.

If you go back in history, you will find there has been Government regulation of food and drugs, which for many centuries were indistinguishable, from the beginning of recorded history. That regulation has existed to prevent two problems: fraud in the marketplace, and the danger to health and safety that occurs if fraudulent drugs are permitted on the market to displace medicine that is indeed safe and effective.

If you think it unusual that this has been a problem throughout history, I will give you merely one example. Pliny the Elder, writing in the first century A.D. in his famous treatise on natural history, complained that the druggists of his day in the Roman Empire, "spoiled all drugs with their fraudulent adulteration." This is not a modern issue. It is an issue that has existed throughout all time.

The first statute enacted by the United States Congress to regulate industry was directed at the drug industry in 1813. It was enacted because Jenner had discovered smallpox vaccine in

the late 1700s and immediately on the market came fraudulent imitations that were neither safe nor effective. The United States Congress enacted a statute to ensure that smallpox vaccine on the market would only be what they called in those days, "the genuine matter." In 1848, Congress enacted a statute to make certain that all imported drugs were safe and effective. That statute continues in effect up to this day.

In 1902, Congress enacted what we refer to as the Biologics Act, a statute that again still exists to this day. That statute was very modern. It required premarket approval as early as 1902 of all biological products put on the market for the prevention and treatment of disease. That statute was delegated to the Public Health Service, and it was the Public Health Service and NIH that implemented the Biologics Act up until 1972. In 1972, it was transferred to the Food and Drug Administration where it resides today.

Four years after that statute, Congress enacted the first nationwide statute to deal with regulation of all drugs in the United States, a statute called the Food and Drugs Act of 1906. That statute, for purely historical reasons, was delegated initially to the United States Department of Agriculture, later to the Department of Health, Education and Welfare, and now of course in the Department of Health and Human Services. That statute did not require premarket approval. It was a simple policing statute. FDA was given authority to take adulterated or misbranded drugs off the market but not to require premarket approval.

In 1938, that statute was replaced by the law that we now have in place, the Federal Food, Drug, and Cosmetic Act, but even then Congress did not require pre-market approval of new drugs. They required only a form of pre-market notification and gave FDA authority to veto the marketing of adulterated, misbranded or unsafe drugs.

It was in 1962 that our current law, amending the 1938 act to its current form, was put in place, following the thalidomide tragedy. Under the Drug Amendments of 1962, FDA is required to approve new drugs as safe and effective before they may be commercially marketed.

There are four stages of drug development that FDA regulates. I want briefly to characterize those four and then explain some of the practicalities of how they actually work.

Here again, I want to emphasize, FDA does not test drugs. FDA regulates how other people test drugs. NIH, universities, the pharmaceutical industry, individual physicians and so on, to test drugs. FDA's role is solely a regulatory function.

The first stage of drug development is the animal research. Basically, FDA does not control animal research. Anyone in the country can begin animal research on a new drug for AIDS or any other purpose without informing FDA, and without getting FDA approval of any kind. FDA has regulations called good laboratory practice (GLP), regulations which lay out general principles in order to ensure that the data from that animal research is valid from a scientific standpoint, but FDA does not otherwise control when it is done or how it is done.

The second stage is clinical research, i.e., research in humans. Here, FDA does enter the picture. FDA requires, under the statute, that an investigational new drug (IND) application be submitted to the agency and approved by the agency before the human research is undertaken. During this investigational stage, the statute itself, the Federal Food, Drug and Cosmetic Act, prohibits the commercialization of a drug. But, as I will explain in a moment, it does not prohibit its use for treatment under appropriate circumstances.

The third stage is the approval itself. Once all the animal and human data are available, FDA can review a new drug application (NDA), and determine that the drug is in fact shown to be safe and effective. This is a rigorous review by the agency to prevent the problem that would be caused if unsafe or ineffective drugs were commercially marketed. It takes two to three years on an average for FDA to complete this process. Once again, no marketing can occur under the statute until FDA has in fact approved the new drug application.

The fourth and final stage is once the NDA has been approved and the drug is marketed in accordance with that new drug application. This is the post-approval stage. Here, FDA requires surveillance in the marketplace and has legal authority to withdraw approval if at any stage it is determined that the drug is unsafe or ineffective, despite earlier indications that it might have been safe or effective.

Let me turn to a few general observations. The first one I want to emphasize very strongly. The statute itself, the Federal Food, Drug and Cosmetic Act, and all of its permutations, is not a barrier to making available any drug to any patient at any stage of any investigation where that patient needs the drug. The statute has general criteria. It has flexible provisions and it provides enormous discretion to the Food and Drug Administration to permit anything that is in the public interest.

I have never seen a situation -- not only in the 30 years I have been working in this area, but going further back in history -- where FDA was precluded from making a wise public health decision because of some rigid provision in the statute.

I urge upon you that the issue is not whether the statute must be changed to prevent a barrier to new drugs. That is not a problem, either at the IND stage or at the new drug application stage.

Second, and this is equally important, I am unaware of any situation where a beneficial drug, even at the experimental stage, has been precluded by the Food and Drug Administration from being made available to patients who need it. Here I want to give you a clear, unequivocal illustration. I am not aware of FDA ever telling someone they could not get a drug where the following four criteria were clearly met. First, the drug company will make the drug available. Second, the physician wants to prescribe it. Third, the patient wants to take it. Fourth, there is some credible scientific evidence that it may be of some utility.

Where any of those four is missing -- where for example, FDA has reason to believe there is no credible evidence of effectiveness or safety, or where the drug company is not willing to make it available or the physician is not willing to take the responsibility for prescribing it -- of course that drug will not be made available. This is not an issue where FDA is standing as a barrier, to the best of my knowledge, to prevent good medicine from being undertaken.

Where there is a problem is in the lack of understanding among doctors and patients, and frequently in the pharmaceutical industry and FDA itself, about how to make this system work. There is a lack of information on how to get drugs, which ones are available, what the criteria are, what the paperwork that is necessary is, et cetera. Where it is done properly, I have never heard of an incident where FDA was standing in the way of good therapy, even at the earliest phase of investigation.

My third general observation is that the FDA personnel from top to bottom, in my judgment and experience going back many years -- and I have known eight FDA Commissioners personally -- are dedicated to public health. They believe very strongly that these drugs, once they are in a position to go out, ought to get out there as fast as they can and be available to anyone who needs them.

Thus, their job is to be a tough regulator, to prevent fraud, to prevent ineffective drugs from getting out there and displacing effective drugs. Their job, and I have never seen anyone in FDA look at it any differently, is not to prevent a useful drug from being made available to a needing patient.

Fourth, some companies are concerned about making available highly experimental drugs at a very early stage of

investigation. These are valid concerns. The first concern is one of cost. If you are a small company and if you are asked to make a drug available without being able to charge for it because you are prohibited from commercialization, it could be the end of your company. You could bankrupt yourself. That is one problem. That is why Dr. Young and his colleagues have recently come up with the idea of a treatment IND where an experimental drug can be charged for. There are needed changes in rules, I might add, to permit Medicare and Medicaid to pay for these experimental drugs, which they currently will not do. If there is any issue that would speed these drugs to the American people who need them, that is probably the most important barrier at this time.

There is also the problem of product liability. A company may not wish to have its drug in the experimental stage widely distributed because it may result in serious product liability.

My fifth general observation is that the biggest problem we face in America with more rapid development of drugs and more rapid FDA approval of drugs is not, as I said, the statute; it is not the dedication to the public health by the Food and Drug Administration; rather, it is a bias that we have developed in our country against putting drugs on the market too fast. The media and Congress have focused upon the risks of drugs, not upon the potential benefits. The only person in the history of the Food and Drug Administration who has received a gold medal from the President of the United States, received that medal for disapproving a drug -- which she quite properly did. Dr. Francis Kelsey refused to approve thalidomide. Thank goodness she did.

But what about all the FDA employees over the last 50 years who have made difficult judgments, on the basis not always of totally compelling data, to permit the marketing of a drug that has saved hundreds of thousands of lives? Those people do not get a reward. They do not get recognition. There is no incentive for them to make that kind of courageous judgment and decision.

I am not certain this aversion to risk taking in our society can totally be overcome, but it is the major impediment to faster approval of new drugs in our country.

My final general observation is that AIDS drugs are no different than any other type of drugs in this respect. Cancer drugs and drugs for other life threatening and serious disease stand in the same position. They have the same problem and they need the same kind of encouragement as do the people who work on AIDS drugs.

In conclusion, I would simply like to say that the requirements for drug approval in our country are sensible. Drugs should not be commercialized until they are shown to be safe and effective. I would hope no one would question that.

Nor is the statute a barrier to providing these drugs at the earliest stage possible to people who need them. I would say, for example, that the criteria that the Commissioner announced some months ago for treatment INDs are flexible criteria. Those who complained this morning that they could not get these drugs, in my judgment, were suffering from the major problem of lack of information, not for lack of a system under which they could be made available. I am convinced, for example, that if it were shown that a new chemical entity was the best promise and the best hope for AIDS or cancer or any other serious disease, even at the end of Phase I or early in Phase II, this Commissioner and his staff would allow it under a treatment IND tomorrow morning.

These are flexible criteria. They are there to help, not to harm the public health. I think you can tell how strongly I believe that we are well served by our Food and Drug Administration and by the efforts it makes on behalf of all of us.

Thank you. I would be happy to answer any questions you may have.

DR. LILLY: Thank you for your advocacy, sir.

Dr. Lee, do you have any questions of Mr. Hutt?

DR. LEE: I believe that while the immediate issue is access, the main problem is the several years it takes at a minimum to get the drug application through: the year or two of animal research before the clinical research, and the one to seven years of evaluation. That is what we are wrestling with. I hope you will wrestle with us.

MR. HUTT: Dr. Lee, the immediate issue is, during that period of clinical research and NDA approval, can the drug be made available to everyone who needs it. The answer is a flat yes. FDA has a system in place that permits that and, indeed, encourages it. I do not think I ought to go into the details because you will be hearing from Commissioner Young on that shortly.

DR. LILLY: Dr. SerVaas?

DR. SERVAAS: I have no questions.

DR. LILLY: Mr. Creedon?

MR. CREEDON: Thank you very much. I found that very illuminating. As I understood what you said, an experimental drug could be made available if it met four criteria.

MR. HUTT: Yes, sir.

MR. CREEDON: One of the criteria is there be credible evidence that it is safe and effective?

MR. HUTT: No. Just that it <u>may</u> be safe and effective. There has to be some basis for giving the drug to the patient, other than sheer hope and hokum.

MR. CREEDON: There is a spectrum between credible evidence and sheer hope and hokum. I'm not sure where along that spectrum someone could make a decision that maybe this drug if it is being used in France or Mexico or wherever, maybe there is some credible -- perhaps "evidence" is too strong a word, some credible -- I don't know what, that it could be helpful. It seems to me it depends on how strictly the words "credible evidence" are applied by the FDA as to whether experimental drugs can really get out there.

MR. HUTT: Mr. Creedon, I agree with you. That is a critical issue. I can assure you that FDA has said that it is not limited to any one form of evidence. For example, it may be based on the structure of the drug. It may be based on the animal data. It may be based on in vitro data. It may be based on human data.

MR. CREEDON: We had a witness here who had two exhibits yesterday. In one, he had a whole grouping of vials which were supposed to represent drugs, and there were probably 30 or 40 of them. In the other, he had just one, which was AZT. He said, here are all these drugs that could have a favorable effect on AIDS, are being used by somebody somewhere because they feel it may be having a favorable effect, and yet, there is only one drug available, AZT.

MR. HUTT: Mr. Creedon, I would have to again state my knowledge and belief. I am unaware that any patient or doctor has approached FDA to gain approval for use of one of these experimental drugs in a patient where FDA has said no.

MR. CREEDON: Is the problem that people do not know what the process is?

MR. HUTT: I think that is probably the major problem. There are also problems, as I indicated, that some physicians are unwilling to take the personal risk of malpractice to prescribe a highly experimental drug on which there is little or nothing available in the scientific literature, and some companies are

unwilling to allow these drugs to be used widespread at that early stage also, for the reasons I explained.

MR. CREEDON: Perhaps there would be a need for legislation in the liability area.

MR. HUTT: I would concur with that.

MR. CREEDON: Under certain circumstances, relieve some of the liability.

MR. HUTT: I strongly agree. I also believe that getting information out to physicians and patients and the general public about how these experimental drugs can become available is of crucial importance.

MR. CREEDON: Thank you.

DR. LILLY: That is a very important point. Cardinal O'Connor?

CARDINAL O'CONNOR: I have a few. Pardon my ignorance. Perhaps these questions shouldn't be directed at you.

There would seem to be a disconnect; in the latter portion of your remarks, you said there is a breakdown in information rather than in reality. This morning we had a gentleman who has been pursuing these things for five and a half years, I think he has said, and he has looked for a list of available experimental possibilities, those that might fall within this general credibility that you talked about. Does FDA provide such a list? Is there a reason why such a list wouldn't be available?

A few days ago or a week ago, I asked to meet with a number of doctors, nurses, staff, others who are engaged in daily hands on activity with persons with AIDS in one of the facilities I'm responsible for. They were very much concerned whereas a number of the things you are talking about might well be available, they don't seem they are available to clinicians in hospitals, they don't seem to be available to us engaged in hands on activity.

Is that controlled by FDA? Is this another matter of misinformation and misperception?

MR. HUTT: Perhaps I could start with your second question. FDA does intend control, as I described it, the availability of any experimental drug. It cannot be made available to humans without FDA agreement. That is true whether that is in a hospital setting or in a home setting or any other

setting. I think both of your questions relate to the same problem and that is one of information.

To my knowledge, there is not available a list of the experimental drugs that FDA or the company has agreed can be made available through -- and I apologize for all this jargon -- a treatment IND, compassionate use IND, orphan drug IND, or various other types of these experimental protocols that FDA approves upon application by a company.

I must emphasize that it is ultimately the company that will decide whether the drug is made available. FDA has no authority to require that it be made available. A list, in my judgment, is one of the needed pieces of information, of the kind you described, Cardinal O'Connor, that is not available today.

CARDINAL O'CONNOR: My final question, and again, I don't know if this is within your province, I don't know what FDA has to do with costs, but again, my concern, and I have no competency in research but I work very closely with patients and persons with AIDS, and this is a very severe increasing problem for us, I am still not happy about the fact that at least one pharmaceutical company has been able to refuse to release its costs, its development costs, its production costs and so on, moreover, there is a broad spectrum of medications required because of the opportunistic infections related to AIDS which would not be AZT, so that in the treatment of the whole person over an extended period of time, the costs are becoming almost astronomical.

Has FDA a role to play in that at all?

MR. HUTT: Let me distinguish where it does and where it does not. First, with regard to the investigational stage before approval of the new drug application, if FDA permits the sale of an investigational or experimental drug, FDA has a regulation in place that says that the company may not charge more than to recoup costs. There are criteria for this that FDA has laid out in its regulations.

As I indicated, the major problem is that HCFA, the Health Care Financing Administration, prohibits at the moment payment for an investigational drug. As I indicated, that is probably one of the most serious impediments that ought to be investigated by this Commission.

Second, with regard to a drug after FDA has approved it for marketing, FDA has no statutory or any other authority to deal with the price of that drug. None at all.

CARDINAL O'CONNOR: Thank you very much.

DR. LEE: I think if Dr. Krim is here, AmFAR does have a list of all these drugs that are currently in trials all over the country.

MR. HUTT: Dr. Lee, I was not referring to drugs that are in trials. FDA has a list of those. I was referring to the drugs that are both in trial and will be made available to any patient through a treatment IND or other mechanism. Thank you for that correction.

DR. LILLY: Thank you very much, Mr. Hutt.

The Food and Drug Administration

DR. LILLY: We will go on now to hear from Dr. Frank Young, who is the Commissioner of the Food and Drug Administration. Dr. Young has brought some of his assistants with him. I think we can get answers to an awful lot of questions this morning. Dr. Young will have a presentation to start off with.

Dr. Young?

DR. YOUNG: Admiral Watkins, Dr. Lilly, ladies and gentlemen of the Commission and those in the audience, I am particularly pleased to be here today to try to explain some of the issues that came up both this morning and those that I have heard throughout the time that we have been dealing with this war on AIDS.

I want to summarize a few points for you and then I would like to introduce the individuals at the table by showing you the structure of who is fighting this war, and then I would like to take some time to discuss the drug evaluation process and possibly answer some of the questions that Cardinal O'Connor raised, Mr. Creedon, Dr. Lee, and others, to focus on what is the current state of the process, where I believe the bottlenecks are, what might be done and what effect that would have.

I think if we can see this whole process, we might be able to look at it clearly. I also believe that you heard the history amply described as to how we got the Food, Drug and Cosmetic Act that we have, and the burden on the agency when it approves a new drug to deal with safety and effectiveness.

I also want you to know that in coming into the agency, I felt particularly strongly about the concept of the treatment IND and am very pleased that we have this available now. I would like to show exactly how the treatment IND fits in.

I would also provide some data that will show you the increase in treatment INDs and will discuss their rate of increase that might be of help to you, the audience, as we look at this particular issue and see the progress that has been developed in this area. I do believe that some of the progress that we are seeing may eventually end some of the frustrations. I will be just as frustrated as Dr. Broder and others were because we don't have a cure at this time. No one can rest until we have a cure for AIDS.

I particularly compliment you for having Dr. Broder here and I want the record to know that he almost single handedly stood for a long period of time working on anti-virals. It is a

good example of the persistence of an investigator in making a difference.

May I please have the first slide?

[Slide.]

DR. YOUNG: In dealing with this war on AIDS, it is important for you to know the individuals that I have brought today and the changes that we have made.

Until this October we had a single Center for Drugs and Biologics. Recognizing the problem that AIDS was going to be for to the agency, we have changed our organizational structure.

Dr. Paul Parkman, who is sitting to the immediate right of my empty chair, is the AIDS coordinator for all of FDA. That means that he has the responsibility in our agency of developing the flow of information across all sections: those working with devices, foods, drugs, biologics, etc. He is also the director of one of the two new centers -- the Center for Biologics Evaluation and Research. That Center, which has approximately 340 individuals in it, is devoting over 75 percent of its total effort to AIDS activities. That includes the blood testing kits, the vaccines, the biological drugs, and the applied research that is required to better understand these particular products. I must emphasize at this point that NIH clearly has the lead responsibility for fundamental research. FDA's research supports our regulatory mission.

A new Center was formed in October for Drug Evaluation and Research. Dr. Carl Peck, who is sitting at the immediate left of my empty chair, joined FDA at that time to take responsibility for this new center. Within Dr. Parkman's center, we created a new office that has the responsibility for antimicrobial agents, antiviral agents and metabolic agents. The new Director of that office is Dr. James Bilstad, who is sitting to the immediate left of Dr. Peck.

On the immediate right of Dr. Parkman is Dr. Ellen Cooper, who was designated as Acting Director of a division which has just been formed to review new antiviral drugs.

We have a number of other activities that we are responsible for. In the area of medical devices, for example, we regulate condoms and gloves, and make sure that devices are safe and do not transmit AIDS. These responsibilities fall under the Center for Devices and Radiological Health.

We also have a field force that is involved in inspecting and validating studies. For example, when AZT was

being evaluated, and before its final approval, we sent inspectors to each of the clinical sites to be sure that there was no fraud in those studies. They had to be validated.

We also have some AIDS-related concerns in the food safety area that we are looking at through our Center for Food Safety and Applied Nutrition.

I am using these examples to show you that we have made major organizational changes to fight this war, and also to introduce the individuals who are with me today to assist in answering your questions.

Now let me focus on the drug review process. The first aspect of exploration of a drug is in a laboratory, as Dr. Broder might describe the example in which AZT was used to check its antiviral activity. That is followed by short term animal tests to examine toxicity. Long term animal tests are frequently done simultaneously and a company might, during that process, conclude that this is something that could be put into mankind.

As was noted by Peter Hutt, only at that point does a new drug come before FDA for the first of its regulatory actions -- the investigational new drug application (INC). The IND's purpose is to determine of the drug is safe enough for numan testing. We have modified our IND procedure in the case of AIDS drugs. We frequently are proactive in working with the company sponsor or the NIH sponsor during this time, so that most of the investigations of new AIDS drug applications are approved in five days. That essentially is as fast as you can turn a piece of paper around by the mail service in these United States today.

And it is not infrequent that I will call in the Chief Executive Officer of a company and ask him to bring in his team to work with the team that we will be setting up in FDA to look at the drug. I did that, for example, most recently with Hoffmann- LaRoche in looking at DDC, and with Bristol-Myers looking at their vaccine.

Once FDA gives a go-ahead for the IND, the drug's study is done by the sponsor. FDA approves the protocols and will interact with the sponsor as the study proceeds, but no testing is done by FDA.

Dr. Peck plans to announce some innovations that will be explored to see whether we can speed up this process.

On the average, from 1980 to 1985, this process took approximately eleven years to go through -- from early laboratory work to final FDA approval. I am pleased to inform you that from 1985 to 1988, that development time -- atleast for new molecular entities -- has decreased from about eleven years down

to 7.3 years. That is still a long time, and not where I would like to see it finally rest, but I emphasize that much of the development time is the sponsor's, not the FDA's.

For most drugs, we do not have the extensive interaction with a company until a mammoth approval application arrives at FDA. To my surprise, less than 40 percent of the companies come to FDA for a formal conference at the end of Phase II studies.

Phase I primarily dealing with safety, 20 to 40 people; Phase II, another portion of the innovative phase, a couple of hundred patients. And then one moves into Phase III, which is the verification phase. Phase III is the expensive phase -- 2,000 - 5,000 people are looked at in the classical drug -- not necessarily in the AIDS related drug.

What we have modified in the AIDS-related approval evaluation is that when we call the companies in, we request them to be in constant dialogue with FDA over this period of time. Let us look at the protocols, let's make suggestions, let's evaluate the data. Let's not surprise each other. Let's try to see what we can do to facilitate the process.

The average new drug application does take approximately 30 months -- a little less than 30 months -- to go through the FDA evaluation. A modification that we put in very early for all AIDS drugs is that we promised that there will be no application that will take longer than 180 days to go through this process.

If we have to pull individuals off other drugs, which we have done, we will do that. If we have to move resources away from other essential actions, we will do that. In the case of AZT, approximately 60 people worked over 107 days with the expenditure of over $600,000 to get that drug approved. There has been no drug for AIDS that has taken longer than 180 days at this time and, as I said, AZT is 107.

This is a major modification of a process that on the average is taking 30 months. That is in itself insufficient and it is insufficient because of the needs for the possibility of treatment IND. But before showing you and walking you through the treatment IND, I would like to give you some data we developed just a short time ago, and it is going to take a few moments, because this is extraordinarily important to understand.

We went back to 1976, 1977 and 1978 for INDs -- remember the INDs are those that are now being tested in human beings -- for new chemical entities. These would be the drugs

that are new and significant, the highest category of drugs prior to getting the IAA classification.

If one looked at 100 percent of these drugs, starting in human beings, 70 percent remain after Phase I, 33 percent remain after Phase II, 27 percent remain after Phase III and 20 percent of these are finally approved.

Now why do they drop out? That is shown [pointing] here. In Phase I the majority of these drugs that fail, fail because they are not safe. You also see some that are not efficacious. The failure here is made in the minds of the company sponsor or the NIH sponsor in not continuing the trial.

There are a lot of thoughts, "Well, what happened in other countries? Where are the drugs there?" In those for which there are no commercial interests, 80 percent of those are never introduced to any other country in the world. Of the 20 percent that are introduced somewhere, they are introduced into a very few countries. Interestingly, France is the country that usually takes anything that is introduced and not introduced widely around the world. I am not trying to disparage that system, but it is a much more permissive system.

Of those 20 percent, they are rarely marketed in more than a couple of the Western developed countries.

In Phase II again one sees a carnage primarily related to safety, efficacy and no commercial interest.

This brings us back now to the treatment IND.

[Slide.]

At the end of Phase II, we have a very high degree of certainty of what candidates are likely that the sponsor -- I emphasize again, the sponsor -- will bring forward to Phase III.

I want to clearly emphasize that the idea of the treatment IND is to bring those drugs that are promising before the whole process is completed.

How do we know? We have some criteria for efficacy for treatment INDs for AIDS drugs that I will submit for the record. But primarily we are saying that we are balancing the relative risk of the disease with the relative effectiveness that might be appropriate for humans to use those drugs.

In the case of a very promising drug, as Dr. Broder mentioned, in AZT, there was not even a Phase III study. In the case of serious diseases, more efficacy information is required

and there we would expect Phase III trials likely to be completed, but the data not completely evaluated.

In these circumstances, my estimate is that between 20 and 30 percent of the total time that would normally be required for the evaluation can be saved by bringing these drugs out early through a treatment IND.

But a treatment IND is not the only way in which we bring drugs to patients. I want to emphasize that we too are concerned about that balance between helping people and getting the scientific information. And in the case of CMV retinitis, with a drug called Ganciclovir, the entire study was done on a compassionate IND. There were no controlled, double-blinded placebo trials, but the trial was done by giving all of the individuals the drug and looking at it from a historical basis.

We also have emergency INDs, which are different from compassionate INDs. Remember, the treatment IND is for everyone; the compassionate IND is patient by patient; the emergency IND is given when we hardly know anything about the drug. So we are not limited to a single way in which we bring drugs to patients.

Now there is another modification that I would suggest for your consideration, which we have seen as we have looked at this. There might be a way in which one would be able to require less data from the Phase III studies if there were a mandatory Phase IV, where studies could be done after the drug is on the market. Now with AZT we did require, by agreement with the company, Phase IV studies. But FDA does not have the absolute legal authority to require those. And thus that puts us more on the knife edge of certainty. I must say that FDA does undergo a great deal of criticism for those who think there is a drug rush.

We had one series of hearings on a drug that took seven years to evaluate in FDA and someone said that was a drug rush. That sends a different signal than the Commissioner who is trying to look at bringing drugs forward as rapidly and as expeditiously as possible.

Another thing that we are doing to improve the drug evaluation process is to form a team, so that when we start looking at the drug a constant FDA team is formed, and that team works all the way through this process. That is much more resource-intense.

So much for the process.

[Slide.]

Now what is in the pipeline? As of January 31, 1988 -- and these numbers are slightly different than your numbers because they are increasingly rapidly -- we have this picture of the number of AIDS drugs that are under investigation in the United States.

Of these 35 antivirals, for example, 17 are in Phase I -- have started Phase I; 17 have started Phase II, and 1 has started Phase III. Of the immunomodulators, 15 have started Phase I, 25 have started Phase II and 5 have started Phase III.

In the opportunistic infections, progress has been more rapid: Three have started Phase I, 27 in Phase II and 1 has started Phase III. In the antineoplastics, one has started Phase I and 3 have started Phase II, and none have started Phase III. The vaccines are all in Phase I.

[Slide.]

If one looks at the rate of increase that we have had of AIDS-related INDs, the rate is quite spectacular.

[Slide.]

Here is 1981, essentially no action, very little action in 1982, very little action in 1983. Beginning in 1984, we received 21 INDs at a rate of 1.75 per month -- 1.8 per month; thirty-one were received in 1984, at a rate of 2.6 per month. Forty-four in 1986 at a rate of 3.7 a month and 50 in 1987 at a rate of 5 per month.

We have a very strong feeling that this curve is going to go up very rapidly. My fear, as you will see in the next slide, is that we may not be prepared. I don't want FDA to be the bottleneck.

[Slide.]

I show you the research dollars increasing in only NIH because these are the only public dollars that we have. Compare the rate of research increases to increases for resources toreview the new products that will result from that research. I must emphasize that the research in the private sector is greater than all of the activity at NIH.

For example, if you were to look at the orphan drug status, which has been given to 15 drugs, only four of the 15 are sponsored by NIH in any way and 11 of the 15 are in the private sector. So this 468 million dollars of activity and growth is if anything an understatement. You can see on the bottom curve here, the increment of resource in FDA to process this increase

of drug research that inextricably is going to be translated into FDA workload in the future.

What we are desperately trying to do for our organization and program is to prevent FDA from being the bottleneck.

The bulk of the AIDS drug research at this time is somewhere in Phase II. We are just beginning to get to the point where I would think we will see a larger growth of treatment INDs coming to FDA. We will act on these expeditiously.

What are the risks for approving treatment INDs? The risks are substantial -- if patients and physicians do not understand the summary basis of approval that this was developed on. And I am pleased that I have an informal agreement with the editor of The New England Journal of Medicine, Bud Relman, and with Jim Salmon, President of AMA, to be able to publish immediately the basis of the approval of a treatment IND, what the indications are, and what the contraindications. And we will do that promptly as treatment INDs are approved.

We will also write consumer articles so that the physician and patient can learn about these drugs in lay language. We have written, and I have submitted for the record, a whole consumer booklet on how one evaluates these drugs.

When I was dealing with a group of individuals on an ethics panel a short time ago, and I asked how we can help the physician and the industry from feeling that they will be under a burden of our litigious society. And they said if you publish the results on which the decision was made and emphasize the benefits and the risks, and emphasize informed consent, and the experimental nature of this, the reduction in suits will be dramatic, and we promised to do so.

We also promised to provide other publications to really do a cookbook approach to how this process works.

I must tell you when I left the deanship and vice presidency of the University of Rochester and came to FDA, I had within the first two weeks to do a television talk show on this approval process, and I didn't understand it, though I had been a physician for a number of years. I want you to know now I know this like the back of my hand, and we are trying to see what we can do to expedite the process. But the physician community and the consumer community other than, I think, the AIDS community, which is much more educated, are really not that familiar with this process. So the burden falls on us to make that more understandable.

Let me now summarize the kind of things that I have already said that could be done that will influence, in my opinion, this process.

First, of course, we have got to have the team of individuals that take this application from the beginning right through with a constant team that doesn't change and that can meet those needs, and have a very strong interaction with the sponsor, whether it be government or private. And I have emphasized that the majority of the research, clinical research and developmental research, is done in industry at this time.

I have also said that it is important to get some way in which the litigious fear and the fear of applying for treatment INDs may be reduced. We are going to put the information out and deal with it in that fashion.

I have tried to focus on the need to see whether we can modify the data requirements for AIDS in this period of time, and couple it with a mandatory Phase IV. Dr. Peck has focused on the need to develop generic research so that we can identify possible bottlenecks and solve them before they occur.

I have tried to focus on the needs for understanding that the treatment IND is a flexible process. You can go back earlier into phase two if it's really a breakthrough drug, you can take longer if it's not, and that we do have standards for efficacy. And I have tried to point out that we have reorganized FDA to try to deal with this in the most vigorous fashion, because to us this is war. We are in charge of the ammunitions factory, and it is our job to be sure that safe and effective bullets are turned out. Safe so that they don't kill the person using the drug; and effective in that they shoot the target that they are aiming at.

I have tried to show you that there is a substantial promise for these drugs now in the pipeline, given you my promise that the agency will look at them as rapidly as possible so we can get these out to people as soon as we have the appropriate evidence of efficacy.

I thank you for the opportunity to present this information. I would be delighted to answer questions and have my staff answer questions as we go through this. Thank you.

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

DR. LILLY: Thank you, Dr. Young. I am sure the Commissioners will take you up on your offer to answer questions.

Perhaps, Ms. Pullen, would you care to start the questioning?

MS. PULLEN: Dr. Young, yesterday we heard from a witness from, I believe, the Institute of Medicine, that a vaccine trial had taken place where the vaccine was tested first in humans before it was tested in animals. They didn't indicate whether that was in the United States. I assumed it was, because that is generally the context of our discussions. Was the FDA involved in approving the human trials before animal trials were done?

DR. YOUNG: If you are talking about the two that are being tested in humans at this time, the answer is yes, and I have to explain that. There is no animal model for effectiveness at this time. Therefore, one cannot do the classical experiment that is usually done in vaccines; namely have an animal model that shows you that antibodies are produced and those antibodies prevent infection. That's the situation today.

There is animal data in these trials that were done to see whether there was toxicity or whether there were problems with safety. Now we were faced with two choices:

One, we could wait until an animal model was developed, and I asked the people at an IOM executive committee, do we have an animal model today. The answer is no. Will we have one within a year? No. Will we have one in two years? Most likely not. One in three years? Probably not. One in four years? Maybe. One in five years? A stronger maybe.

We could wait and look at no effect of toxicity on human beings and antibody levels of response until an animal model was done. No vaccine trials for two to five years.

Alternatively, we could, as we did upon the advice of our scientists and the extramural advisory committee, do what I would strongly defend, of trying a vaccine shown to be safe in experimental animals, to see whether it raised an antibody titer, and whether it had any adverse reactions in mankind.

This does not mean that we are going towards an efficacy test at all, but if we don't get started, it's a longer delay.

Having answered it in a global form, let me ask Dr. Parkman if he would like to add anything further, because it's his center that has that responsibility.

DR. PARKMAN: I think you have answered it very completely, Dr. Young. I don't have anything to add to your statement.

MS. PULLEN: Are you saying then that there have been no such trials in human beings that precede safety trials in animals?

DR. YOUNG: Safety trials were done in animals, but there is no animal model for efficacy. So the choice was a hard one: wait until the model came, two to five years, or start looking at safety in human beings.

In this war effort, we felt that if there's an informed consent, so that the patients know who are volunteering and really sacrificing a lot for humanity, of what the risks and the benefits are, then that should be allowed to go forward, and our advisory committee concurred. But there were safety experiments in animals.

MS. PULLEN: Thank you.

DR. LILLY: Dr. Primm?

DR. PRIMM: Dr. Young, perhaps you could explain for me the monopoly sort of given to Burroughs-Wellcome Company for AZT for 17 years. Could you comment on that and give me a clearer understanding of why a pharmaceutical company would have those kinds of rights for that period of time, creating no competition and no lowering of price and so forth?

DR. YOUNG: I'm afraid, really, Dr. Primm, I cannot. I have, during my watch at FDA, asked the agency to sort of put blinders on. We must only look at safety and effectiveness. Once we start looking at economics, once we start looking at different political issues on whose drug gets tested first and how it goes through the system and order the priorities, once we deviate in these ways, I believe we are betraying the trust of the American public.

As I understand it, though, this is what usually happens, if I'm understanding this:

An organization discovers a drug, it submits that drug for a patent. A patent is granted, and then that discoverer of something that's new, not obvious and novel, is granted a patent for a 17 year period of time.

In this case, the drug was not used, as Dr. Broder said, really for any retroviruses. That just wasn't part of the experimentation.

Then through Dr. Broder's pioneering work of picking out chemicals that might be determined to have the reverse transcriptase, the enzyme that takes the RNA and makes it go into DNA, that drug was then tested. Based on that test, there was a

joint support by the National Institutes of Health and the company, and rapidly that drug was developed.

Though we will look at drug prices for sale under treatment INDs, we have no responsibility, legally, to examine drug costs, nor would I think it would be appropriate, for us to consider those costs in our review.

I do feel it is appropriate for it to be looked at, but we are just not the agency.

DR. PRIMM: I think it would help to make it more available to other populations if possibly there was some competition involved, and maybe the prices could be decreased.

DR. YOUNG: I think if DDC were a valuable drug and Dr. Broder's inklings came true, you would see, as soon as possible, a drug like that on the market. And I have observed from the other times when a discoverer with a single product had other products come on, that there was that type of competition. The marketplace does have a value. But I must also say that I know Congress has looked at the price, and has seen some of the books; we have not, and I think Mr. Waxman might be someone that could answer your question on the fairness of the price.

DR. PRIMM: Thank you.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: I would like to ask for your help and advice in an area that you also supervise, namely the blood supply.

DR. YOUNG: Yes.

DR. CRENSHAW: Most people don't think of the blood as a drug, but it indeed in some sense is, with side effects, transfusion reactions and, of course, infection.

DR. YOUNG: Yes.

DR. CRENSHAW: It has come to my attention, and I have looked at in depth, the availability of the resource of intraoperative transfusion, that it seems to me is widely underutilized, and largely available, that could protect not only against the small percentage of HIV infection that slips through testing, but the other things we worry about, HIV-2, HTLV-1, et cetera, and what I wonder, since blood can be suctioned during surgery, and I understand it applies to the majority of transfusions, and a person can get their own blood back within three minutes of an operation, what you can do to help educate physicians and the general public? Because one of the reasons

this isn't being applied more widely is people don't really know about it.

I also understand, and it was interesting to me to hear, that I hadn't connected, which is that AZT naturally is placing more demand on the blood supply and it preserves the homologous blood supply which we worry about shortages of. So will you comment on that and elaborate, perhaps?

DR. YOUNG: Surely. Let me answer your question and then ask Dr. Parkman, who has the responsibility for the blood areas in FDA, to provide further details, if he wishes.

We look at a number of levels in dealing with the blood supply. The first is to focus on the screening test to see whether or not we can reduce, as you said, maximally the number of units that could have any possibility of infection. That's the first cut. But some will slip through, you are absolutely correct, and the American people need to know, though it's a very small risk, that some risk occurs. It also occurs with infectious hepatitis and other diseases as well.

To counter that, you have two major methods that you pointed out:

One is the donation of your own blood before the surgery, and the second is the method that you raised. Now we can do two things, and are doing two things:

The first that we can do is to provide educational pieces; you saw our first attempt at better explaining the drug approval process, and we now have a number of articles that are coming forward dealing with various aspects of FDA regulation. That's because we realize that our responsibilities are poorly understood, particularly by physicians. We are also preparing similar articles for JAMA.

FDA will be putting some further information out on the blood supply in that fashion. We will be delighted to keep you informed and send you that, because education is important.

On the issue of self-donation, we work very closely with blood banks, and Dr. Parkman is in constant communication with the officials in the American Red Cross and others, to try to educate and deal with those practices, and to help people donate where they can.

In the other case, of the reprocessing of blood, we have approved the devices used in intraoperative salvage, and believe that the process can be a useful aid to the blood industry. However, we must recognize that the procedure is useful only in certain settings, such as in cardiac surgery,

where substantial blood loss exists. Since it is done intrastate, it does not fall under FDA's guidelines, per se.

DR. CRENSHAW: The thing that I think would be such a service is your needing funds and society's pouring funds into research with long term yields and years away, is that I'm hearing more and more stories about these machines standing by unused while people are given someone else's blood and leaving with hepatitis or something else. So if you can help inform physicians and encourage that use, which doesn't have side effects, it would be very valuable.

DR. YOUNG: Right. And that brings in another point, Dr. Crenshaw, which I would like to emphasize. We feel that there is a need, right now a very great need, for what I would call the applied research that goes between that long term fundamental research, which is the clear responsibility of the National Institutes of Health, and that research which is necessary to bring something to the marketplace. So that in the case of blood testing right now for HIV-2, it's Dr. Parkman's laboratory that has to work out some of the just nuts and bolts of building enough samples.

I called a while ago to get through a company in France more HIV-2 positive samples, because we only had 25 and we were making up a panel of 100 test sera. Then we have to go across that. In the same way we could deal with some practical research to see what could be done on making this process even more available, if that's appropriate, or less available.

Paul, could you mention more about the questions raised on the blood supply?

DR. PARKMAN: Well, I think that the question of education, as you are pointing out, is very important, if you are talking about intraoperative transfusion or other things that deal with the blood supply; education of physicians, their patients and the general population is one of the keys here.

In the blood bank, for example, people are screened and that is in part an educational thing to let people who are potential donors know who should not donate blood. And the question of education of the general population is important, too. I am still surprised at surveys which show a fairly substantial percentage of persons who believe that they have a risk of AIDS from donating blood to blood banks. And, of course, that is not correct; there is no risk from being a blood donor as far as AIDS is concerned. And so there are obviously lots of things we need to do more about education of all of those groups with respect to AIDS.

DR. CRENSHAW: The point that I don't want to have get lost, that I think is so important, is that this isn't a research phenomenon. It is a technology that has been available for ten years and we could make such progress if people were simply informed, both the physicians and the public, that it was an alternative that was cost effective and readily available.

DR. YOUNG: We will promise to give you an update on what is presently available that we know of on this technology and submit it for the Commission and then we will develop and keep you informed on how we are putting together educational packages and share those with you as they come out. I think it is a good suggestion.

DR. LILLY: Thank you. Dr. Walsh?

DR. WALSH: Just a brief comment and a couple of questions. First of all, Dr. Young, I want to tell you how impressed I was this morning with the presentation that you have made. I think it clears up for this Commission a lot of misconceptions that perhaps have been presented to us by other witnesses.

The other part of my comment is that as these hearings have gone along, I have been more and more impressed with how much the Federal Government actually is doing and how successfully they have mobilized the resources to attack this disease. It emphasizes for us again that the public and even those who are the victims of this disease are simply not aware of all that has been accomplished and is being accomplished. I wish we could find a way to have the public recognize more what has been done.

My questions are that obviously the burden on the Food and Drug Administration has vastly increased.

DR. YOUNG: Yes; it has.

DR. WALSH: Yet, your funding has not.

When you mobilize a team as you have for the war on AIDS, other aspects of drug evaluation must be suffering.

DR. YOUNG: That is correct.

DR. WALSH: We must keep AIDS in the forefront. What can this Commission do to assist you to a greater degree in getting more resources? We have been impressed by witness after witness that the prioritizing and allocation of resources is so vital and we need help in order to make appropriate recommendations. It would seem to me with the pleas of our first set of witnesses this morning, along with the plans that you have

outlined, that we simply cannot do the job with the manpower you have available.

What can we do to help you?

DR. YOUNG: There are a couple of things that I would like to point out that I think are keys to this type of resolution. The first is that you have hit the nail on the head. Without trained personnel, the system is going to crumble. Regrettably, it takes two years to get a person up to speed. A physician coming in is not going to be ready immediately to properly review a new drug application.

Unlike the usual system where you have a need and then you bring in a person, we have to have a way of anticipating this. We have been surprised by the rapid increase in experimental AIDS drugs. Our budget cycle is such that it is about two years earlier that we begin each year's budget planning. We have in recent times been able to get the people that we requested when the budget was prepared two years before, but it is very hard to catch up with it -- to know possibly what we will need two years later.

One of the most frustrating things, particularly for Dr. Peck, as we were creating the division for Dr. Cooper, is that we have to have the people on board to get the facility to put them in. The way GSA operates, unless you have the FTEs, you can't get the space for them. Imagine the dilemma of setting up for a 40 to 60 person unit to do anti-virals, and as I had to promise Dr. Peck, maybe in a year from now, I will be able to get you some space for the people.

Dr. Parkman has had to convert much non-laboratory space for labs, and I really thank Admiral Watkins for walking through with this staff. In the Biologics Building, for example, we converted a cold room to an office. It does look a little funny because it has one of those locked doors which I guess you can keep propped open. The janitors' closet is a dark room for photographic development. So, we have a problem getting the facilities once we get the people.

I think there has to be a way to more readily convert from the workload that is coming in to the people that we must have within FDA. There is a model for recruiting scientists that goes back to the World War II model.

When we were fighting a war and looking for medical units, we mobilized medical units in universities to be of help. I think a great help would be to develop a novel training program, that Dr. Peck has had some experience with, but which would enable us to support faculty to work with us in particular areas, advice in regulatory medicine, and support some trainees

who could enter the Public Health Service after their residency period. After they have spent two or three years in an AIDS specialty working on anti-virals or immunomodulators with financial support from the government, then pay back that on service in the Public Health Service at FDA.

I've been encouraged the strong support of that idea by Dr. Bowen and Dr. Windom. I hope that such a program can come to pass. That gives us both the immediate solution with faculty that we can use as an extension of FDA and a longer term solution for getting trainees in. That plus our recruiting and having the hiring authority would make a big difference.

DR. WALSH: If it would not be inappropriate, I think what we would like to have is something as specific as possible, because the strength of any Commission report, and I must say I have great admiration for the way Admiral Watkins functions, is that he wants this Commission to come in with specific recommendations, not a lot of general garbage that will be filed somewhere. We need all the help we can get on prioritizing. As I look at the number of drugs coming from the private sector, at the energy of the witnesses we have had this morning at NIH, I don't care how good your intentions are, I don't see how even with your new treatment INDs you are going to be able to turn the stuff out as fast as you would like and still fulfill your obligation to society.

If it is not inappropriate, and you could write it out for us. If it is inappropriate, maybe we can all get together one day and we will write it out after talking with you, so it would be safer, perhaps.

DR. YOUNG: We are always in a difficult position. I must add that I have been very pleased with the support that Dr. Bowen has given us, for the dollars that we have requested have been approved.

The two difficulties we have faced is -- although we have an outstanding review in the Agriculture Committees we go through -- we don't get the largest budget increases possible.

The other thing is we are discovering some things that are causing us difficulties throughout the agency. When the condom program came forward, we immediately diverted resources, yet we can't anticipate these kinds of things.

We have received about 230 new people to work on this but we have diverted 84 of our existing agency personnel from other things.

DR. WALSH: Without wanting to appear negative, it seems to me with limited resources, rather than have Congress authorize sending out 40 million pieces of mail that is already two years old to people who won't read it, think of what we could do with the money in improving the process say at FDA, in its resource allocation.

DR. LILLY: I think I am going to take my place in the line. I would like to verify one thing. Other than trimetrexate, there are no treatment INDs that have been authorized? I think that is what has been said and that is essentially because the sponsoring companies have yet to request them; is that true?

DR. YOUNG: That's correct; with the exception of Ribavirin, which had a treatment IND application, and which we found as we analyzed, that there was insufficient evidence of efficacy for treatment IND approval. With those exceptions, we have no other INDs for treatment use that have come forward from industry for AIDS drugs. We would be most anxious to receive these so we could work on them.

DR. LILLY: That was one of the more striking complaints that we received this morning from the PWAs who were relating their difficulties. Why do you think these have not come forward? Do you think for most of the drugs, they are in the same position that Ribavirin is, there is no indication of efficacy?

DR. YOUNG: There are a couple of things that I would think would be the case, although these are only guesses. First, the drug development industry I must say is really a conservative industry. It changes slowly. I was not at all surprised to see the number of treatment INDs that we had in less than a year, to have essentially 12 in less than a year, and one other one we are negotiating on, to have this many come in since May really surprised me.

We also have to be more clear in the signals that we send out. I think it is a hard thing to understand the drug review and treatment IND processs. We are going to correct that by being much more convincing.

I have been proactive, and so has the agency, in urging drug sponsors to come in for a treatment IND, although, with some drugs a treatment IND may be unnecessary. For example, in the case of gancyclovir, they said, "We already have 1,200 compassionate INDs, we feel that is not something that would help at this time." I think they were right.

We are going back and asking, would you be interested in a treatment IND. We can turn them around very fast but I think the two things that are scaring companies and physicians are liability, will there be a major suit that will come forward, and I think the corporate lawyers are dancing around this point. He and I are also going to write an article together dealing with the litigation problem and why it shouldn't be applicable to treatment INDs. I think that is the first issue.

The second issue is exactly the one you said, where the clinical trials are. I believe based on the data that I have presented and the numbers I raised, that we are just now coming in that up swing of what I think will be good treatment INDs. We were able to get AZT in and out so fast because it was very spectacular.

I think trimetrexate, although it was done on 100 patients, the data was clear enough, not nearly as clear as with AZT. As we get experience and the world sees us doing this, I think as the data comes in, we are going to see more of these come forward. I would encourage that.

DR. LILLY: One last question. When a treatment IND is granted, is this granted for only people with advanced AIDS or is it granted also for people with less severe disease?

DR. YOUNG: It would depend on the severity of the condition. Treatment INDs apply to both immediately life-threatening diseases and serious ones. ARC, or even antibody positivity, would be considered at least to be "serious."

The earlier you go in the course of the disease, the more likely the effectiveness data would have to have more promise because you would worry about the risk. There is always a cost benefit. Although we have guidelines on how to evaluate it, I know it is frustrating to hear it is a judgment but it is a clinical judgment just as you would be treating a patient.

This Commissioner who took all the heat of getting the treatment IND regulation out, is certainly going to be a Commissioner that will see that when it is appropriate, these drugs will be out as well. That is the purpose.

DR. LILLY: Thank you. Cardinal O'Connor?

CARDINAL O'CONNOR: I have two statements and one quick question. The first statement may be a conflict of interest, if so, wipe it from the record instantly. The Archdiocese of New York sponsors the New York Medical College. I listened with interest to your talk about farming some of this activity out to medical schools. I suspect that our faculty, trustees and president would be deeply interested.

Will you please strike that from the record if it is a conflict of interest?

[Laughter.]

DR. YOUNG: If we have these training grants, they will be large training grants. I would imagine that many people will be interested and I would welcome all comers on a peer reviewed basis. I think that is exactly what we need to do.

CARDINAL O'CONNOR: Our interest will probably be in proportion to the size of the grant.

DR. YOUNG: They will be large grants.

CARDINAL O'CONNOR: Secondly and seriously, I was very happy to hear Mr. Hutt and you because it seems to me that this Commission has been looking from the outside, or at least I have been looking from the outside, for some agency that seems to have it altogether, that seems to know presumably everything that is being done in the field, and it ultimately all seems to come to you.

DR. YOUNG: It all comes to us.

CARDINAL O'CONNOR: In listening to you, it seemed to me, if I may grind my own favorite axe again, that if you had a Manhattan type project, much of the red tape with which you are confronted, many of the regulatory procedures, the financial problems, even such nuts and bolts problems as having to have your spaces authorized before you can get physical facilities, if you had the sense of a Manhattan project, if you had that kind of urgency, many of these things would fall into place.

I think you very appropriately repeatedly used the word "war." It was only when we were threatened by the atomic bomb that we responded not simply by trying to probe all of the resources of the United States but to pull them together effectively.

I would hope you would give that some reasonable consideration and that we might ask you about it after you have done so because at least yours is the only agency that I have listened to that seems to be exposed to everything that is going on. If so, you could conceivably have a sense about the possibility of bringing everything together much more rapidly.

I know you cannot speed up research beyond a particular point, but you can certainly speed up an exchange of ideas. You can certainly speed up a move from the spinoffs of basic research to applied research.

My brief question, those with whom I work week after week, perhaps 50 percent of them, have acquired AIDS through IV drug abuse. What do you see on the part of people in research or pharmaceutical companies to try to address the problem of drug abuse? Are there antidotes, if you will, being developed for that with the same intensity as for the retrovirus itself?

DR. YOUNG: Cardinal, I do not have a simple answer for this. I do think that the problem of drug abuse is one of the most terrible problems we face in this United States. Some have said the cause is due to the breakdown of families. Others have said it is related to possibly a lower influence and should be on part of the church. Others with the terrible issue of crack which addicts people so rapidly on even the first use, others in regard to the lack of understanding of how to modify human behavior, others to the problems faced with people that are dreadfully afflicted with this, but I do think a couple of things can be done.

I think that it is incumbent upon the medical community, the community at large, to begin to grapple with this and to try to do a critical point analysis. You are correct in saying that FDA is a mini-Manhattan project. I look at it as running it in that fashion. I'm not convinced whether a whole Manhattan project would help us that much but we have done just what you said amongst ourselves.

We could only do it by scoping out the problem and try to see where we could make the difference. I think that has to be done in the whole drug abuse problem. What we are seeing are the symptoms of a problem, not necessarily the root cause.

I tried to make once a speech about three or four years ago at the Institute of Medicine when we were talking about suicides and the number of deaths therein.

I said if you took that analogy 50 years ago, we would be talking about infectious diseases and we developed a critical point analysis to overcome infectious disease.

We have to develop a critical point analysis to this and as Sam Broder said, to stick to it, to stick to it through thick and thin. One of the problems that I see as a person who has been in academic medicine a quarter of a century is we swing too much on a pendulum. When the going gets tough, the tough get going, that is really what has to be done. We have to get this problem under control. I think it is going to be very difficult.

I would call for a national agenda to do a critical point analysis.

CARDINAL O'CONNOR: Thank you. Your concern is very encouraging.

DR. LILLY: Mr. Creedon?

MR. CREEDON: Dr. Young, were you here when Dr. Gingell, Mr. Lipner and Mr. Callen spoke this morning?

DR. YOUNG: I was here through about three-quarters of it. I was managing another emergency for the first portion.

MR. CREEDON: Well, first I'd like to say that I was very educated, first of all, by your presentation and also encouraged especially with the organizational changes you made in order to focus very specifically on that, and I feel very good about it.

I think there is however -- and maybe what you've done now will help to change it -- it seems to me that the FDA has a perception problem.

DR. YOUNG: Yes it does.

MR. CREEDON: I guess what I don't know is whether the perception is the reality or the perception is different from the reality. I don't know what -- you must be doing things to deal with it.

I guess one of the feelings I have is that especially the Gay Man Health Crisis Group has been a very positive force --

DR. YOUNG: Yes.

MR. CREEDON: -- in getting people to focus on the problem and yet I sense that there is a high level of frustration there and I am not sure whether the people who are active there feel that they have a forum in the federal government for expressing their views and having them listened to in a serious way.

Many of the people involved, as the three people this morning, themselves have AIDS --

DR. YOUNG: Yes.

MR. CREEDON: -- I mean they are under a death sentence. So it is not just an administrative job. It's their lives.

DR. YOUNG: Yes.

MR. CREEDON: I think it is important that they have a good forum where people will listen and take into consideration how they see things. And I wondered, do they have that now?

DR. YOUNG: Let me try to respond to that in this way. When we were developing the first blood test, and it was very sensitive, I had a number of individuals and called to have them come in. While we were waiting to come on, I provided them my phone number -- which is the largest known unlisted phone number I think in Washington -- and urged them to come and see me, as I have with others -- come into the agency so that we can deal with this.

Regretfully, I think government agencies are viewed with disdain by most in the country. I am not a long term government employee. I have been here three and a half years. I must say that is longer than any Commissioner back to the last 22 years, so I think I know the agency a bit better. I have found that the agency has outstanding individuals. But one of the frustrations that I think everyone feels, and I strongly share, is there isn't anything out there other than what we have already approved and the problem is how to get it and how to get the process understood.

I think too, I must honestly say, there is a vested interest of dumping on FDA. Let me stand back for a moment. A congressional hearing: a problem is cited. The FDA is the third witness. Who is the first witness? A group of individuals who have been injured. Who is the second witness? The GAO.

MR. CREEDON: You are the third witness today.

DR. YOUNG: I am the third witness and it starts off almost invariably, "The Sleeping Federal Watchdog Has Failed Again." And I feel like saying, "Woof. I am awake." That is one of the ways it is dealt with.

On the other hand, there are individuals who can gain credibility by attacking it for raising funds for their organization to attack the FDA -- and there is a vested interest there.

Now I will I am sure hear some repercussions from my industrial developers when I say that you can get into the Hall of Fame by batting .400 -- you might even by batting and hitting one out of three times. I don't know whether you get into the industrial Hall of Fame by hitting one out of five times, but that is what I showed you on that data. And I think there is some advantage to calling attention to that data.

Now what have been the changes? I think we have made a number of them, in general, in the drug evaluation process. The goal has been to drop the time it takes FDA to review a drug from 24 months to 30 months on the average to 12 months. I have said it will take about 200 more people to do that. I don't think I have gotten more than about 40 new positions, and we have reallocated 90 to AIDS from other FDA programs.

I tried to say that it is important to update and make the computer programs more available. Fortunately, Carl Peck is very computer literate and we have committed to review an electronic NDA together. We are trying to establish a model for such a new way of reviewing complex medical data.

We have focused on the need to make changes in the procedures, and I think that is helpful. But there is going to be a lag time before we get out the fact that we do have the lowest backlog of NDAs in recent history.

We did for the first time in 1987 have three new drug applications approved in less than a year. Never happened before. And the fastest one -- 107 days. We are making changes, but as Cardinal O'Connor would know, the good thing and the bad thing in having a reputation as a university is if it is good no one will perceive that you've changed until about 10 or 15 years, and if it is bad, the bad part is no one will perceived that you've changed for about 10 or 15 years. We are making a lot of changes. I am very proud of the agency, have been very pleased with the response to the action plans that we have set. You and I think we are getting somewhere. Do we have a long way to go? Absolutely yes.

MR. CREEDON: Will that same frustration be out there a year from now?

DR. YOUNG: About the AIDS drugs? Absolutely! Until there is a cure we are going to remain frustrated.

MR. CREEDON: But will there be more AZT?

DR. YOUNG: Oh, I think there will be much more than AZT --

MR. CREEDON: A year from now?

DR. YOUNG: I do.

I think new AIDS drugs will emerge furst under treatment INDs, because that procedure permits new AIDS drugs to reach widespread use quickly, but I don't see yet in the pipeline anything that is really dramatic, as dramatic as AZT.

MR. CREEDON: Do I have time for one more question, Mr. Chairman?

DR. LILLY: Yes, quickly though, because we are running out of time.

MR. CREEDON: One of the points that has been mentioned is the question of liability, both for the companies and for the doctor who might prescribe something that is still in the experimental stage. And this may be an inappropriate question, but would the FDA be supportive of legislation to try to deal with this in some way?

DR. YOUNG: Yes.

MR. CREEDON: Yes? Thank you very much.

DR. LILLY: Dr. SerVAAS?

DR. SERVAAS: I want to thank you too for an excellent explanation and I hope that you will be invited and accept to come to Indianapolis when we talk about the blood supply. But just in case you don't come, I just have a quick question and that is, where you are on the approval of the tests for HTLV-1, and then the other thing I wanted to quickly ask is, do we need a "Manhattan Project" to further make the blood supply safer? We are told that the FDA guidelines say that if a person has visited a prostitute in the last six months, he or she can still donate blood --

DR. YOUNG: I think it's back to 1978, isn't it Paul?

DR. PARKMAN: (Checking.)

DR. YOUNG: 1978.

DR. SERVAAS: Oh, it's changed.

DR. YOUNG: Yes. 1977 -- excuse me.

DR. SERVAAS: So it is not six months anymore?

DR. YOUNG: No, no, no. You are right, it has changed -- it is 1977.

DR. SERVAAS: One question, then. The HTLV-1?

DR. YOUNG: Yes. That is the highest priority we have right now. We feel that that is a very important test. The way that we do this may be important for you to see. When we do it, we deal with priorities, and that is our highest priority now.

One of the issues that Dr. Parkman and Dr. Peck both feel is critical is that FDA do enough applied research to get the tests on either drugs or biologics or diagnostics out there. Right now there is a laboratory that is working on this, and Paul, I know that you can't say completely where a predictable timetable is, but would you give some details as to who is working on the test and what your general expectations are?

DR. PARKMAN: There is a great deal of interest in research in general in the area of retroviruses currently and that is greatly focused on two viruses. One is HIV-2, the second type of AIDS virus that is endemic -- occurs in populations in West Africa -- and the other is HTLV-1, which is not an AIDS virus but is a virus which has been associated with leukemia, not so much in the United States but particularly in Western Pacific countries.

As you know, the first case of AIDS due to HIV-2 was reported in the CDC's publication, the MMWR several weeks back. The Public Health Service, CDC and ourselves have been involved in keeping a vigilant look at the blood supply and blood donors and other people in the United States to try and see if that virus is coming into the United States. At the moment there have been about 23,000 people screened including people who you might expect at high risk -- people from sexually transmitted disease clinics and so forth, and all of those tests have been negative. So at the moment there is that one case in the United States.

However, there is a good deal of interest, obviously, in developing a test for HIV-2 as well as HIV-1. Dr. Young touched earlier in one of his responses about one of the problems there is of course there are very few patients here. It is somewhat difficult to get the samples that you need to document sensitivity and specificity of a test and we are in the process of getting those reagents now and have made some strides there. I think that we are going to be in a position to have a panel to evaluate tests in the near future.

You could say about the same thing for HTLV-1. Again you need to accumulate reagents to allow you to evaluate tests for a disease which is common in other parts of the world but is uncommon here but we are getting reagents for both of these and we are making progress in looking at the tests that other people are developing?

DR. YOUNG: Can you give any estimate, Paul, for what the time frame might be? Weeks? Months? Years?

DR. PARKMAN: It is little bit hard to go out on that particular limb when you haven't got the data. It's difficult. But we are looking forward to months, I think, and not years

DR. LILLY: Dr. Lee?

DR. LEE: Dr. Young, you have been the most cooperative person that has come before this commission. You have thrown your agency open to us. You came here reputed to be a villain, and it turns out you are the hero. So we want to congratulate you on that.

I was very pleased to hear you talk in the impassioned way you did about the drug abuse problem, because all of us here on this commission are impressed by the magnitude of that problem. It is probably the biggest health problem in the United States today.

Mr. Hutt said that the major obstruction here to getting out new drugs is the inherent bias that is built into the FDA to consider risk more than benefit. Now I totally understand this. If you make a mistake in America today and you hurt two or three people, the legal profession is out there to get you, Congress is out there to get you, and the press will clean up the remains. This is a sad statement, really, because it seems that in our society we are willing to forego benefit for the majority to eliminate risk for a very, very few. And this is what you have to deal with. I think that we deserve as a society the fullest understanding of the discrepancy between the problems of the PWAs and the problems that you face.

If we do have a "Manhattan Project" -- which we love to talk about -- personally, I hope it comes in the drug abuse area, because a few Miami Vice police officers and Mayor Koch aren't going to be able to stop it.

DR. YOUNG: May I respond to that, Dr. Lee, because I think that there may be some areas to dissect that that might be very helpful and some areas of legislation or consideration that might also be looked at.

We have been very impressed with the Orphan Drug Law that Congress enacted and the President signed a while ago. That had the advantage of allowing us to give orphan drug status, which meant there was longer exclusivity and some degree of tax credits. It enabled the agency to give grants, and we have given four grants over this period of time on AIDS and AIDS-related diseases to focus on bringing particular drugs forward from a practical standpoint. They are not the fundamental research, the kind of work that Sam Broder would be doing usually, but targeted from where the discovery is to getting it out.

I think that if one, instead of looking at a global Manhattan Project, possibly looked at what parts might be applicable -- for example, as I tried to say, the industry has really responded in many ways with some interventions and new

work, but not all of the industry. Most of the work is in the little bio-techy companies as you look at the ones that are in our monthly report. But if it was possible, since this disease is -- and the PWAs are going to increase and will eventually get out from our cap of the number of people we are allowed to treat with drugs for orphan diseases and some of these drugs -- if successful -- might be real winners and there would be conflict on orphan status that is usually only given for rare disorders, and AIDS is not a rare disorder at this time at all -- that possibly recognizing the marketplace, what makes a marketplace move -- increased exclusivity, increased tax writeoff with a sunset clause, not to let it go on forever, and narrowly restricted to AIDS might bring private sector resource in.

The Manhattan Project portions that I think are very important, as Dr. Parkman mentioned, is the development of reagents, the development of animal models, the development of things that can be shared in that way.

The university that I was at -- the University of Rochester -- was the biologic component of the Manhattan Project and I know that well and how it was done. But in a sense the Manhattan Project was done really in sub-pieces. We think of it as a big, single Manhattan Project, but there was a biologic component at the U. of R.; the University of Chicago dealt with a physics component and there was a coordination.

I think that you can recognize that some agencies would be helped on being put on a wartime basis. We have some needs that can be met by that approach -- the training issues, the space issues, the sharing with our sister PHS agencies and industry, which is very important.

I see a need for correct information and if there were anything I would put in addition to the private sector incentives it is to get the facts out. I am not sure how to do that best. I think you are doing a very fine job with this Commission in hearing facts and getting facts out. But I am talking of the practical facts of where the drug research is, how the process goes, what we can do to understand and help physicians can deal with it. I think we need a sub-set Manhattan Projects on the litigious problems of this. I would love to see a crash effort done on how to solve this and then take pieces left, such as the drug abuse. Somebody said it is a global project that possibly is different than making a bomb.

I think that someone asked in development of going to the moon, how could it be targeted so easily? It is because you could see up there and see the moon and know where you are going. Here we don't know where we are going. I think there is going to be a bit of pluralism.

I am sorry, that is a longer answer than I should have given, Dr. Lilly.

DR. LILLY: We are under a bit of a time constraint. I would like to get just a very brief comment from you about such initiatives as the Community Research Initiative. How do you think that the FDA is going to be able to relate to this type of, shall we say, consumer-initiated work on drug development and perhaps also -- this may be a big question but I hope you can give a brief answer -- such initiative as has occurred recently in the State of California to develop what some people feel is sort of a "State FDA."

DR. YOUNG: That is a very complex question but I will try to be brief. We would be delighted to see drugs from any organization that feels they are promising drugs. I will, as I have in the past, urge NIH and other sponsors to work on them. I particularly urged NIH to look at Ribavirin, even though we didn't feel anything was there now. A lot of people were concerned about it, put it into a further trial.

I would be interested in seeing that and will be responsive and see what I can do to inform individuals and learn whether there is something out there we don't know about and how to get it into the system. Results are results. We would be happy to see anything that is controlled and able to be evaluated. That would be my concern there.

The second, on the State of California, I think in part there are some pluses and in part that is a political issue. I want you to know there are 34 states in the nation, including California that can do what California is doing without passing a law, and that is intrastate commerce, it is possible for any state, any one of these 34, to put drugs into people for early trials without coming to FDA.

Most states have felt that is unwise up until this time because by coming to FDA early, you can start the process and get it going. I think that is absolutely true. The data that I show you points out that we are turning most of these around in five days whenever we can and certainly not any longer on the average than 30 days. There is a rapid response time.

I think in part it was a political issue. I must also say part of it was frustration and not understanding FDA. I try to go out and work with states. I work with the state of New York. It is my native state. I communicate with Dr. Axelrod quite frequently. I still communicate frequently with California. I have no problem at all with starting individuals in drugs in those states that have those laws on controlled trials, with one exception.

If an accident occurs and when it occurs, it could throw back clinical trials for a long time. As was said, there is a lot of emphasis on the risks. If someone goes and does something silly and a couple of people die, we are going to have a real problem.

My answer is let's make the system work. We are not the confederated states of New York, confederated states of California, the confederated states of Illinois, pick your state, we are the United States of America. Certain things are Federal responsibility. Kick the Federal watchdog; beat on me, and I'll be happy to respond, and let's make the system work.

DR. LILLY: Thank you. Admiral Watkins?

CHAIRMAN WATKINS: Dr. Young, before I ask some questions for the record, I would like to say we are very late here in the timing and certainly any of the Commissioners here who would like to break for lunch right now and move out, they should feel free to do so. I do have to ask some questions. For those who would like to stay, that is fine.

If you do leave, be back at 1:15. I don't see realistically we can get a bite to eat up on the top floors here and return prior to 1:15. Let's be back at that time.

I do need to make some points for the record, Dr. Young. I think if there is any portion of this hearing that is important it is the one we are conducting right now; without any question. I think you are really the heartbeat of inspiring hope in the hearts and minds of the PWAs and that has to be always in our minds. Whether it is perception or reality, you need help. You need advocacy and I and the Commissioners tend to be an advocate for you as long as we are commissioned, until the 24th of June. I believe you do represent a very important switch in that process, that we cannot relegate to the second or third team at the Washington level. I believe frankly that you have not been supported. That's the way I read a lot of this.

I've had the opportunity and privilege to get out and talk to your people. I've had them grab me and pull me in the back room and say, Admiral, you need to help us, we are losing our own personal self esteem as professionals because we don't have the right facilities and the equipment, we are not getting the support, we don't see the full time equivalents coming in, we don't see the training dollars coming in, we don't see the help that we need to make this a balanced program because we are looking at that curve you have up there, of the NIH budget which is not the total budget developing these dollars, as you know, the private pharmaceuticals are outspending the NIH now.

This means we have probably $1 billion, with you level funded at the bottom waiting for that to funnel towards you. How are you going to handle it professionally? Are we going to backlog other drugs for other infectious disease in the nation?

We have to have some of those answers to help you. We have many questions for the record that we have to get from you.

Ms. Peggy Dufour sitting on my right is the staff director for these hearings. I would like she and Dr. Parkman perhaps to get together right after we finish and pin down an approach so that we can "staff out" some of these answers on a rather urgent basis because some don't require a lot of analysis. They really require filling in some voids of knowledge that we have from our prior dealings with you and listening to a whole range of witnesses.

For the benefit of those in the room, some of these questions include the following:

There are issues involving orphan drugs. We have to have some answers on how that might be migrating into something more difficult in the future and we have to worry about that.

Clinical trials. We have talked to you and some of your people. You have some imaginative concepts of how you might go into something in this post-marketing and surveillance period and shorten the pre-marketing evaluation period that you outlined for us. Something that would allow you to continue some trials into that post-marketing period. We need to know more about that. It sounds like it is exciting, particularly if we focus that solely on dealing with the AIDS epidemic.

DR. YOUNG: I think that would make a real difference.

CHAIRMAN WATKINS: We need to know specifically in writing from you. We have to have something formal. I think that would be encouraging to the PWAs.

Interaction with the private sector. You talked a little bit about that. Let's talk about what you need in the way of investigators that might be working much more closely with the pharmaceuticals, with NIH and others, so that you can be there with the separation of powers sacrosanct, yes, but involved early enough so that we are not going down a variety of blind alleys unnecessarily.

It seems to me that your concept that you outlined earlier this morning needs to be looked at in terms of do you need resources to do that and is that among the kinds of FTEs you have talked about in the past.

DR. YOUNG: Yes, we would. That is a resource intense issue.

CHAIRMAN WATKINS: We need to know more about it, maybe for AIDS related drug development it is an area that we can afford to take a hard look at. We would like to have some answers.

This whole issue of personnel. I was inspired when I went through your organization, particularly the facilities out at NIH, to see just what kind of professionals you have. They need help. They want help on the way for their follow-on scientists.

How do we get scientists to volunteer for FDA? How do we get the kinds of training dollars we need to inspire them to come in? The National Health Service Corp, we are losing that. We have taken the funding away. Why? They have to go into the underserved area, couldn't they be the nucleus of some exciting new scientists that can flow through FDA to underserved areas and then perhaps go out and do their turn in the private sector after they have paid back whatever you might have in the way of scholarship grants and the like.

DR. YOUNG: They could do that. That would be very helpful.

CHAIRMAN WATKINS: We need to have your thoughts on that for the record.

The facilities issue I think is critical for you. I do not see how you can continue from my limited and naive vantage point. I have been through a lot of facilities in my life. Frankly, I am embarrassed that we look like Third World in the way we have treated the FDA facilities to do the job. I think we have to move facilities up front for you in particular to try to give your people some hope that they are moving towards the front end of technology, not just on the equipment they use, but in the spaces and allocation and their ability to work on problems.

One of your scientists told me specifically, Admiral, I'm worried about my own professional reputation, because I have worked here for many, many years and I'm dedicated to the task and my people are, but we are worried that a few years from now we are going to be overwhelmed. We should be the best in the nation. We should be able to review the slicks that come in and separate wheat from chaff and people should look at us as the pros and we are worried that we are not bringing in enough new talent.

DR. YOUNG: That's absolutely true. With all the intense pressure, if we are not able to get the resources and not able to have something that will attract people, it is even harder. It is not very glorious to be in a regulatory agency and get beat upon, if you don't have the resources to deal with it. You are absolutely correct.

CHAIRMAN WATKINS: I have just been handed a copy of the presidential budget which was submitted yesterday. I notice in here that the Food and Drug Administration ramps up from $21 million in fiscal year 1988 to $65 million. I just wonder if that is a budget request that you submitted, was it about at that level or has this been an OMB add-on that you are now going to have to go back and restructure where those dollars are going to be allocated within that $65 million or are you up to speed on this particular budget line item at this point?

DR. YOUNG: That is exactly the request we made. That ramp up is really about $25 million of that is the money for the buildings. If you were to look at the real budget, that is a budget of about $25 million. It went from $10 in 1986 to $16 in 1987 to $25 in 1988 to $41 in the 1989 request. The requests have been met.

One of our problems is it is very hard to project what is coming in. In part, we have been surprised by this. I have been very pleased in the recent years under Secretary Bowen that he has been very supportive of our requests. The other part is getting the operation altogether. You yourself saw us at Parklawn, part down at NIH. We need to be closer to NIH where we have our larger interaction. That is a real problem. There is no budget for that at all.

The President has been very responsive to meeting FDA's needs. The problem is the needs have grown faster than we were ever able to calculate. That is what scares me.

CHAIRMAN WATKINS: I understand, and we are sympathetic to that. What we want to do is be your advocate now from this point on with our interim report going to the President in two weeks and make sure we are as punchy as we possibly can be at this point. We won't have all the answers. We are going to include other answers later, by the 24th of June.

Some of these things are so vital and it seems to me this is going to give the kind of new hope to people out there who are extremely concerned that somehow the process is constipated and not doing the job it should be. We are trying to facilitate a reconciliation between the PWA and the highest level of our national bureaucracy. I think we are at the heart of doing that in the kinds of recommendations we can make across the board. We are not just throwing full time equivalents at you.

We have to look at the total logistic support pipeline that feeds FDA and gives you the hope that over the next couple of years when those drugs start rolling out of the pharmaceuticals and NIH, that you are not sitting there swamped, turning down or backlogging important work you have to do in other infectious diseases where we also have a large number of terminal cases facing us.

Am I saying this right?

DR. YOUNG: You are absolutely correct. One of the things that has been difficult is until we got that up sweep, until we began to see how fierce the increase was, we were really not able to make these adjustments, and stimulated by some of your questions. Now we have tried to make a different calculation than we ever presented before, which really takes a model of looking at the up swing based on the mathematics of what we have seen now, projecting it in the future on dollar investments and come with personnel.

In part, the failure has been mine to understand enough of the up-swing of this, and the President has provided the dollars. I want to say that very clearly, in the budget that we requested. It is really the events are now catching us in a sense the success of the events are catching us and we can't afford to be behind.

I would rather over spend a little bit, I must honestly say, and be prepared than to always try to hit the line and possibly miss.

CHAIRMAN WATKINS: The Chairman's recommendations to the other Commissioners here on the panel will be mailed out probably Monday night to them. They will be subjected to public scrutiny as well. It is very important that in that we have the most powerful input that we can obtain and that is why I think we need Dr. Parkman and Ms. Dufour to sit down here now and perhaps with other members of my staff and your staff and drive towards finding answers to these to the extent we can in order to be submitted in a timely fashion for the Chairman's recommendations.

Let's do that. I think there is a great opportunity for FDA in that and we certainly want to give you the kind of support to get out of the perceived image that I think is there for valid reasons, much of which has been outside your control, much of which has been a lack of understanding of just what your role is in this whole process, and frankly a lack of someone up above you that is going to hold the line and make sure that you are coupled with the other resources which then will deliver products to flow through you.

We will do that. We will recess this hearing, and reconvene at about 1:20 p.m.

[Whereupon, at 12:58 p.m., the Commission recessed, to reconvene at 1:20 p.m. this same day.]

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

[1:30 p.m.]

CHAIRMAN WATKINS: Good afternoon, panelists.

I'm sorry we are starting a little late this afternoon for the afternoon session, but we had a very important set of witnesses this morning we just simply had to continue dealing with.

This afternoon we have the pharmaceutical companies represented here, and we are going to be talking about obstacles as they view them, and their recommendations.

Gerald Mossinghoff, President, Pharmaceutical Manufacturers Association; Dr. Patrick Gage, Vice President for Exploratory Research, Hoffmann-La Roche; Dr. David Barry, Vice President for Research, Burroughs Wellcome Co.; and Dr. George Rathmann, President and Chief Executive Officer, AMGEN, Inc., and President of the American Biotechnology Association.

I will turn over the hearing to Dr. Frank Lilly, who will chair the remainder of this hearing.

DR. LILLY: First, Mr. Mossinghoff, would you lead off, please, with your statement?

Pharmaceutical Manufacturers and AIDS-Related Drug Development

MR. MOSSINGHOFF: Thank you, Mr. Chairman.

My name is Gerald Mossinghoff, President of the Pharmaceutical Manufacturers Association. The Pharmaceutical Manufacturers Association, or PMA, as we call it, represents more than 100 of the research-based pharmaceutical companies in the United States that develop and manufacture and market most of the prescriptions used in the United States.

I will begin my testimony by providing a brief overview of the research-based industry, and thereafter, in the order you mentioned them, Dr. Gage will discuss the challenges of viral research and federal private cooperation; Dr. Barry will describe his company's experience in developing Retrovir; and Dr. Rathmann, who is president and chief executive officer of AMGen, but also the chairman of the Biotechnology Industries Association, will concentrate on the role of biotechnology in the battle against AIDS.

Our companies recognize the urgency of discovering and developing drugs to stem the AIDS epidemic, one of the most serious public health problems this country has ever faced. Never before have so many companies devoted so many resources in such a short period of time to combat a single disease. 55 companies are developing, have in development, or have developed a total of 77 products to diagnose, prevent or treat AIDS. This is shown in Appendix A of my statement, Mr. Chairman, which is reproduced for the commission in the charts to my right.

Despite this impressive range of activity, no one should underestimate the enormous challenge of discovering and developing products to combat AIDS. According to our best scientists working in this area, there is insufficient basic scientific knowledge about viral diseases generally, and specifically about the HIV virus and its effects on the body, particularly the immune system. For more than three decades, scientists have been trying to develop drugs to treat viral diseases and only a handful of products with limited application have been produced.

In the relatively brief time since AIDS was recognized as a public health threat, private companies have developed nine diagnostic tests, including screening tests to ensure the safety of the nation's blood supply. They have developed Retrovir to arrest the development of the arrest, and Pentam 300 to treat PCP. Just this week the Food & Drug Administration, by granting a treatment IND, approved the expanded use of another drug to treat PCP.

Contrary to what many people may believe, our companies use their own funds to discover and develop new drugs. The government provides less than one tenth of 1 percent of all the funds our companies use to develop and market drugs. Last year our companies invested a record $5.4 billion of their own funds on research and development in all disease categories. This year they will spend almost as much on all of their pharmaceutical research and development as the National Institutes of Health spent on all biomedical research and development. A more complete discussion of our industry's investment, including the trends of that investment in research and development, is included in Appendix B to my statement.

As a result of this enormous investment in research and development, private pharmaceutical companies discover most, and develop all, of the new drugs that are introduced in the United States market. In working to combat AIDS, each company is concentrating efforts in areas it believes will be most fruitful based on its previous research and its own expertise.

As I have noted, 55 companies are studying, or have developed, a total of 77 products to diagnose and prevent or

treat AIDS. The products now being developed include 15 antivirals, 22 immunomodulators to strengthen the immune system, two anti-infectives, 17 diagnostics, and 10 vaccines.

All of these products are listed in Appendix A, which is based on a detailed survey conducted by the Pharmaceutical Manufacturers Association. This appendix specifies the manufacturer of each product, the proposed use of the product, and the product's development status in the scheme that Dr. Young so ably described to you this morning.

Appendix A also describes the various phases of the drug approval process. Of course, not all the products described in the appendix will prove to be safe and effective. There is a high attrition rate, as Dr. Young again pointed out. A number of them, therefore, will not be developed as testing proceeds, but other products will be discovered and developed as the research continues.

To conquer AIDS, government, industry and academic scientists have worked well together, in our opinion, but the time has come to provide a more effective arrangement to accelerate the development of new therapies. The National Institutes of Health established a network of AIDS Testing and Evaluation Units to facilitate the development of AIDS drugs. In creating the ATEUs, as they were then known, the NIH recognized that there was a finite number of AIDS patients suitable for clinical trials under FDA criteria, and a limited number of qualified clinical investigators and appropriate clinical facilities. The ATEUs have been useful, but with the increasing number of AIDS drugs to be tested, it is time, in our view, to reevaluate their role and administration.

To discuss this and other issues that inevitably will raise as AIDS-related research and development continues, there is a need for a forum where government, academic and industry can meet to assess progress in the battle against AIDS, resolve problems as they emerge, and thoroughly discuss all relevant issues.

In our view, the National Academy of Sciences - Institute of Medicine is uniquely qualified to provide such a forum. It is a highly respected organization, highly respected by the scientific and medical community, and the National Academy of Sciences was specifically chartered by Congress to advise the government on critical scientific issues, and has done so very ably over the years.

PMA knows first-hand, having worked with the Institute of Medicine very closely, how deeply they are involved already in the effort to combat AIDS.

In responding to the AIDS epidemic, the FDA is acting swiftly and effectively. Officials at all levels of the agency, from Commissioner Young, whom you heard, on down, are working extremely hard and effectively in cooperating with our companies to hasten the approval of drug and diagnostic products to combat AIDS and its complications.

It has suggested, and it was mentioned here today, that the country needs a crash program to combat AIDS organized somehow along the lines of the Manhattan Project, or even, we have heard, along the lines of the Apollo Program. We do not believe such an effort would be productive, if what we mean is a massive engineering effort based on existing knowledge, which is what those two programs essentially were. Nor do we believe that a single person or government entity should be given overall authority to direct the efforts to combat AIDS.

The Manhattan and Apollo Projects were massive engineering enterprises that used existing scientific knowledge to accomplish specific programmatic objectives. One of the major difficulties with AIDS is that many fundamental scientific questions remain unanswered, as I have noted. To ensure that scientific research proceeds as rapidly as possible, the federal budget must provide adequate funding to support all legitimate AIDS research proposals for such funding.

In addition, research by private organizations should be encouraged, so that a rich diversity of approaches will be pursued. Development and marketing of products is best accomplished by the private sector which, as I have indicated, develops and markets all the drugs and vaccines introduced in the United States. Establishing a single director or bureaucracy to decide what research should be pursued, and what discoveries should be developed, could be an enormous and counterproductive step, in our opinion, that would really threaten the expeditious development of AIDS therapies.

Before I summarize and conclude my statement, let me comment a bit on the treatment IND which was discussed at great length this morning.

We work closely with Dr. Young in his issuance of regulations to establish the treatment IND. The initial regulations would have put him in a position which we felt was an impossible position to prove that a therapy was not effective, and we thought scientifically to prove a negative was impossible.

We worked with former Commissioner of the FDA Peter Hutt and with policymakers in the government and have turned it around now to get to the test that Peter Hutt described in his presentation.

I think it would be a disservice to the commission if we left you with the view that at least in industry and the manufacturers, that a treatment IND was the whole answer, and that somehow that was a substitute for approval of a drug, prompt and effective approval of a new drug. There is an awful lot of activity occurs in industry following approval: the establishment of suppliers, the establishment of production facilities, the education of the medical sales representative force, the detailing of doctors, the explanation to them, the educational materials that are placed in scientific journals. All of that occurs after the approval, and as long as you have a treatment IND, and if that delays the ultimate approval of the drug, none of those commercial activities occur, and only with the occurrence of those activities can the doctor, the practicing physician, whom we all are going to depend on ultimately to treat, effectively treat AIDS, does not occur.

So the treatment IND is a good idea, it's an idea that may be well suited to the AIDS situation, but it is not a substitute for the suggestions, Mr. Chairman, you were making to provide adequate resources so that the FDA can promptly approve drugs, so that this myriad of commercial activities, which is ultimately what's going to get drugs used properly by the medical profession, occurs.

Mr. Chairman, in summary, the research-based pharmaceutical industry fully appreciates the urgency of discovering and developing drugs to combat AIDS, and has mounted intensive efforts to that end. 55 pharmaceutical companies are developing or studying or have developed 77 products to diagnose, prevent and treat AIDS. The industry supports the conduct of basic research, public and private, to gain basic scientific knowledge about the HIV virus and its effects.

The Institute of Medicine, in our view, should be designated as the forum where the government, academic scientists and private industry can meet to assess the progress and the battle against AIDS on a regular basis, resolve problems as they emerge, and thoroughly consider all relevant issues, including the role and administration of the AIDS testing and evaluation units.

The Food & Drug Administration should be encouraged and provided, along the lines you suggested, with the sufficient resources to continue its fine efforts to expedite the approval of safe and effective drugs and diagnostic products to combat AIDS.

We believe diversity of research and development should be preserved as the way best to ensure progress in the battle against AIDS.

Mr. Chairman, this concludes my prepared marks. I can either respond to questions now or proceed with the other members of the panel.

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

DR. LILLY: Thank you for your presentation. I think we will hold the questions for a little bit later. I'm sure we will want to come back and ask you questions, particularly about your implied, shall we say, dubiousness about the treatment IND.

Our next speaker will be Dr. L. Patrick Gage, who is vice president of Hoffmann-La Roche, the company that is currently developing dideoxycytidine, among other drugs.

DR. GAGE: Mr. Chairman, members of the commission, good afternoon. I am Patrick Gage, Vice President for Exploratory Research at Hoffmann-La Roche. I am responsible for all pharmaceutical discovery research for Roche in the United States and of particular interest here, for our concerted efforts to find new therapies for HIV infection and AIDS. I am also project leader for the Roche development program on dideoxycytidine, or ddC, whose activity as an anti-HIV agent was discovered by Dr. Samuel Broder of the NCI.

It is a privilege to have this opportunity to speak to you today, about what we are doing at Roche worldwide, about what government, academia and industry can accomplish by working together, and about the complexity of the AIDS challenge. We have traveled far since 1984, when the AIDS virus was first discovered, but the road ahead, as we shall see, remains very difficult.

First, I'd like to talk to you about what we are doing in our laboratories at Roche to help solve what may be the most challenging disease to confront the medical community in this century. Roche, together with others in the research intensive pharmaceutical industry, including those who are sharing the panel with me today, is aggressively committed to finding answers. We are investing millions of dollars and significant people resources in AIDS research this year alone.

At Hoffmann-La Roche in the United States, a principal focus is ddC. Last year the government licensed this NIH discovery to Roche for development and clinical evaluation. Although we work closely with NIH scientists, Roche has the primary responsibility for conducting the preclinical development and clinical research required to gain approval of a new drug application for this antiviral agent, as well as development work necessary for efficient production and eventual marketing of the product if it proves effective.

As you may be aware, we have experienced difficulties with ddC, namely the unexpected emergence of serious toxicity in the form of peripheral neuropathy. Dr. Broder mentioned this earlier. We seem finally to have that under control through adjustments in dosage level and schedule, but as a result are somewhat delayed in our clinical program. Several new approaches are being evaluated, including both the use of ddC as a single agent and in alternating therapy with Retrovir, also known as AZT.

As for other Roche efforts, Roferon-A, the Roche brand of alpha-interferon, approved for use against a rare form of leukemia, also shows potential in AIDS therapy. Roferon-A has demonstrated definite activity against AIDS-related Kaposi's sarcoma in clinical trials, and has shown further activity with other agents in cell culture assays in the laboratory.

Roche also supplied its recombinant interleukin-2 preparation to Dr. Fauci at the NIH for tolerance studies in AIDS patients which were undertaken in early 1984. In addition, we have now begun testing recombinant interleukin-2 in an attempt to promote restoration of the immune functions compromised by HIV infection.

Roche began its in-house dedicated HIV drug research program in 1984, and now has a worldwide effort involving our laboratories in the U.S. and in Great Britain, Japan and Switzerland. This program focuses on several HIV proteins as targets for intervention, using the techniques of molecular biology to produce HIV proteins for structural analysis, and for cell-based assays suitable for drug screening.

In addition, Roche will be introducing a new screening test for AIDS this year that promises more accurate results than tests currently available.

AIDS and HIV infection clearly pose an enormous challenge to our health care system. How can government, academia and industry, the triad responsible for our country's remarkable progress in biomedical research, address this challenge most effectively?

The answer lies in the optimization of our synergistic relationship. Each partner plays a special and significant role in the research, development and testing of new medicines to combat AIDS.

The Federal Government, through the National Institutes of Health, the Food & Drug Administration, the Surgeon General's Office, and the Centers for Disease Control, has addressed the challenge aggressively.

We commend Dr. C. Everett Koop, the Surgeon General, for his forthright stand on AIDS education. The Centers for Disease Control likewise have done an exemplary job in assessing the progression of AIDS and predicting its future consequences, and the FDA has taken a strong position in giving drugs for AIDS and HIV infection its highest priority in the review process.

In our own experience with the clinical testing of the HIV antiviral ddC, the FDA has demonstrated a willingness to work closely with Roche to assure that ddC clinical evaluation is performed responsibly and with all possible speed toward obtaining the data necessary for licensing.

Now the NIH plays an essential role in drug discovery and development, that of facilitator. In our view, the facilitator role is most appropriate and has led to steady and significant biomedical progress. We should do everything we can to strengthen the involvement and optimize the contributions of the NIH to the established drug development process within the research-based pharmaceutical industry.

The principal facilitator role for the NIH is as the provider of funds for biomedical research, either extramurally through investigator-initiated, peer-reviewed grants to academic scientists, or through funding of research intramurally in the laboratories of the NIH. This activity fuels advances in biomedical research, lays the groundwork of understanding for applications in the pharmaceutical industry, and elaborates the molecular tools for advances in drug discovery. In the face of the AIDS crisis, this role should be strengthened.

One of the most relevant examples is Dr. Robert Gallo's pioneering research on HIV at the National Cancer Institute. Without work of this kind, the pharmaceutical industry's search for AIDS drugs would be exceedingly difficult.

An innovative approach to funding by the NIH has been the introduction of grants to support research by consortia clearly directed to AIDS drug discovery. These "National Cooperative Drug Discovery Groups," or NCDDGs, provide funds on a peer review basis to research groups representing the government, academic, and industrial sectors. Such funding mechanisms allow active industry input into the design of research programs so that "bottleneck" technical questions can be answered and gaps of knowledge filled on the way toward drug discovery. We strongly recommend that funding of the NCDDG program be increased.

In addressing the AIDS crisis, the NIH has also assumed another rule. Through the AIDS treatment evaluation units, or ATEUs, or as they are now called, the AIDS clinical trials group, the NIH administers a major share of the clinical evaluation of AIDS drugs in the United States.

The ATEUs were established to coordinate the evaluation of AIDS drugs nationwide. This program has contracted with most of the leading clinical investigators and institutions involved in AIDS research and, therefore, controls the main source of clinical expertise and subjects required by an AIDS drug development program.

Although well-intentioned, the NIH-controlled ATEUs do not optimally take advantage of the pharmaceutical industry's drug development experience and capability. For example, once a potentially beneficial compound has been discovered in the laboratories of a pharmaceutical company, the primary goal is then to develop and implement the most prompt and efficient clinical plan to determine the efficacy and safety of the drug, and to gain approval for marketing. Planning of the clinical development program for the ATEUs, however, involves NIH representatives, extramural clinical investigators and the sponsoring pharmaceutical company. The complexities of these interactions can lead to delays in making new drugs available.

The ATEUs attempt to centralize accrual and management of all clinical data from the studies also causes additional delay. We propose that pharmaceutical companies, because of their wealth of experience, be encouraged to handle data management and be responsible for all elements of a drug development program within their capability, while still working through the ATEU program. If the drug sponsor has limited drug development experience or capability, the NIH chould contribute more to the drug's development or, such a company could form an alliance with an established pharmaceutical company.

Finally, the government should continue to facilitate the normal processes of drug discovery and development by supporting fundamental HIV and AIDS research. Furthermore, the NIH should continue to promote the translation of this research into applications by the pharmaceutical industry through collaboration, publication and licensing of promising compounds. Once the research is transferred to the private sector, we should work together to optimize industry's ability to utilize its proven drug development mechanism. This is the best way to assure the public that AIDS drugs will be developed in an expeditious manner.

Now I would like to shift to a brief discussion of AIDS drug discovery.

The pharmaceutical industry has had breathtaking success in developing anti-bacterial drugs. But antiviral drugs, also intended to combat foreign pathogens, have proven largely beyond reach. Now why is this?

Antibiotics were initially discovered using screening techniques and bacterial cultural assays. Research later revealed that these agents interfered with vital biochemical processes unique to the pathogen. Thus, antibiotics could successfully fight infection without toxic side effects because human cells have different biochemical pathways from those of bacteria.

Pharmaceutical researchers tried a similar approach to the discovery of antivirals, but with limited success. Agents discovered by screening either have not been effective against the viral infection, or they have proved too toxic. This is because viruses are essentially parasites that use normal human biochemical mechanisms for their own survival. Viral gene functions that differ from those of the human host, and thus provide specific targets for therapy, are quite limited in number, and until recently we haven't known a great deal about them. As a result, most antiviral agents discovered by random screening tend to target human cell processes and not specific viral mechanisms and thus produce toxic side effects.

We have had recent breakthroughs, however, mostly because of advances in molecular biology, that have permitted detailed analyses of viral gene structure and viral protein function. The biotechnology revolution is having a profound impact on our ability to discover antiviral agents, and, particularly, anti-AIDS drugs.

Gene splicing and DNA sequencing techniques have made possible a thorough structural and functional analysis of the HIV genome, and as a result, we have identified key HIV genes that code for viral proteins essential to HIV replication but not for human cell function. Compounds that interfere with these functions may therefore be effective but less toxic to normal human cells. HIV proteins, such as reverse transcriptase, integrase, tat, art, and protease, are now targets for anti-HIV drug discovery in many of the nation's pharmaceutical companies. For example, Retrovir and ddC selectively interfere with reverse transcriptase.

A second major approach to AIDS therapy takes advantage of the body's own natural antiviral defenses -- interferon and the immune system. Recombinant DNA techniques have for the first time made available large quantities of pure, recombinant human interferon and a number of other human cytokines that can enhance viral resistance and restore immune function debilitated by HIV infection.

A third approach, vital in fighting the ravages of AIDS, is to continue to develop medicines that are effective against various opportunistic infections associated with this

disease. These medicines, a number of them developed years ago for other diseases, are the last resort for many AIDS patients.

What I am saying is that we have the means to develop agents to affect the immune system, treat opportunistic infections, and interfere with the viral replication cycle. These are the primary approaches to AIDS therapy that we are actively pursuing in collaboration with government and academic researchers. I think it is fair to say that we are making considerable progress.

There are, however, some very critical points that I'd like to make concerning future expectations. While drug design programs and "smart" screens are being put in place in industry laboratories at a frenetic pace, targeted approaches to HIV therapy will inevitably take some years to move from discovery to clinical development and finally accrue to the public benefit.

The second point is that even with reasonably selective anti-HIV agents, some toxicity will be associated with the treatment of AIDS. For example, the only agents described to date that have a firm selective basis for activity against HIV are the dideoxynucleosides and interferon, and despite their specificity for inhibition of HIV DNA synthesis, both Retrovir and DDC elicit toxicity in humans because they also interfere to some degree, with normal cell function.

And a third point is, we can expect the eventual use of multi-drug treatment regimens in AIDS. This strategy is based on the expectation, demonstrated already in cell culture and animal experiments, that a multifocal attack on the viral infection cycle together with modulation of the immune system, is likely to be more effective and less toxic than reliance on a single agent.

The last point, and the most important point, is the reason that no cure for HIV infection is in sight. Like other chronic viral infections, HIV implants its genes in the human cell's chromosomes at the time of initial infection. Hence, HIV infection, when it occurs, is for the lifetime of the individual. We do not have a technology for eliminating cells that carry these genes, nor do we see such a technology on the near horizon. The only reasonable goal for drug development at this time, then, is not a cure, but rather the suppression of viral replication, prevention of immune and nervous system damage, and interruption of the progression of the disease.

The excellence of our scientific enterprise has identified the causative agent, HIV, and has provided us with the tools and knowledge to combat it. Based on our current understanding of the disease, we can be cautiously optimistic that therapeutic agents will be discovered and developed that can

suppress HIV replication and slow or prevent the progression of the disease. This process, however, takes time, and while treatments are here now and others are in sight, there are no cures on the horizon.

All of us are committed to conquering AIDS. Our society already has institutions with the expertise and determination to achieve this goal. Academic science is building the foundation of knowledge. The research-intensive pharmaceutical industry is establishing the AIDS drug discovery programs and has the clinical development experience and resources to bring promising therapeutic agents to the public. And the Government should continue to facilitate this overall partnership by aggressive support of fundamental AIDS and HIV research through the NIH, expeditious review of drug development programs by the FDA, invaluable assessment of the epidemic by the CDC and effective public health policy leadership from the Surgeon General.

We applaud all of these efforts and encourage the strengthening of these alliances among the public, private, and government sectors as the very best means to deal effectively with this health crisis.

Thank you.

DR. LILLY: Thank you, Dr. Gage.

Our next speaker is Dr. David Barry, Vice President for Research, Burroughs Wellcome Company.

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

Burroughs Wellcome Company is located in Research Triangle Park and Greenville, North Carolina and is the U.S. subsidiary of Wellcome PLC with headquarters in London. Wellcome employs over 19,000 people worldwide with over 3500 employees in the United States and has been operating continuously for over 100 years since its founding by two Americans, Silas Burroughs and Sir Henry Wellcome.

Wellcome PLC is publicly traded on the London stock exchange, but 75 percent of its shares are owned by a charitable foundation, the Wellcome Trust. Thus three-quarters of our distributed profits are given away to support medical research and education worldwide, and that is over and above the investment we make in research related to our businesses and not connected to it in any way.

Burroughs Wellcome Company first became directly involved in the treatment of HIV-associated infections in 1980, about a year before AIDS was described as a syndrome when we first began supplying intravenous Septra for use in adult patients with pneumocystis carinii pneumonia, PCP, under a treatment IND program. Since that time, we have also supplied Daraprim, Wellcovorin, Zovirax, DHPG, and Wellferon to treat various opportunistic infections or tumors occurring in AIDS and ARC patients.

Besides manufacturing most of the medications used to treat the complications of AIDS, Wellcome also has a long history in the discovery and development of antiviral therapies, including the development of Marboran for the treatment and prevention of smallpox and the complications of its vaccination in the 1960s, Viroptic for ocular herpes infections in the 1970s, and then Zovirax for systemic herpes simplex and herpes zoster infections in the 1980s.

We were therefore in the very rare circumstance in the early 1980s of having an extremely large staff with many years of experience in the newly emerging field of antiviral chemotherapy. In 1984, after Drs. Francoise Barre, Robert Gallo, and Samuel Broder came to our laboratories to talk about the then newly discovered retrovirus, now termed HIV, we made the decision to test some of our compounds for activity against retroviruses.

Among those tested was a compound which was activated by cellular thymidine kinase. This compound, known initially as Compound BW-509U, is now known as azidothymidine, AZT, zidovudine, or Retrovir. AZT, as was mentioned this morning, had initially been synthesized in 1964 by Dr. Jerome Horowitz at the Michigan Cancer Foundation as a potential anti-cancer agent, but studies with the compound were abandoned shortly thereafter because of a lack of activity against animal cancers. Wellcome resurrected it by resynthesizing it in the early 1980s and conducted a number of studies that showed it was quite active against certain species of bacteria.

Studies in November of 1984 in our laboratories suggested that it might be highly active against the human immunodeficiency virus. At that time, however, we did not have the high-containment facilities required to test compounds against the human AIDS virus. But Dr. Broder at the National Cancer Institute kindly agreed to test Retrovir for us and found that it was active against the human immunodeficiency virus. Its mechanism of action against HIV are as a selective inhibitor of retroviral reverse transcriptase and also as a viral DNA chain terminator.

After this confirmation of Retrovir's anti-HIV activity in February of 1985, Wellcome scientists rapidly conducted a series of preclinical studies, including toxicology, pharmacology, and pharmacokinetic studies, the latter being assisted by staff from the National Cancer Institute. These studies supported the decision to conduct a trial in humans with AIDS and ARC. Such a preliminary Phase I study began in July of 1985 at the National Cancer Institute and Duke University, sponsored by ourselves.

The results, which were published in February of 1986, indicated that Retrovir did not induce any unexpected side effects, was well absorbed orally, and penetrated the blood/brain barrier quite well. As was mentioned this morning, there was anecdotal evidence at that time of immunologic and clinical improvement in the limited number of patients studied.

Now when this study was completed in January of 1986, we had a very difficult decision to make as to how to proceed. Traditionally, early clinical studies of new drugs proceed in a very regimented way. They are typically first tested in normal, healthy volunteers and then later in a somewhat larger number of patients with milder manifestations of the illness being studied.

There are several reasons for this approach. The first is that any toxicity seen is likely to be milder in patients whose baseline physical status is relatively good. More importantly, the likelihood of therapeutic success in less ill patients is often greater than in those who are at the severe stages of their disease.

In the case of Retrovir, however, Wellcome believed that there were two counterbalancing elements which required that a less classical approach be taken. The first was that there were hundreds of patients per week dying of AIDS at the time the Phase I study was published. Wellcome also believed that the testing of Retrovir in patients with advanced manifestations of HIV infection was the most rigorous test to determine its clinical efficacy. If it proved to be effective in the most severely ill patients, while exhibiting manageable adverse effects, then it could be expected to be equally or possibly even more beneficial in patients with milder forms of the disease.

With the absence of any effective comparative drug, we therefore made the decision to conduct a double-blind, placebo-controlled study in advanced AIDS and ARC patients in February of 1986, so that the effectiveness of Retrovir could be definitively determined. The results of the study have been published, so only a brief review and update of the data gathered since then is really necessary.

In this study, 282 patients with AIDS and ARC were entered in twelve university-associated medical centers in the United States between February and June of 1986. The AIDS patients had experienced their first episode of PCP within the prior four months, and ARC patients had a number of symptoms of advanced disease and a T4 cell count of less than 500. The study occurred before the establishment of the ATEU program, and all financial and logistic support came from Burroughs Wellcome.

On September 19th of 1986, an independent panel of experts recommended to Wellcome that the study be terminated because they found a significantly higher mortality rate in the placebo group compared to those who received Retrovir. Analysis of the data indicated that Retrovir recipients, but not placebo recipients, had significant improvements in the number of CD-4 cells, delayed cutaneous hypersensitivity, weight gain, activities of daily living, and neurological functioning. In addition, Retrovir recipients had significant decreases, in many cases to undetectable levels, of circulating P24 antigen and significant decreases in the frequency and severity of opportunistic infections. Most importantly, the probability of death within six months of initiation of therapy was 22 percent in the placebo group and 2 percent in the drug-treated group.

Symptomatic adverse reactions were quite common in both drug and placebo groups. This was clearly the result of the very complicated nature of their underlying disease, but nausea, myalgias, insomnia, and headache were somewhat more common in the drug-treated group. The most significant toxicity was bone marrow suppression, which was dependent upon dose and duration of therapy, as well as upon the preexistent bone marrow reserve of the patient. Up to 45 percent of patients with poor bone marrow reserve had significant decreases in either red cell or white cell counts during the observation period. The incidence of such decreases in patients with only somewhat better marrow reserve, however, was only slightly higher than in equivalent placebo groups.

Although there was great heterogeneity in the management of this adverse reaction by the physicians taking care of the patients, the bone marrow suppression could usually be handled by dose reduction, dose interruption, transfusion, or a combination of these approaches.

At the time the placebo-controlled portion of the study was terminated, all patients, including those originally randomized to receive placebo, were offered the opportunity to receive Retrovir in an unblinded fashion, provided they agree to continued follow-up by the original investigator. While most of the patients agreed to continue to take Retrovir under these conditions, a certain number left the study after its unblinding for a variety of reasons. Because of this unblinding, however,

continued follow-up and comparisons of the two groups have been particularly difficult.

Nevertheless, we were able to determine that Retrovir recipients who did not discontinue the drug for prolonged periods of time had a survival rate of approximately 88 percent at 12 months and 78 percent at 18 months. Survival was even further improved to 91 percent and 84 percent at 12 and 18 months in those patients receiving prophylaxis for PCP in addition to receiving Retrovir.

Survival in the AIDS and ARC placebo patients who did not receive Retrovir for any significant period of time was 76 percent at 6 months and 52 percent at 9 months. Too few placebo recipients remained after 9 months to provide meaningful comparison thereafter. In fact, only four of the 28 AIDS patients originally assigned to placebo and who received little or no Retrovir after unblinding of the study were alive at one year after initiation of the study, and all 28 are now dead.

The closing of the original double-blind, placebo-controlled study in September of 1986, however, provided the opportunity to examine the use of Retrovir in a much larger cohort of patients. Wellcome set up a program in conjunction with the National Institutes of Health and the special efforts of Dr. Dan Hoth to dispense Retrovir free of charge to any AIDS patient in the United States who had had PCP at any time in the past. Approximately 4800 patients received free Retrovir under this "treatment IND," sometimes known as "compassionate plea" program, between October of 1986 and the end of March 1987 when the drug became available by prescription.

A number of patient categories not originally included in the Phase II double-blind, placebo-controlled study did participate in this uncontrolled study, including nearly 150 women and over 250 intravenous drug abusers. In addition, 424 patients were Hispanic, and over 500 were black.

After adjusting for the fact that significantly sicker patients could participate in this program, overall survival data were very similar to that observed in the original placebo-controlled study.

Certain prognostic factors of survival were noted. Better survival was associated with higher preexisting hemoglobin and activity of daily living performance levels, as well as the brevity of the period between the first episode of PCP and the initiation of Retrovir therapy. These data, therefore, point to the importance of beginning Retrovir therapy as soon as possible after the diagnosis of AIDS or advanced ARC is made and not waiting until the patient is in a preterminal condition before starting therapy.

Although a great deal of information about the usefulness of Retrovir has been gathered in a relatively short period of time, a very aggressive worldwide program of clinical research is being mounted, including over 4000 patients in over 40 studies worldwide to address many as yet unanswered questions. In the United States, this program is being conducted in part with the cooperation of the AIDS Treatment and Evaluation Unit Program.

The largest group to be studied involves patients with different degrees and severity of HIV infection, including those with advanced AIDS, milder forms of ARC, lymphadenopathy syndrome, and even those who are infected but do not show obvious signs or symptoms of disease. Four studies, in fact, are being conducted in such, "asymptomatic" people with the largest involving 1500 patients randomized to receive one or two different doses of Retrovir or placebo.

A placebo-controlled study will also be conducted primarily in health care workers who have been exposed by cuts or punctures to HIV-infected blood. There is optimism that this approach may be effective in preventing the establishment of infection in such workers, because animal studies have indicated that Retrovir, if begun within a few days of challenge and continued for only a few weeks, may completely prevent the establishment of retroviral infection in those animals. In addition, the relatively brief period of therapy envisaged is unlikely to produce any significant adverse reactions in otherwise health individuals.

Studies will also be conducted in special patient populations, such as hemophiliacs, intravenous drug abusers, and children. Preliminary data from children indicate that the benefits and adverse reactions to Retrovir in children are similar to those in adults, and particularly striking improvements in neurologic function have been noted in pediatric patients, as was mentioned by Dr. Broder this morning. After additional experience with Retrovir has been obtained in neonates, we will also begin studies with short- term therapy in newborns from infected mothers in an attempt to prevent the establishment of infection in these children.

Other studies will examine different dosing regimens of Retrovir as well as combinations with other drugs such as acyclovir, ampligen, interferon and possibly others which are synergistic in vitro with Retrovir. In addition, some compounds, such as granulocyte-stimulating colony factor as well as erythropoeitin, will also be studied because they may counteract the marrow suppressive effects of Retrovir.

Although years may pass before the results of some of these studies enable us to have a more complete knowledge of the full therapeutic usefulness of Retrovir, sufficient data already exist to indicate that it is a valuable weapon in the physician's armamentarium to lengthen and improve the life of patients with AIDS and advanced ARC.

We are not resting on our laurels, however, and intensive research in our laboratories continues on the forefront of basic and applied virology in our search for new antivirals. Most recently, our laboratories were the first to isolate and produce sufficiently pure quantities of viral reverse transcriptase to allow X-ray crystallography, which will permit the design of specific molecular inhibitors.

It should be emphasized that the rapidity and success observed in the development of Retrovir is very atypical and unlikely to serve as a precedent for the development of other compounds found to be active against the AIDS virus in the test tube. A historical review of drug development unfortunately reveals that the majority of chemicals exhibiting in vitro activity never become useful drugs. We saw this morning that of the limited number of drugs which reach the IND stage, only 20 percent even of them ever make it to a successful therapy.

Some are simply not effective, either because the original testing was less than stringent or because conditions which allow viral proliferation and its direct and indirect adverse effects in the human body are vastly different from those in the test tube.

More commonly, chemicals do not become drugs because unacceptable toxicity may be observed in experimental animals or humans that was not evident upon initial tissue culture assays.

Finally, a myriad of other factors including among other poor adsorption following oral administration, rapid excretion, rapid metabolism to an inactive compound, or even poor penetration into the central nervous system all mitigate against successful drug development. Drug development in general and anti-AIDS drug development in particular is a labor and money-intensive venture filled with many promising leads which usually lead to failure and disappointment.

This general lack of success, however, should not lead to cynicism or disillusionment with the entire drug development progress, but should evoke a healthy skepticism among patients who are now using a variety of unproven nostrums. The drug development process requires a great deal of knowledge, skill, and cooperation among experts, as has already occurred with the NIH and the FDA. It also requires time and luck to ensure that a chemical or biological compound is a safe and effective drug.

The last thing any of us wishes is the widespread use of something which proves on later careful scientific examination to be either useless or toxic or both.

Thank you for the opportunity to appear and present this brief overview of the development and use of Retrovir.

I hope my testimony will prove useful to the Commission and I will be happy to answer any questions you may have after Dr. Rathmann's testimony.

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

DR. LILLY: We certainly will be asking you some questions, Dr. Barry.

Our next speaker is Dr. George Rathmann, President and Chief Executive Officer of AMGen and President of the American Biotechnology Association.

DR. RATHMANN: These remarks will supplement written comments that have been submitted.

I am George Rathmann, Chairman of the Industrial Biotechnology Association representing more than 70 members. Roughly two-thirds of these companies are independent biotechnology companies and I am President of AMGen, one such company.

It is the perspective of those companies I will try to summarize. Such independent companies are generally less than eight years old, have limited resources in contrast to the large pharmaceutical companies, many of whom also have biotechnical capabilities.

Independent biotechnology capabilities have been the most successful translators of basic biological science in candidate pharmaceutical products. They have collaborated closely with basic researchers and major pharmaceutical companies. They have pioneered all of today's marketed genetically engineered products, including recombinant human insulin, recombinant human growth hormones, recombinant human alpha interferon, hepatitis B vaccines, recombinant human tissue plasminogen activator.

Independent biotechnology companies are playing a vital part in discovery and development of gamma interferon 2, the immunomodulators, interleukins I, II and III, colony simulating factors and erythropoeitin, these latter two are being tested to combat the bone marrow side effects of AZT, described this morning and just recently.

Several companies are producing candidate vaccines for AIDS and others are pursuing the receptor decoy strategy that has been mentioned and still other therapeutic candidates.

The great strength of these companies, most of which have less than 400 employees, is their close link to academic research and the ability to put small effective teams together and, you might say, Manhattan Projects.

The good news is that research on AIDS is underway at many of these companies. Unfortunately, there are severe resource limitations in these small companies which raises possible funding opportunities to stimulate more research and development.

In conclusion, speaking for independent biotechnology companies, I would add one recommendation to the four made earlier by Gerald Mossinghoff of the Pharmaceutical Manufacturers Association. He proposes continuing basic research, to designating the Institute of Medicine in a coordinating role, encouraging and enable the FDA to expedite approvals, and continuing to encourage all possible parallel and diverse approaches, and we sincerely endorse all of those recommendations and perhaps would add one more, support and promote a substantially broadened participation by biotechnology companies because despite their small size, they have proven to be powerful innovators and developers.

Thank you for the opportunity to participate.

DR. LILLY: Thank you, Dr. Rathmann.

We will start the questions with Dr. Lee this afternoon.

DR. LEE: I will pass, for the moment.

DR. SERVAAS: I will pass.

DR. LILLY: Cardinal O'Connor?

CARDINAL O'CONNOR: Dr. Barry, I know that you are well aware of the continued questions that are raised about the cost of AZT. I have gone through your paper. I have listened to you. I'm sure that you would consider production costs a tremendous amount of money that you talked about putting into research and development and many other variables would seem to justify the costs, and yet I think a sticking point for all of us who are concerned with patient care particularly, is that if I understand correctly, Burroughs-Wellcome still says that the production costs and various facets related to that are proprietary in character and cannot be revealed.

With complete respect and without certainly any intention to malign anyone, it is very difficult to deal with in an situation where you are the sole owners of the only therapy at the moment, however limited it may be, with whatever problems and toxicity it may bring with it, the only one that the FDA approved completely, the only one that is being used on a widespread basis.

If I understand correctly, your ownership, or your exclusive ownership, continues for a period of seven years under the original agreement, six or seven years.

DR. BARRY: No, that's not correct. The period of ownership is determined by the Patent Office, which is completely separate from the FDA. Like all patents, it is good for 17 years.

CARDINAL O'CONNOR: You were able to reduce the price by 20 percent and you have attributed that to a lower production cost. You seem, if I understand correctly, you seem to suggest that the price must remain elevated in general. It went from $182 to $150 for a bottle of 100 capsules. You seem to suggest that the price must remain elevated because of the ambiguity of the future. You don't know what else might be developed. You don't know, from the impression created, I should say, you don't know if it will no longer be a winner, no longer be used.

The unfortunate inference one could draw from that would be that Burroughs would want to get its money out of it before it were no longer a viable product.

I don't know these things. I am reflecting to you what doctors ask me, nurses ask me, persons with AIDS ask me, and I'm not sure we have yet had the satisfactory answer.

DR. BARRY: It is obviously a very difficult issue and a very important issue to us. We don't want to make medicines that are unaffordable for patients either.

The factors that go into pricing are multitudinous, and I am really not the person to ask. I'm the Vice President of Research, not our Chief Financial Officer. Clearly, our President, Mr. Theodore Haigler, has testified on the numerous factors that went into making the decision about the pricing.

The uncertainty of the future usefulness of the drug I think was one of the factors, probably not a terribly major one. The most significant one was the extreme high cost of research. As I mentioned, we have many thousands of patients who are under study receiving the drug now. Almost 5,000 received free drug for the better part of a year, certainly, at least nine months, or six months. There are a large number of costs.

As soon as we had increased efficiency in production, we had a 20 percent reduction in price, in the absence of any competition, and yet we felt there was a clear moral obligation to do that, to make it more affordable.

I would also point out, as I mentioned at the beginning of my testimony, we make many other drugs for the treatment of complications of AIDS. I would point out that some of those drugs, such as Daraprim -- the only real form of primethamine available in the United States -- which is used to treat and prevent both pneumocystis carinii pneumonia as well as toxoplasmosis, costs approximately $0.25 per tablet and the dosing regimen is one tablet per week. Therefore, a year's worth of therapy with another one of our drugs would cost about $10. We have a number of other drugs at costs in between.

As you also pointed out this morning, the costs of Retrovir are just one of the many drug costs that occur in AIDS patients, and certainly many of the hemophiliac patients have to pay much more for factor VIII than they do for AZT if they are on both. Even one mouthwash for the treatment of oral candidiasis can cost as much as $100 a week.

I think the issue is not so much individual cost, but affordability. Certainly the cost of hospitalization at $500 and $600 a day is staggering and no individual could handle it. We have been working with private insurers. We have been working with the Government, so that the patients would be able to afford Retrovir. We have even helped work with the Government to pass special legislation of $30 million to pay for drugs for those patients who couldn't pay for it themselves. This is administered by the states but in many states, very little of that money has been used.

I think we all have to work together, including insurers, on how to make drugs more affordable. We will do our part in continuing very, very expensive research to try to find new and better agents. We will do our best to try to make the drugs affordable. But, there is a certain limit, when you are making an exceedingly expensive drug, below which you can't go if you want to continue to have a functional operation.

CARDINAL O'CONNOR: I don't want to use up an inordinate amount of time. I will make a brief statement rather than question you further because clearly, you are answering within the best of your ability as a researcher since you are not in the marketing end of it.

But you are aware that the American Cancer Institute put $3.5 million into the development of AZT. It seems awfully strange and it would seem to me that it could dissipate a great

deal of the ambiguity and ease a lot of minds if Burroughs would simply open its books, putting it simplistically.

DR. BARRY: I understand that is a statement and not a question. It is obviously a statement that I think is important for me to respond to.

I think we have not opened our books, nor has any other company to my knowledge, making many medications and therapies much more expensive than ours, open to any regulatory, review or governmental group. There are a lot of reasons for that. One is that it would obviously establish a very difficult and I believe not beneficial precedent; and secondly, if you want to have any sort of meaningful figures, if the Government plans to put accountants in and so on, it would clearly be information that would be competitively advantageous to our competitors both here and outside the United States.

I must point out that competition -- although there has been a great deal of cooperation among the pharmaceutical industry in making drugs available for testing including combination testing -- frankly, competition in the drug industry is very important, because it is from the competitive drug industry of the United States and Western Europe that new drugs come. Virtually no drugs come from places such as Eastern Europe where there is very little competition and very little incentive for individual researchers to produce important products.

CARDINAL O'CONNOR: I think at a time at which we are confronted with one of the most critical health care problems that we have had, that Burroughs Wellcome would surely not want to go down in history as a company unfairly marked as having profiteered during this crisis. It would seem to me that if we begin with an assumption that the company is being fair, then we should add the recommendation that the company do a lot more than it has done to demonstrate its fairness in the matter.

DR. LILLY: Dr. Walsh?

DR. WALSH: We know well the extent of money that is being spent by the private drug companies, I believe, this year in research and so on. You are spending more than NIH, I guess, in all drugs.

About what percentage of what you are spending in R&D on drug products is being diverted now to AIDS research?

MR. MOSSINGHOFF: Dr. Walsh, let me respond. When we aggregate our research expenditures for our companies, this is again very proprietary, and we get gross numbers and we don't go below that into individual categories. I do not have an answer speaking for PMA. There were interviews done by Business Week

and others who have written articles about the industries and they came out with an estimate which says hundreds of millions of dollars. I'm sorry I can't refine it any better than that.

DR. WALSH: Your total number in research is about $6 billion.

MR. MOSSINGHOFF: Last year, 1987, it was $5.4 billion. This year, it will be near $6 billion. We had a pretty definitive study done by Professor Wiggins of Texas A&M, an economic study. His estimate was that it cost about $125 million to bring a drug from discovery to marketing. If you just take the drugs that are listed on these charts and begin to multiply by those kinds of numbers, you can get a gross idea about how much is being spent.

DR. WALSH: How many years does it take to make it back, to make back your investment on a successful drug?

MR. MOSSINGHOFF: All too few, they don't make it back. Some of them, they make it back, the really impressive drugs, the things that really break new ground, make a lot more than theirs. On the average, for every one year extra it takes for the FDA to review and approve a drug, it takes three or four years of exclusivity to make that money back.

DR. WALSH: What I am trying to get at is that is one of the reasons I would suspect you have a drug like AZT and so on, it is not only the cost of producing AZT, it is the cost of research and development on a whole host of products of which this is only one. You are in effect trying to recover monies so you can continue your research and development for other drugs.

It is sort of a Catch 22 situation. That is why I am not so enamored with the economic arguments over the prices of drugs for that reason. You can't pull out one drug and say that is too expensive and aspirin cost a penny.

MR. MOSSINGHOFF: The data that were shown on Dr. Young's charts this morning, one out of 20 percent, one out of five make it from IND to actual approval, that is a higher number than I have seen. We usually one out of ten make it from IND to approval and marketing.

DR. WALSH: While recognizing the value of competition, as those of you who know me, I am a great believer in competition, in something like AIDS, which is so critical to so many patients who have a very limited life span facing them, is there much collaborative research and development going on among the companies and are there any anti-trust problems with that collaboration?

MR. MOSSINGHOFF: Let me answer generally, and then refer to Dr. Barry. I would say even the production of these charts which give status, indication and all the rest is rather unprecedented as you well know, in the pharmaceutical industry. This is an unusual display of people opening what they are and what status. In any other area, this would probably be regarded as proprietary and our companies would not provide it to PMA for publication at a public hearing such as this.

Also, the industry does an awful lot of publishing of its articles. As a former patent lawyer, my rules used to be for the clients, as long as they had the patent application on file, they could publish. Those two things usually go in parallel. By the time the articles are peer reviewed, the patent application is on file.

I don't believe there is a lack of publication.

DR. WALSH: On this treatment IND, do you have patent protection?

DR. BARRY: The patent circumstances are completely and entirely separate from the drug approval process, with the exception that there are certain much less limited exclusivity rights than patent under certain Orphan Drug Act provisions as well as certain provisions of the Waxman bill dealing with generic drugs, as well as patent extension. Generally, that is separate, whether your drug has exclusivity or not, whether it is under patent exclusivity, as an approved drug or treatment IND or investigational drug, really they are two separate issues. They are not connected.

DR. WALSH: What I was asking is I assume there are also delays in the Patent Office. For the good of the patient, you are trying to get these drugs out under Frank's new treatment IND. Do most of these drugs have patent applications which protect them before you go into the FDA?

MR. MOSSINGHOFF: I would say as a general proposition of making a decision to even go into the IND and all would probably follow a decision to seek a proprietary patent position.

DR. WALSH: Okay, and I have just one other question. No, two questions, very brief ones.

When you see this tremendous array of compounds, and then Frank testified this morning that there were only Trimetrexate and AZT that are approved, is the holdup that you can't get them out until you are in Phase II, that you can't use them? I mean you have got a lot of things in Phase I and some in Phase II and Frank is talking about 5 days, 30 days and so on.

He confused me a little bit this morning on that score when I see all this. Where are these drugs?

MR. MOSSINGHOFF: I can try and answer that. I think probably a general answer would be that most of these drugs on the chart are at earlier stages in development, in stages where there hasn't been sufficient credible evidence of efficacy or safety to justify going for a treatment IND or for approval.

I can give you a good example with ddC, if you like. At the time we licensed Dideoxycythidine from the government, Dr. Broder had shown in his work enormous promise for the compound both in cell culture experiments against the virus and also in a very limited exploratory clinical trial where ddC seemed to be more potent that AZT in terms of some of its biological parameters. But it particularly had a different toxicology profile and that suggested it might be a very useful agent.

Some people said, "Gee, we should be giving this to a lot of patients." Fortunately, I think there was a more responsible position taken -- it was licensed to Hoffmann-LaRoche and we set about developing it in collaboration with the government.

What we found was, unfortunately, after about 6 months of study with patients, was peripheral neuropathy turned up in the patients which led to really quite extraordinary pain in the feet and it would have been absolutely tragic both for the patients who had gotten the drug and for the drug if that drug has been administrated widely through a treatment IND situation. It is fortunate that it wasn't, because it would have caused a lot of trouble and, as Sam said earlier today, it probably would have been the end of ddC. Whereas today, through very methodical, careful clinical studies we think we have a way to get around this problem and there is a possibility ddC will be a useful therapeutic for HIV infection. I think that is an example of trying to be responsible and good clinical practice for the development of these drugs.

DR. WALSH: On one of the questions that Admiral Watkins raised this morning, I wasn't clear on the answer. He raised the problems again of legal liability during this treatment IND stage.

Do you have adequate protection now, or is that something that this commission should take an interest in?

MR. MOSSINGHOFF: I think it is something your commission should take an interest in, Dr. Walsh. It seems to me Frank Young said that he had an agreement with one plaintiff's lawyer that what was in it was publication and explanation. Well that only leaves 250,000 other plaintiff's lawyers out there who

may not agree with that one he agreed with, so in the whole area of drug development and development of all medical devices -- in fact, throughout industry -- the product liability chaos that exists in the states is something everyone should look at and this is a particularly acute area --

DR. WALSH: Because we have to find a way to do that fast, I think that the PWAs that again have really a certain right to expect that efforts are going to be made at least to prolong or save their lives quickly. And yet there seem to be impediments which will prevent us from making things available to them unless we do something. Maybe you could suggest what we specifically could do.

MR. MOSSINGHOFF: I'd be glad to try to do that.

DR. GAGE: I have somewhat of a different answer to that question. I can say from my own company's experience that liability concerns have not prevented Roche from requesting a treatment IND for something like ddC. It is just good medical practice, and good drug development practice that you don't do that until you have sufficient evidence of safety and efficey to justify it.

DR. WALSH: That's right, but this time we're rushing, you see, and that is what worries me. Okay, thank you very much.

DR. LILLY: Dr. Crenshaw?

DR. CRENSHAW: Dr. Barry, I have a two-part question for you.

The first is that a while back when I was working behand the scenes to accelerate the FDA approval of AZT, I was surprised to learn from Burroughs Wellcome that they weren't eager for the approval to be accelerated and the reason that was explained to me at the time was because since the drug was being made from herring sperm, which was in short supply, Burroughs Wellcome was very worried about once it was approved the demand so far exceeding the supply that they wouldn't be able to keep up with the pressure. I found that understandable.

I understand also now that you have developed ways of synthesizing AZT so that you no longer depend on that supply. My specific question is, of the 30,000 or so AIDS patients and perhaps million and a half HIV infected, if they could afford the drug, how many -- give me an approximte number -- could you service? How many could you actually supply the drug for over the next five years?

DR. BARRY: Well, before I answer that, let me comment that I don't know who you talked to at Burroughs Wellcome. It wasn't my group -- and I was head of the group, and communicated all the way up to the Chief Executive Officer in terms of knowing what was going on.

We were very eager to have the drug approved just as soon as it was shown to be safe and effective. That was proven by the fact that we prepared the entire new drug application within a two and a half month period, and normally that takes -- even at the quickest -- six to nine months to prepare. As soon as it was prepared -- literally hot off the press and steaming -- it was brought to the FDA by special courier.

I think the problem you may be referring to was the fact that we -- because the drug is so difficult to produce and because some ways of producing it could produce a very explosive intermediate -- we had to work very fast to ensure that every patient who was started on the drug would, in effect, have a guaranteed supply because we felt that nothing would be crueler than to start someone on the drug and then halfway through say, "Well, this batch did not come out, so you don't get anything" and then have them deteriorate. And patients who do go off the drug do have a deterioration with the natural course of AIDS and ARC.

So what we did was to have a very rapid development program beginning with herring sperm, which was the original source of thymidine. But there were only about 20 pounds per year, and we were the primary users of it for another drug, Viroptic, used to treat ocular herpes infection, it's also a beginning drug there. When we told them, well, gee, we need a ton next week, they said there are just not enough herring in the ocean -- better think of another way.

So we worked very hard ourselves and with a number of outside collaborators and groups to have a synthetic method to produce thymidine.

All of this occurred during the period of the Phase II study, and the very beginning of the treatment IND program, which started two weeks after the results of the Phase II study became known.

We were very worried that from week to week we would not be able to guarantee the supply for the new patients coming on to that study and we had very tight limits of entry that if we exceeded them we would have to stop. We never exceeded those limits, but we literally had to have our staff, particularly in our production unit in Greenville, North Carolina, work basically full time. All of the production workers were working

a schedule of 28 straight days on and 2 days off, and many of them working 12 and 18 hours a day to get to that stage.

We were even concerned that at the time of approval on March 20th, 1987, FDA approval for general sale, there might be a sudden rush, up to a maximum of one and a half million people to use it. We just didn't know how many. So what we did was say that to start out we are going to have a controlled distribution system, somewhat similar to the treatment IND program that we already had running. The physician had to certify that his patient had the package insert indications, because we felt that we had a pretty tight number on that, and we felt we could meet it.

It became very clear that, as our production facilities increased in their efficiency over the course of this summer, we could be those demands. So, on September 15th, that requirement was removed and the physician could prescribe it just as he did any other drug.

I know that is a long preamble to your question, but the answer is that we could supply certainly well over 30,000 people and well under one and a half million people right now. I think it's unrealistic at this time, or within the next year or two, to think that all one and a half million people who are infected with the virus could be eligible. We have a lot of clinical research to do before then. Right now, I think we are at the stage we are with virtually all of our other drugs and that is we can meet the expected demand, whatever it might be, as long as it is within reason.

DR. CRENSHAW: So to summarize then, I understand there was a problem at one time with supply and that that partly explained what was one of the factors in why the early studies were so limited to the perhaps terminal patients and not made available to the HIV positive individuals because there wasn't enough to go around, but now basically the supply problems are relieved and you could, if the funds were available, accommodte the 30,000 plus some unknown number?

DR. BARRY: The latter part of your summary is correct. The first part isn't the way it really occurred. The number of persons in the Phase I and Phase II study were determined by what the FDA and our statisticians and their statisticians thought would be sufficient numbers to answer the question.

However you are right in the sense that we were very fortunate and worked very hard that we had just enough drug at those points -- that is, September of '85 and February of '86 -- that could just meet those demands. I think it was a happy coincidence and would have meant if the numbers were higher that

those workers who were getting two days off a month wouldn't have even gotten those two days off.

DR. CRENSHAW: And then the last part of my question is, I know you are under siege and that although you are the only drug company that is currently making a prescribable, approved drug available to people who are infected, you are being picketed and criticized and challenged. This must be very discouraging for other potential pharmaceutical companies who are entertaining the idea of contributing to the AIDS effort.

What can you tell us that would help you and that would inspire and motivate drug companies to pitch in without the apprehension and the fear of the kind of pressures that have been experienced by the pioneer?

DR. BARRY: Well I think that is a really excellent question. We could ask for a lot of sympathy, because there is no question that some of the things we have heard are much like the ingratitude of a child that Shakespeare said stung "sharper than a serpent's tooth."

But frankly, we're in the business and we have to be tough, and I think it is very important for people who are going into this to realize you do have to have a tough skin, but you do also have to perserverate. If you do think you have a successful drug, there are rewards -- there are scientific rewards, there are rewards to the patients, there are financial rewards that, as Dr. Welch said, allow you to continue to do your research not only in AIDS, but in many other areas where diseases are poorly treated or not treated at all. So I think toughness and I think the companies that are in this now have a great deal of toughness and I have a lot of confidence that private industry is actually enthusiastically pursuing these goals.

DR. CRENSHAW: Is there anything we can do to help?

DR. BARRY: Not that I can think of, but let me defer to Mr. Mossinghoff in case I have lost the opportunity and forever remain silent.

MR. MOSSINGHOFF: I would just like to say on behalf of the industry we appreciate the question also. I am obviously not with a company. I deal with the people at all levels in the organizations and these are some fairly tough-minded people, the CEOs and all, that aren't playing with their own money -- they are playing with all their shareholders' money and they make some very, very tough decisions for everything that they put on the market and are very willing to make those decisions because of the great progress that comes from them.

DR. GAGE: Maybe if I could just make a comment as well, Mr. Chairman.

I think the thing what I would say is that you should not do is you should not to establish some sort of extraordinary new way to develop AIDS drugs, you should let the institutions of our society that are already established to do so, do so and try to optimize process.

DR. LILLY: Now Ms. Pullen, do you have any questions?

MS. PULLEN: Does any of you see any circumstances under which it would be advantageous for the FDA's approval authority to be limited to safety rather than efficacy or to lighten the standards of efficacy in going into a treament IND at the time the decision is made to go into that?

MR. MOSSINGHOFF: We considered that question very carefully when the first regulations were proposed. They were not regulations, they were proposed rulemaking that the Food and Drug Administration came out with on the treatment IND and there -- those regulations would have put the burden upon the commissioner to show that a drug was not effective and the PMA unanimously took a position against that. We thought that that would have led to quack medicines being on the market -- that plus the ability to sell medicines that were still under experiment and we think the last thing the health care system in the United States needs is that kind of problem and so we took a position which was agreed to ultimately by the government and by Dr. Young in his final regulations: that there must be some evidence -- some scientific basis or evidence for the fact that this is an effective treatment. We really believe in putting the burden on the commissioner to prove that it was not effective or alternatively, just to remove the effectiveness requirement would have led to all kinds of mischief that would have helped no one.

MS. PULLEN: There is a lessened -- a reduced standard of evidence, of effectiveness on entering a treatment IND, though, right, because you are still in the --

MR. MOSSINGHOFF: It is --

MS. PULLEN: Because you are still in the trial phase although you are making it available.

MR. MOSSINGHOFF: That's right. The words in the regulation are different and I think lower standard of efficacy for treatment INDs than for actual drug approval itself. At the end of the political issue when we working with Dr. Young, we finally concluded that you can't regulate or legislate common sense and we have a high degree for the common sense of the people at FDA and we think they are going to deal with the

treatment IND regulations in a very sensible and appropriate way but that efficacy will be something that they will have to consider.

DR. RATHMANN: There is a somewhat more unfortunate issue with treatment INDs and the meeting that was just held in Washington dwelt on about two days of issues that are really unresolved. Most companies don't know how to deal with that degree of uncertainty as to how extensively should these patients be monitored, what are the liability issues, what are the potential delays both because of the dilution of your own efforts in trying to manage a very diverse group of patients all across the country without being assured that you will have the resources to dedicate to the eduction that is necessary to be sure that these products are being used correctly.

Unfortunately the treatment idea is still kind of a shadow and that is one of the reasons there haven't been very many companies volunteering to have treatment INDs.

I think it may be that it's correcting itself but it was not clear from that meeting that it was out of the shadow, and it would seem almost as though if the FDA looks at those modified understandings that are necessary in both efficacy and safety that they could take the treatment IND issue out of the shadow if they could simply award a license for those products at that stage and put them into the category where they now are fully licensed, and many of the confusions go away. Whether the FDA has the authority to do that -- I understand that they do not -- but under the circumstances where those drugs would be licensed and provide additional provisions from compulsory Phase IV or whatever it is, it seems as though something has to remove that shadow. Maybe time will do it but it is a shame to wait.

DR. LILLY: I'd like to ask you, Dr. Mossinghoff, just for a little bit more information about the relationship on the theoretical and practical level between ATEUs and the testing that is done by the developers in the pharmaceutical houses. In your talk you certainly registered a bit of dubiousness about the ATEUs and I would like a little more information about that.

MR. MOSSINGHOFF: Mr. Chairman, I do not have very much direct experience with that but PMA put together an AIDS Resources Group and it was senior people, three of four of whom are at the table today, of the major companies so that had an identifiable group we could deal with as part of our efforts to try to coordinate. The general feeling that I got and I think my colleagues here can better expand on it was that these ATEUs are not set up for the large scale phase three tests which we believe are needed to get a drug to an NDA position and approved by the Food and Drug Administration. That is a very broad statement. I would defer to my colleagues.

DR. LILLY: Does that fact that they are not equipped to do that interfere with the capacity of the company to do it?

MR. MOSSINGHOFF: That was the general feeling of the group that we had set up that met discussing this and other issues involving AIDS. That was the general feeling. It is certainly well intentioned. It was useful in the beginning. We are not throwing bricks at anyone. We do think that Dr. San Their and the Institute of Medicine being kind of a neutral floor that everybody levels with and levels within, might be a place where this could be considered by the Government, by academia and by the industry.

DR. GAGE: May I could just add from Hoffmann-La Roche's perspective on our experience with ddC. Probably the focus of our concern is principally where the ATEU system has extended from the beginning. I think this is changing. They have learned. They have tried to do everything that the pharmaceutical company might do normally in the development of drugs.

The area that we found to have the greatest problem is in managing the data coming out of the studies. This is absolutely essential if you are trying to put together the data into a form where you can get registration with FDA. We found from our perspective that this is the most serious deficiency in their program. It is not for lack of trying. They have done an incredible job getting that program up. You can't expect this agency to do this, essentially reproduce a major pharmaceutical company overnight.

I think in the cases where there is a working relationship between an established pharmaceutical company and the ATEUs, there is a possibility that the pharmaceutical company should do everything it knows how to do well and the ATEUs take less than a role, then in the case where you are working with a small company that maybe doesn't have that capability, then the ATEUs could take that other larger role.

DR. LILLY: In this last point that you have made, since one of the comments we have had several times today, that the ATEU system seems preoccupied with further testing of AZT, is this a help or detriment to development of AZT?

DR. BARRY: I think as you mentioned, we have more experience with the ATEU than anyone. We really tried to get involved before it was even formed. Many of the investigators, virtually all of them that we chose in February of 1986, later were appointed as ATEUs. I'd say the process, the ATEU management, supervision and execution, is in the process of evolution and flux. I like the direction it is going. I think

the Director, Dr. Dan Hoth, is an extremely capable person and has a lot of experience in that area.

I think there has been an agreement in principle and even a recent review by outside experts of some things to do and some of the principles agreed to, for example, would be in certain circumstances, the drug company would be able to hold the investigational new drug documents, which is very important in determining exactly how a study is done, that the sponsor would be able to directly supervise some of the studies, particularly those as Dr. Gage mentioned, that are pivotal to a drug approval process. Drug companies, and I might as well beat our own drum, because a lot of other people don't do that, but I think in the business world, they are seen as quite efficient operations. Because clinical research is so expensive, you need greater efficiency and you need great zeal, speed and precision to get from point A to point B.

Other companies at times, and we have also, felt frustrated because we are used to doing something over a weekend, getting a protocol written, getting agreement by the investigators in a week, and this may take much longer in the AIDS treatment and evaluation unit.

What we have seen recently is much more improved over what has been seen in the past. I think what Mr. Mossinghoff suggested and I believe the rest of us agree is that basically there needs to be a forum where it can be discussed among experts, if there are disagreements.

A company and the Government may have two different goals in dealing with the same drug or even the same study. There has to be an accommodation for both. I think a suggestion that the Institute of Medicine be used as such a forum would be lauded on both sides. Dr. Hoth will be testifying and you can ask him.

Certainly, this was a forum that was used at the very beginning of September, 1987, where everyone discussed their issues, experts, Government, industry, academic people, and it seemed to work out well. I think it is a good model.

DR. LILLY: Thank you. Chairman Watkins?

CHAIRMAN WATKINS: We are going to be sending you all some additional questions. We just don't have time today to go into them all. For the benefit of others here today, I wanted to lay out the kinds of questions you will getting, and some of them are repetitive to some of the questions being asked here.

This goes down a sequence chronology that I think makes some sense. Federal interaction with private industry, under what circumstances should the Federal Government contribute to the development of drugs and vaccines that can be subsequently sold to the public for profit. We need to have some comments and we have specific questions under that.

In what ways should NIH and private industry collaborate, should it be in the form of screening compounds, assist with clinical trials. Let's focus on this emergent crisis, not trying to make this a precedent setting for every other kind of drug we are developing. They may have positive spin offs in that direction but I'm talking about focusing on an emergent crisis in the nation like this.

When the Government and in this case the taxpayer also pay a big contribution up front in the initial stages of drug development, should in fact there be a flat or amortization regime allowed, in the form of a lower cost of the drug. I think somehow that has to be looked at in the special context of this crisis.

If there are ways to cooperate, such as orphan drug research grants, assist with protocol designs or drug provisions and market exclusivity and tax incentives, which of those do you see may be significant as we try looking at it and take some lessons learned from experience.

We will ask you a little bit about the orphan drug law, how successful is it as an incentive to develop and market products, if you think there should be changes, what should they be, particularly if we look ahead and perhaps see a migration from the fine line between AIDS and say asymptomatic HIV, how is this going to affect the laws.

We want to talk more about collaborative R&D. As I mentioned before, we had a specific congressional relaxation of anti-drug to encourage 12 major companies in this country to come together for microchip development, so the Americans could be competitive in the next generation of supercomputers. Is there not, and maybe Mr. Mossinghoff can answer this question, isn't there a way to take a look at a new concept of collaborative R&D for this specific emergent disease that might be a little different, that might require us to look into our own way of doing business and share in both the joys and the sorrows of victory and failure together, and share the prizes and the glory. Is there not inside that, if you review it very carefully, a way to perhaps have our cake and eat it, too, twice as fast.

We will be talking about the treatment use regulations and why, again going back to Dr. Rathmann's comments earlier, I think it is very important that we understand those obstacles and

we need to know what process we need to follow to expedite that. Let's not let the obstacles sit there and fester for eight months if we can move aggressively and try to resolve them.

For example, do we need legislation to take a look at liability laws specifically for this disease. Is this something we need to look at.

I think that succession of questions coming from each of you and particularly from PMA's viewpoint would be very valuable to stack those up and see if we can't really do something here and not just let the old way of doing business be good enough for this particular disease.

I'd like to have two short questions. Those questions will be coming to you officially under my signature. I would like to ask any of you, because it keeps coming up and I would like to get the pharmaceutical viewpoint, could we eliminate placebo controls and trials for AIDS patients and maintain scientifically valid results, and if so, how would we do that?

Clearly, we had the point made earlier on today and there is a lot of sensitivity to the ethics involved in placebos with AIDS. We have heard it now from people with AIDS from all over the country, not just in this hearing. Many of those health care providers around the nation bring it up. We haven't resolved that issue. It won't go away. We need to understand it a lot more. We have heard from very competent people that think it can be done with large groups and the question is how do you look at it?

DR. BARRY: We have had to confront this question from both sides. One, when there was no active product and now that there is. I think the consensus in the scientific community, and this is supported by a number of discussions at the National Academy of Sciences, the Institute of Medicine, the Food and Drug Administration and NIH, that for patients with AIDS and severe ARC, you should no do placebo controlled studies. You should do active control with AZT, retrovir, as the benchmark, and the other drug being compared in its ability to influence the longevity and quality of life with retrovir. I think that is well established.

You don't need a huge population of epidemiologic studies. You can do it with just about the same number of people, you can get your answer as if there were placebos, if you have a positive control.

I think there is also agreement that in patients who have milder forms of HIV infection, who are less in danger of immediate death, then placebo controlled studies can be accepted. The one area to my knowledge where there is any controversy at

all is in those patients who have neurologic disease, whether it is justified to have a placebo there or not. I don't think we need to get into that discussion because I think it is being worked out now.

I think, however, there are individuals who do not believe in the scientific method, and who don't have any real evidence that the nostrum that they are promoting is effective. They will sometimes use as an excuse the lack of ethics or the ethical inability to do a placebo controlled trial. I think the scientific community has found a way around it in the severely ill patients, use a positive control, in those less threatened with death, than placebo is justified, provided you have an outside independent group as we did, look at the results on a regular basis to make sure one group isn't doing so poorly or so well that it would be unethical to proceed.

CHAIRMAN WATKINS: Anyone else have a comment?

[No response.]

CHAIRMAN WATKINS: Dr. Gage, last question because you mentioned it briefly, your industry, for example, put aside competition to work with FDA and develop a computer software package that could be used for clinical trial data to speed up FDA review, and if so, how long would it take?

When we were out at FDA, it was very clear to us that we were using somewhat archaic techniques today to contribute to facilitation of the process.

The question is when you get into building such a software package, are you opening Pandora's Box and is there not a way to close it again with modern technology to provide controlled access and the like?

MR. MOSSINGHOFF: Mr. Chairman, maybe I can comment on that. PMA several years ago established a Board of Directors Committee to work with the FDA chaired by Irwin Lerner of Hoffmann-La Roche, the CEO. That committee has several pilot projects underway with various of our companies to work with FDA and Jerry Myer, particularly, to develop an electronic NDA precisely for the reasons that you suggest.

If we know anything it is that you can add on massive amounts of data very quickly by machines and that is not being done at FDA.

CHAIRMAN WATKINS: What can the Commission do to expedite the placement of that?

MR. MOSSINGHOFF: We would be pleased to submit to you a briefing, briefing materials on what we are doing. We will jointly prepare those with Dr. Young and submit what we are doing, the pilot projects, and you can look at those. If the Commission believes that is a good idea, which we think it will probably end up being, and you can lend your advice to us and to the FDA.

CHAIRMAN WATKINS: Is that something you can provide us fairly quickly, that particular piece of information?

MR. MOSSINGHOFF: Yes.

CHAIRMAN WATKINS: It is off-the-shelf?

MR. MOSSINGHOFF: It is not off-the-shelf but I can find a shelf and we will work it.

CHAIRMAN WATKINS: Thank you very much.

DR. LILLY: Thank you, gentlemen. It has been quite an informative session.

NIAID Clinical Trials: Testing AIDS-Related Therapies

DR. LILLY: Now we will go to consideration of the aspects of NIAID's testing program for AIDS therapies. We will have two speakers in this session, both representing the ATEU system from different viewpoints.

The first of our two speakers will be Dr. Donald Armstrong, who is the principal investigator of an ATEU at Memorial Sloan-Kettering, where Dr. Armstrong holds a staff position.

Dr. Armstrong?

DR. ARMSTRONG: Thank you, Mr. Chairman, Dr. Lilly, members of the Commission. I welcome this opportunity to talk to you. I am the head of infectious diseases at Memorial Sloan-Kettering Cancer Center and a principal investigator for one of the first 12 ATEUs. I am also the principal investigator for a national drug discovery unit for AIDS at Memorial Sloan-Kettering Cancer Center and I am chairman of a committee for access to care and treatment trials of the advisory council of the AIDS Institute of New York State.

The ATEUs started in July of 1986 and as we prepared our protocols and met and deliberated and were ready to get off the ground in September, AZT was released.

DR. LILLY: Excuse me, I wonder if the audience could be a little bit more quiet so that we can hear.

DR. ARMSTRONG: The release of AZT made a great deal of difference as far as our movement of various protocols was concerned. Suddenly we were going from what we thought would be in-patient trials to out-patient trials and we had a drug against which we would have to compare all other drugs.

Very quickly, AZT became available by compassionate release and we had to inform our patients that they could get the AZT, that some of our protocols were not ready but they could get AZT by compassionate release so a number of them chose to do that and not wait for protocols.

So we did not get off the ground as quickly as we expected. The other thing that we found from the investigator's point of view was that this is a tremendously complicated program. There was a large number of people that we had to deal with. Some of us had done clinical trials before dealing just with a drug company. Now we had the drug companies, the FDA, the

NIH program, other investigators among the ATEUs, and consultants, so that there was a tremendously complicated business of just developing the protocols.

From the practical point of view at the centers where the trials were being run, teams were developing, teams of nurses, social workers, psychiatrists, doctors, administrators, data managers, again a much more complex development of a team effort than I have seen in many years of a cancer center and many years involving studies of antibiotics.

So for both antibiotics and anti-cancer drugs which I had seen developed over the years, for reasons that I think you probably have some idea and for reasons about which I am not certain, the complexity of developing the anti-HIV trials were much greater.

We also had laboratory support that was really extraordinary. Suddenly retrovirus laboratories had to be developed, complex immunology tests had to be developed and put into place, even neurological evaluations required new testing systems that had never been used before.

So we found that we were doing extremely intensive research, very, very intensive research and I think that we will find that this is going to be very productive research. We have already seen a number of abstracts submitted to the AIDS meeting in Stockholm from the ATEUs and I think it has been productive.

I think that we have a lot of scientific knowledge that is developing and a lot of practical knowledge about how to run trials in such a complex setting as HIV infection and the disease AIDS.

Well, is this enough? Is the intensive sort of trials that we are using, is the knowledge that we are getting, enough? I don't believe that it is enough for what we have here in New York. I see many patients who do not fit protocols for various reasons. Most of the protocols now are for ARC. There are relatively few for AIDS for various reasons and we need to develop protocols for patients with AIDS as well as for those with ARC.

There are a number of patients who cannot take AZT who need protocols, who need these protocols developed and implemented for them. They are essentially there without any treatment even if they have AIDS, much less ARC.

So there is not enough to take care of the number of infected and diseased patients that we have in New York at this time.

Are there drugs that are not being developed? Again, are there drugs that are too expensive to be developed in an ordinary industrial situation? I am not sure about that but I think those are questions that we have to ask.

How can we get trials to individuals who don't have access to, for instance, the ATEUs? I think we have to develop consortiums among hospitals. For instance, in southern Manhattan, there is not a hospital that is an ATEU. In Brooklyn, there is not a hospital that is an ATEU. In Harlem, there is not a hospital and in the South Bronx, there is not a hospital that is in the ATEU.

These are areas where we need access to care and access to treatment and we could set up consortiums. We could set up teams to work in these areas and we should. We should have, and we are initiating in New York, Community Research Initiatives, and this is an exciting area.

If the questions are the right questions that are asked, I think they can be answered in the setting of a Community Research Initiative, and the people who have developed the Community Research Initiative are talking to the ATEU people and we expect to see them working together.

Finally, these are extraordinary measures, setting up Community Research Initiatives, trying to get money to set up consortia among smaller hospitals which may not have the experience in clinical trials where we try to supply them with experiences investigators. These are extraordinary measures but we have an extraordinary situation.

Is this not a public health emergency? Is it not a public health crisis and I think all of you know as well as anybody that indeed it is. Should we take extraordinary measures? Should those measures include direction of drug production? Should we tell drug companies what they should do? Should we ensure rapid drug production as you have heard discussed today? I think we should.

If this were a war, we would be producing munitions in various industrial settings that were requested by the government. Indeed, there should be a war, there should be a war on HIV infection and we should take extraordinary measures.

Finally, if we are having trouble and I think we are having trouble getting personnel, getting personnel in the right place at the right time, experienced people to carry out the administrative and the medical duties that are necessary, we should get the personnel. We should assign the personnel.

For instance, I am in the United State Public Health Service Reserve. I could be requested to report to duty someplace else in the nation although I think I have something to do here in New York. I still could be requested to do so if it was felt that this was enough of an emergency.

There are public health officers all over the United States who could be pulled out of their present positions if this was an emergency and if the appropriate powers were given to the government to pull them out and reassign them to do the job that we believe we need to get done.

Thank you.

DR. LILLY: Thank you, Dr. Armstrong. Our next speaker is Daniel Hoth who is the director of the AIDS program for the National Institute of Allergy and Infectious Diseases, NIAID.

DR. HOTH: Thank you, Dr. Lilly and the panel. I am delighted to be here to have this opportunity to explain the clinical research program at the NIH which is attempting to discover effective therapies and develop effective drugs for the treatment of this epidemic. May I have the first slide, please?

[SLIDE.]

DR. HOTH: What I propose to do in approximately the next 25 minutes is present to you a brief history of the National Institute of Allergy and Infectious Diseases program of clinical trials, the ATEU program, a summary of an evaluation recently conducted of the program and then move on to tell you the future directions that we plan to go and I hope that this talk will address many of the concerns that have been addressed in the last two days.

This program began with its initial intent to establish a national clinical trials capability which was oriented to the evaluation of new drugs, namely, Phase I and Phase II.

It should be recalled that this was in the days prior to the discovery of the usefulness of AZT. Hence, all of our efforts were thought to be needed to be directed at early trials, at new drugs, to discovery something useful and as you may know, it is a very different kind of clinical trials capability required to do Phase I studies than Phase III trials.

[SLIDE.]

DR. HOTH: Now in the autumn of 1985, an RFP was issued to request people to propose for AIDS Treatment Evaluation Units to conduct these Phase I and Phase II trials. In January 1986 just to present a parallel study the Burroughs Wellcome

Corporation initiated the controlled Phase II AZT trials. In June of that year the 14 contracts were awarded.

[SLIDE.]

DR. HOTH: In September, a Clinical Trials Coordinating Center contract was awarded. This is a data management and statistics center to receive the data from the ATEUs. In that same month we had, of course; that is, scientifically and medically we had success in that the placebo controlled trial of AZT did show some benefit with the drug in terms of prolonging survival.

Of course, the practical thing that that required was an abrupt and major change in the approach to the clinical trials program which I will show you in two subsequent trials. In January, 1987, the first ATEU protocol was initiated and five additional units were established and finally in September there were 17 awards made for something we refer to as Clinical Studies Groups which essentially are groups that perform clinical trials in AIDS and I will come back to that in a moment.

[SLIDE.]

DR. HOTH: Now, as I mentioned, the discovery of the clinical efficacy of AZT in September had several consequences. Number one, it mandated the study of AZT in other stages of HIV infection. We have heard much concern about the amount of this research that is going on with AZT in this program. By analogy, if you had a drug which was active in one type of cancer, wouldn't you want to try it in all other types of cancer? If you have a drug which is active in a late phase of HIV infection, isn't it logical to test it in many other phases to explore its full potential?

[SLIDE.]

DR. HOTH: Hence, it added the requirement for large multi-center Phase II trials which required the re-writing of many protocols which were in draft form at that time.

Finally, there was a drug scarcity as we have heard described. I might point out that at that point we also collaborated with the Burroughs Wellcome Company in establishing the treatment IND and so we were very well aware of the demands for the drug supply.

[SLIDE.]

DR. HOTH: Now what has been accomplished is demonstrated on this slide. I wonder if we could focus the bottom of that just a bit. The timeframe here shows you the time

in late 1986 when the efficacy of the drug was established; the treatment IND was established in October, 1986; protocols were re-written and we finally got the first ATEU protocols off the ground in January 1987. Depicted here then is the cumulative accrual to all of the ATEU-sponsored studies. Last week, the total accrual passed the 3,000 mark.

[SLIDE.]

DR. HOTH: That is a summary of where we were until last summer.

[SLIDE.]

DR. HOTH: At that point Tony Fauci appointed a clinical trials advisory panel, to review the progress of the AIDS clinical trials program and to make recommendations for the future.

[SLIDE.]

DR. HOTH: This panel was chaired by Dr. Robert Couch of Baylor and included representatives from the Food and Drug Administration, from academe, from other parts of NIH and importantly the pharmaceutical industry and they met from July until October and have issued their report which has been provided to you.

[SLIDE.]

DR. HOTH: Their major recommendations are number one, to establish a cooperative group, that is to transform the clinical trials effort into a collaborative, cooperative group which incorporated both what were formerly referred to as ATEUs and the CSGs as full partners to give emphasis on the expedition of protocol development about which I will say more later, to increase the flexibility in ideas to be tested, that is, to allow more different kinds of ideas, clinical ideas, drugs to be tested, to define very clearly the relationships with the pharmaceutical industry --

[SLIDE.]

DR. HOTH: -- to improve the information about the drug selection process, communication at all levels, both between investigators and the NIAID as well as between the clinical trials program and the general public and the patient population, to improve data collection in management, to increase AIDS program staffing and to establish an advisory committee to have an on-going oversight role.

[SLIDE.]

DR. HOTH: Well, the first thing we did then and that summarizes their overall recommendations, I am now going to describe to you how we have already begun to implement those recommendations. What I am going to describe to you is a process of an evolution of what had existed. Much of what we have heard in the last two days are concerns and criticisms that related to the program which is now in a considerable degree of evolution. I will now present to you our new directions.

Number one is we established four goals for the program. The first is that the overall and most important objective is to conduct clinical trials which ultimately yield timely information which guide physicians in selecting the most appropriate therapy and this is a key point.

Why do we clinical trials? We do clinical trials so that clinicians can know what is the best treatment to give to their patients in any particular situation. You must study asymptomatic patients, ARC patients, KS patients, patients with the opportunistic infections. We must have a clinical trials program capable of studying the total range of the HIV epidemic.

[SLIDE.]

DR. HOTH: Second is that it is likely and we heard Bill Haseltine allude to that yesterday that we will very soon have more things to test than there will be resources as measured in any of a number of ways. Patients, physicians, institutions or dollars, we must always assure that we are addressing the questions, the scientific questions, of the highest priority. A mechanisms has been established to do so which I will describe later.

[SLIDE.]

DR. HOTH: Thirdly and very importantly is the goal of developing new agents from pre-clinical studies to final FDA approval. I want to make the point that this is not the entire effort. This program is more than a drug testing program. Its objective is to test AIDS therapies, whether they be single drugs, combinations of drugs or therapies that might not involve drugs; for instance, radiotherapy in AIDS-related malignancies and bone marrow transplants. It is a broader objective than drug development.

Nevertheless, drug development is important and hence, we believe that it is important for there to be the opportunity to conduct new drug application or product license application trials; that is, those studies which result in FDA approval for marketing of a drug not only because it is commercially important but because it is medically important that such approvals be made since they result in the greater availability of AIDS drugs.

Therefore, one of our policies is to foster and encourage such trials to be done wherever we can. Finally, we feel that the clinical trials program should be regarded as a national resource for drug development to the drug industry and I will have more to say about that in a moment.

[SLIDE.]

DR. HOTH: Finally, the fourth goal is that it is not enough to do research. You must transfer that research, the results, the fruits of that research from the research setting to the routine patient care setting and the most important method of doing that is the involvement of community providers in clinical research.

We believe it is important to do so because community providers, particularly in this disease, that is, providers outside of the major medical centers are very interested, often very knowledgeable about the latest state of the art, the latest research and we also believe it will help them improve their use of the treatments and finally they may contribute ideas which may be creative and may add to the overall effort.

We believe it is important to communicate about advances in treatment and also the approval of an NDA and treatment IND is another way to do technology transfer.

[SLIDE.]

DR. HOTH: Now let me make a comment about the involvement of community providers. We believe that this is so important that we have a separate initiative that we are going to be publishing very soon encouraging organizations such as the CRI to apply for funds which will directly support clinical research sponsored by them.

We intend to call a meeting within the next two months of community providers to help us plan that program. We have already had a number of informal meetings. Our staff has been up here to New York and talked to several of the groups here. We also think it is important to study care in the real world as it occurs outside of major medical centers.

[SLIDE.]

DR. HOTH: Now given these goals, what then are the requirements for a clinical trials program to accomplish these goals? Number one is that it must be able to conduct studies looking at the total spectrum of problems presented by the disease from Phase I to Phase III multidisciplinary, not only anti-HIV. We have heard much concern that the emphasis is too much on that.

We have a separate effort in opportunistic infections, biologic response modifiers, anti-cancer drugs, pediatrics and other areas as you will see demonstrated in a few moments.

Secondly, the involvement of as many as possible of the brightest clinical investigators, not only in the development of individual clinical trials but in the development of overall research priorities.

We think it is important to increase the notion of investigator initiated research and that is one of the major new directions of our program.

[SLIDE.]

DR. HOTH: The final slide on requirements is that protocol development must be rapid so that the studies can be completed in as timely a way as possible since we all know that there is a window of opportunity during which questions can be asked and answered.

Flexibility is very important. The program must be more flexible to new ideas, to a wider range of drugs to be able to shift priorities should more important ideas come along and to have room for innovation and creativity while at the same time doing the studies at the highest level of conduct.

[SLIDE.]

DR. HOTH: Now we believe and our advisory panel recommended that the embodiment and the method of accomplishing that goal is a cooperative clinical trials group which by definition is a standing organization which can continuously develop and carry out the highest priority multi-disciplinary trials.

[SLIDE.]

DR. HOTH: Now what is this cooperative group? It has three major components. The AIDS program at the Institute is coordinating a clinical trials coordinating center which is data management and the heart of it is the member institutions, what were formerly called the ATEUs and the CSGs and we have coined a new term, these are AIDS Clinical Trial Units so ACTUs refers to the totality of the 35 institutions now funded to do this work and the total effort is now referred to as the AIDS Clinical Trial Group.

[SLIDE.]

DR. HOTH: Here is a geographic representation showing where these 35 centers are and I believe that listing in the material available to you.

[SLIDE.]

DR. HOTH: Now what is a cooperative group? How does it work? Well, it really is very simple. It is not really very complicated. It consists of the leading investigators in each of these specialties in AIDS research working together in a collaborative effort.

The actual science occurs in these committees. Primary infection, these are where the anti-HIV studies originated, OIs, oncology, pediatrics, BRMs as we have discussed and the very important pharmacology studies. This is the primary research, resources for virology, immunology, nursing and patient care and data management that relate to all of these research efforts.

It is coordinated by an executive committee. Now I will explain a little bit more about how this notion works.

[SLIDE.]

DR. HOTH: What you have is a spectrum of studies ranging from Phase I to Phase III. Phase I trials are pilot studies of new ideas. They should be innovative, usually have small accrual requirements using a few institutions, small studies. These drugs or ideas have potential for further development, a low level of committee or bureaucratic scrutiny but are usually fairly data intensive.

Only a few of these ideas wind up in Phase III as, in fact, Dr. Young's slide showed you. Much is tried but only a little bit makes it to these final evaluations. Phase I asks the question, "is a drug safe?". Phase II asks the question, "is it effective?" and Phase III asks the question, "fine, it is safe and effective, but is it any better?" and that is, it is a comparative question and implies that you need large numbers of patients, a randomized study.

Many institutions are involved. There are usually simpler questions. A high level of consensus is required and it is very demanding of system resources.

[SLIDE.]

DR. HOTH: Now that is the overview of what we expect the way the group process will work. The advantages are that it will provide a standing mechanism to serve as a national resource capable of evaluating many therapies, fosters collaboration between investigators and not only with investigators but also

with the pharmaceutical industry. I will have more to say about that.

Investigator-initiated trials are now the emphasis in the process. It should set standards for all of these trials to avoid duplication but yet to assure that no stone is left unturned.

[SLIDE.]

DR. HOTH: Now protocol development has received a great deal of attention. We have given a lot of thought to that and here is how we plan to deal with that.

[SLIDE.]

DR. HOTH: We wish to make it rapid, adaptable, high quality, multidisciplinary and well-coordinated and the way we have done that is to define a simplified process. So we have defined a protocol development process, we have simplified it. We have established a notion of a team that writes the protocol and develops the concept.

We have increased the staffing devoted to it by beginning the recruitment of full-time individuals whose entire duty is the development of protocols and improving the process by the early involvement of statisticians, the pharmaceutical firm and the Food and Drug Administration.

[SLIDE.]

DR. HOTH: Now this is an overview of how that process is envisioned. An idea usually originates from an investigator. The pharmaceutical industry may also provide ideas. This process is totally open to industry. An idea is submitted, the committee looks at it and sets an overall priority and says, "Yes, we think this is important. We wish to do the study."

The research committee again remember is composed of investigators from the AIDS Clinical Trial Group and then a protocol team actually writes the study and you get an active study in collaboration with the participating investigators. So that is the anatomy of an individual study.

[SLIDE.]

DR. HOTH: Let me make a comment about flexibility and innovation. We want to emphasize that we are increasingly flexible to move into new scientific areas quickly, to be responsive to new ideas and to increase the opportunity for diversity in Phase I and pilot studies.

The overall objective of this entire effort is to provide an umbrella or a framework, an architecture if you will, for a national system of clinical trials.

[SLIDE.]

DR. HOTH: Now let me talk about the interactions with the pharmaceutical industry. We believe this is very important and we have designated that or displayed that as so by our making it one of our four major goals.

This slide shows that our interest are in substantial overlap but not precisely congruent with that of the pharmaceutical industry. I would characterize industry's goal as to develop and test new drugs to their final FDA approval. The NIH's goal is the development of potential therapies for HIV infection.

Now that is, as I said, largely the same ut there are areas of unique interest to both parties and that defines, however, an area of consensus and collaboration and we think it is very important that we do so.

[SLIDE.]

DR. HOTH: Now the role of the cooperative group then, this AIDS Clinical Trial Group, in drug development is as I said to serve as a national resource, to conduct studies of investigational drugs which support FDA applications. We should, however, and intend to be extremely flexible about this while at the same time evolving a set of standard procedures so that the units do not have to utilize a different standard for each company which is very confusing to them.

So I think the important thing here is not that there is a straight jacket or a funnel through which all companies must pass. It is not that. There is no proscription from any company dealing with any ATEU or AIDS Clinical Trial Unit privately outside of this system. We view that as perfectly possible and we believe that in many cases that is the optimum way to go. If a company wishes to be involved, then we encourage their approaching the group and working with the group.

[SLIDE.]

DR. HOTH: Now let me just talk a little bit about an overview of AIDS drug development, a slide that you have seen a number of times just to emphasize there is a continuum from the discovery phase through pre-clinical development and through clinical trials just to show you where this fits in the overall picture.

The point that I wish to emphasize is that if you view this as the entire process of drug development, you could envision a line here for the NIH and a parallel line for the pharmaceutical industry and the NIH has all of these resources within it as do many of the major pharmaceutical firms.

The proper role for thee NIH in this is to be a facilitator so that drugs and we have heard the example of AZT, there are other examples, ddC as Dr. Gage mentioned where a drug may start here, come up here for a formulation or a toxicology, go back for clinical trials, perhaps we might be involved in discovery, industry will do this phase of development and then ask us to do some of the clinical trials.

I could point to make examples of that. It is a collaborative process recognizing that only a few of the major pharmaceutical firms have the total resources necessary to do all of the effort but we do believe that wherever companies do have such resources that we wish to accelerate their independent development or in collaboration with us in either case, either way.

[SLIDE.]

DR. HOTH: Now let me talk a moment about the drugs that are in trial. Just to give you a notion, these are the anti-HIV drugs that are actually in trial, single agent, these four in combination study --

[SLIDE.]

DR. HOTH: -- therapies for opportunistic infections, a number of drugs. We have heard much about the treatment IND for Trimetrexate which we are now running.

Just a comment, we have established within the program a unit to administer treatment INDs and we now have a full capability of expanding the treatment IND program and we have a number of other candidate drugs we are looking at for treatment INDs right now and in the anti-cancer area, also.

[SLIDE.]

DR. HOTH: Now the accomplishments to date are the establishment of a clinical trials capability with 35 funded institutions, 27 active protocols and 17 agents that are under study.

[SLIDE.]

DR. HOTH: This is a list of the drugs that are near clinical trial, anti-HIV drugs, immunomodulator drugs and

opportunistic drugs. We have approximately 75 protocols that are in some stage of development either as concept sheets or actually in far advanced draft. So there is a great deal happening.

[SLIDE.]

DR. HOTH: Now to summarize, what do we need to achieve national needs to identify effective AIDS therapies and to identify which therapy a physician should use? We need rapid protocol development, rapid accrual, flexibility to move into new scientific areas as quickly as possible, always keeping our eye on answering the most important question.

The way we accomplish this is by bringing the investigators together in a group. We held the first meeting of this group in December of this year. There were 300 clinical investigators from all over the country. There were representatives of approximately 20 pharmaceutical firms at that meeting.

The next meeting will be in late March and we intend to hold quarterly meetings so we have provided a forum which essentially is open to the pharmaceutical industry and open to the clinical investigators to develop clinical ideas and clinical research to find these answers.

[SLIDE.]

DR. HOTH: Future directions of the program, we have established goals, established a cooperative group. We are increasing the opportunity for innovation. We are accelerating protocol development.

There are improvements that are needed in the functioning of the Clinical Trials Coordinating Center including data collection and management. We are converting the funding instrument from a contract to a cooperative agreement.

The relations with the pharmaceutical industry, let me pause on that for just a moment, we believe that this is so important that we intend to call a meeting in the very near future, I believe it should be within the next eight weeks, of representatives from the pharmaceutical industry in order to discuss and formalize these avenues of collaboration, to improve the drug selection process, to improve our communications about what is happening and very importantly, program staffing. We are operating on a very short staff at the current time.

Well, that summarizes my prepared presentation. I will be happy to answer any questions.

DR. LILLY: Thank you, Dr. Hoth. Ms. Pullen, would you like to start the questioning.

MS. PULLEN: To what degree is there access for experimental therapies and what are the strategies for increasing their access for children, women, hemophiliacs and people who live in states or cities which do not have groups located in them?

DR. HOTH: Okay. I will try to remember your categories. Pediatrics, we are establishing a pediatric initiative. We issued two weeks ago what we call a RFP, a Request For Proposal, to establish a Pediatric AIDS group to work within the overall committee. There are two protocols which are about to be initiated in collaboration with the Burroughs Wellcome Corporation and we will be participating in a meeting of pediatricians in late March, the Department actually is calling a meeting to develop a national agenda for pediatric research.

Hemophiliacs, we are about to initiate a clinical trial with the National Hemophilia Foundation to look at the efficacy of AZT in that population and that project is going to be budgeted at about two million dollars, a little over, I will get you the exact number, to accomplish that study.

Women, I believe was your next category. There has been a lot of concern expressed to us about the access of women, the eligibility of women to these clinical trials. What I can tell you is that the only protocol whichever excluded women was protocol one which was for Kaposi's sarcoma which is very rare in women and that protocol is closed now.

All of the other protocols permit women into the trial and, in fact, the only exclusion is an exclusion which is intended to protect the fetus. That is, there is a standard clause which exists not only in HIV research but all therapeutic research asking that a woman not be pregnant, have a negative pregnancy test and be willing to use barrier contraception which is again for the protection of the fetus.

The other thing I want to point out is that we have analyzed the percentage of women in our trials and the percentage of women in the ATEU trials is the same percentage, approximately the same percentage, as there are women with AIDS. It is in the seven to eight percent range.

You asked about access to clinical trials in areas that don't have AIDS treatment units, was that the thrust of the question?

MS. PULLEN: Yes.

DR. HOTH: That would require an expansion of an additional funding and at the current time we do not have any additional funding to expand the program.

MS. PULLEN: On your map, I saw no indication that there were any such groups located in the State of Illinois which has a fair concentration --

DR. HOTH: There is a unit in Chicago.

MS. PULLEN: I am glad to hear that. Can it be accessed by other people in Illinois or just people who live in the city limits?

DR. HOTH: No. I think any patient may go to that unit.

MS. PULLEN: Thank you.

DR. LILLY: Dr. Walsh.

DR. WALSH: You heard Dr. Hoth, of course, the expressions of concern by the previous concern about the ATEUs. Would you want to comment on that for us?

DR. HOTH: I think that the process of clinical research is extraordinarily complicated. That group, the pharmaceutical industry, is expert. They certainly understand how complex it is. It is sometimes hard for those of us in the clinical research field to adequately communicate that complexity to others.

The NIAID Clinical Trials program started from scratch about 18 months ago. I believe a lot has been accomplished. However, criticism is justified. For instance, you heard the recommendations of our advisory panel who said there are improvements that are needed. We believe that we are putting in place the improvements that are required.

We believe that a lot of it has already occurred and, in fact, the main point I want to leave you with is that we started that process in December and so an awful lot of change has occurred. A great deal of what we need to do is to adequately communicate what we are doing.

DR. WALSH: Is there any likelihood or concern that you may extend this type of operation outside of the AIDS category, in other words, to other areas of drug testing? I would think that if I were in the business I would be concerned about very frankly because you have developed a prototype here which if it works, but I am just curious as to what your thinking is.

DR. HOTH: The prototype exists already. The National Cancer Institute has had in place for more than two decades a clinical trials effort which is vastly in excess of this but we have no plans to expand it. Our goal is HIV research.

DR. WALSH: All right. Thank you.

DR. LILLY: Mr. Creedon.

MR. CREEDON: I wasn't sure what Bill's question was, the beginning part of your question.

DR. WALSH: The beginning part of my second question, you mean?

MR. CREEDON: No, your first one.

DR. WALSH: I asked Dr. Hoth to comment on the expressions of concern of the previous panel.

MR. CREEDON: The immediately preceding panel?

DR. WALSH: Yes, the immediately preceding panel on the ATEU set-up.

MR. CREEDON: Dr. Hoth, have you been here the last two days?

DR. HOTH: Yes.

MR. CREEDON: Good.

DR. HOTH: I have been firmly planted in the audience!

MR. CREEDON: As you know, we did have some testimony this morning particularly from Dr. Gingell and Mr. Lipner and Mr. Callen which seemed to indicate that some of the people with AIDS have had difficulty in getting access to the clinical trials or getting access to the kind of medicine that they feel that they need.

I wonder how you would respond to their comments and specifically whether you think there are now things being done to address those comments.

DR. HOTH: Well, one of the major initiatives that we are undertaking and it is partly for that reason is the community provider initiative so that we have set aside approximately five million dollars at the current time and we will see how far that goes for the funding of folks who want to be involved in the community in the clinical research project process so we are expanding it.

MR. CREEDON: How quickly will that happen?

DR. HOTH: It will probably take six or eight months in order to get those awards out. That is the competitive process. May I just expand on my answer, however? I think we must distinguish, some have said that, between and I think what we heard this morning was the very important desire of people to have access to experimental drugs which is not necessarily the same as to wish to be in a clinical trial.

MR. CREEDON: I thought they said both really.

DR. HOTH: Yes, that is true. What I want to point out is, however, that a well done clinical trial such as the one with the placebo trial of AZT of 282 patients produced results which helped thousands of patients.

So I think the point of good research is not the size of it but how quickly it gets an answer so that it may be generalized to a large population.

MR. CREEDON: Well, I wasn't being critical really but I was asking to what extent do you think that you are directly responding to some of the questions that people had this morning.

DR. HOTH: Right. Well, the other thing that we have done is to establish a treatment IND unit within the AIDS Program which will address the concern about access to experimental drugs. However, I don't believe that we will ever completely answer their concerns as long as the regulations require both safety and efficacy be shown prior to a treatment IND, and few drugs have shown efficacy.

MR. CREEDON: Thank you.

DR. LILLY: Dr. SerVaas.

DR. SERVAAS: No questions.

DR. LILLY: Dr. Lee.

DR. LEE: That as a very "un-NIHy" presentation.

[Laughter.]

It is very refreshing that you are reaching out into the real world. You are talking to the community doctors. You say you are trying to involve, and I know you are, the people who addressed us this morning, and I think you are doing a terrific job.

For the sake of those in the audience who don't know Dr. Armstrong, I work with him and have known him for 25 years. He is a true "worker in the field." He is dealing with patients with AIDS, with massive numbers of them. He is very highly respected across the country and I have a few questions here that I would like to have you go back and forth on from the point of view of the physician administrator at the Center, to the physician out in the field.

First to give us an idea about some of the problems that you are facing from both sides of the coin. What is the hold-up on these two drugs: the first is Ampligen and the second would be aerosolized Pentamidine? Where are those things stuck in the system, and why?

DR. HOTH: You are asking both of us?

DR. LEE: I am asking both of you, yes, if you have anything that would illuminate.

DR. HOTH: With respect to aerosolized Pentamidine, there are approximately six protocols that are in development. The process is complex because there are two pharmaceutical firms which are competing with each other.

There are different sets of investigators who do not see eye-to-eye and what we believe is that the establishment of this cooperative group process which started in December has provided a means to resolve that and we see those protocols as accelerating the development.

I do not sit here, however, and defend the overall time it has taken to get those protocols going because I believe we should have done that much earlier but the process is going now.

DR. LEE: How about Ampligen?

DR. HOTH: Ampligen was a very difficult story. You are going to hear a full hour on this, I believe, after. Just to comment from our standpoint and that is that the interactions were very complex and not moving very well until the duPont Corporation became involved in November and it has been our perception that following that, things have moved much more quickly.

There was initially a request for us to provide what ultimately would amount to between $500,000.00 and a million dollars to the Corporation for that for the drug for one trial and that caused a great deal of concern for us.

What I can tell you though is the first trial of Ampligen in this system is beginning next week at Johns Hopkins or is beginning very soon, in the IND has been granted, that is Ampligen that they have developed.

We have signed an agreement last week with DuPont so we have concluded agreement and we expect that within the next week or so the drug should actually be arriving or so I am told. I guess they will tell you.

DR. LEE: Do I understand that the Ampligen people were demanding money from you?

DR. HOTH: They wished us to buy the drug, yes.

DR. LEE: How does that fit into the normal scheme of things? Has that happened?

DR. HOTH: Well, it is relatively unusual. I must say that I have only been in this job about three months so I am not sure I know all the details prior to my arrival but I am not aware of any other drug that we have bought.

I am not saying it is always unreasonable for us to help a small firm but we thought the amount of money being requested was very high. That would amount to, if that dose was extrapolated to an annualized basis, a cost to patients that would have been several times the annual cost of AZT. So it seemed to us to be an extremely high cost.

Now we understand that the cost of production is high but it is not that high.

DR. LEE: Very illuminating. Now the next question is you are going to be collaborating with the pharmaceutical industry --

DR. HOTH: I would say are collaborating.

DR. LEE: You want to.

DR. HOTH: We want to increase it. We have daily dealings with literally dozens of companies. I think what we heard from the previous panel is the importance of us sitting down with them and articulating a policy which makes it clear what our intent is. They must perceive the government to be a stable partner, a reliable partner and that may not have always been the case.

DR. LEE: One question that we had when we were working this thing up was, what is the status of working up some sort of software computer program that could interconnect with the

pharmaceutical industry and you so that a lot of this paperwork could just go a lot faster.

DR. HOTH: I think everyone recognizes the need for an information exchange. I don't know whether the details of whether that should be a computer medium or exactly how that should work can be addressed here but we think that it is important. I think you discussed that with Dr. Young previously and we would like to establish such a thing.

I am actually hiring, attempting to hire, an individual right now. We have somewhat of an FTE problem but we are trying to hire a person right now to actually do that, to have a national surveillance of what is going on in drug development.

DR. LEE: Do you anticipate cooperation with the pharmaceutical industry overall. or to a degree?

DR. HOTH: No. My assessment is actually that overall in general there is a dramatic improvement in the interactions with the pharmaceutical industry. I think that many of them have not yet been made fully aware of some of the evolution that has occurred in the last eight weeks or so.

DR. LEE: Now the last question -- maybe you could make a mental note and give it to us in writing if you know the numbers because this is the type of thing we would be terribly keen about for this report that is going out early next week -- what increases in your full time equivalent positions would you like so that you could get these programs underway and what actual staff and money requirements do you have, if you have some numbers to put this excellent program into effect?

DR. HOTH: Well, I will give you a very brief synopsis. I think there are two things I would like to say about that. The current staffing, authorized staffing, for AIDS program responsible for epidemiology, molecular biology, vaccine development, pre-clinical drug development and clinical trials is 47. I need, our staffing plan is approximately 120. That is an interim staffing plan. That would take us through the next year but we are currently authorized to 47. So we are far short of that.

DR. LEE: You need 120.

DR. HOTH: Yes, 120. Moreover, I would like to state that is what you, the Commission, as well as the public should do is look to us as program managers and say, "Hold us accountable for getting results." On the other hand, do not tie our hands with process. By this I mean specifically things such as the complexities and procedures of hiring, some of the

complexities in the budgeting process, some of the complexities in FTEs.

For example, I only have two physicians in the treatment branch right now. It is hard to recruit them because their office is four miles from the hospital where we would like them to be working. That would be my most important recommendation.

DR. LEE: I wish we could promise you less bureaucracy. I don't know that we are going to be able to do that but we sure would like to. Thank you very much.

DR. LILLY: Mr. Creedon has another question.

MR. CREEDON: Well, this question, excuse me, is really triggered by Dr. Lee's question about Ampligen. We have had testimony that there are quite a few different kinds of drugs or treatments that some people with AIDS are experimenting with, in some instances getting the drugs from France or Mexico or someplace else.

I wonder if we were able to get either the GMHC or someone to supply us with a list of those drugs, whether we could present them to you and get a reaction as to where we stand, where the government stands with respect to those.

DR. HOTH: We would be delighted to. The American Foundation for AIDS Research, with our support, does publish a directory that has much of that in it but if you would like the rationale and evaluation of a list provided by anyone, we would be happy to do so.

MR. CREEDON: I think that would be helpful and especially, I guess, a lot of it depends on this credible evidence of efficacy.

DR. HOTH: There is a committee of scientists, The AIDS Clinical Drug Development Committee, which reviews this evidence which is not just government scientists. Dr. Armstrong, for example, serves on that committee which has reviewed dozens and dozens of compounds and we can submit the records of that committee for your records.

MR. CREEDON: Mr. Chairman, I think that that would be helpful to us if you could arrange that.

DR. LILLY: I have several questions. First of all, this is a technicality that I would like to clear up, in recent discussions with the principal investigator of an ATEU I was told that very recently after the NIH had encouraged them to expand their studies beyond those planned with the very strong

implication that there would be money to support those studies beyond those budgeted for that would come forth later, that they, in fact, got only what they had originally planned once they had already beefed up their operations a great deal. Is this true?

DR. HOTH: The answer to that is that we had budgeted this year a 30-percent increase in the budget for the units and we asked the units for a budget and they came in with a request that was virtually double their current budget so it was much greater than a 30-percent increase.

They perceived the 30-percent increase as a cut from expectations. We are very concerned about that. In fact, this week as we are meeting we have invited the principal investigators from each of the centers to come to Washington to meet with us so that we may develop a realistic understanding of what the cost of conducting AIDS clinical research is.

Dr. Armstrong alluded to that in that we have a suspicion that the cost on a per patient basis may be higher than other areas of therapeutic research. If we discover it is so, we will come forward with that information.

DR. LILLY: The ATEU system costs an awful lot of money and I am just wondering if this is perhaps money that might otherwise have had to have been spent by the pharmaceutical industry. To what extent are you, in fact, relieving the pharmaceutical industry of developmental costs in drugs and should that be reflected in the costs of the drugs once they are released to the public?

DR. HOTH: I think that we are relieving them to some extent but I think it should be emphasized, remember the two circles did not precisely overlap. We are doing some studies that they might not, in fact, do. They need to do some studies that we might not do. So we are not relieving them of the entire burden.

DR. LILLY: But you are relieving them of part of it.

DR. HOTH: I think that does exist to some extent.

DR. LILLY: Given the quite large emphasis up to the present at least on AZT, that should perhaps be reflected in the cost of AZT ultimately.

DR. HOTH: Let me just point out that Burroughs Wellcome provides to the system, last year I understand they provided free drug to the tune of one metric ton of drug. So while we did provide the funding to the units for that study, it is not as though they got a totally free ride on that either.

DR. LILLY: All right. Another question, there are, of course, a lot of people with AIDS, vastly more people who are infected with HIV, does the work that you are doing in the ATEU system in some sense use up the populations that the drug companies might need for their own studies, for example?

DR. HOTH: I think that the important emphasis there is on our notion of flexibility, that this system should be viewed as we are evolving it so that a drug company can come in and do a Phase III trial or an NDA trial in the system if they wish because we are very sensitive to that. This is a precise national resource.

We all need this resource. It must work. It must work well. It must have access to everyone who needs it and we are not going to put some bureaucratic limitation on it that only if it is some special procedure that there can be access.

So I think we are fully cognizant of how important this is. Clearly there are many researchers and AIDS patients who are not part of this system so there is opportunity. A number of the companies have put together major trials well outside of it but we still view this as a national resource.

DR. LILLY: One more question, I am just wondering to what extent your system as a whole is using the drug user population as subjects.

DR. HOTH: I think that is an excellent question, Dr. Lilly. I believe that while we have some of our units that are in areas where the drug user population exists, that is an area we need to improve on. In fact, I intend to add that to my list of program future directions. We have to put some attention to increasing our efforts in that area.

DR. LILLY: Let me see if I can find any others. One more question, do you have PWAs in your advisory groups?

DR. HOTH: Not that I am aware of.

DR. LILLY: Don't you think that would be a rather good idea.

DR. HOTH: I intend to form an advisory committee. Dr. Fauci and I have discussed the formation of a program advisory committee in which we will invite a representative from the infected population.

DR. LILLY: I think that would be an excellent idea.

DR. LEE: Dr. Armstrong, you do get advice from the PWA community, don't you?

DR. ARMSTRONG: Yes.

DR. LEE: You have a lot of input from the GMHC and so forth?

DR. ARMSTRONG: Correct. I think that the ATEUs do also. I know that Dan has met with them, with various organizations on a number of occasions.

DR. HOTH: If I could just emphasize, actually, Dr. Gingell himself was at the December meeting and he was invited to attend all of the meetings so, in fact, there has been input.

DR. LILLY: I think that is very good. I simply think that it is not a bad idea under the circumstances to have a PWA as a formal member of at least some advisory groups.

DR. HOTH: Yes, we agree.

DR. LILLY: Admiral Watkins.

CHAIRMAN WATKINS: Dr. Hoth, just one quick question. I notice in the Presidential budget submission yesterday under NIAID's budget line, a ramp up from the 1988 figure which is an estimate figure still but it is $100 million dollars over the 1988 figure in 1989.

DR. HOTH: Yes.

CHAIRMAN WATKINS: Was that your recommended number? Does that solve your funding objectives that were submitted to you throughout your various departments?

DR. HOTH: If you are referring to the matter that Dr. Lilly brought up, namely, the funding request from the AIDS Clinical Units themselves, that matter has just come to light in the last few weeks and as you know the federal budget process started approximately a year ago before the numbers that were let out yesterday. So that number does not reflect any new requirements that might arise from the units.

CHAIRMAN WATKINS: But is this $100 million dollar increment over the 1988 figure, is that something that you have already allocated?

DR. HOTH: Yes. We have budget plans for the Fiscal Year 1989, for those figures, yes.

CHAIRMAN WATKINS: But was that your requested figure at the time the budget data had to be in or is that below what you had requested?

DR. HOTH: Since I am new to the program, those numbers were submitted months and months ago, I believe that is our request but I will get you a formal answer on the record for that.

CHAIRMAN WATKINS: You talked briefly about the personnel resources you needed and the concerns you have about being able to handle the trials coming up in the future, the larger number that you are projecting. Is it just FTEs? Is it recruiting problems? Is it training slots as well to prepare, to train them to do the monitoring that is required or all of the above and is all of that part of your budget submittal within that $100 million or are we talking about another increment above that in order to do that kind of thing properly?

DR. HOTH: Well, the solution to the staffing problems is for the most part not a budget issue since at least at NIH the personnel costs are a relatively small fraction of the total budget. The impediments on that are the FTE ceiling, the physical location of the staff. We need to get them on campus.

Most of the extramural programs at NIH are put off campus and there is a severe need to have a building on campus where the physicians can work on these types of programs and then go across the street and see AIDS patients. They will do a better job at that program. I have a hard time recruiting because of that. Dr. Young experiences similar things.

I believe the notion of establishing a training program where people could work in the laboratory, work in the clinic and then move into these jobs which are more at a policy or overall development level would be an excellent program.

CHAIRMAN WATKINS: Do the FTEs give you the training slots in addition or as a part of the FTE number? It is my understanding that would mostly come out of the total manpower?

DR. HOTH: That is correct. You are absolutely correct. We would need additional slots.

CHAIRMAN WATKINS: I noticed when we talked to Dr. Young about this he has the same problem, that throwing FTEs at the problem only throws an important portion of the human resources you need but it certainly does not cover it all and now we are beginning to rob Peter to pay Paul again out of other kinds of manpower that you need in order to handle the training portion and the planning of that training.

DR. HOTH: To broaden the concept, the training is not only needed for NIH staff but to train researchers in AIDS in general. We do need an increase in that program, yes.

CHAIRMAN WATKINS: Is that part of the increment that you talked about earlier? Is it part of the basic budget that goes to the $100 million?

DR. HOTH: I don't believe so.

CHAIRMAN WATKINS: Would you give us in writing a little better picture of this aspect of the budget.

DR. HOTH: Yes, I think we should supply something.

CHAIRMAN WATKINS: What you requested, what your people are now saying they need as an increment, what those FTEs are and the other ancillary training slots and other concerns you have to pull the staff resources necessary and then let us know because at some point, not in the Interim Report, but downstream we are going to be looking at facilities across the board and there isn't one group that has come before us that doesn't say the facilities are a shambles in terms of adequacy for future growth, they are busting at the seams now, no long range plans, disallowed funding for that kind of thing and at some point we are going to have to start paying the piper on that and the question is, how do we add your needs into all the other needs for facilities at the right time and with the right kind of ramp function that can get there realistically.

So at some point we are going to need that from you as well. I don't know what it means to get your people on campus. There are a lot of people trying to get on the NIH campus including FDA in a much bigger way than they are today. So can it absorb it all or will it sink into the Potomac?

DR. HOTH: Well, we think it is reasonable for the NIH staff to be located on the NIH campus.

CHAIRMAN WATKINS: All right. Thank you.

DR. LILLY: Thank you, gentlemen. That concludes this portion and mirabile dictu, we are slightly ahead of schedule so I would like to declare a three-minute recess while we are setting up for the next group.

[Whereupon, a short recess was held.]

Developing a Drug:
Ampligen: A Case Study

DR. LILLY: I would like to call the meeting back to order, please. The next panel is a special one in the context of the kinds of things we have done today. We will have three speakers who are going to be presenting a case study concerning the development of Ampligen. We are going to follow it through. Our first speaker is Dr. William Carter who is Chairman of HEM Research.

DR. CARTER: Thank you very much, Dr. Lilly. I am a co-discoverer of Ampligen and have been one of the principal catalysts in the development of this product over the last several years.

I would like to briefly describe the environment in which Ampligen was discovered and nurtured and then introduce Dr. Mollica who is to my left and who is the Director of Pharmaceutical Research at DuPont and he will describe the present efforts at large scale manufacturing and the extent of our nationwide clinical evaluation program.

Then Dr. Lenox who is a principal investigator at one of our key hospital participating sites will overview some of the many tedious and necessary tasks which are required to implement a definitive study of a promising agent, anti-HIV agent at the clinical level.

Ampligen Was discovered by Dr. Paul Ts'o and myself in the 1970's at John Hopkins University. The conceptual background for this was that we were searching for a component which was common potentially to many human virus particles which would be capable of stimulating both the body's immunological defenses and also the antiviral mechanism at the single cell level.

Earlier work at Merck had suggested that double-stranded RNAs had a potentially broad range of therapeutic activity but the products being developed at Merck turned out to have unacceptable toxicity and very low therapeutic ratios.

Accordingly, the field was basically stagnated and there was no clinical progress at that time. I should say that the primary initial target of double-stranded RNA was untreatable human cancer, particularly the solid tumors.

As some of you may know, double-helical RNAs are somewhat exotic structures but they actually look like two-winding staircases which intertwine at a given frequency and I know you all are familiar with the shape of double-helical DNA and actually Ampligen is rather similar in this helicity that the compound has.

This by the way turns out to be a difficult compound to synthesize and Dr. Mollica will speak more about that as our discussion progresses. We have felt from the beginning that a molecule which was both antiviral and immune modulatory was worth the effort even though the synthesis might be quite difficult.

The essence of the discovery which we made was that we could produce little molecular out-pouchings or what we call mismatches on this staircase and this resulted in a dramatically different biological effect.

What we had done was to create a very fragile molecule which was able to trigger a variety of biochemical responses which were associated with the first line of immune as well as a first line of antiviral defense but then unlike the earlier Merck compounds our product underwent rapid biodegradation and it lacked and continues to lack any significant toxicity.

Ampligen really is a type of artificial virus and as I said we initially developed it primarily for the treatment of human cancers and really only less than 24 months ago did we recognize that it might have and indeed does have an anti-HIV activity.

I should point out that our early work in cancer was supported primarily by the NIH. HEM Research is a small business and we are especially indebted to the National Cancer Institute, Dr. Vince DeVita and his colleagues in the Division of Cancer Diagnosis and Biology. They have been consistently long term believers and supporters of the scientific merit of Ampligen.

Just to give you an example of their support over the years, they have provided several million dollars on an ongoing basis for the production of Ampligen for kidney cancer. Those of you that are oncologists will know that kidney cancer in America only affects 20,000 Americans but those 20,000 people are obviously very important to all of us as physicians.

Dr. Hoth, the previous speaker, misspoke when he stated that quote, "the projected cost of Ampligen is several times that of AZT on an annual basis," unquote, since the cost even at our present very minuscule production levels is really quite equal to that of AZT.

We were, in fact, shocked to say the least that the NIAID did not find it worthy of further consideration when as a small business we requested support at the manufacturing level for this product. We had no intention to make profit. We were simply trying to produce high clinical grade Ampligen to continue the work which had been supported by the National Cancer Institute over the years.

Ampligen was not an overnight eureka. It was indeed a logical discovery after years of laboratory research. We had very concrete objectives. In the late 1970's and early 1980's, we began to cautiously expand the therapeutic potential of Ampligen by laboratory studies which suggested that many human viruses might also be susceptible to its unique immune enhancing and antiviral mechanisms.

I think the broad spectrum antiviral feature of Ampligen may prove especially important in people with HIV infection since it is well established that many other viruses are often isolated in these individuals, particularly as their immune statuses undergo further deterioration over time and Ampligen may be the first opportunity therefore to have a powerful probe of the potential role that other viruses have in what we now interpret as HIV-induced disease progression.

The development program of Ampligen is a model one in that the concept was initially developed in an academic environment. Hahnemann University in Philadelphia, working with the company, was central to strengthening the Ampligen's scientific underpinnings between 1980 and 1986.

I share with you here a hardbound copy of the scientific productivity for one 14 to 18-month interval. These are copies of all the scientific articles written in peer reviewed press in a period of approximately 14 to 18 months.

By 1986, however, it was very clear that we really needed a more entrepreneurial environment with the discovery of the anti-HIV activity and the realization that hundreds of individuals as opposed to dozens would require evaluation both before, during and after Ampligen treatment.

I should say at this time that the American Foundation for AIDS Research under the leadership of Dr. Krim who has always believed in biological therapy as a promising modality, double-stranded RNAs and Interferon, they were very instrumental in that they provided a critical seed grant which rapidly allowed us to bring the first ten patients onto therapy very quickly.

Those results were published in Lancet about eight months ago and to my knowledge, that was the first study in which independent quality assurance auditors were allowed to study all data, all original data, prior to publication. We opened up all the notebooks.

Independent laboratories were used and for those of you who have looked at this article, you will see there is a quality assurance report provided by a third party that the representations in the article agree with the raw clinical data as reported in different laboratories and in the clinic.

We are indebted to Abbott Laboratories which contributed diagnostic technology, Maryland Medical Laboratories cultured the virus and I am especially indebted to my outstanding clinical colleague, Dr. David Strayer, who is sitting immediately behind me who master minded the initial clinical study and continues to play a pivotal role in the study which is now ongoing and involves several hundred individuals with HIV infection.

Nonetheless the entrepreneurial environment needed more, we recognized that and apparently the NIAID also recognized it. This led us ultimately to the relationship with DuPont, a joint venture and the scope of this will be addressed by Dr. Mollica.

I should point out that DuPont was already greatly committed to AIDS research and had diagnostic products on the market and it was then and it appears now to have been an outstanding marriage. I know you will often hear stories that entrepreneurial spirit is not alive in large companies.

I can assure you that the intellectual freedom to publish, the entrepreneurial spirit which clearly has been alive and well in the Ampligen scientific program continues to be alive and well in this joint venture and I have come to believe that there can be very positive cooperative efforts when a large and small company work together particularly if they share common dreams about scientific excellence and the potential to be contributory to medical care and in some instances these relationships can actually be superior to those of a purely academic setting.

Now we believe, I think, first and foremost that the integrity of any scientific study especially in the HIV area which is understandably such an emotionally charged disease area cannot be short-cut.

The short-cut processes that we have tried to date and I believe have successfully avoided include short-cutting the process of rigorous peer review such as by going straight to the lay press with interesting new findings or by avoiding FDA sanctioned clinical studies.

There are ways, of course, to avoid FDA clinical studies in the United States, sanctioned studies. At the end of the day, it is our feeling that these short cuts only compromise the care that HIV-infected individuals will receive.

Accordingly, we always publish first our data in a recognized scientific journal and only after publication do we provide limited releases to the lay press which fully conform with both the spirit and the guidelines as set forth by the FDA.

The FDA states and the law is you do not promote a drug until it is approved by the agency.

Where possible, we try earnestly to present all data with a full biostatistical analysis so that the reader can evaluate for himself or herself the likelihood that the data will be reproducible over time.

Suffice it to say that we have found that our recent data which includes T4 cells, virus load, skin tests, et cetera, with some 18 months, that is a year and a half, of experience in HIV treatment agrees well with the interpretations that we reported in Lancet which was based on only one month or two month data.

Accordingly, we believe that no patients, no families and no physicians have been deliberately misled by any attempt to hype the promise of Ampligen. We now have over 2,000 patient study weeks and these data agree nicely with the pilot data because from the inception of our work we had quality assurance mechanisms which were in place at the laboratory and at the clinical level from the beginning of our work.

Quality assurance mechanism is a feature of the pharmaceutical industry. It is not historically a feature of the academic activities because the goals are different.

We are acutely aware of the special needs of the patient population and we are working towards treatment programs with Ampligen which will utilize community physicians. We are making every effort to provide treatment for AIDS and ARC in a non-hospital setting.

Indeed, one of the real promises of the preclinical work with Ampligen is the suggestion that it may evolve as what we term the "base biological" treatment and by that we mean it may increase the effectiveness of many other anti-AIDS drugs.

By allowing a reduction in the dosage of a potentially toxic though necessary therapy, Ampligen may be able to reduce dramatically the need for hospitalization with its devastating effect both on personal finances as well as morale.

I want to make a point about close ongoing scientific contact with the FDA and especially the Bureau of Biologics which has provided invaluable assistance in the accelerated development of Ampligen. Our own experience suggests a remarkable level of readiness on the part of the FDA to assist all manufacturers, whether small such as ourselves or large such as DuPont, in accelerating clinical programs.

We can find no basis whatsoever for the occasional bashing of the FDA on the grounds that the agency is quote, "proceeding too slowly" unquote, to follow up possibly important leads.

To the contrary, our concern is that pressure groups might cause certain administrative or scientific disruptions with the agency and in the name of progress very effective teams within the agency could give way to new cadres which would, of course, need to get up on new learning curves, explore new ways to collaborate with manufacturers, et cetera.

We fell very strongly that the agency is discharging its functions well and that the regulatory mechanisms in place will accelerate the work of all manufacturers in the anti-HIV arena.

I can assure you that I am very much involved in every aspect of the clinical and laboratory work. We are trying to rapidly and we are indeed expanding our clinical programs each month. At present we have over 300 males enrolled in our HIV-treatment programs and we intend to include females as an integral part of our future study plans.

Our goal in brief with the cooperation of the FDA is to compress a process which might normally require eight years to hopefully more like two years.

I want to say to you in closing that our staff at HEM Research have made dramatic commitments to Ampligen and they recognize the magnitude of the epidemic and the potential of the approach that we are developing.

Many of staff members work 60 to 100 hours a week and this has been the key to the progress of a small organization being able to make a contribution that may be significant. A believe that a similar commitment has been made by DuPont and I would like now to turn it over to my colleague, Dr. Mollica.

DR. LILLY: Dr. Mollica, I am afraid we are using up our time very rapidly and I hope you will be able to abridge somewhat your presentation, I am sorry.

DR. MOLLICA: Admiral Watkins, Dr. Lilly, members of the Commission, I am Joseph Mollica, Director of the Pharmaceuticals and Biotechnology Research and Development Division of the DuPont Company. I am here today representing the partnership between DuPont and HEM Research who will develop and commercialize Ampligen pending successful clinical trials and approval to market.

I do appreciate very much the opportunity to appear before this commission to discuss our efforts in developing a drug to help combat this most dread disease. Let me move on just very briefly.

I think in this century DuPont has become synonymous with polymer and fiber technology, having invented both nylon and teflon 50 years ago. In the past two decades, however, DuPont has increasingly turned its attention to health care.

For example, DuPont invented one of the very few effective antiviral drugs. DuPont is a major supplier of medical X-ray film and equipment, clinical laboratory diagnostic equipment and tests, as well as biomedical research products such as our new automated DNA sequencer. Our AIDS antibody tests have helped make the nation's blood supply safe.

At this time one year ago, HEM Research had fewer than a dozen employees, Dr. Carter himself being on the faculty of Hahnemann University and no products to sell. It was and is a privately held company. Its chief resources were Dr. Carter, himself, several co-workers and a product opportunity called Ampligen.

HEM Research was seeking a partnership; with a larger company who could provide the financial resources, people resources and business experience to help develop what their initial studies had told them was a potentially important drug to combat a devastating disease.

DuPont was one of the companies targeted because of our involvement with AIDS antibody testing, our manufacturing capability and our reputation as an ethical business concern. DuPont has been a major contributor to HIV research.

We have brought to market antibody tests to help assure the nation's blood supply as well as a confirmatory test, the Western Blot. In cooperation with scientists at NCI and Washington University, we were the first to sequence the AIDS genome.

In May of last year, less than four months after discussions were initiated, DuPont signed an agreement to take a small equity position in HEM Research which gave HEM much needed capital. Additionally, we agreed to negotiate a contract to help develop Ampligen and to begin the necessary toxicology studies regardless of whether an agreement could be reached.

Fortunately, our two companies did come to such an agreement in October of 1987. I should note that while negotiations were proceeding, DuPont began putting an organization in place anticipating this agreement. However,

confidential material on the composition and manufacturing of Ampligen was not available to us so we had to wait to pursue this avenue in depth.

Since we signed the agreement in October, a large multi-center double-blind, randomized, prospective trial in male patients with ARC has been accelerated. Today, the study is well under way at centers here in New York, Philadelphia, Washington, Atlanta, Houston and Miami.

The trial should be completed within one year. As the trial is blinded, we have instituted the appropriate statistical procedures for interim analyses while still maintaining the integrity of the trial. There is no charge to patients for the drug.

Later this year, as more drug becomes available, we will initiate additional studies to evaluate other regimens, patient populations, disease status, combination therapy and so on.

We are collaborating with the NIH to support study protocols developed for the AIDS clinical study groups and we are developing collaborative relationships with local organizations such as Community Research Initiative. O course, we are also continuing to treat the patients who enrolled in the pilot programs.

Meanwhile, manufacturing represents a considerable challenge and we currently have more than 75 chemists, molecular biologists, pharmacists and engineers working on this problem.

Manufacturing Ampligen is extremely difficult, involving converting three nucleotide monophosphates to the diphosphates, then converting them to single-stranded RNA's and then joining the two strands together. This process involves more than 17 separate steps.

The present drug source is only producing laboratory-scale quantities of less than ten kilograms of drug per year. Each patient on Ampligen requires twice weekly intravenous infusion, and current production would only provide dosage for a few hundred patients. As you can see, this alone limits our ability to more aggressively pursue clinical trials.

However, the current process is being increased to a maximum capacity to support about 5,000 patients, enough for trials, but not enough for commercialization. To meet anticipated needs for further trials and possible commercialization, we are proceeding as rapidly as possible along multiple paths.

Through our established contacts around the world, we have been calling upon other manufacturers competent to do individual segments of the production, still not efficient, but hopefully satisfactory until we can establish production of sufficient capacity.

Normally, designing, scaling up and testing a new process, building a plant capable of meeting anticipated demands would take about five years. We have set a goal to cut that in half. We believe we are moving ahead as rapidly as possible. Next to successful clinical trials, obtaining sufficient supply of product is our paramount concern.

In summary, DuPont this year alone is committed to spending tens of millions of dollars to develop Ampligen. We already have 100 people working on this project full-time and many more part-time. Our partners, HEM Research, are actively involved in conducting clinical trials.

Equally important, they continue to do research in the area of mismatched, double-stranded RNA in order to better understand the substance, its mechanism of action and its work in the body and I will conclude my comments there in the interest of time. Thank you.

DR. LILLY: Thank you, Dr. Mollica. The last speaker then is Dr. Lenox from New York Medical College at Valhalla.

DR. LENOX: Thank you, Dr. Lilly. I am Dr. Lenox, Assistant Professor of Medicine at New York Medical College at Valhalla, New York and an attending physician in Infectious Diseases at Metropolitan Hospital Center, one of the city operated hospitals in New York City. I have been asked to describe my experience in establishing and running the Ampligen trial at my hospital.

For the sake of time, you have or should have a copy of my presentation. I will try to summarize it as much as possible.

The biggest problem in Metropolitan Hospital in trying to do any type of research at all is going though the IRB's. We actually have three IRB's that must give approval for any protocol that gets underway. Because we are a major affiliate with a medical college, we have to first submit the protocols to the medical college, to the IRB for approval. From there, it comes to the research committee at the hospital for approval and finally it goes down to HHC headquarters downtown, for final approval. You can imagine how much time this may take on some occasions. On one other project it took us an actual six months just for everybody to agree on the consent form involved.

When I was approached to do the study, the IRB from the college had already been approved and I got underway the workings for Metropolitan Hospital and HHC. Within ten days I was able to actually get verbal approval from HHC and written approval from the hospital. This was a very, very short period of time and I think it is because people realize the importance of getting this study done very quickly.

However, verbal approval from HHC did not allow us to start enrolling clients. It took another month before we got written approval and before our first client could actually be enrolled.

During this process our second obstacle was to try to hire a staff to implement the protocol. Since we have not done much major research in the past we did not have the clinical staff available at that point and we had to hire them. So we hired two nurses, one of whom has the clinical and technical background who also has done extensive counselling at GMHC.

This counseling experience has been one of the most important and vital assets I think we have been able to get from our clinical staff so far. Most of our clients in this study are healthy working men and because of this, a lot of them have been able to minimize sometimes the fact that they actually are HIV infected.

Once they enter a trial like this, they are forced to remember at least twice a week when they come in for their infusions they indeed are HIV infected and that the possibility of deterioration of their own health has to be faced on a daily basis.

One of our clients experienced nightmares prior to his first infusion because of the uncertainty of what was going to happen once he started the infusions. Once he had started the infusions, these nightmares have ceased.

Other clients are extremely anxious and a calming force is important for them and also for us if we hope to keep them in the study for a total of nine months. The level of their anxiety is often heightened once they have entered the study.

Another major obstacle for us was finding space at a large inner-city hospital. People are vying for space all the time and we had to include our name in the list for space to implement this study. This, however, still has not been finalized and we are still trying to find the amount of space we actually need to implement the study.

Right now the study is being done primarily in my own office which not only now holds myself, two infectious disease fellows and our two nurses but also at this point now the clients that come in for the infusions and evaluations. This obviously is not the most ideal of situations and we are trying to remedy this as soon as possible.

There have been other types of hang-ups and problems that occur from day-to-day that the city bureaucracy has seemed to help along. We need telephone lines to be put in for a printer to receive the blood test results from Maryland Medical Laboratories and also for a fax machine to get the randomization results from DuPont.

It took us three weeks just to get administrative approval just to get the lines run into the offices. Once they were put in, no one decided to turn the lines on. We found this out a week later and when we had to go back and submit work orders to have these lines turned on we were told, "Fine, we will get to them soon" and as of this morning and it has been two weeks now, no one has turned the lines on.

We were informed on Tuesday morning that because of construction in the area of the hospital where we are located, the electricity will be turned off for approximately two weeks starting next week. So even though we may have the lines put in sometime soon for telephone wires, now we have no power to turn on the fax machine or the printer. This then will require us to telephone call Maryland Medical Laboratories or DuPont to get this information.

In order to do that, however, we have to get approval first through the Medicine Office for every phone call that we make including collect phone calls and this sometimes will take quite a while as well.

The next problem came with the recruitment of clients. My own patient population is primarily IVDA and therefore, we had to recruit entirely from outside our own population, the patient population.

I have written letters to all of the local infectious disease attendings in the area and used lists of resources published for PWA's and PWARC's and wrote to appropriate groups. Most of our referrals have come from private physicians. Several organizations have called us regarding the eligibility criteria and have promised to refer clients to us.

As of this morning we have taken a minimum of 120 phone calls and begun or completed active screening on 28 clients, eliminated 12 for reasons that do not fit the protocol and

actually have begun infusions for five clients with three more to begin next week.

The total number of calls is actually misleading because a lot of this time spent on these phone calls is spent in counselling clients on what they may or may not do, what the options are available to them.

Many calls request information or the clients are disqualified very quickly either because they don't fit the protocol criteria and these calls have not been counted. Clients have usually decided not to enter the protocol for mostly three reasons; first, an unwillingness to take a chance with the placebo trial, secondly, an unwillingness to stop PCP prophylaxis or antiviral or immunomodulating agents several of which are being used frequently in New York at this point or third, the rigorous demands of the study, that is, twice weekly infusions for nine months.

In conclusion, doing a research trial such as this in a setting such as mine is full of frustration and disappointment and it takes a lot of hours. My staff and I are encouraged at this early date by the very positive, appreciative response which we have received from our clients.

We feel that we must never lose sight of the number of lives already lost to this epidemic and use whatever resources available to get effective therapy to as many people as possible. We should never allow ourselves the complacency of designing trials because that is the way it has been done before.

We must continue to question whether it is still ethical to run placebo trials and when must we stop denying clients adjunctive therapy which may be beneficial to them. Must we define an endpoint as one in which the patient, the client, becomes seriously ill and accept the possible loss of lives as a necessity?

I would recommend the following points:

--One, counselling support which is something that is not frequently brought up, counselling support for the clients as well as the staff involved in these trials become a part of future research projects. Everybody involved needs emotional support to complete a long study such as this.

--Two, an up-to-date clearing house for dissemination of available trials with information regarding the protocol eligibility requirements. I am aware that some are available but people are telling me that sometimes these clearing houses will give old or incorrect information. I have recently have seen printed information about the Ampligen study which is

totally erroneous and actually very detrimental to our trying to enroll clients.

--Three, incentives to public institutions to encourage the development and implementation of research projects.

--Four, the involvement of private physicians to assist in the development and implementation of research projects such as the recent beginning of the CRI.

--Five, the inclusion of all persons at risk in future trials.

--Six, the redefinition of end points to eliminate the necessity of expecting serious illness or further loss of lives and one I have also added, number seven, a concerted effort to disseminate information to minority PWAs. We have had a difficult time at this point in reaching some minority PWAs and thus far, we have screened only four minority PWARC's and we have actually enrolled only one at this point and we are trying to reach more at this point. Thank you.

DR. LILLY: Thank you for your presentations. Dr. Lee, would you like to start the questioning?

DR. LEE: First of all, there are a couple of small points here. Is it correct that you do think that the cost of Ampligen is going to be approximately that of AZT?

DR. CARTER: What I stated was that the previous speaker had misspoke when he stated, quote, "the projected cost is several times that of AZT on an annual basis" unquote. We offered the product, keep in mind this is prior to the DuPont relationship, we offered the products to the NIAID at the same price that the National Cancer Institute had been paying for years.

Our books are open to federal auditors. Indeed, federal auditors have from time to time analyzed our records. I simply stated that even at our low present and crude manufacturing price, I found no basis whatsoever for that statement.

As far as the price for the future, that is a consideration that Dr. Mollica and his manufacturing team will uncover and he may wish to comment on that.

DR. MOLLICA: I think at this stage of development one really cannot comment on the price. If one looks back at the history of drug development, the first few milligrams of

penicillin or the first few milligrams of cortisone cost an astronomical amount of money.

I think what Dr. Carter has said is based on the price that existed at that time was how he set his price. Right now that is one of the challenges one has in any process is scaling up and coming up with an efficient, practical, commercially feasible product.

DR. LEE: We have another small point here. In New York, the PWAs are rather sophisticated. We have heard from many of them that when they are in trials such as yours they may be taking AZT on the side as well. Do you have any method of screening for that?

DR. CARTER: All of the patients sign a patient consent form, all the individuals who participate, I should say, in the Ampligen studies, be they pilot or what is termed in regulatory parlance the "pivotal" study meaning the several hundred patient study.

They execute a form in which they state that they understand that to take a product specifically such as AZT for which there is the statistical data that you have seen earlier today that that is a violation of this protocol. If they wish to take AZT, they are certainly allowed to do that but they can't participate in Ampligen work.

We do randomly test for the presence of AZT metabolites in blood and urine. Those individuals in which that is found will be eligible for expulsion from the study. It should be no secret that AZT causes other abnormalities in the blood count which our computers can rapidly pick up. This provides us a facile manner to identify those individuals who are not complying with what is the present regulatory requirement for a pivotal study in ARC, in AIDS Related Complex.

We also ask and we remind the patients, I should say, the individuals who participate in the study twice a week that they should not be taking other compounds which may interfere with the interpretation of the work and here again, twice a week they execute a form in which they represent to us that they are not doing so.

We are testing for other products which people may desire to take but for which there is no demonstrated efficacy in their disease. Obviously, if there were demonstrated efficacy, a clinical test would be conducted in a different manner but we cannot, there is no basis in scientific and ethical medicine to ask or require that people take medications which are not proven.

So I guess the answer to your question, Dr. Lee, is that we have major testing underway. We will also do, I should say, random testing and we hope that the participants in our work will recognize the importance of complying with the request once they enter the study.

I should also say as you probably know, Dr. Lee, the CDC in collaboration with the NIH have further defined the progression of the disease such that full blown AIDS can be diagnosed more rapidly than before with better parameters and what we have tried to do carefully working with our clinical investigators is to provide what we believe is the very best present safety net for anyone who might progress onto full blown AIDS.

First of all, rapid diagnosis of any possible disease progress; secondly, the patient, all patients, are given the opportunity if they desire to go on a very high dose of Ampligen, a substantially higher dose than is being done in the placebo controlled trial. Obviously, also, any individual is fully entitled if he or she -- he, since we only have males at the present time -- if he determines or his physician determines that he should be on AZT, he simply discontinues participation in the Ampligen study.

What I am trying to say here in a roundabout way, Dr. Lee, is that we are trying to provide the best medical care that we or anyone else knows about given that it is February 19, 1988 and at the same time as Dr. Mollica suggested, we are earnestly trying to conduct a study which is scientifically and medically unimpeachable.

We use, for example, only central laboratories, the first time in this country that central laboratories have been used in the execution of a major study. We use independent laboratories in Illinois and in Maryland. They have no vested interest in the outcome of the study. They don't even know the nature of the sample. We think that is the best way to build further clinical data on this particular product and hopefully a model for other products which will come along.

DR. LEE: I think you answered my question. I have one other series of concerns here as do other members of the Commission. This is an epidemic, a worldwide epidemic, and Burroughs Wellcome has taken a lot of heat from this Commission and from a lot of other people for possibly profiteering on AZT.

Now I know something about Ampligen. I think it is going to turn out and I think you know it is going to turn out to be rather a good drug. It may be one of the best things that we have on the horizon. It may be much better than AZT. It may be much better for an enormously larger group of patients.

This drug has been around since the 1970's. We have heard from the NIH that there has been a tremendous amount of backing and filling, and arguments, and hold-up on getting this drug into trials. We are interested in your side of that story.

We are also interested, I do not want to know here but I am sure that eventually this will be known, what you sold your interest in this drug to DuPont for. My understanding is that this was an extraordinary amount of money and this amount of money, DuPont is going to have to make back when it sells the drug to PWAs.

If there is real profiteering here, I am sure there are going to be a lot of additional questions. Now can you tell us why this drug has taken so long to come to market when we have heard how fast they brought AZT?

DR. CARTER: We have approximately four or perhaps at latest count five peer reviewed scientific publications on Ampligen. That is probably more publications than the totality of clinical data that have been published. There have been three papers to my knowledge on AZT and a paper here and there on products like HPA-23.

We did not communicate with DuPont or any other organization to seek an expansion of the clinical work until we were confident that independent quality assurance of the work suggested the reasonable likelihood that the data would be reproducible.

I am primarily an academician. I have had NIH grants now for 20 years. I think I have never lost an NIH grant and that may sound immodest to you, perhaps it is, but I believe in first and foremost, you produce the laboratory and the clinical data and then if there is an opportunity for commercial development you pursue it.

We did not know that there was an inhibitory effect on this virus until less than 24 months ago. We had to reproduce that effect in several different laboratories. We had to find seed money to fund the pilot project.

The NCI had been extremely and continues to be very generous in the area of our cancer work but as you know as a recipient of federal grants, you cannot take funds allocated for kidney cancer and suddenly switch them to another disease however important that disease may be. There are processes you go through.

I indicated to you that our seed money was provided by Dr. Krim. As relates to the ATEUs, I have no ax to grind with them beyond this simple statement. Number one, if they are dealing with a small manufacturer of drugs classified as a small business and they are interested in the product, they should consider procuring the product. They can always send in auditors to determine whether or not we are profiting prematurely during the IND phase.

But more fundamentally, I had and I continue to have the question as to whether what is termed "good laboratory practice" is widely practiced in the ATEUs. Good laboratory practice is an esoteric area of pharmaceutical practice which is pertinent to the reproduceability of subtle laboratory data.

It is not appropriate for academic labs to spend a lot of money standardizing equipment to conform with the federal requirements which are all written out nicely in the federal register as to what good laboratory practice is.

I was and I remain today to be very honest with you, Dr. Lee, I remain skeptical as to whether the laboratory capacity in the ATEU network reflects good laboratory practice. I know they will do good research.

I believe that, but that is different and it was only when Dr. Mollica and his colleagues from DuPont came to the table and began to have dialogue with the ATEUs and the people involved that they began to convince me that it might be possible over time to have a good laboratory practice in these ATEUs.

DR. LILLY: Dr. SerVaas.

DR. SERVAAS: No questions.

DR. LILLY: Mr. Creedon.

MR. CREEDON: This is a related question to the one raised by Dr. Lee. As I understood the testimony from Commissioner Young of the FDA and I may have misunderstood, it was my impression that the FDA would be willing to approve the use of a drug either on an emergency basis or on a compassionate basis if the FDA felt there was reasonable efficacy to the drug and if a doctor recommended its use and if the manufacturer were willing to supply it.

I guess my question is, recognizing Dr. Carter what you said, the importance of having very rigorous trials to ultimately test the efficacy of the drugs for commercial purposes, is there any reason why the drug could not be made available if a doctor were willing to prescribe it.

DR. CARTER: I personally would have no objection to that. However, we are in a situation where out freeze-dried chambers literally product the Ampligen which will be used in several weeks and I recognized when Dr. Barry was talking and he described the role of someone sitting down there trying to figure out each week was there enough AZT to meet the commitment of the people on trial, that is exactly the situation we are in right at the moment.

We are stretched to the limit to try to maintain the 300 patients that are enrolled in our present studies and they must come first. We have stated that individuals who participate in clinical investigation with Ampligen have the first entitlements.

MR. CREEDON: How quickly can the volume of the drug be produced beyond the needs of the clinical study group?

DR. CARTER: That, of course, is Dr. Mollica's job, that and explaining why he is not going to profiteer.

DR. MOLLICA: Mr. Creedon, I think Dr. Young also made one other comment, one that the efficacy has been established. We in collaboration with the investigators, with the FDA in testing the hypothesis are now going through that. We will reach an interim analysis at certain defined points in the trial.

If we do indeed establish that the drug has shown to be safe and efficacious for the treatment of ARC, the trials will be stopped, application will be made and moved ahead. We have not reached that point yet.

MR. CREEDON: But the impression I got from Dr. Young and I may be wrong is that the FDA would be willing to approve the use of a drug even though it hadn't gone through all the trials that might be necessary for it to get to commercial use.

Now if Dr. Lee whose opinion I value very highly feels that this drug could very well be a very effective drug and this is going to take two years for this process even though that is better than eight years, how many thousands of people may die in the interim and could we help them.

DR. MOLLICA: As I say, we are in the process now and hopefully it will be done in less than two years of establishing indeed whether or not Ampligen will retard the progression of ARC to AIDS and we are, I believe, moving down that path. The first interim analysis has not been conducted yet to give us, Dr. Lee, Dr. Young the assurance that indeed the data is significantly working in that direction.

We have an open label pilot studies. We are maintaining those patients on the drug and are running this large study now that Dr. Lenox and other collaborators at five or six or seven centers are participating in.

MR. CREEDON: If the FDA were willing to approve the drug, would you be willing to supply it assuming you get beyond the point where you are --

DR. MOLLICA: Yes.

MR. CREEDON: You would be?

DR. MOLLICA: Of course.

MR. CREEDON: Very good. Thank you.

DR. LILLY: Dr. Walsh.

DR. WALSH: I am sorry but I disagree somewhat with some of my colleagues on the Commission with this persistent concern or implication of profiteering in such a critical area. If we wanted to shut off research, we couldn't find a better way to do it than to constantly be accusing those of you charged with that responsibility that you are in it purely for profit.

To me, I don't know any of you but I a make a judgment here that here is Dr. Carter and he has had this thing on his laboratory table since 1970. He is obviously a very careful, conscientious scientist. I can understand the frustration certainly of the people with AIDS and this is an example of why they are frustrated but he finally came to a point where he found in effect a partner who could finance it.

You come from a company that has been traditionally a careful conservative company, be it nylon or pharmaceuticals. It makes no difference. I don't think that because we are faced with this particular disease we are going to change the world or we are going to change the habits of companies or would we want to change the habits of a very careful scientist who has something which he thinks will finally have a monumental impact on a dread disease.

I think the point that you make that from the time that you two got married that you had less than two years that you have made again remarkable progress. I, for one, would hate to see loused up very frankly at this stage because my impression of Ampligen is that it does hold great promise, that you have overcome virtually the whole toxicity problem, that it appears to be less toxic, that you are willing to spend the money as a company to get this drug on the market in a form in which it may

save or at least prolong the lives of thousands of thousands of people.

I feel that you are probably more impatient at this point than either me or my fellow Commissioners or the PWAs because you would like this concluded and out in the market. Yet when we see the problems of clinical trials, it makes us learn once again that all of those diagrams we see, all of these plans from NIH and the institutes out there are only as good as the people that make them work.

So as I say, my point is I am making more of a comment than a question because I think you are very close. I don't know how close and I commend you for your persistence, you for your risk and you for your patience and I think we are lucky to have you.

DR. LILLY: Dr. Primm.

DR. PRIMM: This is a question for really the whole panel. I am quite concerned about research protocols that are intentionally exclusive because they have to be in many instances.

We do research in our corporation and unquestionably the protocols are sometimes exclusionary. What I mean by that is that I represent a particular group, I feel, on this Commission and that group is primarily intravenous drug users and that is where my expertise really lies and there are some very other very obvious reasons that I probably sit on this Commission, very obvious.

[Laughter.]

DR. PRIMM: I would like to ask you if you exclude intravenous drug users from the population that you would be, of course, doing your trials on and your protocol, why, that is number one and I think I can understand why but I would like for you to state that.

You exclude women, also, and I would like for you to state your reasons why that is because we are getting an increasing number of women and more minority women than any other women who are involved with this problem who certainly need every hope and need to hang their hat on every hope that they can have to do something about changing the progression of their disease.

If indeed it turns out to be that the drug is efficacious and it passes all of the clinical trials, et cetera, et cetera, how much longer, will it take two more years before you begin to put on intravenous drug users or you would put on

women who might have the same problem? It creates a problem for me and I am sure if you were in that same situation, it would create a problem for you.

DR. MOLLICA: I think first of all the trial that is designed now, there are a couple of points, number one, we are treating patients with ARC and I think even this morning there were some questions as to whether it is an ethical consideration to run a placebo controlled trial in this patient population or not. These are not patients with full blown AIDS.

We believe in conjunction with the Food and Drug Administration that this is the most rapid way to give ourselves and them and the medical community assurance that indeed Ampligen is a safe and efficacious therapy for this patient population.

As soon as we have finished this trial as I indicated to you we are now expanding the trials which will include women, which will include other patient populations, other status of the disease, other regimens, combination therapy and so forth but I think we want to reach the point to assure ourselves, the medical community, the FDA that indeed Ampligen is safe and efficacious.

We, too, along with Dr. Lee have been very much impressed with the status of the data that Dr. Carter has generated to date but I think we would agree that is the Phase I, Phase II open label data. It is very, very encouraging but I think sound medical practice dictates that one should move ahead.

I would like to thank Dr. Walsh for his comments. I think over the years at many times in the history of this country that DuPont has come to the aid. We were involved in a Manhattan Project. We ran the Savannah River Project for many years at no cost.

We believe we have some unique capability. Ampligen is a unique molecule. It is a polymer. So we think we have something to contribute in the manufacturing of that particular molecule as well as having some experience in the conduct of clinical trials.

So as soon as we assure ourselves and you, I think that is the most important thing that we can do is to give ourselves through a rigorous trial that indeed Ampligen is safe and efficacious for this patient population that we are testing and we then will move on to include all the other subsets, various patient populations, other regimens, other dosage schemes and so forth.

DR. PRIMM: That doesn't quite answer my question. I am not satisfied with that answer. Perhaps you could do better, Dr. Carter.

DR. CARTER: Well, you spoke about two other groups that can be infected with HIV, namely the IV drug abuser and the female receiving the virus through sexual activity. The reason why the female was excluded in the initial study is that they obviously have a fundamentally different physiology and HEM Research was prepared to undertake a major trial even if we had been unable to convince DuPont to participate. It might have taken us into bankruptcy and it probably would have but we were --

DR. PRIMM: I don't think you could ever bankrupt DuPont.

DR. CARTER: But we were prepared to do that.

DR. PRIMM: There is no way you could bankrupt DuPont.

DR. CARTER: One of the things we had to consider was the homogeneity of the population group and that meant that people who had fundamentally different physiology, different metabolism which obviously had to exclude the female at least at the initial phase and in my written testimony you will notice that we are fully aware that that is a deficiency in our work to date and we plan to have up to one-third of the participants in our next study be females even though they only represent less than ten percent of the HIV-infected group.

With respect to the IV drug abusing group, here again it was a decision that HEM Research reached and with which DuPont concurred as we formed our marriage. We were acutely aware of the cost which will run as Dr. Lee implied, the study that we are doing runs into millions and millions of dollars and we felt that every time a patient leaves the study, that is a loss of the scientific knowledge needed to analyze the efficacy or lack thereof the compound, in this case, Ampligen.

We simply felt that it would be a safer approach to have individuals who would report, were likely to report, twice a week for a very tedious laboratory study and a very tedious intravenous infusion and report for what turns out to be one month before they go on what is termed active therapy.

They report twice a week for tedious tests of their immune system, their HIV load. They go on tread mill machines and as some of the gay newsletters have indicated, there has never been and I think I am being accurate in this quote, there has never been a more tedious scientific study than Ampligen.

By the way, they are not altogether understandably happy with the tedium but hopefully they will bear with us because I think the vast majority of individuals who know about what we are doing recognize that we are serious in what we are doing and that we are conducting it in as ethical a manner as we know how.

But we felt that the inclusion of a different population group, namely the intravenous drug user, might cause disturbances in the ability to actually prosecute the study; that there might not be the ability to adhere to a tedious schedule.

DR. PRIMM: We call that "creaming" in my center. I treat 2,100 addicted individuals and these patients come in, the majority of them every day, sometimes seven times a week to pick up their medication and for counselling so I think it is rather ridiculous to assume that these patients are irresponsible particularly when a protocol like this denies them of some treatment that could be efficacious to that group and would not have to be proven later on.

I think maybe that should be taken into consideration the next time around, that some way, somehow, DuPont and, of course, you, Dr. Carter and you are from Hahnemann and there are a lot of addicts in Philadelphia who are terribly responsible people, could indeed be found that could have participated in this study and would have been faithful in coming to their treatment.

DR. CARTER: Well, you have made an excellent comment, Dr. Primm and the only thing that I would disagree with you on hopefully constructively is I did not suggest that they were irresponsible. I suggested that the gay population is a group of people committed and trying to engage in a variety of educational pursuits, they have come to us and stated that they wished to participate in a variety of Ampligen trials.

To date, there has not been a constituency either of females or of IV drug users who have come to us and said, "We want to participate. Here are the numbers of individuals who are prepared to participate in your work."

DR. PRIMM: I want to thank you for comments and if you had something to say about that, Dr. Lenox, I would be glad to hear it. You had indicated that a number of your patients are intravenous drug users and you had to turn away a number of people who called about the study that were both women and intravenous drug users.

DR. LENOX: As I said before, I do primarily treat IVDAs in my practice at Metropolitan Hospital and unfortunately a lot of my patients did hear about the study and I was asked by a

number of my patients about getting onto the Ampligen trials so I had to turn them down.

I do agree that most of my patients who I have been treating are very forthright and would be glad to get involved in a study such as this and I feel very sure they would be coming on a regular basis if they were given a chance to do so.

We have received a number of phone calls from individual women and women's groups wondering whether or not women were involved in the study and why and why they were not including some very irate phone calls from time to time as well.

DR. PRIMM: Thank you.

DR. LILLY: I will then turn the meeting back over to Admiral Watkins.

CHAIRMAN WATKINS: I have one question before we close it out. Dr. Mollica, I read your paper here and one of my biggest concerns is produceability. If the lid were completely lifted off and we were ready to move in a whole series of trials and expand it as we just heard from Dr. Primm and others, I read in here quite a concern that you have about produceability, the ability to put the drug out there in sufficient quantity. You are limited in quantity today.

So I have been a great proponent of this drug listening to persons with AIDS from our field visits and so forth and talking to those who have had to go to Paris to get on an Ampligen protocol or eventually have gotten up to Philadelphia to get on special protocols and so forth to be able to really move and there seems to be a great interest among the persons with AIDS to move in this direction so all of a sudden if we move you say, "Wait a minute, I can't quite produce the Ampligen in the right quantity" or "It is going to be so expensive that it is going to be prohibitive."

I question whether or not you have been given everything you need to lay the ground work for eventual produceability in quantities sufficient to handle any kind of a set of trials that might be forthcoming here.

How hard to we push it? Are we off two years from something that might be of high enough quantity to be able to deliver at reasonable price? In other words, what do you need from us to help you make it go faster? Do you need tax incentives? Do you need the Master Drug Formulary given to you bu HEM? What is it you need?

Your paper sounds very worried. Your biggest concern, you say, is the composition and manufacturing of it and this is a paramount concern to successful clinical trials, yes, but then obtaining sufficient product to get with it above the 5,000 patients you might have to support. What is the obstacle?

DR. MOLLICA: I think part of it is just scientific understanding. Dr. Carter alluded to good laboratory practices. We want to assure that we can reproduce Ampligen time and again. It is a very complex molecule. It requires a great deal of quality control, of reproduceability steps, quality of raw materials all affect the ultimate process.

CHAIRMAN WATKINS: Are you telling us that you may not be able to produce in sufficient quantity?

DR. MOLLICA: I am not saying that at all. I am saying we have well under way with a competent staff and I believe we are uniquely qualified to do so, we will be able to produce that material. If it can be done, we will do it.

CHAIRMAN WATKINS: You have proven its produceability?

DR. MOLLICA: We are in the process of doing that at this time.

CHAIRMAN WATKINS: But at this point you have not proven its produceability in large quantities?

DR. MOLLICA: No. That is what we are doing now.

CHAIRMAN WATKINS: But you don't see any technical hurdle in your path that would tell you that you are heading into harms way on this? We have had non-producible things in the past in the world where we have laboratory work that is exquisite and done beautifully, it has been unable to produce certain things and I am just wondering if we are walking into something with the concerns you have expressed in here, how serious are those.

DR. MOLLICA: My concerns were, I think, addressed at this particular point in time. The available material is sufficient to support the ongoing trials, the patients that have enrolled. I think we have an ethical responsibility to maintain and continue those patients who have enrolled to date. That is the present state of the knowledge.

The reason HEM came forward to DuPont is that we do have the resources to put a large number of technical people on this, as I say, engineers, pharmacists, chemists who are now looking very rapidly at what it takes to bring this forward, reproduceability of starting materials, reproduceability of the

process and so forth. So I am confident we will do this job, yes.

CHAIRMAN WATKINS: So you could expand then to do the kinds of things Dr. Primm would like to see done and also expand into the female community and so forth and that would not be a problem for you or is the limit 5,000 people in trials at this point in time?

In other words, what is the ramp function we are talking about? How many people can we handle today with the produceability? How many a year from now, two years from now?

DR. MOLLICA: At this point in time as I indicated the amount of material are enough to support several hundred patients. We could easily take that existing process ten to 20-fold and that gets us up to 5,000 patients; that is, more patients than is indicated that are presently in the ATEUs so i am confident that we can indeed treat all the experimental population at this particular time.

Now the next step is to go another order of magnitude for full scale commercialization.

CHAIRMAN WATKINS: I just wanted to clear up that that was not an obstacle. Supply was not an obstacle to expanding the trials along the line Dr. Primm said.

Thank you very much. The Commission will stand adjourned now until tomorrow morning at 9:00 o'clock here.

[Whereupon, the hearings were adjourned at 5:45 o'clock p.m., to reconvene at 9:00 o'clock a.m., Saturday, February 20, 1988.]