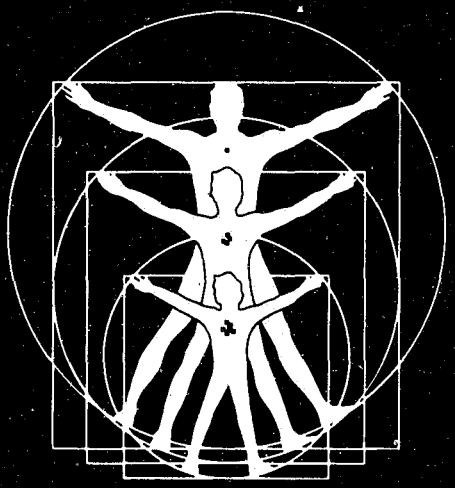
A TOWN FORUM ON AIDS

Latest Advances in HIV/AIDS Vaccines and Treatments



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This report was prepared for the Institute for Advanced Studies in Immunology & Aging by Ann Giudici Fettner. It is based on a public forum sponsored by the Institute, held at The George Washington University in Washington, D.C., on Wednesday, June 2, 1993. Funding for this report was made available in part through the Office of AIDS Research, National Institutes of Health.

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ACKNOWLEDGEMENTS

The Institute for Advanced Studies in Immunology & Aging is an international non-profit medical research and education organization. Since 1985 the Institute has helped to accelerate the pace of scientific discoveries by disseminating the latest scientific information regarding the body's complex immune system and its potential role in the prevention and treatment of disease.

The Town Forum on AIDS represents an important education program of the Institute. The planning and design of the Forum involved many individuals, representing the scientific and lay communities, and including the public and private sectors. All of these individuals volunteered their time because of their personal commitment both to issues related to AIDS and to the Institute's mission.

On behalf of the Board of Directors, I want to especially thank the scientific panel members who so generously gave of their time and expertise in making this meeting possible. We acknowledge Drs. Anthony S. Fauci, Robert C. Gallo, Enrico Garaci, Robert R. Redfield, and Michael S. Gottlieb.

The success of the Town Forum on AIDS can be credited, in great part, to its dynamic and insightful moderator, Ms. Carole Simpson of ABC News. Ms. Simpson expressed the passion of the public for finding any early cure for AIDS and brought out the best of the scientists in addressing just where medical science is today and where it may be in the near future.

I wish to acknowledge the advocacy and journalist panel members for their thoughtful and well targeted questions. We thank Drs. Robert J. Darga and Peter Hawley, Ms. Vivian L. Torres and Mr. Jon Cohen. We also thank the audience members for asking a wide range of questions reflecting the concerns and frustrations, as well as the willingness of many to come together in response to this disease. Strong support was expressed for continued and focused AIDS research to find effective prevention and treatment methods.

We acknowledge and thank C-SPAN for its repeated broadcast of the Town Forum throughout the United States; and the U.S. Information Agency WORLDNET Television for its broadcast to 145 countries around the world. We appreciate the assistance of the American Red Cross for broadcasting the Town Forum live, making it available across the United State to their offices as well as to television stations, AIDS groups, health centers, public health departments, medical schools, and anyone with the capacity to receive the program from satellite.

Approximately 1,000 participants came to the meeting. In order to organize this meeting and cover the expenses, including the publication of this report, generous assistance was provided by the following collaborating organizations: the National Institutes of Health, Office of AIDS Research; Adworks, Inc.; American Red Cross, Burroughs Wellcome Co., and Olgilvy, Adams & Rinehart. In addition, numerous other organizations and companies supported this meeting; all are listed at the end of this report.

We thank Rita and Patrick Ewing, the Glen Eagles Foundation, the Eugene and Agnes E. Meyer Foundation and the Pharmaceutical Manufacturers Association for sponsoring the *High School Student Symposium on AIDS Research* conducted by the Institute in conjunction with the Town Forum.

On behalf of the Board of Directors, we want to express our appreciation to all of these individuals and organizations that enabled the Town Forum to be so successful.

Richard J. Hindin, Chair
Board of Directors

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A TOWN FORUM ON AIDS

Latest Advances in HIV/AIDS Vaccines and Treatments

Tables and Figures

LIST OF PARTICIPANTS

WELCOME

Richard J. Hindin, Chair
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Chairman
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MODERATOR

Carole Simpson
ABC News Senior Correspondent

Washington Anchor
"World News Sunday"

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Dr. Robert C. Gallo
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Dr. Michael S. Gottlieb
Leading AIDS physician

Assistant Clinical Professor of Medicine,
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ADVOCACY/JOURNALIST PANEL

Dr. Robert J. Darga
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National Association of People with AIDS

Dr. Peter Hawley
Medical Director
Whitman-Walker Clinic, Inc.

Ms. Vivian L. Torres
National Minority AIDS Council

Mr. Jon Cohen
Staff Writer
Science

Mr. Richard J. Hindin, Chair, Board of Directors, Institute of Advanced Studies in Immunology & Aging, welcomed the audience and introduced Dr. Allan L. Goldstein.

ALLAN L. GOLDSTEIN, PH.D.
Scientific Director
Institute for Advanced Studies
in Immunology & Aging
Professor and Chair
Department of Biochemistry
and Molecular Biology
The George Washington University
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Dr. Goldstein welcomed the audience to the second in the series of Town Forums on acquired immune deficiency syndrome — AIDS — and gave a brief overview of the present magnitude of the worldwide pandemic.

Dr. Allan L. Goldstein: In the early 1980's, just as health experts were predicting the eradication of smallpox and polio — two of the great infectious diseases of our time — AIDS appeared. Within a few years it became clear that this strange disorder was not a garden variety disease, but one that would not easily be brought under control and thus had the makings of a major public health problem. The scientific community found itself confronting a faceless enemy that through unknown mechanisms was causing massive destruction of the immune systems of those afflicted.

Thanks to the contributions of Drs. Robert Gallo, Luc Montagnier and others, by 1984 the pathogen responsible for the illness was identified as a virus. This eventually would be called human immunodeficiency virus or HIV. Almost ten years later, however, there is nothing available that can do more than temporarily relieve some of the opportunistic infections that characterize immune system failure. And there is only one class of approved drugs that is thought to slow viral reproduction.

The World Health Organization estimates that at least fifteen million persons have been infected with HIV. One million of these are children who contracted the virus parentally. By the year 2000 — six-and-a-half years from now — over forty million people will have been infected with more than twenty million living with HIV.

In the U.S. and Western Europe, the majority of AIDS patients are members of the gay community or IV drug abusers. Throughout the rest of the world, the vast majority have become infected through heterosexual intercourse. This is fast becoming the major mode of transmission in this country as teenagers and children increasingly are found to be HIV positive.

On a worldwide basis, sub-Saharan Africa has borne the brunt of the worldwide epidemic, and it is there that one finds over eight million of the fifteen million total persons infected. The virus has spread rapidly on all continents. In Asia, public health experts are finding alarming sero-prevalence of HIV and estimate that, given the size of the population, the epidemic in Asia may ultimately dwarf all others in scope and impact. For those of us who have experienced the personal loss of AIDS, it is staggering to

Table 1. Worldwide Prevalence of HIV and AIDS, 1993

Region	Estimated cumulative adult HIV infections [1]	Estimated cumulative adult AIDS cases [2]	Reported cumulative AIDS cases [3]	Distribution of adult HIV prevelance Men	Women	Current Trends
Australiasia	> 25,000	< 5,000	3,963	85%	15%	HIV transmission through heterosexual contact is increasing—especially among urban populations with rates of STDs and/or IV drug use.
North America	> 1 million	> 3oo,ooo	249,035	85%	15%	
West. Europe	500,000	> 120,000	78,049	85%	15%	
Latin America and the Caribbean	1.5 million	> 240,000	64,048	80%	20%	HIV infections among IV drug users is growing. HIV transmission through heterosexual intercourse is increasing dramatically. The epidemic is more severe in Central America and the Caribbean.
Sub-Saharan Africa	> 8 million	> 1.5 million	210,376	45%	55%	HIV transmission through heterosexual contact is increasing rapidly. Perinatal HIV transmission also is growing quickly.
South and South-East Asia	> 1.5 million	> 30,000	1,445	65%	35%	HIV trasmission is increasing rapidly through heterosexual intercourse and female sex workers. HIV prevalence among IV drug users is increasing dramatically.
East Asia and Pacific	>25,000	1,000	663	85%	15%	Limited data reveals that a large portion of those with AIDS are hemophiliacs who received HIV-infected blood products in the early to mid 1980s.
Eastern Europe and Central Asia	50,000	> 3,000	2,850	87%	13%	The magnitude of HIV/AIDS remains poorly defined. Unscreened blood remains an HIV transmission challenge.
North Africa and the Middle East	> 75,000	10,000	1,160	80%	20%	There is high incidence of HIV infection among female sex workers and IV drug users.
Global Total	**> 13 million**	**>2.2 million**	**611,589**	**60%**	**40%**	*[1] including deaths; [2] estimated as of June '93; [3] as of 4 January 1993 – adults and children*

Source: World Health Organization in 1993 World AIDS Day Resource Booklet, American Association for World Health

consider the global implications of this epidemic. AIDS has and will continue to devastate individuals, families, neighborhoods, communities, regions, nations and has affected their economies and governments.

In the face of this specter, the urgency of our research is clear. Twelve years into the epidemic, research has revealed much. As science examines many of the virus's effects on the body, knowledge of the genetics, immune regulation and virology will help solve other medical problems and already are playing a role in treatments for AIDS and many other diseases. But much more remains to be learned.

Today, the Institute has brought together five of the scientific leaders in the war on AIDS to discuss their progress with us and to chart the future directions of research. The Institute conducts these forums because we are committed to building a dialogue that draws together the insights of researchers, clinicians and patients. The Institute believes that this type of forum will help the public better understand the complexities of the scientific process and the need to continue to support the young men and women scientists in the laboratories throughout our nation and the world who are the unsung heroes in the battle against AIDS. On behalf of the Institute, I would like to thank you — the scientists, clinicians, advocates, journalists and audiences members — who share our commitment to building this dialogue.

At this time, it is my pleasure to introduce the moderator for today's "Town Forum," one of America's most distinguished and respected reporters, the well known, award winning journalist, ABC News Senior Correspondent and Anchor for ABC's "World News Sunday," Ms. Carole Simpson.

Table 2. Estimated and Projected HIV Prevalence in Adults by "Macro" Region

	Mid 1993		2000	
"Macro Region"	Estimated prevalence[1]	Estimated population aged 15-49 years (1990)	Projected HIV prevalence	Projected population aged 15-49 years
Australasia, Europe & North America	>1.2 million	646 million	1 million	675 million
Latin America & Carribbean	>1.3 million	227 million	>2 million	282 million
Africa	>6.5 million	289 million	>9 million	397 million
Asia	2 million	1527 million	8 million	1843 million
Global Total	>11 million	2689 million	>20 million	3197 million

[1] Total number of HIV-infected people currently alive.

Source: World Health Organization, 1993

INTRODUCTION

MS. CAROLE SIMPSON
ABC News Senior Correspondent
Washington Anchor "World News Sunday"

Carole Simpson: Twelve years ago this week, the Centers for Disease Control published the first report of the epidemic that would become AIDS. Today, almost 200,000 Americans are dead and more than a million more are infected with HIV, the virus that causes AIDS. Over these years, the AIDS epidemic has radically changed our approach to medical research. Never before have patients and primary care physicians been so deeply involved in the process of developing treatments. Never before have care-givers and researchers worked as a team with patients and their families to develop treatment strategies. Twelve years ago a meeting like this would never have happened, but because of AIDS the scientific, medical, and patient communities have come together in new ways. The AIDS model has been adopted by other activists, such as those for women's health and breast cancer.

Today you will have an opportunity to preview the scientific discussion that will begin in a few days at the International AIDS Conference in Berlin. There are many scientific questions on our collective minds. What is the effectiveness of AZT in light of recent studies? Does our current therapeutic approach attack the virus too late in the cycle, after it has already infected the immune system? Are we making progress in the development of an effective vaccine and in finding new drugs to treat AIDS?

We will hear from the scientists who are at the leading edge of the fight to find answers to these questions. Five prominent scientists will each address an individual aspect of AIDS research. Following their brief presentations, our panel of AIDS advocates and medical journalists will question the scientists, followed by an opportunity for questions from the audience.

Leading the U.S. government's research effort into the causes and treatments of AIDS is **Dr. Anthony Fauci.** Dr. Fauci is the director of the National Institute of Allergy and Infectious Diseases within the National Institutes of Health. Dr. Fauci has made numerous pioneering scientific discoveries that are central to the current understanding of the regulation of the immune system. Among the issues Dr. Fauci will address are the lack of latency of the HIV virus and the potential impact of the Concorde Study on clinical practice.

Universally recognized for his achievements in molecular biology and for his pioneering achievements in the field of human retrovirology in which he identified the first cancer-causing retrovirus, **Dr. Robert Gallo** heads the Laboratory of Tumor Cell Biology at the National Cancer Institute of the National Institutes of Health. With his co workers and scientists at the Pasteur Institute in Paris, Dr. Gallo is credited with discovering HIV, the virus that causes AIDS. Dr. Gallo will speak about new directions in AIDS research, including the innovative exploration of the utility of antisense treatments.

As one of the leading European biomedical researchers, **Dr. Enrico Garaci** is well known in the American scientific community for his contributions in the field of immunology, which includes the

use of natural hormones to reconstitute the immune system. Dr. Garaci is president of the National Research Center of Italy — the Italian equivalent of our National Institutes of Health and National Science Foundation combined. He is also professor of microbiology at the University of Rome "Tor Vergata." Dr. Garaci will brief us on recent developments in combination therapies and on trends in European AIDS research.

Dr. Robert Redfield is the chief of the Department of Retroviral Research at the Walter Reed Army Institute of Research and a staff physician at Walter Reed Army Medical Center. Dr. Redfield was one of the first researchers to chart the natural history of HIV's impact of the immune system and is currently conducting advanced trials in vaccine therapy using GP160. Dr. Redfield offers an update on the status on vaccine research and other strategies for immune restoration.

The first published report on the pneumonia that has come to characterize AIDS — PCP — was based on the investigations of **Dr. Michael Gottlieb.** A faculty member of the UCLA School of Medicine, Dr. Gottlieb has headed the effort to fight this disease through his clinical research, as well as through his leadership at AIDS Project Los Angeles, the California Task Force on AIDS and as a founding member of the American Foundation for AIDS Research. Dr. Gottlieb will tell us about the state of the art of current clinical approaches, including the treatment of opportunistic infections.

Joining our scientific panel on the stage is a distinguished group of advocates and an important AIDS journalist, all of whom will question the scientists. **Dr. Robert J. Darga** is director of programs for the National Association of People with AIDS in Washington, D.C. and vice president of the Carl Vogel Foundation — two organizations which work to improve the lives of people living with AIDS. Equipped with his training as a physician, Dr. Darga is a powerful advocate for people living with AIDS.

Ms. Vivian L. Torres is an AIDS activist and educator from New York representing the National Minority AIDS Council. Ms. Torres is active at the front lines of the epidemic, working both directly with people who are HIV infected and at the policy level on the implementation of the Ryan White Care Act. She has been particularly active in advocating for services to communities of persons of color affected by the epidemic.

Dr. Peter Hawley is medical and laboratory director of the Whitman Walker Clinic in Washington, D.C. Dr. Hawley is responsible for overseeing medical care for Whitman Walker's 2,000 HIV infected clients and directs the clinic's extensive community based research programs. Under Dr. Hawley's leadership, Whitman Walker has become one of the leading national sites for community based clinical trials.

Mr. Jon Cohen is a staff writer for *Science* in Washington, D.C., where he directs the magazine's coverage of AIDS issues. Mr. Cohen is uniquely qualified to cover scientific issues with a degree in science from the University of San Diego. He has written extensively on a wide range of health and science issues and has been published in *The Washington Post, The New Republic, The Village Voice* and many other publications.

THE SCIENTIFIC PRESENTATIONS

ANTHONY S. FAUCI, M.D.
Director
National Institute of Allergy
and Infectious Diseases
National Institutes of Health

Dr. Anthony Fauci: I have been asked to briefly discuss several subjects that will set the stage for some of the other discussions and, hopefully, for the questions that we will get to later on. The first topic is related to work that was conducted in my laboratory and a number of other laboratories over the past couple of years. The primary focus of that work has been to more precisely delineate the mechanisms of the pathogenesis of HIV disease. In other words, how does HIV virus ultimately take part in the destruction of the body's immune system?

Many mysteries have emerged as we have gained insight into the pathogenesis of HIV. One of the more important and puzzling mysteries with which we have been faced is that in infected individuals, there is often an initial burst of viremia — during which the virus is detected in the peripheral blood — but after a period of weeks to months the virus becomes undetectable. This event is usually associated with the appearance of an immune response in the form of antibodies against HIV. In the usual course of the infection, individuals go for a median of ten years before they develop the AIDS defining illnesses.

Given this scenario, one explanation could be that during the quiescent or clinically latent period only a very little virus can be detected in the blood because the virus fails to replicate efficiently. This explanation became inadequate after we were able to follow the status of HIV-infected individuals over the years and evaluate the gradual decline in their CD4 cell count — an immune system cell that is the primary target of HIV. This decline suggested that something deleterious was going on in the body even though very little virus could be detected in the peripheral blood where there theoretically should have been evidence that the virus was replicating.

Based on the recent observations of viral replication in lymph tissues, we did a prospective study looking at individuals at different stages of disease: from the very early clinically asymptomatic stage (when they still have more than 500 CD4 cells) to individuals who were intermediate in their course of disease, namely 200 to 500 CD4 cells, to those individuals with advanced HIV disease (fewer than 200 CD4 cells). We looked at their peripheral blood and examined their lymph nodes, and, to make a long story short, we found something very striking.

Even early in the course of infection when there is little, if any, indication of viral activity or viral replication in the peripheral blood, there is an extraordinary amount of virus trapped within specialized cells in the lymph nodes that are scattered throughout the body. When we examined a lymph node from someone and quantitated the amount of virus within it and compared it to the amount of virus in the peripheral blood in the same person, we found the following: During the clinically latent period, the amount of virus in the nodes is considerable and, indeed, viral

replication is going on. When we follow individuals as their disease moves to the intermediate and late stages, there is a close correlation between the amount of virus detectable in the blood and the destruction of lymphoid tissues in the lymph nodes — the cellular elements as well as the micro environment of the lymphoid tissues. This concept will become very important when we discuss the concept of immunological reconstitution. The conclusions we have been able to draw from this research is that the virus is present and continuously replicating in the lymph nodes from the very beginning. This gives us strong scientific rationale to start therapy as early as possible after one becomes HIV infected. Of course, to take advantage of this discovery we need to develop drugs that are effective against the virus while it is hidden within the lymph nodes.

The drugs we have today that work against HIV are the nucleoside analogs, AZT, ddI and ddC. These drugs provide only temporary benefit. After a while, particularly with single drug therapy, individuals become resistant to the drug. This raises the problem of balancing the possible advantage of starting therapy very early — when someone just finds out that they are HIV infected and still has a relatively normal CD4 count — against the disadvantage of the development of drug resistance. Alternatively, should therapy be initiated later when a patient is sicker, to avoid drug resistance? However, we at least know now that there is a scientific rationale for starting therapy — once the appropriate drugs are available.

This leads to the next topic, which is, where are we now with the available drugs? The recent report of a study that was performed in Great Britain and France — the Concorde Study — indicated that although benefits were found both when AZT was started either early or late in HIV infection, after three years on AZT alone there was no difference in survival. These results are leading us to rethink how and when to begin antiretroviral therapy. Immediately after the Berlin AIDS conference, scientists from throughout the world will come together at a consensus conference sponsored by NIH to examine all the data we now have on antiretroviral therapy.

ROBERT C. GALLO, M.D.
Chief
Laboratory of Tumor Cell Biology
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Dr. Robert Gallo: From the point of view of a laboratory/medical scientist, I would like to cover some of the approaches that are currently being thought about and beginning to be put into practice in treating HIV infection. The first priority in treating this disease, of course, is the reduction of virus — at least relative to the number of uninfected cells. One approach might be to just give the person a transplant of more uninfected cells. This is, in fact, an effort of Project Immune Restoration under Project Inform (a non-medical research/advocacy group) is attempting to catalyze. One specific tactic is to store viable frozen cells from people known to be infected very early in disease, in the hope that their uninfected immune cells could be used as a transplant to help later in the course of the disease. However, the far more conventional approaches for most of us are to identify ways to block HIV replication.

We have had little success so far in medicine in developing antiviral agents against this virus or, in fact, almost any virus. Thus, it is fallacious to assume that anti-HIV therapy is a wrong approach since AZT has not worked as well as we hoped. The key point is that we have not had adequate agents. Presently, the most common approach is to block one enzyme needed by the virus with drugs such as AZT, ddI, and ddC, which target the enzyme reverse transcriptase (RT). There has been speculation recently that maybe we should target several enzymes in the virus' replication cycle, because this virus is able to mutate so fast that it finds ways to escape the single drug attack. However, viruses require components and activities that are available through both their own genes and proteins *and those of the infected cell as well.* This suggests the possibility of targeting *cellular components vital for replication,* if it becomes possible to do so without creating unacceptable toxicity.

Eons ago, viruses developed from cells, so there is nothing that is entirely specific only to viruses. Because viral genes came from cells' genes, when you hit a viral enzyme like RT with a drug, cellular activities that require enzymes similar to RT (cellular DNA polymerases) are negatively affected. This creates the toxicity in patients.

What about other approaches against a virus that mutates so much? One could try to hold it down and not let it escape from an infected cell. To do this, you attempt to make drugs that interfere with parts of the virus' genes that make proteins which are conserved and don't change without killing the virus. For example, there is a protein called nucleocapsid protein, which has a sequence or string of amino acids that are common not only to HIV but to all retroviruses that infect animals ranging from chickens to man. That string of amino acids must be vital for the function of that protein, and that protein is vital for the virus to form and to escape from the cell. A lot is known about the structure of this nucleocapsid protein, and attempts are being made to design drugs to interfere with it.

Targeting conserved regions of the virus may also be done at the level of the viral genes or nucleic acids by the technique known as antisense, an area of research on which my laboratory is spending a considerable amount of time. What does antisense therapy mean? How might it work? Basically, we identify nucleic acid sequences that are compli-

mentary and can bind to and inactivate essential parts of the viral sequences. We can target conserved, needed regions of the viral nucleic acids and block virus replication by building sequences that bind to the viral gene and block the important activity required by the virus to replicate. Presently this works in laboratory culture systems. Problems with this technique that many are working now to solve include getting enough of these antisense sequences built and finding ways to properly deliver them so the nucleic acid does not get degraded in the patient's blood serum. These are technical, logistical and economic problems which, I believe, will be solved, and there will be clinical trials with some antisense molecules. This technique may not work initially, but it holds considerable promise for the future. Clinical trials with the first antisense against HIV will be initiated this year.

I'll briefly mention two other approaches. Everybody has heard of gene therapy for correcting genetic diseases. The present emphasis is on its use is in therapy against these inherited disorders and for some kinds of human cancer, but, at least in theory, gene therapy can be used in AIDS. There will not be any dramatic success in the next year or two with gene therapy, but it is something that will soon be tried. The rationale for this is that one can insert genes into cells that prevent HIV from being able to infect that cell. Now the plan with HIV-infected persons is to take out a bit of their bone marrow and from this to obtain some of the bone marrow stem cells — the primitive parent cell that gives rise to the immune system and other blood cells. The majority of these will be uninfected. The inhibitory gene is inserted into these cells. These cells are then given back to the patient, in whom they should form the progenitors of HIV-resistant blood cells, gradually repopulating the immune system. Major technical problems still exist, but theoretically they are solvable problems. I expect HIV-infected people will benefit from such therapy within this decade.

One other thing that deserves mention is that as well as virus replication and the direct effects of HIV which in my mind are the key problems — there are now strong suggestions that there are numerous indirect harmful effects of HIV, including harm to *uninfected* cells of the immune system. For example, even uninfected T-cells seem not to always behave normally. Why?

By this I mean that in people who are HIV-infected, these cells are not producing the biologically important molecules that regulate immunity. Both Dr. Fauci's and my laboratories are attempting to identify what roles this dysregulation plays in AIDS. There seems to be a similarity with conditions known to be caused by autoimmunity, in which one's own cells are seen and attacked as "foreign" by the immune system. For example, there is some evidence that the antibodies that attack HIV also attack normal cells. Also, some components of HIV mimic normal cell components in such a way that even without stimulating a harmful autoimmune response, the mimicry may allow competition with cells activities and interfere with normal functions. In my opinion, it is the effect of HIV proteins — especially its envelope protein — that induce such harmful effects, even on uninfected cells. As Professor Daniel Zagury in France has suggested, this in turn fosters dysregulation of biologically important cell regulators (the cytokines) which in turn may greatly magnify the immune disorder. Specific treatments designed to correct these abnormalities will be of importance.

ENRICO GARACI, M.D.
President
Consiglio Nazionale delle Recerche
(C.N.R.)
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University of Rome "Tor Vergata"
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Dr. Enrico Garaci: As Dr. Goldstein indicated in his opening remarks, AIDS is rapidly growing worldwide and there is a great need for continued close international cooperation. I will briefly review the current state of affairs in Italy, including a promising new approach using a combination of antiviral drugs and biological response modifiers.

In Italy, approximately 200,000 people are infected with the HIV virus, and of these 17,000 have already progressed to AIDS. The number is increasing rapidly. The majority, approximately 70 percent of HIV- infected individuals, are intravenous drug abusers. In Italy, unlike the United States, homosexuals represent only a minority of HIV infected patients.

The success we have achieved in Italy with monotherapy such as AZT has been similar to that seen in the United States. There is no question that this drug is helpful and does improve the quality of life for many patients infected with HIV. However, there is now recognition that drug resistance develops in many, and also that the current doses of nucleoside analogs are substantially toxic during long term treatment.

A big problem with regard to single drug therapy is that all of the anti viral drugs that are currently approved for use are inhibitors of reverse transcriptase, an enzyme of the AIDS virus that is involved in the early stage of the virus life cycle. Unfortunately, the approved antivirals — AZT, ddI, and ddC — are not efficient in inhibiting virus replication in chronically infected macrophages. We have found that chronic infection of macrophages causes the production of prostaglandins, which results in an increase of apoptosis, or cell death of uninfected T-cells in the thymus gland and in other immune system organs.

Scientific work in my own group has clearly shown that the inhibition of HIV replication in chronically infected macrophages may significantly slow down the rate of T-cell loss. My group has clearly shown that inhibition of HIV replication in chronically infected macrophages can be achieved by utilizing novel drugs that inhibit key enzymes of HIV called proteases. We have found that these effects are consistent and sustainable over time.

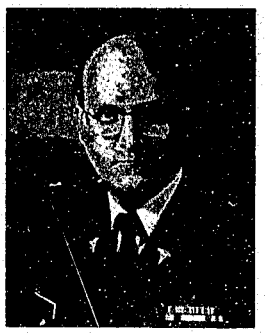
A number of scientists in the United States and Europe have shown that the decline in cellular immune responses, including IL 2 production, precede a significant reduction in CD4 cells by at least 12 months. This raises the issue of identifying and treating with agents that can restore immune response, and using these in association with anti-retroviral chemotherapy.

Over the past several years, published experimental cancer studies from our group at the University of Rome "Tor Vergata" have established that the combination of biological response modifiers, such as thymosin alpha combined with low doses of interferon or IL 2, have been able to significantly improve the immune response of immune suppressed mice and to cure them following challenge with mouse

tumor cells. This animal model, which has provided the scientific rationale for the use of the combination of chemotherapy with biological response modifiers, has been translated to the clinic during the past two years in cancer patients and in AIDS patients.

Our experience with these studies in AIDS patients has been as follows:
In 1991, we started a Phase II clinical trial in a group of forty eight patients with CD4 counts of between 200 and 500 cells by cubic millimeter. The patients were divided into four groups. The first group was treated with AZT, the second with AZT and alpha interferon, the third with AZT and thymosin-alpha-1, and the fourth group received a combination of AZT, thymosin-alpha-1 and alpha interferon. The results of this study indicated that the group treated with this last regimen experienced a substantial, stable increase over a one year period in the number of CD4 cells and have a sustained enhancement in immune function as measured by recall antigen presentation to tetanus and Candida challenge, as well as a decrease of HIV DNA copies in circulating blood lymphocytes as measured by special analysis. By contrast, each of the other groups — after a transient improvement of most parameters in the first six months — experienced a continued decline in CD4 cells and in immune function. The most important result of this preliminary trial is the maintenance over time of the improvement achieved by the fourth treatment regimen.

It should be emphasized that the results are based on a relatively small number of patients and needs to be confirmed in a larger study. I am pleased to report that this larger study approved by the Minister of Health in Italy is now underway and involves a large number of clinical centers in the country. We plan to enroll at least 200 patients with less than 500 CD4 lymphocytes. We believe that the combination of antiviral agents with biological response modifiers holds significant promise for improving the treatment of patients infected with the AIDS virus.



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Dr. Robert Redfield: HIV is a unique chronic viral infection. Other chronic viruses — such as chickenpox, shingles and genital herpes — actually cause intermittent periods of viral production in clinical disease, which are followed by periods of viral latency and complete disease resolution. As Dr. Fauci has said, HIV is different in that there actually are no periods of viral latency that occur in the course of HIV infection. Even healthy early asymptomatic patients have significant quantities of virus, particularly in their lymph node tissue.

The human immune system is an extremely powerful organ. It is capable of orchestrating an almost infinite number of immune responses that equip us with the capacity to defend and defeat numerous infectious pathogens. Many of these organisms cause acute self-limited diseases, because our immune system produces an immune response that combats those pathogens and clears the infection. It stands to reason, then, that chronic viral infections are chronic because our immune system is not capable of generating a successful immune response.

Patients with HIV infection do mount an immune response against HIV which, however, is not capable of clearing the virus or effectively controlling the virus. Despite the presence of these responses, the virus continues to replicate, and a progressive debilitating disease process ensues. The careful description of the natural immune response of these patients has provided some insights into why the human immune response may fail in controlling the virus. Most notable to me is that there is extremely poor recognition by the immune system of some of the conserved regions of this virus.

An important question that remains to be answered is: why doesn't the body's immune system recognize the outer coat of the AIDS virus? Recently, Drs. Zagury and Salk and our own group began to investigate whether we could improve recognition or augment or redirect this response by active immunization. It was the demonstration that HIV vaccines administered to patients who were chronically infected could safely augment the immune repertoire against HIV. This enhanced the enthusiasm about this concept of vaccines that could be used as therapeutics. No longer does natural infection with HIV define the limits of the human potential for the immune system to generate specific immune defenses. No one today knows what immune responses are important in terms of the control of HIV, and this is a critical question. However, it is likely that the human immune system could generate those important responses if we understood which responses are critical in the control of this virus.

Currently, a variety of different therapeutic vaccine products are in early clinical evaluation to determine their safety and their impact on the ability to alter the anti HIV immune response. The comparative evaluations of these products will determine the similarities and the differences in their ability to alter the relevant immune responses and what variables of the vaccine are important. The variables include: which of the many known viral strains would be the best to use; which

cell line would best produce viral proteins; how would one administer the vaccine in terms of its conformational structure; and which adjuvants (enhancers) would be most effective to include with the vaccine proteins.

I am confident that this approach will define which immune responses are critical for the control of HIV, and that the ongoing trials of these numerous products and additional products planned for the future will provide the needed insights to define both the antiviral activities and the clinical consequences of particular immune responses. I don't believe we are limited by our biotechnological abilities but rather by the current state of knowledge about how the immune system works in terms of controlling HIV. Once we understand that, the biotechnology industry will be able to apply this knowledge to design very specific vaccines to induce very specific immune responses. Several of these products are currently being evaluated in clinical trials to determine if vaccine therapy results in any clinical benefit to patients.

The recent report by Dr. Steve Strauss — a member of Dr. Fauci's group — has demonstrated that in recurrent genital herpes virus infection, using a vaccine made of that virus's outer protein coat, they have been able to achieve a clinical benefit by reducing the number of recurrences of active herpes in infected patients.

As Dr. Gallo mentioned, other immune-based therapies are under development and these include passive antibody immunization, immune cell replacement and combination cytokine therapy, as well as attempts at the development of new strategies to reconstitute the human immune system itself.

Finally, I think that vaccine therapy and immune based therapies will likely provide a unique potential to better understand the nature of the inadequate immunity against HIV and how it can be altered to more effectively control HIV replication. This information can then be exploited in the development of a preventive vaccine. Personally, I remain optimistic about the potential of vaccine therapeutics for the treatment of HIV infection, but independent of its ultimate clinical utility, I am confident that its pursuit will provide progress in our understanding of HIV, other chronic viral diseases and cancer.

Table 3. AIDS: Some Vaccines in Development

Vaccine Name	Company	Indication	U.S. Development Status
ALVAC (rgp160)	Pasteur Laboratories	HIV positive	–
AIDS vaccine (rgp160)	Immuno AG	AIDS	Phase I
HIVAC -1e (rgp160)	Bristol-Myers	HIV positive	–
VaxSyn HIV-1	MicroGeneSys Wyeth-Ayerst	Early HIV infection HIV negative	Phase II as therapeutic Phase I/II as vaccine
HIV-1 (rgp120)	Genentech	HIV infection and prevention MN strain / III B strain	Phasel/II
EVN 2-3 (rgp120)	BIOCINE	HIV positive	Phase I
HIV-1SF2 (rgp120)	BIOCINE	HIV negative and positive	Phase I/II
HIV killed virus gp 120 depleted (RG-83894)	Immunization Products Ltd.	Treatment of asymptomatic HIV-infected patients	Phase II/III as therapeutic
HIV vaccines (gp120)	Chiron CIBA-GEIGY	AIDS	2 in Phase I
HGP-30 (p17) vaccine (r p24)	Viral Technologies	HIV prevention	Phase I
Theravir murine monoclonal anti-idiotype antibody vaccine	IDEC Pharmaceuticals	HIV positive asymptomatic patients	Phase I as therapeutic
VaxSyn HIV-1 (rp24)	MicroGeneSys	AIDS	Phase I as therapeutic
VLP-p24	British Biotechnology	HIV negative	Phase I

Source; AIDS Medicines in Development, Pharmaceutical Manufacturers Association. October, 1992.; and AIDS Clinical Trials Information Service, 1993.

MICHAEL S. GOTTLIEB, M. D.
Leading AIDS physician
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Dr. Michael Gottlieb: AIDS has changed my views about the relationship between doctors and patients. I have come to believe that when dealing with a new disease about which there are so many unknowns, the information transfer between doctors and patients must be a two way street on which patients are encouraged to share their unique experiences and to propose new ideas to the doctors, including information on alternative therapies. I believe that people with a life threatening disease must have the freedom — within reason — to seek out the treatments they feel they need.

I wonder how many healthy people have ever thought about how it feels to be a person with HIV and to read and hear the news coverage of research developments? One of my patients gave me a cartoon that describes this emotional dilemma better than anything I have seen. It shows a man walking along a sidewalk with a sad face and eyes downcast as he approaches a sign in his path which reads: "Abandon Hope." Just a few feet beyond him is another sign that reads: "Resume Hope." Many people with HIV are living their lives on such a lose hope, get hope cycle, experiencing alternating feelings of hopelessness and fantasies of an imminent cure. It is a roller coaster propelled in part by the way newsmakers release their findings and in part by the way the media covers them. Doctors like me are forced to deal with the fallout the next day.

Word from Dr. Fauci's group that the virus is hidden in the lymph nodes or that the Concorde Study casts doubts on AZT's usefulness causes people to lose hope, especially if they have been taking the drug for several years. Cover stories in national news magazines about a young Harvard researcher's eradication of the virus with a triple whammy combination in the test tube fuels the fantasy that a cure is imminent. Optimism quickly crumbles and turns to frustration and hopelessness again when patients learn that there is only a small chance that they can participate in early clinical trials, and that certain drugs will not be made available through the FDA's Expanded Access Program. We wonder why more drugs can not be made available through this program. (This type of program has been devised by the Food and Drug Administration to allow much wider accessibility to clinical trials by persons infected with HIV.)

However, while there is no question that many problems remain, I can say without qualification that doctors today have better medical treatments to offer the person with HIV than we did five years ago. Combination antiretroviral therapy — which combines AZT with it's FDA approved cousins, ddI and ddC — is now widely used in clinics early in HIV infection. Another relative of these drugs, d4T, is available through Expanded Access and the initial experience with it in my practice is very favorable. Drugs newly approved for treatment of the opportunistic infections are welcome additions. Atovaquone is a backup treatment for pneumocystis pneumonia, and fifabuton is preventative against Mycobacterium avium infection.

Growth factors such as G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte/monocyte) dependably reverse white blood cell depletion caused by AIDS or drug toxicities. Also, human

recombinant erythropoietin is useful in managing AIDS-associated anemias. Unfortunately, many insurance companies set dangerously low limits for blood counts before agreeing to reimburse for these expensive pharmaceuticals.

But major gaps remain in our armamentarium. There is no effective drug for cryptosporidium — a devastating intestinal parasite — or for the worrisome, drug-resistant TB that is becoming epidemic in this country. Sometimes we worry and ask: Does the drug industry have sufficient incentive to aggressively look for drugs for these diseases?

Despite widespread desire by patients to participate in immune boosting treatments and therapeutic vaccines, the prospects for participating are slim. You probably have heard about new research tests that measure the amount of HIV in the blood to see if drug resistance has developed, or to test whether a more damaging syncitium-producing strain of HIV has evolved.

None of these tests are available on a routine basis to help us guide therapy. When modifying doses and schedules of antiviral drugs in our clinics, we are making the best guess as to what will be effective, but such decisions should be made based more on science than on intuition.

Doctors and their increasing number of women patients need gender-specific information on hormonal and other changes caused by HIV itself or as a result of medication used to treat the virus and the complicating opportunistic infections. This information can only be generated by specific designs of trials that ask these questions about the effects of HIV in women and more affirmative action to smooth the access for women to participate in clinical trials.

With respect to children, while we now understand more about the course of HIV, problems remain in the area of treatment. Pharmaceutical companies are reluctant to commit resources to test drugs for AIDS in kids and to manufacture formulations of their drugs that can be studied in pediatric patients. HIV disease in children is largely a problem of the poor, and resources to make treatments available are lacking at many of the public hospitals where the poor receive care.

In recent years, as the HIV problem has become more complex, many Americans have joined together to urge more funds for AIDS research be allocated and to elicit a stronger acknowledgment from the White House of the scope and seriousness of this problem.

Figure 1. Estimated Global Distribution of Cumulative HIV Infection by Continent or Region, Mid-1993

Source: World Health Organization in 1993 World AIDS Day Resource Booklet, American Association for World Health

Q. Carole Simpson: One of the main reasons I accepted the invitation to be here today is because of my own personal experiences with AIDS. I have covered the issue as a correspondent for ABC News, but it has also touched my family in a very tragic way. I had a first cousin, Gregg Scott, who was reared as my little brother. We could not have been any closer. He was gay. He lived in San Francisco with his life partner and in 1988 he had a bout with pneumocystis pneumonia that almost killed him. I rushed to San Francisco General Hospital from Washington to be with him. His mother and I learned that what we thought had been a bad case of the flu was actually a case of full-blown AIDS. He recovered enough to go home and then began an odyssey of medical trials and alternative medicine and spiritual healers and macrobiotic diets and pyramids and vortexes, and he took AZT and ddI and ddC. He was part of all of the trials out at San Francisco General. He so desperately wanted to live.

I made five more trips to San Francisco during his various crises. AIDS is a terrible disease; it attacked every part of my dear Gregg's body and mind. It was even worse to watch the deterioration of a relatively young person. He died last year at the age of forty. So, I am here today for Gregg Scott and others who have died from or are living with AIDS or infected with HIV.

I want to begin our discussion by asking our panel if we are going to find a cure?

A. Dr. Fauci: It is unlikely, if we think of cure as ridding the body completely of the virus because of HIV's ability to integrate itself into the cells of the body. What is feasible, however, is to identify a combination of drugs able to suppress the virus' rep-lication safely and sufficiently so that you can tell someone who is HIV infected that their lives can be extended by decades. That is the goal that we all work for. If that is considered a functional cure, I think we can do that. That is what we are all working for.

How soon? It is impossible to predict. It would be folly for any of us to say that in a year, four years, five years, six years, this will happen. It would be inappropriate and would raise false hopes. We want to be able to be scientifically sound about it and do it as rapidly as we possibly can, but it is impossible to give a specific time.

A. Dr. Gallo: I work in an institute that's called the Cancer Institute, but 80 percent of my time is spent on AIDS work. If I didn't believe we could cure this disease, what the heck would I be working on it for?

A. Dr. Garaci: We are optimistic for the future, but although in the last years of research we have made really extraordinary progress, we can't perform miracles. In my personal view, the combination of several antiretroviral drugs with biological response modifiers point to the possiblity of immunological reconstitution. In this manner, while we cannot completely cure the disease, the possibility exists to eliminate almost all clinical manifestations and to thereby lengthen the survival of patients. Our preliminary data obtained using Zidovudine combined with thymosin-alpha-1 and alpha interferon are very encouraging.

A. Dr. Redfield: I believe very strongly that science is going to solve this problem which presently seems insurmountable. I am reminded of the late 1940's, when a mother brought her healthy child into the hospital with an infection called periorbital cellulitis around the eye. Those parents were told that child would probably be dead in five days or ten days, no matter what the doctors tried to do. No one predicted in five years that penicillin was going to come along. Today, 95 to 100 percent of those children are cured. I believe that science is going to solve the AIDS problem. None of us can predict when, but I believe it is going to be sooner rather than later.

THE ADVOCACY/JOURNALIST PANEL

Q. Dr. Robert Darga: There are mixed feelings whether a cure will ever occur, but some persons survive for very long periods of time, doing quite well. Many in our community wonder why the long-term survivors haven't been studied adequately, and they have begun to question whether we may have been chasing the wrong cell line and focusing exclusively on the decrease in CD4 cells. Long term survivor studies show there is a significant role of CD8 cells in the survival in some fraction of patients.

Dr. Gottlieb, as a leading clinician, do you see correlation between survival and CD8 cell counts? What treatments, either from standard or alternative medicines, do you think help maintain those levels. How important in your mind is the role of cellular immunity in survival of this disease?

A. Dr. Gottlieb: Let me take the last question first. I think that cellular immunity is critical in survival with HIV disease, but I don't think its simply quantitative — that is, the number of CD4 cells. I think it is a functional thing related to a specific type of CD4 cells, and I think it is critically important to know more about people who are long-term survivors and whether that correlates with a CD8 subpopulation of cells. As to what drugs or alternative treatments augment that specific population, I could not even venture to speculate, since we haven't identified the critical subpopulation of CD8 cells.

Q. Dr. Darga: The recent reports by Dr. Gene Shearer at the National Cancer Institute and Dr. Salk from the Salk Institute have raised the issue of two different types of immune response: a TH-1 response which is primarily a cellular response versus a TH-2 response which is antibody production. It is speculative at this point, but, Dr. Garaci, it seems like some of the work you are doing would favor this theory.

A. Dr. Garaci: The TH-1/TH-2 hypothesis certainly is something that needs to be pursued. Hopefully, we can do so both in an animal model and in long term survivors. We are examining many of these to see if there is a predominance of the IL2, interferon-gamma or TH-1 response over that of the IL4, IL5, IL10, TH-2 responses which — at least theoretically — might be detrimental in certain models of chronic infections such as cutaneous leishmaniasis. Whether or not that pertains directly to HIV is uncertain at this time. So, although it is an interesting theory and certainly needs to be pursued, it is really unclear whether that imbalance between TH-1 and TH-2 is, in fact, going to be the answer. I think it is worth vigorously pursuing which one can do through the cytokine network, since different subsets of T-cells secrete different cytokine profiles.

Q. Dr. Darga: I would like to ask Dr. Fauci if his new lymph node studies shed any further light on the TH-1 and TH-2 question?

A. Dr. Fauci: We are actually looking at that right now. We've developed specific probes for the whole array of cytokines and are now probing the lymph node's CD4 and CD8 cells to determine if there is any change in the cytokine profile as the disease progresses in people with early — versus intermediate — versus advanced — disease. We are also in the process of admitting several people who have been infected with HIV for ten years whose CD4 counts show a positive curve up. We are going to study their CD4 count, and by probing with quantitative PCR (polymerase chain reaction), we should be able to determine if there is a unique ctyokine profile in people who are long term survivors.

Q. Dr. Darga: Mention was made earlier about CD4 counts, and with the recent results of the Concorde Study (a long-term European study indicating that the use of AZT — both when started early and late in infection — made no difference on patient outcome) have thrown in doubt CD4 counts as surrogate markers (indirect measures of disease progression and/or drug efficacy). That's still open to interpretation, so could you comment on what roles surrogate markers should have in determining treatments and in managing patients. Can we rely on CD4 counts to determine choices for prophylaxis therapy?

A. Dr. Gottlieb: I haven't seen enough of the Concorde Study data to know whether what you say is true. In other words, whether CD4 as a useful marker has been seriously damaged. My opinion is that CD4 is one of the most reliable parameters which we have at this point with respect to when to initiate prophylactic treatments of opportunistic infections. I think we have good data on that subject. As I said earlier, we need better tests to evaluate syncytia-forming strains (the more aggressive, immune system damaging strains of HIV) and better tests for determining resistance in patients in order to be able to make better clinical decisions.

A. Dr. Redfield: I think it is important to acknowledge that we all understand the importance of CD4 cell numbers in patients, but as we begin to explore both drug and vaccine interventions, we really haven't validated the best way to understand whether these surrogate markers equate with prolonged survival. It is important to recognize that not just the CD4 cell numbers but ways to assess their functional capacity are important. We do need to validate what markers to use clinically, in terms of whether they really indicate that prolonged survival can be influenced by different drugs. I think there is a possibility that there can be dislinkage between some of these surrogate markers and prolonged survival.

Q. Dr. Peter Hawley: We have heard how the HIV virus starts to multiply and continues to multiply throughout the life of an HIV-infected person. This suggests that early treatment would be of primary importance if we wish to stop the ravaging effects of this disease. On the other hand, we have the results of the Concorde Study which suggest that, at least in the case of AZT, treating patients too early may not be of much long-term effect. What advice do you have for physicians and patients right now, as far as deciding when to start retroviral therapy and what to start it with?

A. Dr. Fauci: I think the answer to that question will be clarified at the consensus conference NIH is sponsoring in June. All of the data from the Concorde study, as well as the data from any of the other studies, will be available for consideration. On a practical level, if you put somebody on AZT and their CD4 cell count continues to decline, or if they show other signs of disease progression, you don't leave them on monotherapy with AZT. You either switch them to another drug or add another drug in combination. I would be hesitant to make a recommendation prior to the consensus conference, but I think the Concorde data and data from other studies may lead to a change in the current recommendations. It's a personal trade-off. Do you start antiretroviral therapy early when the CD4 cell count is 450 knowing that may compromise a benefit later on, or do you wait and see and thereby avoid all the possibilities of toxic side affects? What I pay more attention to than the absolute number of the CD4 cells is the slope of the decline of the CD4 cell count. If somebody

has a CD4 cell count that is 475 and it remains stable, I won't put the person on AZT under any circumstances. If somebody starts off with 600 and then goes to 500 then 300 and the decline is rapid, I would initiate antiretroviral therapy to try and cut off the viral replications. So I don't think we should be wedded so strictly to evaluating the absolute number of CD4 cells, but look at the whole patient and evaluate their clinical course.

A. Dr. Garaci: In Italy, it is recommended that therapy with AZT begin when the number of CD4 is down to 500, but as I said before, I think that much more important is the study of functionality of CD4s. So I think it is better to depend on the functionality of CD4 as the indication of when to begin the therapy.

Q. Mr. Jon Cohen: Last fall, the Food and Drug Administration (FDA) passed a regulation called the Accelerated Approval Regulation which calls for speeding the approval of new treatments based on endpoints in trials that are short of disease and deaths. In other words, looking for things like CD4 count changes and changes in viral load and other parameters. I am curious what the panel thinks would be convincing evidence to them that a therapy was working. What would you need to see if you were sitting on an FDA Advisory Panel in order to say: I think this should be conditionally approved and later taken off of the market if it doesn't, in fact, improve health and slow death?

A. Dr. Gottlieb: I think stability of or increase in the CD4 count over time, decline in plasma viremia or, if we had a better test, to get at viral activity in the lymph nodes, an observed improvement there. These endpoints might convince me — short of survival.

Dr. Redfield: I once thought it was going to be pretty straightforward that we could validate surrogate markers. For example, the rate of CD4 decline or some absolute CD4 cell number. I think, again, that it really is important to try to validate these surrogate markers in terms of what they mean in terms of survival. I don't know exactly how this consensus conference is going to come out regarding different therapeutic advancements, but I do think that there is a tendency for us in our desire to make rapid advancements to sometimes make mistakes. I think functional immunity associated with prolonged survival and the absence of developing clinical immune deficiency is what's going to be the most meaningful to me at this time. If we spend the energy to validate what these surrogate markers mean, once and for all, then all of HIV therapeutics could take advantage of them. We would know that they mean something and this would truly accelerate the whole process of AIDS therapeutic approval. Until we do know that for certain, we will continue to debate and change our opinions.

Q. Mr. Cohen: If I could paraphrase you, are you saying that the FDA Accelerated Approval Regulation isn't really meaningful until we have validated surrogate markers?

A. Dr. Redfield: I think people know that in the past I was a big proponent that CD4 cell count and viral burden measures would basically lock this up, and thought we would be able to prove that drugs work or vaccines worked. I am more skeptical now. This is new technology we are applying, and we are not sure what many of these new assays mean in terms of overall viral replication. For example, I am not sure what plasma viremia means to total body viral load. I am not sure what a CD4 cell count of 300 means in an anergic patients,

when the count rises to 600 and they remain anergic. I am not sure what it means if someone's CD4 cell count is 300 and they drop to 100 and still retain functional immunity. I think that if we designed trials that could prove different therapeutic strategies in such a way that they would also validate these endpoints, then we all could take advantage of them and could lay this to rest. That would be a great advantage for all therapeutic vaccine development and, eventually, I think the process will be accelerated so that you know if the plasma viremia goes down it means that's a good thing, or if the CD4 cell count stays stable that's a good thing. Right now there is still a lot of uncertainty that needs resolution.

Q. Mr. Cohen: It seems to me that there is a question about the value of the FDA's Accelerated Approval Regulation and what it means. After listening to Dr. Redfield, I am having a hard time coming to terms with what it means, and I am curious whether others are too. If they can make some sense of it, how can it be applied in 1994? Does it have value right now?

A. Dr. Redfield: I think we need to reconsider what an early transient rise in CD4 count means. Hopefully, the Concorde Study will give us more information on that, but what it is starting to look like, at least with the nucleoside analog such as AZT, is that a transient increase in T4 cells may not be prognostic of what is going to happen during the course of the infection in any specific person. Whether that invalidates any assumptions that were made about drug approval it is difficult to say, but we need to face the fact that an early little blip may not necessarily mean much — depending upon what the drug is. Personally, I would hope that as we get more available, inexpensive ways to quantitate virus, actually show that there are changes in viral replication, and collaborate that with what is going on in the lymph nodes. That would be a viral based test that tells us we are actually cutting down viral replication. I don't know whether we are going to have that, but to me that seems to be the soundest way to do it, because maybe you actually cut off the viral replication. However, it's possible that a person's immune system is incapable of spontaneously regenerating itself, and although you don't see any affect at all on the CD4 count, an antiviral may really be a good drug. That could be the case.

Q. Ms. Vivian Torres: Dr. Fauci, since women have different reproductive and hormonal cycles then men do, and since many women have reported menstrual irregularities when they are going through drug trials, why docsn't an experimental trial ever document gynecological symptoms? I am an example myself. I just joined a d4T (antiviral drug under investigation) profile trial and in none of the information they have given me is there a specific warning that if this or that female-specific symptom appears, what to make of it, and whether or not it should be reported. How are you going to make sure that these assessments on gynecological problems become part of overall clinical assessments?

A. Dr. Fauci: You make a very good point. There should be, and there will be. In fact, in association with the Women's Committee of the AIDS Clinical Trials Group we are going to do just what you are talking about. Not only to make assessments of the kinds of things that are gender specific for women, but also to add examinations that are not routinely done part of the evaluation process so that we can get a better handle on the array of opportunistic diseases specific to women — such as chronic pelvic inflammatory disease and cervical dysplasia that may lead to cervical carcinoma.

Q. Ms. Torres: Generally women with AIDS have been using drugs that have been experimented with on men. I have to educate my women so that when something goes wrong, they know to go talk to the doctor, even though they did not tell you that this might happen. They always talk about neuropathy. They talk about pancreatitis. They talk about all of this, but they forget about women's symptoms. And when a women gets a recurrent discharge or vaginal infections, they think it is natural for them to get this, because they are HIV-positive, instead of linking the problems to the new medications they are taking.

A. Dr. Fauci: There has been a problem in getting women accrued into drug trials, which relates to multifactorial problems within the healthcare delivery system. In an inner city area, where people are disenfranchised anyway, it is very difficult to get any kind of health care, particularly for people who are HIV infected. To overcome this problem, we are developing community programs that go into the inner city areas and recruit more women for the trials. Also, as part of the competition for clinical trial funding, we are making it very clear that applicants will be judged on their ability and their intention to enroll more people of color and women in clinical trials.

A. Dr. Gottlieb: I think it is very difficult for women with HIV infection to access the healthcare system even for basic care, and clinical trials represent a step beyond that in terms of sophistication. Until recently, they have been badly isolated with HIV infection and may not know other women with HIV infection. It is only in the last couple of years that groups have formed to advocate the need for more services and research for women and more opportunity for women with HIV to interact with one another and to decide what their priorities are.

Ms. Torres: There have to be more agencies funded by the government that are willing to help these women, so they can join these trials and be a part of them. Another very important thing is that while you can get the women to come into the clinical trial, women who are HIV infected not infrequently have a child who also is HIV infected, as well as a lover or husband. They don't come to clinic because they can't afford transportation, so we need to add funding for the ancillary services such as this and for child care. This is part of the whole healthcare delivery process that, obviously, needs revamping.

Q. Dr. Hawley: As the demographics of the HIV infected have continued to expand to include new groups, there is one group to which little attention seems to have been paid. One is the aging population in this country. Are there any data on the difference in pathogenesis of HIV infection in older people, and if so, are there any studies planned specifically to look at the importance of the modifications in those advancing in HIV disease, as far as treatment advances go?

A. Dr. Fauci: There are not enough people: if one thinks of the median age of HIV-infected individuals, you are talking about the twenty- thirty- forty-year old group. With the exception of some transfusion recipients, there are few HIV infected patients in the aged population. What we do know from prospective studies is that in the hemophiliac population there seems to be a greater rate of progression of disease in the older patients than in the younger patients. This may be a clue to the integrity of the immune system which generally diminishes with age. It may be that the reserve of a youngster who gets infected is greater than the reserve of someone who gets infected at age 65. Although, if we are successful in

delaying the onset of disease in the HIV infected population, we will have the opportunity to study older people who have been infected for thirty years and are still alive and well. I hope we get to that point sooner rather than later.

The only studies that we have that really compare older individuals with younger individuals are the hemophiliac studies, and they clearly indicate that older people do not do as well, even if the mode of infection is exactly the same.

This is not the case with infants, however. You have to be careful when you are talking about infants. If an infant — a fetus — becomes infected in utero, it is very likely that there will be a very fulminant course of illness, given that the virus has had the opportunity to destroy precursor cells very early on in the development of the immune system. On the other hand, if an infant becomes infected at birth or immediately after birth, the infant will have a disease that is somewhat similar to the adult.

Q. Mr. Cohen: Everyone, from Bill Clinton to AIDS activists, has been calling for a Manhattan-style project to speed the search for a cure and a preventive vaccine. Being that Drs. Redfield, Gallo and Fauci come from three different parts of the United States government, I am curious about what they think of that proposal and whether they think they could collaborate more and set a research agenda more tightly and speed the search for a cure and a preventive vaccine.

A. Dr. Redfield: There is no question that the efforts can be better coordinated. Clearly, the big issue behind this idea of a Manhattan project is to develop an overall plan with milestones and assignments in a coordinated fashion. A careful, coordinated process that goes from step to step to step to step, building to an ultimate solution to the problem in which a variety of different approaches are better coordinated wouldn't be unreasonable at this point in time.

A. Dr. Gallo: I think that this idea means different things to different people, but my answer is yes. I do think such an effort makes sense, but I don't know if we have time to discuss what I would think would work. However, briefly, yes, we can do better, and none of us are ever going to say we are doing the best we can do. I think an experiment that brings together the very best people in all areas of AIDS research would be useful, interesting and inspiring. This would not be in competition with NIH funding, and I can't say what the monetary level should be, but I think it would be inspirational to combine some of the best people to devise strategies — from basic research to therapy. We have to have international cooperation obviously, but often we don't define what we really mean. Without that understanding, we end up talking and meeting each other a lot, saying the same things again and again. To me it would be inspirational to see a focused, hyperactive, concentrated effort of the best possible people defining the priorities together and then funding a limited, very specific new type of multidiciplinary study.

Mr. Cohen: Just as food for thought: There is a $100 million discretionary fund in the new Office of AIDS Research at the NIH, and there are people who are talking about siphoning off some of that money to fund such a mini Manhattan project.

AUDIENCE CONCERNS

Carole Simpson: Now we are going to broaden our dialogue to include members of the audience. We begin with an important group of young people who earlier today participated in a *Student Symposium on AIDS Research.* These seventy minority students who have chosen career paths in health care, join us from the "Health and Human Services Academy of Eastern High School" in Washington, D.C. and from the program "Raising Hispanic Academic Achievement" in Maryland. I will begin our audience question period by having one of these students ask the first question.

Q. My name is Maria Segata. I am eighteen and attend McGunther High School and the Raising Hispanic Academic Achievement Program in Silver Spring, Maryland. My question is: What kind of central efforts, nationally and internationally, are there to advance research and treatment in AIDS?

A. Dr. Gallo: Scientific collaboration comes as advances occur and, with them, the mutual ability to help one other. There is quite of bit of interchange, quite a bit of contact via fax and telephone and at scientific meetings. For example, where I work at the National Cancer Institute at NIH there are collaborative research agreements that form between different groups, nationally as well as internationally. For example, we have several vaccine development projects that involve our laboratory with foreign laboratories and even foreign companies. This is not done formally but are official NIH collaborations that involve international relationships, one institute with another institute.

A. Dr. Fauci: There are a large number of collaborative efforts and consortia that are organized through the federal government and implemented through universities in this country as well as internationally with the health departments of other countries. A good example of the kinds of exchange of information is going to take place in Berlin next week at the International Conference on AIDS. There the broad scope of all AIDS research will be considered. There is also a considerable amount of collaboration and exchange of information at the national and international level on subtopics within AIDS research such as vaccine and therapeutic research.

A. Dr. Garaci: We have many types of collaboration in Europe. For instance, we organize some clinical trials such as those showing the association between AZT, ddC or ddI, or the association between AZT and interferon. We have also very intense collaboration between Italy and the United States. However, we need to increase the level of international collaboration as I think that only together can we win the fight against AIDS.

Q. My name is Darien Cane. I attend Eastern Senior High School Health and Human Services Program. My question is: What is the difference between envelope and p17 treatments or vaccines and what are they?

A. Dr. Redfield: The virus has many different proteins. Dr. Salk's vaccine, for example, uses the whole virus in which one of the viral envelope proteins has been

depleted. The vaccines that the Genentech company makes have just the envelope protein called GP120, which is one of the outside proteins that covers the virus. The MicroGeneSys' company GP160 product that we have also worked with has both of the outside proteins. Dr. Goldstein's vaccine is made of one of the inside proteins, p17. So, there are a series of the different components of the virus, and they all should be looked at because none of us know what the critical Achille's heel of the AIDS virus is. I assume that other people will make other vaccines that use different pieces and combine them and make them in different ways. In that process, we will learn what the Achille's heel of this virus is, so then we can more directly make second and third generation products.

Q. My name is Dawn Eden Goldstein from New York City. I have a friend there named Charles who is HIV positive, and I would like to ask this question on his behalf. Late last year Charles was in the hospital diagnosed with cryptosporidium, which Dr. Gottlieb spoke of as one of the ailments for which there is no cure. While Charles was in the hospital he was told that there was a 100 percent mortality rate for AIDS sufferers with cryptosporidium. Well, miraculously, he got better. A few weeks ago he was back living independently at his own place, going to work, gaining weight and everything. So, my question to you, Dr. Gottlieb, is in two parts. First, is that 100 percent mortality rate that Charles was given true, and, if so, does that mean that as far as the medical profession knows, Charles will have a relapse?

A. Dr. Gottlieb: No, it is not true. People who are not immunocompromised get cryptosporidium. There was a big outbreak in Milwaukee recently, and it was a self limited illness with two to three weeks of symptoms. Some people with AIDS or HIV infection are able to throw off cryptosporidium, which usually correlates with the CD4 count.

There are also a number of medicines which are tried for cryptosporidium, such as the antibiotics called paromomycin and azithromycin. It is not a hopeless situation, but we don't have a cure for cryptosporidium in the person with very advanced AIDS and very low T-cell counts. Dr. Fauci, did you want to add something to that?

A. Dr. Fauci: I just think it is unfortunate that a physician would say to a patient that they have a 100 percent chance of mortality when they have a certain infection.

Q. My name is James Watson from Watson, Walker and Associates lobbying firm. Dr. Mohammed from Washington, D.C. came up with Kemron and Immunex, two drugs for people with melanin in their skin. It seems to help them as far as HIV is concerned. It seems to arrest the disease at some point. The government told him he couldn't work with it anymore. Then NIH decided that maybe there was some promise with Kemron and Immunex. So, all of a sudden, NIH is doing a project with Kemron and Immunex. My question to you is: Do people with melanin in their skin respond differently to different drugs such as AZT, Kemron and Immunex, and is there a better response with Kemron and Immunex and, if so, why and how?

A. Dr. Fauci: A number of studies have indicated that, all others things being equal, an African-American will respond the same way to a drug like AZT as a white person

will. The Kemron Study that you are referring to — which actually is a number of studies — has shown that patients show no objective changes. Some physicians, including Drs. Mohammed and Justice, have indicated that when they treat their predominantly African-American patients with low-dose oral alpha-interferon (which is the sole ingredient of Kemron or Immunex), their patients report positive subjective changes; that they actually feel better. On the basis of these reports and in collaboration with Drs. Mohammed and Justice, there will be a NIH-sponsored trial looking at low-dose alpha-interferon in several clinics. This clinical trial will ask and, hopefully, answer the question of whether the drug works. If it does, we want to make it available as quickly as possible. If it doesn't, we will encourage patients to discontinue their use of the product.

Q. My name is Reshita Cooley. I am a student of Health and Human Services at Eastern Senior High School, and my question is about newborns. Is it possible or has there been a case where newborns diagnosed with HIV or AIDS are able to overcome it because of a strong new immune system, and if so, are they able to contract the AIDS virus again?

A. Dr. Fauci: There have been a number of studies that show that about 20 to 30 percent of the children born to mothers that are HIV-infected become infected with HIV. That means that 80 to 70 percent don't become infected. Investigators have begun to try to carefully characterize the immune responses directed against the virus in these children in the first year of life. There have been several preliminary reports that suggest the possibility that the cellular immune response of some infants may clear their infection. These results are still speculative, because another possibility is that the child mounts a cellular immune response which is a result of their exposure to the virus proteins of the mother.

There is an enormous amount that we could learn in terms not only of treating HIV infection but also in understanding how to prevent HIV from being transmitted, by continuing to study the mechanisms of perinatal transmission. One would also hope that such studies will eventually lead to an effective therapeutic intervention for HIV-infected pregnant women to prevent transmission to their infants.

Q. My name is Mora Montoya. I am the director of the HIV Legal Clinic at the D.C. School of Law. I was diagnosed with HIV in October of 1991 and went into a serious depression. But I have always believed that action equals life and silence equals death, so I pulled myself out of it, and I am doing all kinds of things now. I am a poster child with the Living with HIV Campaign. I am part of the HIV Peer Network, going out and speaking to my peers, lawyers, professors and judges. I am also a candidate for the D.C. City Council because I believe we need to have people who are HIV infected in the seats of power. My question is something Dr. Gottlieb alluded to: During my depression my T-cells dropped to 320 and two weeks after I filed for D.C. City Council they bounced to 797. So I believe that taking action and taking charge of your life has a serious effect on your immune system. I would like to find out what you believe in terms of the effects of somebody's mental state on the immune system?

A. Dr. Fauci: The immune system is an organ system that we still need to learn a lot about. There are no hard data that demonstrate that if someone gets depressed that their CD4 cell counts will drop, and if they get out of a depression that their CD4 cell count will go up. But the point that you bring up transcends this issue. A positive attitude — like you apparently have now — is clearly a great benefit to people with any kind of illness, particularly an illness that can become a chronic illness like HIV disease. We may not be able to quantitate this benefit like you quantitate a CD4 cell count, but at least in my own experience with patients, people who have a reason to get up in the morning and really want to do something and make a contribution seem to do better than people who have essentially given up.

A. Dr. Gottlieb: I have two things to add. First, I think there is at least one study that I saw in abstract form from San Francisco that suggested that a serious depression was a negative predictor with respect to CD4 counts. I agree with Dr. Fauci that people who take charge, who are empowered, who empower themselves have a good prognosis, functionally. But I hasten to add that there are some people who take charge of their lives and don't do well, and I don't think there is anything deficient about their response.

Q. My name is Steven Thomas. I am an associate professor in the Department of Health Education at the University of Maryland. My question is about recruitment of minorities and women to clinical trials. But to set the premise — Dr. Redfield, help me out here: If an HIV-negative person takes a vaccine would they then be HIV positive?

A. Dr. Redfield: If an HIV negative individual is vaccinated, for example, with an enveloped based vaccine like the ones we have been using, they would develop antibody that would recognize the envelope of the AIDS virus, and the standard screening test would be positive. But by doing other tests, you could show that they weren't actually HIV infected.

Q. Mr. Thomas: So when they went to give blood at the Red Cross, they would be HIV positive?

A. Dr. Redfield: They would be screening-test reactive and their blood would not be utilized for transfusion. However, they would have the second test, which would be non-confirmed as HIV infected.

Q. Mr. Thomas: A lot of people who are HIV positive face tremendous discrimination in this country, and I think that scientists like yourself must recognize that your breakthroughs may fail to have an impact if we still have a social environment where people will be discriminated against because of their HIV status. People can't buy a home because they are being requested to take an HIV test in order to get insurance for their house, for example. Can any of you speak to the extent to which the current social environment, homophobia, racism and discrimination might actually impede your ability to come up with an effective treatment and cure for AIDS?

A. Dr. Fauci: There is absolutely no question that all of us are proponents of the importance of early diagnosis. If you are diagnosed with HIV early you can seek and get treatment and learn to reduce the risk of unknowingly transmitting this virus to

someone else. The perceived negative social consequences of being HIV-infected discourages those at risk from being tested. There is absolutely no question that if people are afraid to know if they are infected, it inhibits their ability to get optimal healthcare and impairs the public health community's ability to try to decrease the spread of this disease. In addition, this clearly inhibits the scientific and medical community's ability to work towards a solution for this problem.

A. Dr. Gottlieb: I don't think you are going to get much disagreement from the members of this panel with respect to what you said, and if anyone has heard Dr. Jonathan Mann (former director of AIDS for World Health Organization) recently, he has identified discrimination as the single most important factor related to the spread of HIV around the world.

Q. Sandra Quinn, from the Minority Health Research Laboratory at the University of Maryland. I have a question about pregnant women and clinical trials. To what extent are any of the antivirals effective in preventing transmission to the fetus, and is there any evidence of birth defects or other genetic damage to that fetus from the medications?

A. Dr. Fauci: Clinical trials concerning this issue are ongoing. If there was 100 percent HIV transmission rate from mother to infant, it would be easy to give the mother AZT and determine whether or not the virus was being blocked. But since there is only a 20 to 30 percent rate of transmission — and this rate varies with the stage of disease in the mother — the answer to the question of whether or not AZT can inhibit transmission is going to be very difficult to determine.

Q. My name is Allen Ritter, and I am with Act Up, D.C. Dr. Gallo, the current research effort is following the National Cancer Institute's model, which is early detection followed by toxic treatments that extend life for a few years at best. In fact, the first three approved treatments for HIV — AZT, ddI and ddC — are actually abandoned cancer chemotherapy treatments that were taken off the shelf and tested against HIV. I think this rigid approach has stopped creativity and led to a lack of new, perhaps non-drug, approaches. Do you really think that the failed War on Cancer should be the model for AIDS research?

A. Dr. Gallo: I don't know how to begin to answer you. I don't run clinical trials. I work in a research laboratory, but I will tell you what I think. There isn't any simple model for the National Cancer Institute, but if you mean — did the AIDS program get at least partially modeled after what NCI has done in the past with cancer therapy? — I think the answer is yes. In terms of notions of combination chemotherapy, in terms of pharmacological studies, in terms of dealing with the FDA, etc. — the Cancer Institute's administrative and clinical people provided some help in organizational studies and FDA relationships as well as sharing expertise in pharmacology studies with other institutes that didn't have that experience at the beginning of the AIDS research. I have no model for AIDS. I have a model of what I see in laboratory studies, what I see in my own research studies. We use our minds collectively, and we try to understand how the virus works and try to think how to solve the

problem to the best of our ability. That is how it goes. I don't have an institute or a clinic. I have a laboratory. I can't answer your question any better than that. But when you talk about cancer you are not talking about one disease but perhaps fifty, a hundred or two hundred different diseases. You have to understand that.

Q. My name is Eric Turner. I am a thirty-two year old African-American male and work as a HIV and AIDS educator/counselor. As Dr. Gottlieb said, when are we going to be allowed to work with these doctors for living a life of better quality as opposed to quantity?

A. Dr. Fauci: We get very important information from our patients and the activist community. One of the important aspects of the AIDS epidemic is that the HIV-infected community has become involved in the decision-making process related to the treatment of their disease. I think we will see this activist model adopted by other patient communities in the future. We do listen to our patients and constituencies.

A. Dr. Gottlieb: I would agree with what Dr. Fauci said. There is no other illness or condition where there has been such a close knit relationship of patients and physicians and activists. Other disease constituencies are using the HIV epidemic as a model for turning more attention to both quality and quantity of their lives. At the primary care physician level, there is a lot of give and take between physician and patient.

Jackie Sadly, D.C. public schools' HIV/AIDS Education Program. I would like to ask you to please do not say HIV virus. You either have to say HIVD virus or the AIDS virus. Otherwise, our young people think there is a virus that causes HIV and a virus that causes AIDS. So, if you will, for the sake of our young people say HIVD virus or else the AIDS virus.

Carole Simpson: Thank you. I would like to thank the audience members and members of both panels for the excellent questions and informative answers we have heard this afternoon. What we have heard gives us some guarded hope that we are on the right track toward finding treatments for HIV infection and its opportunistic infections, but we should not leave here tonight without focusing for a minute on one scientific fact that is uncontested: that is that HIV transmission is preventable. While these scientists struggle in the labs to find the vaccines and treatments for HIV, we must all commit ourselves to redoubling our efforts to stop the spread of HIV in our communities. We must all continue to inform, educate and advocate if we are to bring about the end of this epidemic.

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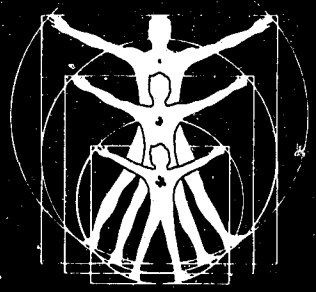

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