TREATMENT ACTION GROUP

Basic Research on HIV Infection: A Report From the Front

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Introduction

For over five years now, AIDS activists have focused their energies on clinical research and the drug development process, hoping to speed promising therapies for HIV infection to the people who need them. We have watched as AZT and then its cousins, ddI and ddC, have slowly crawled through clinical studies and on to the market. However, as the preliminary results of the British-French Concorde study have underscored, AZT and the other nucleoside analogues have only a limited usefulness.

Our efforts have not only been concentrated on treatments targeting HIV. In December of 1991, AIDS activists with ACT UP New York's Treatment and Data Committee launched a campaign, Countdown Eighteen Months, to expedite research on the opportunistic infections that affect people with AIDS and the development of treatments and prophylaxes for these conditions. More recently, Project Inform of San Francisco has enlisted prominent AIDS researchers to take part in its Project Immune Restoration, a think tank devoted to developing immune-based interventions for people with AIDS. Despite all our efforts, new treatment strategies are desperately needed for people living with HIV, yet there are few new drugs on the horizon.

In 1992, the Treatment Action Group commissioned a study of the AIDS research programs sponsored by the U.S. National Institutes of Health. While AIDS activists had scrutinized the clinical trials networks run by the federal government in excruciating detail, no one had ever taken a look at the entire portfolio of AIDS research activities being sponsored by the NIH. TAG issued its report on the NIH AIDS research program at last year's International Conference on AIDS in Amsterdam.

The report cited a lack of coordination and direction within the program as a whole, and proposed a sweeping reorganization in the management of the effort. In particular, the TAG report outlined a proposal for the strengthening of the NIH's Office of AIDS Research to serve as the central coordinating and planning body for all research on the disease throughout the NIH. TAG's proposal for the Office of AIDS Research, with the support of the Clinton administration, prominent extramural scientists, and members of Congress, has been included in the reauthorizing legislation for the NIH and will be signed into law in the near future.

However, even our best attempts to grease the wheels of clinical research and to bring a coherent management strategy to the administration of AIDS research as a whole will draw us no closer to a cure unless we make significant advances in our basic knowledge of its pathogenesis. Right now, we stand on the edge of a vast abyss of scientific ignorance which we must traverse if we are to develop rational therapies for HIV infection. The lives of millions of people worldwide hang in the balance. The world of basic research on AIDS is the final frontier for AIDS activists; it is here that we make our last stand.

We must forge a partnership with those scientists who have devoted their lives to studying the basic biology of HIV and the immune system and quicken the pace of discovery. This will demand new collaborative efforts and structures to link pathogenesis with clinical research.

The progress of science is often said to be incremental with as many advances developing out of serendipity as grow out of years of diligent experimentation (though controlled data are never cited to prove this assertion). The idea of accelerating the rate of scientific progress in AIDS research may therefore sound hopelessly naive. Nonetheless, TAG decided to ask thirty-six leading basic scientists working on AIDS in the United States to outline the scientific challenges for the field in the years ahead and the ways in which they thought their work could be better facilitated.

The following report is a synthesis of the comments of these researchers. It is intended to provide a survey of the state of basic research on HIV infection from the scientists at the bench. We also hope that the report will highlight the importance of the work being done. Unlike clinical research in AIDS, basic research has not had a powerful constituency to advocate on its behalf. The relevance of basic science to the lives of PWA's is far less apparent than clinical studies which hold the promise of proving a new drug's efficacy. Yet, new treatment options for people with HIV and a vaccine to protect the uninfected largely depend on the success of basic investigation. Finally, the report offers an assessment of the non-scientific obstacles confronting these scientists in their day-to-day work and practical recommendations to move these hurdles aside.

Materials and Methods

Thirty-six basic scientists working in AIDS were interviewed, in person or by telephone, during April and May of 1993. The majority of those interviewed were academic scientists affiliated with universities, medical schools, and teaching hospitals. The others interviewed were predominantly drawn from the ranks of intramural researchers at the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, NIH, with two others representing, respectively, industry and Department of Defense-supported research. The researchers interviewed work in a variety of disciplines, including virology, immunology, and molecular biology and have a wide range of specific professional interests. An attempt was also made to talk to both senior established investigators, as well as up-and-coming younger scientists.

Each researcher was asked to address two general topics:

- The key scientific questions facing basic AIDS research;
- The practical, non-scientific problems confronting their work.

While individual contributions to this project are acknowledged below, their specific comments will remain unattributed. The promise of a certain amount of anonymity provided a degree of candor in these discussions which may not have otherwise been achieved.

The report is divided into three sections. The first addresses the scientific issues brought up in the discussions; the second, the practical problems of most concern to researchers; and the third outlines some practical means of remedying the situation. While there was wide agreement on the importance of many scientific and non-scientific issues, no opinion was shared by all. A few topics strongly divided the scientific community sampled in this report. An

attempt was made in this report to present both sides of the contentious issues as well as dissenting opinions where most agreed.

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Part I: Scientific Issues

Three scientific areas were mentioned so often that they deserve to be recognized conceptually as encompassing many other points, and for these reasons we list them here first. Each area points to the need to take basic AIDS research from the pristine in vitro laboratory setting to more difficult, but critical, work with wild-type HIV isolates and clinical samples, often using in vivo settings with animal models or humans. After twelve years, we may "know more about this virus than any other in history," as researchers constantly chorus, but we yet lack the most crucial knowledge of all - how it makes people sick.

Correlates of Immunity

The correlates of immunity to HIV infection - both immunity protecting against infection after exposure, and immunity protecting against immune dysregulation after infection - hold the key to designing effective vaccine and treatment strategies. These can be broken down into the cellular and soluble components of the cell-mediated and humoral branches of the immune system, and their interaction with HIV infection and other pathogens at all stages of HIV disease. Thus, many researchers interviewed asked a plethora of questions focusing on this labor- intensive, understudied area.

For example: What is the specific nature of the immune response one would hope to elicit in designing an effective prophylactic vaccine against HIV? Would one hope to evoke a strong neutralizing antibody response, a strong cytotoxic T-lymphocyte (CTL) response, a combination of the two or none of the above? Against which part of the virus would one hope this immune response would be directed: the outer sugary envelope of the virus, its capsid proteins, its RNA-bearing core, or yet some other viral component? What will protect against infection? Does infection most often result from cell-free or cell-associated HIV? Most who commented in depth on the topic agreed that a successful vaccine will induce a broadly-reactive neutralizing antibody and CTL response, although there were several individuals that stressed the importance of the latter in protection.

There were numerous specific questions raised regarding the nature of the correlates of immunity to HIV infection. The first group of inquiries focused on the humoral response to the virus, including: What is the extent of cross- reactivity and cross-neutralization by anti-HIV antibodies against various virus isolates? When protection is achieved, what parameters of antibody specificity and reactivity correlate with protection? Can protection be achieved against primary isolates as well as laboratory isolates? What is the difference in the way primary isolates and laboratory isolates are neutralized and why do they appear to have different levels of sensitivity to in vitro neutralization? Does antibody confer sterilizing immunity? Does antibody prevent against infection with cell-associated virus? What is the extent of cross-reactivity and cross-neutralization between the five subtypes of HIV-1 that have been identified on the basis of sequence analysis? Which neutralizing antibodies, if any, will protect in vivo? Do anti-CD4 binding domain antibodies (or other antibodies to host proteins carried on the viral envelope) have a role in in vivo protection? Are there conserved epitopes for neutralization (if so, these will be critical in developing vaccines for worldwide use)? What, if any, is the in vivo role of enhancing antibodies to HIV?

The remaining questions in this area spanned a wide array of scientific and practical issues: Are there particular phenotypic virus variants which are important to target, such as macrophage-tropic, non-syncytium-inducing strains? Do immune responses to cellular proteins associated with the viral envelope offer in vivo protection? Is the type of helper T-cell response (TH1 vs. TH2) generated by immunization important in conferring protection? Can we generate protective immune responses using epitopes in gag, nef, or pol as targets for CTL or antibody? Do we need to know correlates of immunity to proceed with vaccine trials now? Can one protect against different strains, infection through mucosal routes and through cell-to-cell contact? What is the role of IgA antibody in mucosal protection?

"In Vivo Veritas"

One frequently mentioned issue that cut across virtually all of the scientific areas discussed was the need to move way from in vitro analyses of HIV infection and to start looking at the interaction of the virus with the complete host ("in vivo veritas"). By many accounts of the history of AIDS research offered by those interviewed, basic research on the disease began with a greater attention on the nature of the disease in vivo, but with the discovery of HIV, molecular analyses gradually superseded the earlier focus on the body. Many of the interviewees criticized the relevance of in vitro work ("pristine, beautiful, irrelevant systems"). In moving back towards an assessment of the disease in vivo, many recommended the use of primary isolates, cells and tissues in experiments, rather than tumor cell lines and laboratory strains of virus. Where clinical samples aren't available, many suggested taking greater advantage of animal models, particularly the SIV-infected macaque, in looking at questions of disease pathogenesis.

Many investigators wanted in vivo corroboration of data previously established in vitro or postulated on the basis of in vitro evidence, while many asked for in vivo answers to new questions. Some of the topics needing further investigation in vivo mentioned over the course of the interviews include: antibody and CTL responses to autologous virus; the quantitative CTL response; cell tropism of viral strains; cytopathic effects of the virus; the role of defective virions; rate of turnover of virus population; rate of the development of viral resistance to therapy; rate of viral spread within the host; mechanisms of CD4+ cell depletion; viral gene function in different cell types; virus-mediated dysregulation of macrophages and other antigen-presenting cells; occurrence of syncytia; and localization of the virus in various tissues and organ systems.

The Pathology of HIV Infection

As a corollary to the increasing emphasis on the need for in vivo analyses, many researchers stressed the importance of developing a better descriptive profile of the pathology of HIV infection. Recent new studies have focused the attention of many of the researchers interviewed on the lymph node. These studies have offered a trajectory of lymph node pathology beginning with acute viremia, clearance from the peripheral blood by a strong host immune response; viral seeding of immune cells throughout the body and viral deposition on

follicular dendritic cells (FDCs) in lymph node germinal centers; the progressive degeneration of the FDC network with an eventual spillover of virus back into the blood in late-stage disease.

The mechanism behind the destruction of the FDCs is unknown, although several researchers interviewed postulated killing of FDCs was mediated by CD8+ cells or cytokines (for some reason, no one postulated that antibodies might be involved, though the FDC-associated virions are coated with them). Since the FDCs in germinal centers may be T-cell dependent, their degeneration may be due simply to the progressive loss of CD4+ T-cells in the disease (the reverse may also be the case). Several researchers also pointed out that the fate of the lymph nodes in HIV infection was noticed by researchers early on in the epidemic, and that the current interest is a revival of an old concern.

In addition to the lymph nodes, researchers were interested in the pathology of HIV infection in the thymus, an important organ in T lymphopoiesis. The disruption of the thymic microenvironment and the infection of thymocytes and thymic epithelial cells by HIV could make the organ an important site in the pathogenesis of the disease. There is a virtual vacuum of knowledge about thymic function in adults, although bone marrow studies in cancer patients hold out the possibility that there is residual thymic function and an ability to reconstitute a functional immune system. Researchers were also concerned with the pathological effects of HIV in the brain, gastrointestinal tract, and in the bone marrow. In general, the researchers wanted to know where HIV is sequestered in the body: in what cell types, tissues and organ systems, at which stages of disease. Then, they wanted to know the virus's varying local effects.

Events in the Viral Life Cycle

Transmission

Many of the researchers interviewed had strong interests in sexual and vertical transmission of HIV infection. Several thought it was important to discern whether cell-free virus or HIV-infected cells are the primary vector of infection in sexual transmission. Is there free infectious virus present in vaginal secretions or in the seminal plasma? Are spermatozoa themselves infected with HIV or carrying HIV bound to their surface? Are monocytes or macrophages in cervical-vaginal or seminal fluid infected with HIV? Why, twelve years on, are well-controlled studies of sexual fluids only now being initiated?

Other investigators were concerned with characterizing the nature of the viruses passed on from one person to another. Recent studies have reported that, within an individual, early in infection, sexually transmitted viruses demonstrate a relative homogeneity of envelope sequences, a tropism for macrophages and are non-syncytium-inducing strains. In addition, the strain transmitted usually represents a minor variant within the population of viruses of the person who transmitted the infection. What accounts for this effect? (This phenomenon appears to be at work in vertical infection as well.) Is there selective transmission or amplification of these strains? If there are preferentially transmitted strains, what are the implications for vaccine development?

The Viral Life Cycle

There was considerable interest by researchers in the various phases of the viral life cycle. In addition, many of the investigators interviewed mentioned in passing that it was critical to determine the mechanisms behind viral latency and activation. However, there was more active interest in the virus's needy relationship with the cell over the course of its residence.

Several researchers thought it was important to more finely elucidate the steps in viral uncoating and its dependence on cellular enzymes. One researcher commented that in a murine model of retroviral disease, infection is blocked at the level of uncoating in mice strains missing certain enzymes. Other researchers believed that the mechanism behind the transport of the preintegration complex to the nucleus was still relatively obscure. In particular, the way in which the preintegration complex negotiates its passage across the intact nuclear membrane of the cell remains to be clarified. Transport of the preintegration complex to the nucleus is also dependent on the cooperation of the cell. HIV can bind to and enter a resting(G0) T-cell, but transport of the preintegration complex to the nucleus and integration of the viral genome is an ATP-dependent process which requires activation of the cell.

Several researchers stressed the importance of defining these early phases of the virus life cycle, especially for the development of therapeutic interventions. Others stressed that current therapeutic modalities (mostly attempting to inhibit viral reverse transcriptase) were of limited durability, and that therapy should be targeted towards chronically infected cells. Obviously it would be more useful to shut off viral replication at its source rather than to temporarily shield uninfected CD4+ T cells from new infection.

HIV also does not replicate in resting T-cells. The contribution of T-cell activation to the activation of HIV out of latency was also a concern of several researchers. Activation of T-cells by antigens, mitogens, cytokines or with the help of the gene products of other viruses such as Epstein-Barr virus, cytomegalovirus, hepatitis-B virus, or herpes simplex virus can spur high levels of HIV replication, probably mediated by cellular transcription factors, including the NF-kappaB proteins, Sp1 and TFIID. In addition to T cell activation, macrophage activation by HIV or other antigens remains a critical area for future study.

Several researchers were particularly concerned about the adverse clinical implications of immune activation in HIV infection. Whether by secondary infections, HIV itself, or even by vaccination (including therapeutic HIV immunogens), immune activation may speed the progress of the disease. There is considerable interest in using in vivo models, such as nonhuman primates, to assess the role of selective immune inhibitors in delaying or preventing retrovirally-mediated immune destruction.

Envelope Structure and Function

The envelope of HIV is obviously of critical importance in the virus' interaction with the immune system. The researchers interviewed were particularly concerned with the envelope's role in dodging immune surveillance, in facilitating viral entry into cells, in viral cytopathicity, and in viral tropism for different cell types.

The role of the virus' envelope in the failure of the humoral response to HIV infection was a strong focus of several researchers' comments. Some said that HIV's envelope glycoproteins do not elicit strong antibody responses (although there are those who maintain the opposite). Some have had trouble measuring consistently high titers of neutralizing antibody even to autologous virus over the course of infection. Antibodies that do develop must contend with the high variability of the viral envelope which allows the virus to escape their recognition.

A number of researchers interviewed are attempting to more clearly define the structure of the envelope and the regions, both variable and conserved, responsible for key steps in infection, such as viral binding with the CD4 receptor and fusion with the cell, including delineating the conformational changes associated with interactions with various cell types. Others are trying to assess the maximum allowable variation in the envelope permissible for infectivity and its underlying conserved structural properties. Most researchers interviewed stressed the importance of work of this kind for the development of a vaccine and possible therapeutic strategies.

The envelope's role in viral cytopathicity and in the development of pathogenic strains was also an object of concern among the investigators. The envelope glycoproteins may be important in mediating direct killing of CD4+ cells either by syncytium-formation or by the accumulation of gp120-CD4 complexes within the cell's organelles. Indirect immunopathology may be mediated by soluble envelope proteins or by defective, replication-incompetent virions still able to transduce inappropriate signals to uninfected CD4+ T cells. In addition, the Dutch work on macrophage-tropic, non-syncytium and T-cell-tropic, syncytium-inducing strains described

above has identified a correlation between these phenotypic variants and changes in the structure and charge of the viral envelope. The development of more highly pathogenic forms of the virus during the course of infection, as well as the tropism of the virus for different cell types may therefore hinge on characteristics of the virus's outer shell.

Mechanisms of Viral Persistence

Earlier assays of HIV replication and burden in the blood originally led researchers to believe that there was minimal viral replication throughout much of the course of HIV infection. Now, with more sensitive detection methods, it has been shown HIV is a chronic viral infection with measurable viral replication at all stages of disease. Unlike other viral infections, it now appears that HIV is never completely latent within an infected host, although at any given time most infected cells are not replicating virus. This implies either that a few chronically infected cells are manufacturing most of the virus measured, or that virus cycles rapidly through CD4+ T cells in short lytic infectious bursts.

How can either mechanism survive the apparently vigorous initial immune response? Very early on in HIV infection the immune system mounts a potent, multipronged attack on the virus; starting, it seems, with a cell-mediated response which is joined soon after by a humoral response, including the development of neutralizing antibodies. How does HIV persist and replicate at such high levels in an apparently immunocompetent host? In a related question, if HIV, a cytopathic virus with a tropism for CD4+ cells, is so successful at replicating at high levels right under the nose of the immune system, why is the course of HIV disease so often protracted, variable, and slow?

These questions raise the issue of which cells and tissues serve as reservoirs for HIV. (Although the recent lymph node work has shown virions attached to FDC processes, no one is implying that the FDCs are producing HIV - it most be coming from elsewhere.) Several researchers postulated a central role for the macrophage in the mechanism of viral persistence. One individual went as far as to say that HIV infection is a monocyte/macrophage disease. Some researchers report that the macrophages of primates who develop retroviral immune dysregulation (such as humans with HIV and rhesus macaques with SIV) are infected with these viruses, while primates which do not become sick (chimpanzees with HIV or African green monkeys with SIV) do not experience macrophage infection (others dispute this).

This, if true, implies that to cause disease, HIV or SIV must replicate in both CD4+ T cells and in macrophages. Still other mammalian retroviral diseases depend on dysregulating multiple arms of the immune system (e.g., MAIDS is a T cell dependent B cell disorder). Recent studies have suggested that macrophage-tropic, non-syncytium-inducing strains are selectively transmitted in the passage of HIV infection from one person to another. Once transmission occurs, HIV may use the macrophage as a "Trojan Horse" to disseminate itself throughout the body and as a reservoir of heavy viral production. Indeed, some studies report large numbers of viral particles localized almost exclusively with intracellular vacuoles in macrophages, with little or no virus detected at the plasma membrane. With little virus at the surface of the cell, the infected macrophage may be able to produce large amounts of virus without being "seen" by the immune system. Release of infectious virus and infection of other macrophages and T-

cells can occur upon some event that perturbs macrophage function. Other immune cells, such as skin Langerhans cells and blood dendritic cells, may play a role in fostering viral persistence as well, though further research here is required.

Clearly, the immune system is able to control HIV replication to some extent for some period of time, which accounts for the slow progression of the disease in most cases, yet it is not able to eradicate it once infection has taken hold. The researchers interviewed stressed the need for studies of the natural history and pathology of HIV infection to elucidate the mechanisms of viral persistence. We need to know where HIV goes when it enters the body, where and how it hides from the immune system, what cells is it killing, and what cells are producing virus.

Events in the Host Life Cycle

Exposed, but Uninfected

There are two other unique cohorts of individuals that the interviewees thought deserved special scrutiny: those people who show signs of exposure to HIV without detectable infection, and those people who are extremely likely to have been exposed to the virus, yet remain uninfected. The first set of individuals includes gay men and intravenous drug-users who have continued to practice high-risk behaviors as well as health care workers who have received accidental exposures to HIV. They all remain seronegative, yet their helper T-lymphocytes proliferate or produce IL-2 in culture in response to HIV envelope peptides. The second set includes gay men who have continued to engage in unprotected sex and a cohort of Kenyan sex workers who have done the same, with members of both groups remaining seronegative. (Perhaps the most common group of individuals who may have been exposed to HIV, yet do not become infected are the two-thirds or so of initially HIV-antibody positive children born to HIV+ mothers who serorevert some months after birth. However, this cohort has characteristics distinct from the others and is really a separate case.)

The researchers interviewed thought the lymphocyte proliferative responses and IL-2 production seen in response to viral peptides in HIV-individuals needed further confirmation in other experimental systems, in larger numbers and perhaps in an animal model (these findings have apparently been confirmed in a monkey model). If there is indeed exposure to HIV in either cohort of people, there are a number of hypotheses to account for the phenomenon.

There may be a low level infection present undetectable with the methods used in these studies. It is also possible that these individuals may have some sort of genetically determined resistance to infection. The persistently seronegative individuals in the Kenyan Sex Workers Study actually share common HLA alleles (Aw28, Bw70). One researcher interviewed offered the hypothesis that these individuals might have been immunized by defective virus. Lastly, it is conceivable that these individuals have mounted a successful and sterilizing immune attack on the virus, perhaps through the agency of CTL's. Certainly HIV-specific CTL precursor frequencies in exposed, uninfected persons should be compared with those in low-risk seronegative persons.

Acute HIV Infection

Although the importance of natural history studies was stressed throughout the interviews, there was a particular interest in the initial phase of infection for many researchers. In acute infection, which is sometimes marked by flu-like illness, high levels of virus are detectable in the peripheral blood. However, within several weeks, this acute viremia subsides. The mechanism by which virus replication is brought under relative control in acute infection was the primary focus of the comments on this topic.

Several researchers made reference to recent data suggesting that CTL responses to the virus are responsible for its control in acute infection. A early rise in HIV-specific CTL responses has been observed in several individuals and correlates well with the initial reduction in viral load.

Neutralizing antibody responses specific for the infecting strain occur later and after the viremia has ebbed. However, one researcher postulated that antibody may still be involved in controlling initial viremia, but not detectable in serum and bound to cells.

While additional studies of acutely infected persons will be important, such persons will be difficult to identify, and the public health impact of such early monitoring will remain elusive as long as this remains the case. Indeed, it is still unknown what proportion of initially-infected persons display the acute clinical syndrome, since those without symptoms will not present for medical surveillance. The symptoms themselves are far from HIV-specific, and could reflect virtually any acute viral episode, and questions such as whether those without symptoms experience viremia will remain hard to assess. This area is ripe for intensive studies using primate models.

Long-Term Non-Progressors and Long-Term Survivors

Most individuals with HIV infection experience a gradual decline in CD4+ cells over a period of time with a deterioration in clinical status accelerating as CD4+ cell counts drop below 200/mm3. There is a small group of individuals, however, who have not experience a drop in CD4+ cell numbers even a decade or more after infection with HIV and another group that despite having very low CD4+ counts have remained clinically stable for three years or more. These two cohorts of individuals have been dubbed "long-term non-progressors" and "long-term survivors" of HIV infection. Two years ago, TAG members began a drive to get the Division of AIDS, NIAID, NIH to sponsor studies of these unique populations. This year, the Division of AIDS held a conference on the topic.

Many of the researchers interviewed suggested that both cohorts of individuals merited intensive investigation. Others described actual experiments being planned within the Multicenter AIDS Cohort Study (MACS) in the U.S. on matched "triplets" of those who manifest no, average, and rapid immunological progression. The experiments will look at CTL responses, comparatively, using different targets, different strains; lymph node pathology; antibody responses; natural killer (NK) cell activity; suppression of HIV by a putative novel soluble factor secreted by CD8+ cells; viral load; rate of viral mutation; genotype and phenotype of viruses; HLA alleles associated with protection or progression; and other parameters of interest.

Others spoken to had firmer opinions on the correlates of long-term survival. Several individuals postulated the existence of naturally attenuated strains of HIV based on a cohort of long-term survivors in Australia who were all infected with the same isolate. Other hypotheses advanced included CD8+ cell-mediated suppression of HIV and the possibility of the retention of key certain CD4+ cell subsets in long-term survivors with low CD4+ cell counts but without clinical progression.

Mechanisms of CD4+ Cell Depletion

How CD4+ lymphocytes are destroyed in vivo during HIV infection was the topic most frequently cited by the researchers interviewed as one of the key unanswered questions in

basic AIDS research. The hypotheses offered ranged from those who believed the direct cytopathic effects of the virus alone ("its the virus, stupid") were responsible for CD4+ cell loss to those who maintained that CD4+ cells are killed by indirect effects of the virus or by the immune system itself ("AIDS is a virus-induced immunological disease"). However, most researchers settled on a middle ground maintaining the possibility or likelihood of a multifactorial etiology for CD4+ cell decline in HIV infection.

Those who maintained that direct cytopathic effects of the virus alone are killing CD4+ cells referred to recent work from the laboratories of Shaw, Fauci and Wolinsky, respectively, that have identified higher levels of viremia in the peripheral blood and lymph nodes and a greater number of infected CD4+ cells than previously believed. (Of note, however, in the first mentioned paper, only 1/60,000 plasma virions appeared to be infectious, implying that most were defective, and thus incapable of direct infection or subsequent cell killing.) The direct cytopathic mechanism which may be responsible for cell death was not often discussed, but those postulated included single cell lysis upon viral budding through the cell membrane, lysis after accumulation of circularized viral DNA intracellularly, and the accumulation of intracellular CD4-gp120 complexes. Syncytia formation between infected cells bearing gp120 on their surface and uninfected cells via CD4 was also mentioned as a possibility.

Several researchers entertained the possibility that the immune system itself may participate in CD4+ T cell depletion through one of several mechanisms. For example, CD8+ T cells may be killing uninfected CD4+ cells - either because the uninfected cells have bound soluble gp120 onto their CD4 receptors, or because the immune system responds to cellular proteins on HIV's envelope, and then mounts an attack on the cells whence the virus emerged, e.g., the CD4+ T cells themselves. The role of CD8+ T cells remains controversial. Some hypothesized that CD8+ cells are mainly protective, either using MHC class I restricted HIV-specific CTLs, or by releasing a putative cytokine which inhibits HIV replication. Others maintain that some CD8+ cells are immune suppressive and inhibit cell-mediated immunity. Some postulate that CD8+ cells may be involved in lysis of uninfected CD4+ cells or of thymic and follicular dendritic cells.

Detailed immunopathologic studies with in vivo samples from HIV-infected persons at all stages of disease will be required to answer these questions. Technologies for detailed subset analyses of lymphocytes and the other arms of cell-mediated immunity remain at a primitive state in comparison with antibody studies, and substantial investment will be required to bring this critical area up to speed.

The potential of aberrant cell signalling leading to programmed cell death or apoptosis of CD4+ cells was another topic often brought up. The primary hypothesis advanced is that HIV gp120 or gp120-antibody complexes can inappropriately prime T lymphocytes through the CD4 receptor to undergo apoptosis upon restimulation by antigen through the T-cell receptor (TCR). (This hypothesis does not address the fact that most T cells never meet their antigen, and thus does not explain why all CD4+ T cells are eventually depleted.) Variations on this hypothesis proposed that MHC class II proteins associated with the viral envelope and/or portions of the envelope itself acting as a superantigen can inappropriately activate CD4+ cells, leading to programmed cell death. Finally, some hypothesize that HIV-mediated signals result in a state

of antigen unresponsiveness (anergy) which allows antigens to escape immune surveillance, leading to CD4+ cell killing.

Immune Dysregulation

HIV infection induces a spectrum of profound immune dysregulation as well as its hallmark depletion of CD4+ cells. One researcher interviewed has often said she thinks AIDS would be more accurately called an acquired syndrome of immune-dysregulation, rather than immune deficiency because some functions of the immune system are clearly debilitated, but others are performing with wild abandon. The researchers interviewed stressed the importance of a wide selection of the immune abnormalities seen in the disease, involving a broad range of cell types and tissues.

Several researchers were interested in the mechanism behind early defects in CD4+ cell function, which include the inability to respond to recall antigens such as tetanus toxoid and influenza A virus, to alloantigens and to mitogens. Each of them postulated a different cause of these defects: the selective killing of memory (CD29+) T-cells by HIV; defects in antigen presentation by antigen-presenting cells; and active immune suppression mediated by cytokines.

Another immunological abnormality characteristic of HIV infection is the polyclonal activation of B-cells and an attendant hypergammaglobulinemia. Several researchers were interested in the origin of the B-cell disorders in HIV infection and their contribution to the pathogenesis of both the lymphomas seen in AIDS and the primary immune dysregulation of the disease. In this regard, it is striking that the HIV isolated from lymphoid tissue localizes to the B cell rich germinal centers, where the virus may elicit cytokines (e.g., IL-4, IL-6, IL-10) which contribute to a B cell activation cycle, possibly leading in some cases to malignant transformation of B lymphoblasts and later lymphomas. If MAIDS is a T-cell dependent B cell disease, perhaps, one investigator suggested, AIDS is a B-cell dependent T cell disease.

Further immunopathological studies correlating immune activation (including cytokine expression, and cell subset populations) with HIV progression will shed light on the role of inappropriate immune activation on the pathogenesis of AIDS.

The derangement of lymphopoiesis in HIV infection was another topic that recurred several times throughout the interviews. Several researchers wanted to know why the immune system is unable to reconstitute the CD4+ cell population. Where is the defect? Are stem cells or thymocytes infected? How does the immune system monitor the level of lymphocytes in the body? What is the signal which spurs the production of new lymphocytes? Is the rise in CD8+ cell population seen in the disease a byproduct of the immune system's attempt to compensate for the ongoing loss of CD4+ cells by producing more lymphocytes? Isolating the interruption of lymphopoiesis - at the level of the bone marrow, the thymus, or the peripheral lymphoid tissue - will be critical in devising strategies to protect and reconstitute the immune system.

In addition to a descriptive profile of the pathology of HIV infection, several researchers suggested we specifically need a profile of the immunopathology of the disease. We do not yet

have a clear picture of the activity and function in HIV infection of each of the different types of cells and tissues that make up the immune system. Such work will be difficult, expensive and labor-intensive. Substantial resources and ingenuity will be needed to ensure that this critical area receives the attention it deserves.

The Final Phase of CD4+ Cell Decline

The pattern of CD4+ cell loss in HIV infection rarely proceeds in a straight downward-sloping line. In fact, two sets of investigators, one with the Multicenter AIDS Cohort Study (MACS) in the U.S. and the other with the Amsterdam Cohort Study of HIV Infection and AIDS in Homosexual Men in the Netherlands, have noted a biphasic decline. According to the Dutch group, until eighteen months or so before developing AIDS, the number of CD4+ cells declines slowly and continuously. After that point in time, CD4+ cell loss occurs at a rate three to five times faster than before.

Many researchers interviewed were interested in the cause of the second, precipitous decline in CD4+ cells. The Dutch have hypothesized a correlation between the second phase of CD4+ cell decline with the emergence of high-replicating, T-cell tropic, syncytium-inducing (SI) strains of virus which overgrow low-replicating, macrophage-tropic, non-syncytium-inducing (NSI) strains. In feline leukemia virus (FeLV), a similar shift from low-replicating, less cytopathic to high-replicating, more cytopathic viral variants precedes the onset of the symptomatic phase of disease. While a shift from NSI to SI viral strains often seems to coincide with the shift from asymptomatic to symptomatic disease in HIV infection, it is not always the case. People die with AIDS without SI viruses. In addition, recent experiments using the SCID-humouse model have shown that viral isolates which are macrophage-tropic and non-cytopathic in in vitro assays can induce a rapid decline in CD4+ cells in vivo, while highly cytopathic in vitro strains can induce a restrained decline in CD4+ cell numbers.

While many of the researchers interviewed were interested in the in vivo evolution of pathogenic strains and its correlation with clinical progression, others postulated an immunological event as the trigger of the final, rapid decline in CD4+ cells. (For example, thymic or lymphoid involution might mark the end of the immune system's ability to contain HIV, resulting in renewed viremia and final destruction of CD4+ cells in the periphery.)

In particular, several researchers hypothesized that before the onset of symptomatic disease there is a switch in the nature of the T-helper lymphocyte response from a TH1 to a TH2 state. A TH1 response is carried out by clones producing IL-2 and IFN-gamma and preferentially mediates CTL activity. A TH2 response is carried out by clones producing IL-4, IL-5, and IL-10 and preferentially mediates antibody responses. Cytokines produced by TH1 clones can downregulate the cytokines produced by TH2 clones and vice versa. When TH1-mediated CTL activity is downregulated, HIV escapes immune control and virus is allowed to grow relatively unchecked. While provocative, the TH1/TH2 hypothesis needs further confirmation in human, rather than murine, studies. In addition, the contribution of other pathogens (e.g., herpesviruses, parasites) to TH1 or TH2 immune states needs further investigation.

In sum, it is apparent that ambitious new efforts need to be carried out to correlate insights on HIV's behavior in the test tube with its behavior in the bodies of infected people. The mechanisms of CD4+ cell depletion in vivo are the critical events which must be explained in order to delay progression to AIDS, and the multivalent nature of the damage to the immune system must be defined if immune reconstitution is to become a possibility. Researchers are enthusiastic about attempting to conduct basic research in a more clinically relevant fashion. Meeting this need will be a major challenge for the administrators of AIDS research over the coming years.

Part II: Events in the Researcher Life Cycle

The Funding Crunch

Far and away the most often cited topic by scientists was the crisis in funding of basic research. There was a level of chronic, serious demoralization on this issue among the extramural researchers interviewed, which bodes extremely ill for the future of basic research on AIDS.

Most researchers are spending between 30-40% of their time writing grants. In one lab, six out of seven M.D./Ph.D.s were busy writing grants at the time of these interviews. Another researcher submits between one to four grant proposals for each of the review cycles for AIDS (January, May, September) in addition to responding to Requests for Applications (RFAs). Still, this individual is downsizing their laboratory. This person's concerns about funding have "tripled over the past two years." Many researchers complained that instead of writing papers or planning experiments with graduate students of post-doctoral fellows, they are forced to spend much of their time trying to solicit funding. One researcher put it plainly and said the constant, grueling search for funding adversely effects the quality of research.

In addition to believing that too much of their time is taken up with searching for financial support for their laboratories, many researchers feel as if they can't count on support from one year to the next. With increasing numbers of people entering the field and funding levels remaining stable or decreasing slightly, the competition for funding has become intense.

One researcher said it is no longer enough to be an excellent scientist. Many of those interviewed, some being current or former members of study sections, believed that the there was no qualitative difference between the top 20-30% of grant applications and the top 10%, except that only the top 10% or so gets funded. The competition for funding is so acute that many believe the peer review process has increasingly resorted to finding minor, often irrelevant excuses to send grants back for revision, or to reject them altogether.

Many laboratories are being forced to scale back research plans, putting off hiring post-doctoral fellows, and letting go of technicians. The funding crisis in basic research is affecting both the younger, up-and-coming scientists and the more senior, well-established researchers. One senior investigator commented that they had a program project grant for $500,000 for four years, but it is split between five researchers to keep the laboratory going.

Needless to say, Congressionally-imposed pressure on universities to account for and cut back on indirect costs is resulting in a climate of fiscal contraction throughout the nation's biomedical research infrastructure. Another Washington-imposed headache results from Congress' reluctance to fund much-needed construction of new laboratory facilities, which means that many AIDS researchers work in inadequate, antiquated facilities.

Clearly, the present climate is inhospitable to basic research, as one scientist described the situation. Too much time is devoted to writing grants, the competition for research dollars makes each funding cycle a game of chance rather than competence, and there is simply not

enough money around to adequately support the current scientific infrastructure. Some scientists are leaving academia for industry, where their research can be sufficiently and consistently supported. Younger researchers are being discouraged from pursuing a career in science at all. Of course, these problems are not unique to AIDS research and mirror the state of basic biomedical research as a whole.

However, in the case of AIDS, the lack of adequate support for basic research has grave implications for the development of a cure for the disease and a vaccine for the uninfected. In the current fiscal climate in the U.S., it will be difficult to secure additional funding for biomedical research. Yet our failure to support basic research on AIDS and other diseases will have a devastating impact on the health of our nation and its economic future.

The Future AIDS Researchers of America

In particular, one researcher who is involved with his university's M.D./Ph.D. program is concerned with the decreasing number of U.S. students in graduate science programs. Many Ph.D. candidates in biomedical science are foreign students, some of whom intend to return to their countries of origin after completing their education, while others are becoming indispensable to the U.S. research and health care system. Another scientist, who is the director of his medical school's training program, worries about the caliber of U.S. students entering the program in recent years. Both researchers believe that the infrastructure of American science is in a precarious state. (It's the education system, stupid!) Without a steady source of talented young scientists, biomedical research in the U.S., once the finest in the world, is headed for a period of decline.

Researchers see several reasons for the problems facing graduate science education in the U.S. First, the current problems facing the field, particularly around funding, have made the profession less than attractive to young students. As one researcher put it, "People are suffering in basic research...you give up almost everything but your family for science, and then you're jerked around by bureaucrats... Budgets are flat, when labs should be growing." Science education, especially the M.D./Ph.D. programs, is expensive. M.D./Ph.D. candidates are ideally situated to carry out the synthesis of basic and clinical research which many scientists believe holds the key to progress in the future. One researcher estimates the average cost of training an M.D./Ph.D. student at $200,000-$300,000. Thus, support for these programs is hard to come by. One researcher said the NIH subsidizes only five out of twelve M.D./Ph.D. candidates at his university. Several scientists thought the pharmaceutical industry should be approached to financially support graduate scientific education through donations to universities.

Pilot Grants

Several researchers also suggested a new system of pilot grants in basic AIDS research to be funded by the NIH. The purpose of these awards would be to encourage the work of junior researchers in AIDS; to entice senior investigators in related fields to pursue projects in AIDS research; to encourage the pursuit of novel, "risky" approaches; and to encourage work in neglected areas of research.

The awards might amount to $100,000 per year and would involve a short, simple application followed by an expedited peer review process. Several scientists suggested that the American Foundation for AIDS Research (AmFAR) might consider shifting its basic research portfolio to accomplish some of these goals.

Investigator-Initiated Research

The NIH's R01 award, the investigator-initiated grant, is the primary funding mechanism for much of basic research. Most researchers interviewed thought that the number of R01 grants awarded in AIDS, currently around 12% of the total number of submitted applications, needed to be significantly increased. As was mentioned above, the top 10% and top 20-30% of applications were thought to be indistinguishable in quality.

Researchers interviewed believed the R01 was the most successful and productive mechanism for supporting basic research. In addition, the R01 was thought to be a comparatively good bargain. For example, the recent $20M appropriation for a large simple trial of therapeutic vaccines in HIV infection could support approximately 50 R01 awards. Suggestions were also made to shorten the length of the proposals and to extend the awards from three to five years.

Block Grants

Several researchers thought that a new mechanism was needed to fund basic research on AIDS which would provide a single source of significant and consistent funding to fully support the most productive researchers in the field for up to five years at a time. The primary model raised for this new mechanism was the British system of five-year program grants in AIDS. The awarding of these block grants would be done strictly through a peer-reviewed process, with funded investigators returning to the applicant pool at the expiration of their award. However, their was a dissenting voice on this matter, one researcher thought scientists receiving these grants would become "fat and lazy."

Perhaps AIDS research could adapt a model successfully used in the academic setting. Currently, The Howard Hughes Medical Institute funds researchers at approximately 50 sites around the U.S. in basic biomedical science. Researchers are supported for either three, five or seven years. Investigators and their labs are fully supported for these periods of time. Researchers are characteristically up-and-coming scientists in their thirties, and are chosen by the Institute. Applications for these awards are neither solicited nor accepted. The Institute currently favors non-disease-specific work in genetics, cell and structural biology, immunology and neuroscience. Several researchers interviewed thought it would be useful if the Institute would consider initiating a program in basic AIDS research.

Peer Review: the Good, the Bad and the Ugly

While most researchers interviewed thought that peer review was the best and fairest method for selecting which scientific proposals merited funding, many scientists had harsh words for

the current state of the process. In particular, many investigators questioned the competence of some study section members. Often the individuals sitting on study sections were criticized for lacking knowledge of the most pressing issues in AIDS research or for having little experience with the field at all. In addition, some thought that study section members were frequently not senior, well-respected scientists.

The intensely competitive funding environment has also put a strain on the peer review system which is forced to justify the rejection of excellent applications simply because there is not enough money to go around. A vicious cycle has been created where those whose grants were rejected on the basis of minor or irrelevant points do the same to others when they are sitting on a study section.

On a constructive note, several researchers suggested that peer review incorporate appraisals of productivity into the decision-making process. Looking at researchers' track records would help insure that grants were supporting the most fertile minds in the field.

Big Science vs. Little Science

Much of basic research is supported by the relatively small R01 grant. It was not surprising then that many of the basic researchers interviewed looked to the larger AIDS research programs run by the NIH as a source of wasteful spending. However, their criticisms were often justified and merit serious attention.

There was extremely strong concern among many of the researchers interviewed about the NIH's HIV vaccine evaluation program. In particular, the new PAVE (Preparation for AIDS Vaccine Evaluation) program which is preparing the infrastructure for both domestic and international large-scale efficacy trials of prophylactic HIV vaccines, was thought to be a grossly premature endeavor. Many of the scientists thought we were far from having a viable candidate immunogen for testing, and some doubted that we ever will. It was commonly felt that pushing for large-scale testing of vaccines at this point was motivated primarily by political considerations and had little basis in scientific reality.

The AIDS clinical trials networks run by the NIH were also a source of great consternation among the basic scientists. The AIDS Clinical Trials Group, NIAID, was singled out as an expensive, inefficient, unproductive, colossal mess. There was a general feeling that the system was unreasonably large, with 35 adult ACTUs alone, and that the studies being conducted were often of little scientific value or clinical significance. Several of the researchers interviewed thought that the ACTG should be scaled back and that pharmaceutical companies should either take responsibility for clinical trials of already approved agents or offer some form of financial support for the studies within the ACTG.

The Women and Infant Transmission Study (WITS) was also a target of special scorn by several researchers. Apparently, a majority of the samples stored by the WITS were improperly cryopreserved and are useless. Thus the large investment of resources into this epidemiological cohort study has gone to waste.

Despite the importance of animal models, the Regional Primate Research Centers (RPRCs) were thought to be ill-equipped to conduct AIDS research. In addition, the RPRC principal investigators keep a tight reign over use of their monkeys and the RPRC's charge researchers unaffiliated with their centers $2,400 per monkey with a $4.60 per diem surcharge.
The researchers interviewed were split over the usefulness of the Centers for AIDS Research (CFAR) program. Those interviewed who were not at a Center questioned the program's productivity as a whole, while those who were part of a Center admitted that some of the CFAR's were not performing up to par.

Although these researchers' appraisals of many of the larger research programs were harsh, the criticisms are largely true. While no one questions the necessity for some of these programs, there is a serious need to rigorously evaluate their productivity and base future funding on their performance. Basic researchers clearly feel that they are held to a higher standard when it comes to funding and only wish that "everyone was judged by the same yardstick." Basic researchers might feel better if there was some effort made by NIH to streamline clinical research and ensure that clinical trials were both efficient and relevant. Clinical trials might even become useful sources of material for basic researchers, if there were a mechanism in place to link up the disciplines.

The Decline of Molecular Biology

Enormous strides have been made in understanding the molecular biology of in vitro strains of HIV over the past decade. The HIV genome was sequenced and cloned; its proteins synthesized and studied in many model systems. Now, there is a growing feeling that molecular biological studies of the virus have often become an end in themselves with little concern for their own significance in vivo. While many researchers outlined areas of viral gene expression which are still not fully understood, others thought their might be an overemphasis on the study of the regulatory genes of the virus, and that we are seeing diminishing returns from studies in this area. Many thought molecular biologists need to be prodded into working with clinical materials and animal models where possible to expand the relevance of their insights.

The Rise of HIV Immunology

With a growing emphasis on in vivo analyses of the pathogenesis of HIV infection, there is a growing coolness among researchers to solely molecular approaches. Along with this shift, there seems to be an attempt to redress previous imbalances in research priorities. Several researchers commented on the relative lack of attention in basic research on AIDS to the immunology of the disease and the host response to the virus.

As an example, one researcher pointed to the small amount of time devoted to immunological topics at the major basic scientific meetings on AIDS in the U.S., such as the Keystone Symposia. Others lamented the absence of the U.S.'s top immunologists from AIDS research, and wondered how they might be enticed into taking on some critical aspects of HIV disease. Perhaps fundamental immunologists are too comfortable with the highly artificial use of inbred mouse models to deal with polymorphic humanity.

Many scientists felt that studying the immunology of the disease and the host's response to the virus was technically exacting and that investigators have shied away from this kind of work. As one research put it: "People study what's easy to study and molecular virology in tissue culture is relatively easy. HIV immunology is hard to do, you can't manipulate a chimp like a piece of DNA." Another researcher, in discussing the difficulty of CTL assays, compared the practice of cellular immunology to the work of an artist. In addition, the complex nature of the immune system and the limits of our current knowledge of its workings make the study of the immunology of AIDS a daunting task. Yet, many researchers interviewed thought that a new emphasis needs to be placed on the host response in the coming years.

Collaborative Efforts: New Ways of Working

Many researchers interviewed made a strong point of their opposition to and the limited usefulness of directed research. Yet, many researchers also made it clear that new ways of working, especially those stressing collaboration, might have a place in basic AIDS research. Several investigators made it clear that the current scientific culture is not well-predisposed to cooperation and teamwork, but thought it was important to start bringing researchers together within single institutions and between different institutions; within single areas of emphasis and between related fields.

Two models of a collaborative effort arose in these interviews: the Manhattan Project and the Ariel Project. The Manhattan Project, of course, was the massive development effort undertaken by the U.S. to build the atomic bomb during World War II. Activists and researchers are still awaiting a coherent explanation of how the World War II nuclear physics model can be applied to the post Cold-War biomedical problems we now face. While one researcher interviewed was an adamant booster of a Manhattan Project for AIDS, another commented "A Manhattan Project for AIDS scares me: the same people in charge with more power is frightening."

The Ariel Project to Prevent Transmission of HIV from Mother to Infant is a more recent endeavor sponsored by the Pediatric AIDS Foundation. The model of The Ariel Project, however, had wide support among several researchers. This collaborative effort to elucidate the virological, immunological and clinical mechanisms of vertical transmission was praised as bringing researchers together to work on well-defined topics while retaining individual initiative. One researcher said The Ariel Project "points in a direction, rather than directs."

There were other suggestions for fostering collaborative relationships between researchers. Several investigators stressed the importance of funding scientists in their own environments, but thought it would be a good idea to bring them together on a regular basis, perhaps in small regional meetings on specific topics, to compare notes, to brainstorm, to hash out what we really know and don't know about the issue at hand. A few researchers thought the NIH program project grants and centers programs were useful mechanisms for promoting collaboration within institutions. Finally, some suggested that NIH could foster collaboration between institutions by funding individual researchers as part of consortia in certain scientific areas - as is already widely practiced in applied research programs such as the National

Cooperative Drug Discovery Groups, National Cooperative Vaccine Development Groups and the ACTG.

Cross-Pollination

Many investigators interviewed thought that basic AIDS research could profit from greater interactions with work being done in related fields. In particular, several researchers wanted to see a greater effort made to entice basic immunologists into working on AIDS, perhaps by offering individual scientists pilot grants as described above, or by setting up AIDS programs within the nation's best immunology centers. Several researchers thought the vaccine development effort would be enhanced by involving scientists working on human genital tract and mucosal immunology or vaccines against other sexually-transmitted diseases.

Researchers also thought new advances in understanding HIV gene expression and the mechanisms of viral latency and activation are going to need to turn to the work of scientists studying the cell cycle and cellular gene expression. Others thought we could learn some lessons about HIV from looking at other viral diseases. For instance, Mason-Pfizer Monkey Virus induces a lymph node pathology similar to the one seen in HIV, yet MPMV does not target the CD4+ cell. Are there any common pathways in the two infections that might lead to the same effect?

National Network of Tissue and Cell Repositories

Several researchers expressed concern at the difficulty of acquiring clinical samples for basic research. Many basic researchers have little or no contact with the clinical setting. In addition, the collection of clinical material other than from a blood-draw, such as lymph node tissue, is hard to get. Retrieving specimens from special populations, such as long-term survivors or those individuals presenting with acute infection, are especially difficult. Obtaining samples from the epidemiological cohort studies run by the NIH is reported to be an arduous task, and, as is the case with the WITS, the quality of the material is not assured.

As a solution, several researchers suggested the institution of a national tissue and cell repository system with strict quality control procedures. However, supplying basic researchers with clinical samples is only half the solution. Basic researchers will have to learn how to collaborate with clinical researchers and real live infected people if this is to work.

From the Bench to the Clinic

Several interviewees hope for faster translation of new laboratory insights into clinical settings. Current clinical trial mechanisms do not provide for such a fast-track setting. Many agents currently under study both for vaccines and for therapy reflect the outdated insights of five or six years ago.

There was little agreement though on who should provide the support to help translate the insights of basic research into clinical applications. Some thought that pharmaceutical companies need to take a greater interest in developing therapies based on rational drug

design strategies because they have the development capacity which academic labs don't have. Others believed that the large pharmaceutical houses also needed to become involved in vaccine development, which has been the province of small biotechnology firms thus far. However, several researchers said that the pharmaceutical industry was unlikely to follow risky, innovative approaches (e.g. live, attenuated HIV vaccines) and that the government needed to expand both its drug and vaccine development efforts, including an enlargement of NIAID's National Cooperative Drug Discovery Groups and National Cooperative Vaccine Development Groups. Others cautioned that the vaccine effort could easily become a sinkhole of bogus science sucking millions from more productive fundamental or therapeutic research.

Part III: Conclusion and Recommendations

Conclusion

A wide range of scientific and structural issues were brought up in the course of the thirty-six interviews which are the source of this report. Only a small offering of the total collection of concerns mentioned are presented here. These are the leitmotifs running through all of the conversations.

The red thread running through all of the scientific discussions was a new concern for the body in basic research. "In vivo veritas" seems to be a current call-to-arms. This trend was manifested in the acknowledgement by researchers of the importance of trying to conduct experiments in conditions that more closely approximate those found in people with HIV infection. It was also apparent in the focus on all stages of the natural history of the disease (from acute infection through the final decline in CD4+ cells and the development of symptomatic disease), its pathology in the tissues of the body, and the interaction between the virus and its human host, including both the defensive immune response and the aiding and abetting of HIV by cells and their machinery.

The degree of frustration in the AIDS research community as evidenced by these interviews was remarkable. Although the concerns about the level of funding and the enormous amount of time and paperwork taken up soliciting these scarce resources are shared by investigators throughout biomedical research, an inhospitable climate for basic research on AIDS is no place from which we should expect a cure to grow. The researchers interviewed were not shy about what they think is wrong with the state of their profession and what they think needs to be done to set things right. They had a number of suggestions about how to foster the current work of basic researchers and provide for a new generation of scientists.

What was missing from these conversations with researchers was almost as important as what was mentioned by them. Particularly noticeable by its absence was a discussion of the opportunistic pathogens affecting people with AIDS, their pathogenesis and their contribution to the progress of the underlying HIV infection. In addition, the basic mechanisms behind the neurological manifestations of HIV infection, the development of Kaposi's sarcoma and cancers seen in the disease, and the pathogenesis of the profound wasting syndrome often accompanying AIDS, were mentioned only by a few of those interviewed. These underemphases can largely be accounted for in a selection bias in the choice of scientists interviewed who are almost exclusively virologists or immunologists.

Recommendations

This report marks the beginning of a campaign by the Treatment Action Group to focus attention on the importance of basic research on HIV infection to the development of a cure for the disease and a vaccine for the uninfected. TAG will also be advocating for changes in policy to insure that the work of basic scientists in AIDS are supported with the funds, resources and leadership necessary to speed their progress. We make the following recommendations:

On Scientific Issues

1. The Office of AIDS Research (OAR), NIH with the cooperation of the National Center for Research Resources, should encourage the Regional Primate Research Centers to provide greater access to their animals to extramural researchers not associated with their institutions for in vivo studies of the pathogenesis of SIV and HIV.

2. The OAR should encourage both the epidemiology and clinical trials networks funded by the NIH to provide greater access to clinical samples to basic researchers in AIDS.

3. The OAR should convene an ad hoc advisory group of clinical and basic scientists to assess the need for and feasibility of establishing a new national repository for clinical samples, which might include, but not be limited to samples from unique populations such as long-term survivors, individuals presenting with acute infection, etc.

4. The OAR should sponsor a major conference in 1993 on the immunology of HIV infection and encourage the attendance of immunologists not currently working in the field.

5. The OAR should consider encouraging the establishment of novel programs which would foster collaborations among basic, clinical, academic and pharmaceutical company researchers. Basic researchers could have access to clinical materials; clinical researchers could initiate therapeutic protocols based on insights of basic research; pharmaceutical researchers could develop new molecular entities based on the latest, instead of the oldest, ideas on pathogenesis.

On Research Review

- The OAR should conduct a review of all its study sections on AIDS, their composition, their scope (for instance there are no study sections for work on opportunistic infections or neoplasms) and consider restructuring where necessary.

- The OAR should institute a system of ongoing program review for all its AIDS efforts, including the larger directed programs. These reviews should rigorously consider the programs's productivity and scientific merit and should be the primary basis for future funding.

- The OAR should institute a system of ongoing portfolio review for all its AIDS efforts, which will assess the gaps and redundancies in research and make recommendations for reallocation of resources when necessary.

- The Division of Research Grants, NIH should establish a plan with the advice of extramural scientists to streamline the grant application process for both AIDS and non-AIDS research.

- The OAR should set up a Pathogenesis Working Group (modelled on the current Vaccine Working Group sponsored by NIAID) to prioritize, strategize and evaluate the overall NIH effort.

On Research Funding

- Congress should mandate a uniform flat rate of between 25-50% for indirect costs paid to universities for research.

- The Howard Hughes Medical Institute should initiate a program to support basic researchers in AIDS, similar to its existing programs in genetics, cell and structural biology, immunology and neuroscience.

- The OAR should consider initiating, on a limited basis, a new competitive mechanism of program grants (based on the model currently in use in the U.K.) to fully support the most productive basic researchers in AIDS for a period of five years.

- The OAR should institute a new program of pilot grants in basic research on AIDS. The awards should offer approximately $100,000 for each of two years to: junior researchers in the field; investigators pursuing novel, or "risky" hypotheses or understudied areas of research; scientists working in related fields (e.g. T-cell immunology, the cell cycle), but who have not thus far worked in AIDS; teams of investigators wishing to pursue collaborative projects in single research areas. The applications for these awards should be short, and the time from the submission of the application until receipt of funds should be from three to four months.

- The OAR should initiate a mechanism to issue expedited awards to researchers in new areas of emerging scientific importance. Currently, there is a two-year lag from the identification of a critical issue until the awarding of a grant in that area.

- Large pharmaceutical companies should be encouraged to offer targeted donations to universities for graduate science education in AIDS-related disciplines and to support basic scientific research in AIDS.

Table 1

Review of Current (FY 1993) NIAID Supported AIDS Pathogenesis Research Grants[1]

The following is presented for descriptive purposes only, to suggest the balance of extramural work funded through the major supporter of basic extramural investigator-initiated AIDS research, the NIAID Division of AIDS (DAIDS). This data reflects awards made by the DAIDS Pathogenesis Branch (PB), with a few from the Developmental Therapeutics Branch (DTB) and others. Work supported by other divisions of NIAID and other NIH institutes, centers and divisions is not summarized here. Thus, it reflects only a part of the diverse spectrum of AIDS related basic research currently underway (perhaps $60-70 million, or 25%, of the $230 million NIH spends on basic AIDS research).

TOPIC	AWARDS
Molecular Virology of HIV Reproduction + Regulation	118
HIV entry through CD4 receptor	22
HIV entry through other receptors	5
3-dimensional structure of HIV envelope	5
Mechanisms of HIV integration into host DNA	12
Mechanisms of HIV reverse transcriptase	11
Mechanisms of HIV tat + associated cellular proteins	20
Mechanisms of HIV rev + associated cellular proteins	11
Mechanisms of HIV regulatory genes, etc.	18
HIV virion synthesis + maturation	14
Cellular + Physiological Immunopathology of HIV Infection	26
Natural history of acute (primary) HIV infection	3
Levels of viral expression in different tissue reservoirs	9
Mechanisms of HIV entry into CNS + neuropathology	6
Technologies to improve detection of HIV	8
Viral Factors Affecting HIV Progression	38
Genetic variation within individuals + populations	7
Viral gene variation affecting disease progression	19
Viral variants affecting transmission or progression	3
Genetic determinants of cellular tropism	9
Host factors regulating HIV disease progression	50

Viral escape from protective humoral immunity	9
Viral escape from cellular immunity	16
Host genes, proteins, cytokines affecting HIV course	19
Mechanisms of host resistance to HIV infection	4
Non-genetic co-factors affecting progression	2
Cofactors affecting disease progression	13
Effects of co-infection with other viruses	10
Effects of co-infection with other microbes	3
Direct/indirect mechanisms of HIV immunodeficiency	29
Role of CD8s, NK, B cells, macrophages, DCs, FDCs	6
HIV-induced aberrant signalling + superantigens	21
T cell homeostasis	2
Animal models of HIV-mediated pathogenesis	49
Viral genes affecting pathogenesis	23
Time course of infection	10
Clinical course of disease with tropism variants	1
Lentivirus effects on T cell development/regulation	1
Autoimmunity, viral escape, antibody enhancement	14
Mechanisms of sexual/mucosal transmission	8

Subtotals:

Viral factors	156
Host factors	99
Cofactors	13
Animal models	49
Sexual transmission	8
TOTAL	331

Table 2: NIAID Extramural AIDS Funding Trends FY 1990-1994

AIDS awards (N)	**1990**	**1991**	**1992**	**1993 Est.**	**1994 Est.**
Total reviewed	776	536	580	620	662
Total recommended	713	475	459	546	583
Total funded	215	191	198	227	258
AIDS awards ($ in Millions)					
Total reviewed	210	148	297	302	256
Total recommended	147	114	222	257	267
Total funded	45	47	67	71	81
Award rate	39%	40%	43%	42%	44%
Success rate	28%	36%	34%	36%	39%
NIAID AIDS payline					
Percentile for unsolicited:[2]	22%	18%	16%	14%	10%
Percentile for all awards:	22%	25%	23%	19%	15%

Award rate = grants deemed fundable by study section.
Success rate = grants actually awarded given fiscal realities.
Percentile = grants awarded as proportion of applications.

Source: Wayne Crum + Steve Berkowitz, Financial Management + Information Systems Branch, NIAID, NIH, 28 May 1993.

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Founded in January, 1992, the Treatment Action Group, or TAG, is the first and only AIDS organization dedicated solely to advocating for larger and more efficient research efforts, both public and private, towards finding a cure for AIDS.

TAG supports the work of approximately fifty treatment activists as they meet with researchers, pharmaceutical companies, and government officials, ensuring a voice for people living with HIV in the process of finding and accessing promising treatments. TAG's treatment activists, most of whom are living with HIV, strive to develop the scientific and political expertise needed to transform policy.

In 1993, TAG successfully lobbied for a radical restructuring of the management of our government's AIDS research effort. Our recommendations for change, first presented in 1992 at the International AIDS Conference in Amsterdam, were incorporated into the 1993 reauthorizing legislation for the National Institutes of Health. Through the creation of a powerful Office of AIDS Research, this legislation will finally provide for the coordination, strategic planning, and leadership that our government's AIDS research effort has lacked to date.

TAG is a 501(c)(3) tax-exempt organization, and can be reached by writing to 147 Second Ave., #601, New York, NY 10003, or by calling us at (212) 260-0300, or faxing to us at (212) 260-8561.

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Joseph Mike McCune
John Moore

James Mullins
Yvonne Rosenberg
Michael Saag
George Shaw
Gene Shearer
Robert Siliciano
Joseph Sodroski
Ralph Steinman
Mario Stevenson
Bruce Walker
Steven Wolinsky
Flossie Wong-Staal
Jerome Zack
Susan Zolla-Pazner

[1]Source: NIAID Division of AIDS Program Review: HIV Pathogenesis workbook, 20 May 1993, tab VII.

[2]This is the payline for unsolicited investigator- initiated R01 research grants.