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0.0 INTRODUCTION

They [political leaders] simply don't care -- and they're allocating just enough money so it looks good on paper; not good, but at least on paper their asses are covered so in the future when the finger of responsibility points in their direction they can say, "But we did something."

-- David Wojnarowicz¹

The continued ban on the immigration and travel of HIV-infected persons entering the United States is the Bush Administration's most blatant attack yet on people with AIDS. No medical justification for the continued policy was even offered. Ignoring the opinions of the Centers for Disease Control, the World Health Organization, the International Red Cross, the International AIDS Society and the National Academy of Sciences, the Bush Administration decided to formulate public health policy based on politics, rather than science. It indicates that the Administration has no real interest in addressing this epidemic, but rather, sees AIDS policy as a bone to throw to fundamentalist Republican dogs.

The failure to provide adequate education, health care and support has already cost hundreds of thousands of lives. The failure to adequately fund research will cost the world millions more. Clearly, over the last year, the United States government has shown that it is much more interested in wreaking death and destruction than in promoting more humanitarian goals, such as ending disease, hunger and ignorance. We have never been so ashamed of our country as in the last six months.

This is a call to action. You cannot expect us to stand alone any longer, voicing our rage at the US government's genocidal response to this epidemic. You, who are the leaders, who have taken on the task of handling this crisis - the educators, the scientists, the doctors, the administrators - we call on you to speak out: to speak out against discriminatory policies such as the immigration ban; to speak out against a government which refuses to provide health care for its people; to speak out about inadequate funding for research; to speak out against pharmaceutical and insurance industries that place profits before people. If you are committed to ending AIDS, then this is part of your job. It is not enough to be a researcher or a doctor. Your responsibility must extend further. Do you consider yourself leaders in the response to the AIDS epidemic, Drs. Fauci, Hoth and Corey, Novello, Healy, Kessler, and Peck? Then you had better open your mouths. It's about time that AIDS becomes as uncomfortable for you as it is for us.

You, who are representatives from governments from around the world, must now openly condemn the United States AIDS policies. The world is depending upon the U.S. to conduct the research to find a cure. But, the Bush Administration is cutting the research budget. Instead, the U.S. is spending its time and money testing and restricting immigrants, health care workers, prisoners, job trainees and military personnel, while providing health care to no one. You must express your outrage.

The United States has prevented the success of AIDS education programs by prohibiting and de-funding the production of sexually explicit materials, censoring information about needle cleaning, condemning needle-exchange programs, de-funding drug treatment programs, and censoring family planning programs worldwide. The failure of the U.S. to educate its people about HIV

¹ David Wojnarowicz, Close to the Knives: A Memoir of Disintegration. Vintage Books, New York, 1991, p. 106.

transmission has caused infection to spread throughout America and the world, especially in South America and Asia. As we sit in Florence and listen to the many reports about new and soaring infection rates, we must remember that the United States is to blame for this and we must speak out in anger.

There has been much criticism directed at prior AIDS conferences for being too focused on AIDS as it effects the U.S. AIDS is an international crisis and we must look at the totality of the issues. But in doing so, we must acknowledge that, like its military and economic policies, the United States AIDS policies have a global impact, which, thus far, have served to worsen the crisis for everyone. The United States, the only industrialized country other than South Africa that does not guarantee health care to its citizens, must be made accountable for its role in neglecting and mistreating people with HIV infection and for its failure to prevent widespread infection when it had the opportunity.

1.0 BASIC RESEARCH: Unanswered Questions

1.1 Overview

For several years now, ACT UP/New York's Treatment and Data Committee has rigorously examined and criticized clinical research on AIDS, focusing most of its attention on the National Institute of Allergy and Infectious Diseases' AIDS Clinical Trials Group and the pharmaceutical industry which have carried out the bulk of the investigations into treatments for primary HIV infection and its opportunistic sequelae. As we begin the second decade of the crisis, we have realized that there is another fundamental problem: the disorganized state of basic scientific research on AIDS. The improvement of therapeutic strategies against AIDS and thus the lives of millions of people worldwide are dependent on advances in our basic knowledge about the nature of the disease and its pathogenesis. The current paucity of treatment options for PWA's is, in large part, due to the limits of that knowledge.

In some ways, AIDS research was in a better state before the human immunodeficiency virus was discovered. Scientists were investigating a range of phenomena and potential causes as they tried to elucidate the mechanism of pathogenesis. Research was being done on epidemiology, cofactors, and the range of immunological manifestations of AIDS. Researchers had begun to describe a range of immune system abnormalities that were all part of AIDS. These included abnormal levels of cytokines, appearance of auto-antibodies, and chronic inflammation. Then, when the AIDS virus was discovered, the virologists took over and the research into the physiological manifestations of AIDS dwindled off and was ignored. Those who would find the cure retreated to their tissue culture hoods and microtiter dishes, remembering physiology only when they needed another blood sample. AIDS IS NOT A DISEASE OF THE BLOOD; IT IS A DISEASE OF THE IMMUNE SYSTEM. AIDS IS NOT A DISEASE OF THE TEST TUBE; IT IS A DISEASE OF THE BODY.

These points while seemingly obvious have already been ignored many times since HIV was co-discovered, co-stolen, co-mislabeled, co-misnamed, and co-renamed in the early eighties. The perpetual debate over the discovery of HIV distracted attention from the poor quality of the early virological work. For example, the canonical virus strain, now agreed to be from a French homosexual, "LAI," who visited the US between 1977 and 1979, is quite rare in the infected population, and appears both more cytopathic and more susceptible to therapy (in vitro) than many if not most wild-type isolates. Nonetheless, this strain has been used to develop the ELISA test and to assay most experimental therapeutics. Thus the inadvertent (self-) selection of HTLV-

IIIB/LAV/LAI as the reference strain of HIV may have yielded a distorted picture of the behavior of HIV *in vivo*. Comparing the properties of different strains early on, an important part of basic virology, could have resulted in the selection of strains that were physiologically relevant.

To give just one example of how this distorted clinical research, HIV-LAI has a very high binding affinity to the CD4 receptor. It is, at least *in vitro*, quite susceptible to binding inhibition by recombinant soluble CD4. Wild-type isolates, however, are much less susceptible to rsCD4. As David Ho pointed out in perhaps the most stimulating (and depressing) talk given during the 6th International Conference on AIDS in 1990, much if not most *in vitro* work with HIV may be irrelevant because it uses artificial lab strains rather than wild-type HIV isolates:

Studies performed under experimental conditions [must] attempt to mimic the situation *in vivo*. More relevant studies would utilize, for example, normal primary cells (instead of transformed cell lines) and fresh clinical isolates of HIV that have not been (or are only minimally) selected through passages *in vitro*. Appropriate studies must take into account ... the quantity and heterogeneity of HIV. This is especially critical with respect to the issue of viral resistance to drugs. Our recent findings with soluble CD4 *in vitro*, *ex vivo*, and *in vivo* illustrate several of these points... Too often, *in vitro* studies are conducted with laboratory HIV isolates, such as HTLV-III_B, which is a strain heavily influenced by multiple passages through cell cultures. HTLV-III_B is not very like wild type clinical HIV isolates. H9 lab cells are far from normal T4 helper cells. *In vivo*, there is a multitude of isolates at any one time. Experiments should be set up to mimic the *in vivo* situation.

Recombinant soluble CD4 (rsCD4) inhibits viral infectivity by 90% at 100 ng/ml-100 ug/ml concentrations *in vitro*. *In vivo*, however, in a 12-person phase study of 1, 3, 9 + 30 mg/day of the Biogen rscd4 for 28+ days, there was no consistent drop in HIV titers despite concentrations of over 200 ng/ml, which, according to the lab studies, would have been more than enough. No one had made sure that rsCD4 worked in the presence of HIV-positive human plasma. Lab isolates of HIV (i.e., HTLV-III_B) were easily neutralized by rsCD4. Primary isolates were refractory to the drug rsCD4. It required 100 to 1000 times more rsCD4 to neutralize primary isolates in the test tube.

It is scandalous that the ACTG diverted resources from more useful therapies to schedule eight clinical trials of clinically useless rsCD4 and CD4-IgG and has continued to stubbornly defend this decision.² Moreover, two recently closed studies at the NIH Clinical Center used CD4-IgG in conjunction with syngeneic bone marrow transplants, AZT and alpha interferon -- a vile, invasive experiment performed on HIV+ volunteers with HIV- identical twins.

The lack of appreciation for the physiological picture of the pathogenesis of HIV is only one symptom of the neglect of basic scientific research on HIV. Good clinical research is built on a foundation of information about immunology, virology, and epidemiology. The lack of this infrastructure cripples our battle against HIV as well as many other immune system disorders such as lupus. In the sections that follow, we shall outline some crucial neglected areas of AIDS research, starting with immunology and proceeding to basic virology and finally finishing up with epidemiology. We still don't know how much HIV dwells in cells during various stages of infection, which cells and organs are the primary reservoir of HIV (macrophages or lymphocytes), or how the various immune cells and soluble factors contribute to pathogenesis on their own. We still don't

² CD4 trials: ACTG 066, 101, 133 (withdrawn), 147 (withdrawn); CD4-IgG trials: ACTG 121, 134, 139 (withdrawn), 146 (pending). ACTG 146 is a trial of CD4-IgG in HIV+ pregnant women, who seem to be the last hope of the developers who poured millions down this therapeutic dead end.

know what actually kills T-cells in vivo. We lack a clear understanding of the contribution of endogenous and exogenous cofactors (including inflammatory mediators, cytokines, autoantibodies, coviral and other microbial antigens) to AIDS: are they necessary stimulants to immune destruction, or do they hasten what would otherwise be a slower process? Is the immune dysfunction of AIDS mediated by a period of immune hyperactivity? Why do some people remain immunologically intact after infection with HIV for over 10 years? Why do others, with very low CD4 counts, remain free of opportunistic infections? What are the mechanisms by which these questions can be answered?

1.2 IMMUNOLOGY

1.2.1 CYTOKINE DYSREGULATION

In AIDS, levels of a number of different cytokines have been found to be persistently elevated, or produced spontaneously by blood cells isolated from patients and maintained in culture. The ability of blood cells to produce some other cytokines when appropriately stimulated is impaired. Among those that are elevated are alpha interferon, tumor necrosis factor alpha, interleukin 6, transforming growth factor beta and interleukin-1. Abnormal levels of these cytokines may account for many of the symptoms displayed in AIDS.

Some of the cytokines released during the immune response activate HIV in the test tube (IL-2, GM-CSF, TNF-alpha), while others may be linked to both HIV activation and Kaposi's sarcoma (IL-6, TGF-beta). Few interventions have been studied to correct abnormal levels of these cytokines. In fact, these cytokines have been proposed and tested as treatments at the behest of biotechnology companies, even when their physiological role in AIDS was poorly understood.

Alpha interferon (IFN-alpha) was the first cytokine found, in 1981, to be elevated in a majority of people with AIDS. Interferon is known to have the following effects, all of which are abnormalities seen in people with AIDS:

- * Blood abnormalities, including suppression of CD4 lymphocyte production, stimulation of B cell differentiation, upregulation of MHC class I antigen expression (possibly implicating IFN-alpha in the elevations of beta-2-microglobulin, a component of MHC class I Ag), inhibition of platelet, white and red blood cell precursors, leukocyte inclusion bodies and low blood tryptophan levels;
- * Systemic symptoms, including fevers, anorexia and cachexia, the latter indicated by elevated triglyceride levels and lowered cholesterol levels

It is probable that the sustained presence of interferon in the circulation contributes to these abnormalities in people with HIV. Several studies indicate that the appearance of circulating interferon in an HIV infected individual has an adverse prognostic significance. Why does AZT therapy appear to lower levels of circulating acid-labile alpha interferon?

There are additional abnormalities in the interferon system in AIDS. Blood cells from people with AIDS are unable to make interferon on appropriate stimulation despite the presence of large amounts of interferon in the circulation of the same individuals. Interferon receptors are down-regulated in AIDS. Finally, the intracellular antiviral pathway normally stimulated by interferon is dysfunctional in people with AIDS, despite (or perhaps even because of) elevated circulating IFN. One enzyme, the 2-5A dependent endonuclease, is undetectable in AIDS patients' lymphocytes, and this appears to be an AIDS specific abnormality. The utility of this enzyme as a surrogate marker could have been evaluated by now. Incidentally, it was claimed a few years later that this enzyme

reappeared in patients treated with Ampligen.

To this day we do not know which cells make interferon in AIDS patients nor what the inducing agent is. Studies on whether endogenous interferon plays a role in the pathogenesis of AIDS would require that correlations be made between the appearance of interferon and its levels with clinical and immunologic markers. In 1985, a correlation was made between increasing interferon and decreasing CD4 numbers, (and interestingly a correlation between increasing interferon levels and increasing IgA levels), to pathogenesis. No large scale studies of the correlation of interferon levels with clinical, hematologic and immunologic markers has been reported, and almost nothing on the nature of the interferon inducer and absolutely nothing on which type of cell is making the interferon. If endogenous interferon should prove to be a factor in pathogenesis we have lost time in developing methods to control its production or to counteract its effects.

Interleukin-2 (IL-2), which is produced by activated T cells, stimulates T and B cell growth and differentiation, and increases killing activity by T cells, macrophages and natural killer cells. Lymphocytes from PWA's are defective in their ability to produce IL-2 on appropriate stimulation. However, the IL-2 that is produced may play a role in the spread of disease by stimulating replication of HIV-infected cells. IL-2 also exacerbates Kaposi's sarcoma through an unknown mechanism. As IL-2 has already been tested as a treatment, in conjunction with AZT and low dose alpha-interferon, its physiological role needs to be more clearly defined.

Interleukin-6 (IL-6), originally known as B-cell stimulatory factor (BSF), is produced by fibroblasts or macrophages and stimulates B cells to differentiate into immunoglobulin-secreting plasma cells. Immunoglobulin levels are elevated in AIDS patients and IL-6 may be a factor in producing this characteristic abnormality. Autoantibodies are among the immunoglobulins produced by overactive B cells. There is also some evidence that IL-6 is a factor promoting the growth of Kaposi's sarcoma cells.

Transforming growth factor (TGF-beta) is produced by platelets and activated macrophages, and attracts other immune cells to sites of tissue damage. TGF-beta has both growth-stimulatory and growth-inhibitory activities. TGF is known to suppress CD4 cell proliferation. It also enhances IgA production. High IgA levels carry an adverse prognostic significance in people with AIDS. TGF-beta enhances HIV expression in acutely infected cells, whereas it suppresses HIV in chronically infected cells. TGF-beta has been found in brain tissue of people with AIDS, implicating it in neuropathology. TGF-beta may be a promoter of angiogenesis (blood-vessel growth), and, as such, may be implicated in the pathogenesis of KS. TGF-beta can suppress HIV expression normally stimulated by mitogens (PMA) and certain cytokines (GM-CSF, IL-6), but does not suppress TNF-stimulated HIV expression.

Tumor necrosis factor (TNF) alpha is a cytokine released by activated monocytes and macrophages and by activated B cells in response to many viral and bacterial antigens. Along with IL-1, TNF stimulates polymorphonuclear leukocytes, fibroblasts, endothelial cells, and T and B lymphocytes to perform various immune functions. In addition to its ability to cause hemorrhagic necrosis of cancerous tissue (first noted in the 1890s), TNF is a central orchestrator of the inflammatory and immune responses. Like other cytokines, including the interferons, TNF has both therapeutic and pathogenic activity.

Healthy persons rarely have TNF circulating in their blood. People with HIV often do, and its incidence rises as their disease progresses. Some effects of TNF resemble features characteristically seen in AIDS patients. Wasting is a consequence of the prolonged action of TNF. Elevated triglyceride and low cholesterol levels are typically seen in AIDS patients, and such lipid changes result from the action of TNF on lipoprotein lipase, an important enzyme in the

metabolism of lipids. TNF also can inhibit the development of lymphocytes and red blood cells and the levels of these blood cells are low in patients with AIDS. TNF is also a potent activator of HIV out of latency and promotes its replication. It is likely that TNF contributes to the above abnormalities, and evidence for this may come from trials of pentoxifylline, an inhibitor of TNF. Whether or not TNF is a major factor promoting the replication of HIV *in vivo* as it is *in vitro*, remains to be seen. In addition, other viruses which often coinfect HIV-infected individuals, including cytomegalovirus (CMV) and Epstein-Barr virus (EBV), are also capable of stimulating TNF production.

In spite of these observations, and in the apparent belief that the putative antiviral and antineoplastic activities of TNF might prove therapeutic to persons with HIV infection, a team from the University of Seattle, in conjunction with Genentech, the manufacturer of recombinant human TNF, conducted a 12-week Phase II trial of rTNF with or without recombinant gamma interferon through the US NIH AIDS Clinical Trials Group (ACTG 025). Toxicities noted included fever, grade 1 constitutional symptoms and local reactions in 100% of the 30 study subjects. The investigators claimed that HIV culture isolation from peripheral blood lymphocytes decreased from 92% before therapy to 84% after therapy, and that plasma viremia decreased from 56% to 29%. The investigators concluded that "this study demonstrates that TNF alone or in combination with IFN-gamma does not appear to hasten the progression of HIV infection either clinically or virologically," and that further study of the therapeutic potential of rTNF is warranted.

1.2.2 IMMUNOSUPPRESSIVE VIRAL COFACTORS

The role of herpes virus infections, in particular, infections with cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in directly contributing to the immune dysregulation of AIDS has been largely ignored since the discovery of HIV. Recent interest in CMV, EBV and human herpes virus 6 (HHV-6) has focused on the potential role of infections with these viruses in activating and promoting the replication of HIV. While it is important to clarify this aspect of infection with these viruses, CMV and EBV are themselves immunosuppressive, in ways resembling AIDS. Some of the adverse immunological effects of CMV infection include:

- * Lymphocyte changes, including elevated CD8 suppressor/cytotoxic lymphocytes (with a reduction in CD4/CD8 ratio), and depressed lymphocyte response to antigens and mitogens; impaired NK cell function, including impaired gamma interferon production.
- * Monocyte/macrophage changes, including induction of suppressive monocytes, decreased responsiveness of monocytes to antigens, decreased IL-1 production; and elevated neopterin.
- * B-cell and humoral changes, including non-specific polyclonal B-cell activation, and elevated IgG synthesis; production of autoantibodies.

CMV also raises levels of circulating beta2-microglobulin. CMV bound to beta-2-microglobulin can use the class I HLA antigen as a receptor for entry into the cell.

The clinically significant role CMV plays in disease progression is suggested by several studies, including a British study of HIV infected hemophiliacs in which those who were CMV+ HIV+ progressed faster than those who were CMV- HIV+, and a European-Australian study in which people randomized to high dose Acyclovir (for CMV) and AZT lived longer than those taking AZT alone.

Reactivated Epstein-Barr virus (EBV) infections also may contribute to the immunologic

abnormalities of AIDS. Almost all adults are infected with EBV, a virus that may remain dormant in B lymphocytes for the life of the individual. Evidence of frequent EBV reactivations in patients with AIDS and with lymphadenopathy was obtained as early as 1983. EBV may contribute to the high immunoglobulin levels that are characteristic of AIDS, as well as being associated with the appearance of autoantibodies which are well documented in some EBV infections.

Whether reactivated EBV infections contribute to the immunologic disorders of AIDS is still a question that remains unexplored. It is in fact quite possible that active EBV infections do contribute to the pathogenesis of AIDS, as such infections are associated with T lymphocyte subset changes, and can be responsible for increases in suppressor T lymphocytes with a reduction in the ratio of helper to suppressor cells.

1.2.3 AUTOIMMUNITY

Autoimmunity describes immune responses (autoantibodies or autoreactive immune cells) directed against the body itself. The clinical manifestations of autoimmunity will depend on the type of target tissue attacked by autoantibodies. For example, antibodies against certain types of cell in the pancreas result in diabetes while antibodies against thyroid cells can result in an underactive thyroid. Antibodies to platelets can cause thrombocytopenia, and red blood cells can be destroyed by antibodies directed against them.

Many different auto-antibodies have been described in patients with AIDS. Some have been shown to be clinically important. Anti-platelet antibodies can be associated with low blood platelet levels (thrombocytopenia). Idiopathic thrombocytopenic purpura (ITP) in persons with HIV may be caused in some cases by platelet binding to HIV antigen-antibody complexes; paradoxically, ITP in early infection may have a beneficial prognostic significance.

Some cases of neuropathy are associated with auto-antibodies. Antibodies to red blood cells have caused anemia. Numerous other autoantibodies have been described in people with AIDS. There are antibodies to T lymphocytes and it is possible that these contribute to CD4 cell depletion, although this has not been proven.

We do not know the full extent of autoimmunity in AIDS, nor whether or how it contributes to the overall immunedysregulation. We have no idea as to what the mechanisms are that provoke the production of autoantibodies. Some attention has focused on HIV as potentially able to induce autoimmunity. Virus induced autoimmunity is a well documented phenomenon. Several mechanisms are possible. One mechanism depends on the resemblance of viral components to cellular components. An example is the HIV gp41 antigen which has parts that resemble part of the HLA class II molecule, a cell membrane protein important in lymphocyte function. Antibodies against gp41 might then recognize and react with HLA class II molecules on the lymphocyte and thereby exert an immunosuppressive effect. However, even if HIV is able to induce some autoreactive antibodies by this mechanism, it is beyond the capacity of HIV to mimic all the antigens against which the large variety of autoantibodies in AIDS are directed. Clearly other, as yet undetermined, mechanisms must be responsible for the appearance of autoantibodies. One likely possibility is the inappropriate activation of B cells to make immunoglobulins including autoantibodies.

Another phenomenon sometimes seen in HIV infection is the classic autoimmune phenomenon known as Sjogren's syndrome, in which salivary glands become swollen and the mucous membranes, particularly of the mouth become dry. Intriguingly, people with HIV who develop Sjogren's syndrome have a relatively slow course of disease progression. Research on these individuals might

provide a clue as to why some individuals do relatively well. Already it appears that people with AIDS who develop Sjogren's syndrome have a specific genetic makeup.

In 1981, when interferon was found in the blood of AIDS patients it turned out to be unusual form of alpha interferon unstable in acid. A year or two before the AIDS associated interferon was found a similar type of interferon was found in the blood of people with lupus and other autoimmune diseases. The presence of this unusual acid unstable interferon seemed to be a feature of autoimmune diseases, and so a systematic search for autoimmunity in AIDS was made. Ample evidence for autoimmunity was indeed found and reported on in 1983.

We have thus known for the past 8 years that whatever else AIDS is, it is also an autoimmune disease, but this aspect has remained largely unstudied. We have no idea of the extent of the problem, and apart from a few instances, no information about its clinical significance. There are treatment approaches to autoimmunity, and should autoimmunity be of importance in contributing to the overall immune dysregulation of AIDS as it has already been shown to be important in some manifestations of AIDS, time has been lost in developing therapies directed against autoimmunity.

Autoimmune inhibiting therapy. Few interventions have been designed and carried out to determine whether these autoimmune reactions are treatable. There are many similarities between murine and human retroviral immunodeficiency virus-induced disease. The immunosuppressive drug cyclosporine restored normal T-cell function and depleted infected cells in a mouse immunodeficiency virus model (MuLV "MAIDS"). A pilot study of cyclosporine was done in PWAs in France. What were the results?

1.2.4 **MACROPHAGE DYSFUNCTION**

Macrophage function in AIDS is severely disturbed. It remains to be determined which macrophage dysfunction is related to direct infection by HIV, and which to the impaired molecular signal transduction found in AIDS.

Among the impaired functions of macrophages in the context of HIV infection are impaired chemotaxis (travel to the site of infection); impaired phagocytosis (ingestion of antigen); impaired oxidative burst activity (reducing the ability to digest phagocytosed pathogens); impaired recognition and clearance of pathogens; and degenerative changes in tissue macrophages such as skin Langerhans cells and lymph node follicular dendritic cells, and many others (see below).

Many of the circulating soluble factors recognized as hallmarks of AIDS progression (such as neopterin, and many cytokines, e.g., TNF-alpha, IL-6) are produced by macrophages. Many of the monokines produced can exert an amplifier effect favoring cellular activation and proliferation and leading to a hyperstimulation of the immune response, including an elevation in the number of T-lymphocytes (initially), B-lymphocyte activation, hypergammaglobulinemia +, alpha-interferon production. Macrophages may well be the major reservoirs for HIV during all stages of infection and are also a vector for the spread of the disease to different tissues within the body. The study of the pathophysiology of macrophage infection and dysfunction in AIDS has taken a back seat for too long to the study of HIV and its relationship with the T helper lymphocyte.

1.2.5 **ALLOIMMUNIZATION**

Exposure to antigens found in blood or sperm from other persons causes a process known as alloimmunization, which may well be yet another of the many unexplored mechanisms of acquired

immunosuppression. Clearly such exposures could not in themselves produce AIDS, as they are not new; but they are known to produce measurable changes in some immunologic tests and could contribute to disease together with other factors. In fact, multiple blood transfusions are administered to individuals who are to receive a kidney graft in order to make it more likely that their immune systems will not reject the transplanted kidney. Among the known immunosuppressive effects of blood transfusions are increases in suppressor T cells, increased suppressor cell activity, and reduced natural killer cell activity. In addition, foreign cells can activate latent viruses, including CMV and HIV. In fact, the routine isolation of HIV involves mixing lymphocytes containing dormant and unexpressed HIV with foreign lymphocytes from another individual as a means of activating HIV out of latency. Finally, there is a theoretical possibility that repeated alloimmunizations could lead to the appearance of self-reactive antibodies (autoantibodies).

1.2.6 INFLAMMATION

The inflammatory process is an integral part of the body's immune function and involves a general restorative response of tissues to soluble chemical mediators after injury. Under normal conditions the inflammatory response is an acute event which subsides after the offending agent is eliminated.

However, it is clear that in AIDS a pathophysiological state of chronic inflammation is initiated by the continuous presence of irritating agents among them HIV and other pathogens. Elevated levels of some acute-phase reactants, prostaglandins and metabolites of arachidonic acid in PWA's are a few of the manifestations of this aberrant inflammatory state. There is also evidence that the complement system, a group of about 20 serum proteins, whose overall function is the control of inflammation is activated at every state of HIV infection. The cytokine dysregulation that is a hallmark of AIDS contributes to chronic inflammation as TNF and IL-1 among other cytokines are potent inflammatory mediators.

The constant activation of the inflammatory response in AIDS clearly contributes to the pathogenesis of the disease. Prostaglandin E2 for instance has been shown to promote HIV replication. The tissue damage observed in HIV infection may be attributable to the activation of the complement system by the high level of circulating immune complexes in PWA's. There is also evidence that the combination of components of the alternative complement pathway and antibodies to HIV may combine to enhance HIV infection.

The pathogenic effects of chronic inflammation in AIDS need to be investigated more fully. Anti-inflammatory therapy could be a valuable part of the therapeutic management of the disease.

1.2.7 CHRONIC IMMUNE ACTIVATION

Early on in the AIDS epidemic, several theories of disease progression, posited that immune system overload, led to immune suppression. These theories lost favor once HIV was discovered. Recently, similar theories have been proposed again. However, the experiments to prove these theories remain to be done.

The latest versions of these proposals posit several points:

1. Primary HIV infection stimulates an effective immune response resulting in specifically limited infection of T cells and minimal viral expression. Infected macrophages express viral components on their surface which interact with T4 lymphocytes through affinity for

CD4.

2. The effect of macrophage presentation of viral products [gp120] is to cause generalization of immune activation, which is normally localized to tissue sites of infection as a result of MHC restriction.
3. Due to systemic activation, lymph nodes become sites of non-specific recruitment and trapping of lymphocytes resulting in hyperplasia and lymphadenopathy.
4. After exposure to infectious challenge, failure of T cells to escape from activation signals results in progressive anergy to specific stimuli. Anergy occurs faster or only under conditions of specific challenge.
5. Cell death may result as part of the immune system's cycle of stimulation and retrenchment. HIV may play a role in triggering cell death.
6. Treatment should avoid additional stimulation and could be designed to: (a) block inappropriate T cell activation at the level of the T cell/macrophage interaction; (b) target a cytotoxic response to infected cells; and (c) non-specifically decrease the manifestations of generalized cytokine release through inhibitors of their action.

Competing theories of the pathogenesis of AIDS should be fostered and encouraged. It is irrational this early in our investigation of the disease to become wedded to any model, particularly when our current models are based on test-tube rather than physiological evidence.

But there is trouble in store for anyone who surrenders to the temptation of mistaking an elegant hypothesis for a certainty.³

1.3 VIROLOGY

Virology encompasses much more than molecular biology. Classical virology includes studying viral tropisms and quantitation of virus in different tissues. These topics have been bypassed in much AIDS research. How can we have a complete understanding of the disease if we do not know which tissues the virus infects, when these different tissues are infected, and what the viral loads in the different tissues are. An effective early intervention strategy would attack the virus where it lurks soon after infection. Sadly, we still do not know where the virus is. What follows is an outline of what we do know and some crucial questions in need of answers.

The Blood: Looking Where the Light Is. Pronouncements are routinely made about the pathogenesis of HIV in the entire body based on observations of the blood alone.

For example, in 1989 one prominent NIH team declared that CD4 cells were the principal reservoir for HIV in the peripheral blood. This is fascinating. However, more relevant is the question "what is the principal reservoir of HIV in the body?"

Only 2% of the body's lymphocytes (and none of its macrophages) are circulating in the blood at any one time. The rest of the lymphocytes are emerging in the bone marrow, being trained in the thymus gland, coursing through lymphatic ducts or awaiting pathogenic stimulation in the lymph glands and spleen. Macrophages rather than lymphocytes are the major reservoir of HIV infection in these tissues. Certainly some of the most notorious cellular products associated with symptomatic HIV and progression (such as TNF-alpha, IL-6 and neopterin) are produced by macrophages.

³ Levi, Primo The Periodic Table

Levels of macrophage infection would not be detected in blood assays, however, for while lymphocytes recirculate frequently between lymphoid tissue and the blood, monocytes live in the blood for only a brief time and then enter tissues, there to irreversibly differentiate and never return.

Infection of circulating blood cells has been the focus of research because they are so easy to observe; however, much of the actual immune suppression takes place in other organs, and the viral load may in fact be far higher in various tissues (varying by individual according to tissue tropism). Methods for investigating organ infection need improvement.

There is now solid evidence ... that consideration of the low numbers of infected cells in blood alone grossly underestimates the viral load in the HIV-infected patient. In certain bodily tissues, such as those of the central nervous system, lymph nodes, or lung, the frequency of HIV-infected cells may be 10,000- to 100,000-fold higher than in the blood. In each of these tissues, the predominant cell type infected with HIV is not the CD4+ T cell, but rather the macrophage.⁴

Naturally there are logistical issues in conducting a full examination of the pathophysiology of HIV infection in all its stages and sites. Blood is relatively easy to extract, process and fractionate; hence its use for most diagnostic and prognostic assays. Blood is probably not, however, the main arena of pathogenesis. The lymphoid system, mucosal tissue and many organs of the body are where the disease progresses, first insidiously, then clinically. These tissues are difficult to examine, however, without messy, frequent, invasive biopsies -- and hence most questions about basic pathogenesis remain unanswered. Investigators who seek funds to conduct such investigations are often accused of wanting to go on a "fishing expedition," and their grant proposals are turned down in favor of "harder," more "quantitative," (though often less relevant) molecular biology and virology. **This must change!**

Macrophages + Mucosal Tissues: HIV is known to infect macrophages. In fact, as the majority of people with HIV are infected through sexual transmission, the first tissues encountered by HIV in its potential new host are mucosal tissues where the sentinels of immunity are macrophages, not CD4 cells. Thus, HIV may infect macrophages before CD4+ cells. Understanding the properties of HIV-infected macrophages may be key to thwarting the virus.

Cells of the monocyte/macrophage lineage may also play a passive or an active role in disseminating HIV through the organs of the body, with attendant elevated risks of opportunistic organ involvement or idiopathic inflammation and tissue destruction. Certainly CD4+ Langerhans' cells in the skin display a high level of HIV infection. These cells were infected in 20% of the skin samples analyzed from 40 HIV-positive patients. The frequency of infection may match that of CD4+ cells in the blood.

The Bone Marrow: Different investigators have examined whether HIV infects pluripotent hematopoietic stem cells in the bone marrow. The answer appears to be an unambiguous yes and no. Certainly HIV has been found in the bone marrow, but it is as yet unclear whether these viral infiltrates were within stem cells, which are themselves rare and difficult to isolate.

The Thymus Gland: The thymus gland is said to be the Ecole Normale Supérieure for T lymphocytes. Few are called, and fewer chosen, to leave this rigorous finishing school to patrol the body, coordinating the awesomely powerful, rapid, well-coordinated and self-limiting cell-mediated

⁴ MS Heltzer, DR Skillman, PJ Gomatos et al. "Role of Mononuclear Phagocytes in the Pathogenesis of Human Immunodeficiency Virus Infection." Annu Rev Immunol 1990. 8:169-94.

immune system. Unfortunately, most of our knowledge of the thymus and immune development is known from mice. We still do not know what role the thymus plays, if any after childhood.

Since inflammatory cell infiltrates have been observed in the thymus of AIDS patients, their potential role in pathogenesis cannot be ignored. If the thymus gland remains vital throughout life, and is continually selecting T cells, HIV infection of thymic cells and precursor T cells (which are, for a period, both CD4+ and CD8+) could interrupt the maturation of competent T4 cells by several mechanisms:

- Through a direct cytopathic effect, i.e., killing of double positive (CD8+ CD4+) or single positive (CD4+) lymphoblasts in the thymus, infected by cell-cell or free virus-cell contact; or
- Through an autoimmune mechanism, by a failure of self-tolerance (which could be localized to the thymus or any other organ, or generalized), due to the development of 1) killer T cells cytotoxic to uninfected CD4+ cells, 2) anti-CD4-antibody dependent cellular cytotoxicity or 3) complement-dependent neutralization.

If the immune system is being destroyed by its own T cells, this would of course clarify why anti-HIV therapy alone does not halt disease progression. Such killing of uninfected T cells in HIV-infected humans has been demonstrated.

Other Tissues: The role of other lymphatic tissues of the body, including the lymph glands, lymphatic ducts, and spleen, remains to be elucidated. Certainly the lymph glands would seem to serve as a site for productive infection of both lymphocytes and macrophages, and tissue destruction there must contribute to immunopathogenesis. Ultrastructural studies of lymph nodes reveal a pattern of explosive follicular hyperplasia in the early stages of HIV disease, followed by involution and aplasia.

These issues could have been explored after the virus was initially found. Big game virus hunters who wish to find conspicuous targets rather than explore fundamental viral questions should turn their sights on other tasks. For example, there appears to be an outbreak of autoimmune conditions amongst the inhabitants of the White House. Tissue samples from canine (Millie), porcine (John Sununu) and asinine (George Bush) sources should be thoroughly analyzed.

1.4 EPIDEMIOLOGY

Since the start of the epidemic, epidemiology, immunology, and infectious disease have exhaustively scrutinized the people in the final stages of disease. At the same time they have ignored the patient populations that have successfully fended off disease. These unusual, but not rare, patient populations could help unravel many questions about viral mechanism.

Why do some people have severely depleted CD4 cells and yet remain healthy? Many people are walking around with fewer than 100 CD4 cells, yet remain healthy and free of opportunistic complications. Obviously the CD4 cell alone does not account for the entire disease process. An urgent priority for immediate research must be the identification and characterization of immune factors common to long-term, healthy HIV+ survivors. Why some persons with HIV remain AIDS-free after more than 10 years of infection (for example, 10% of the men infected by 1978 in the San Francisco Men's Cohort are said to remain free of immune suppression 12 years later (ref.)). Two cohorts of this group should be intensively analyzed: 1) those long infected who still have high CD4-cell levels; and 2) those with very low CD4 cell counts who are still healthy. What are the

cytokines and other immune factors which these people have which fend off immune suppression and AIDS?

Are there genetic correlates of immunity or susceptibility to HIV? The question of the relation between HLA subtypes and propensity to progression is often raised and seldom answered. Do different HLA-D subtypes have different binding affinities to gp120? While the technology to subtype HLA antigens is labor-intensive, the question is important enough to the resources necessary to answer it. Analysis of a representative cohort (of progressors vs. non-progressors) from within ACTG 016 or 019 might answer this question once and for all.

There is also remarkably scant data on the incidence and prevalence of opportunistic infections. The Centers for Disease Control dutifully records the AIDS-defining infections that fit its narrow definitions. People with AIDS then are ignored until their deaths are reported. Maintaining data on all of the opportunistic infections that PWA's get would answer some basic questions such as:

- 1) Do opportunistic infections coincide with particular T-cell levels? How true is the generalization that people do not get MAI or CMV-retinitis until their T-cells fall below 50? This information is vital for prophylaxis studies.
- 2) Are there correlations between different OI's? For example, does getting cryptococcal meningitis make one more or likely to get toxoplasmosis? This kind of information is vital for physicians.

The CDC's role in the epidemic has been to exclude people from treatments and benefits (see the Woman's Treatment Agenda) rather than to collect the information that PWA's, their physicians, and clinicians need. Current Observational Database projects may answer some of these questions and should be funded by the CDC.

1.5 DEMANDS

The system of basic scientific research on AIDS is not a system of research set up to deal with a crisis. In fact, the manner in which basic biomedical research on the disease is conducted differs little from the way in which basic biological research as a whole is carried out in this country. The model of basic research on AIDS has never taken into account the urgent needs of this epidemic. Our research effort on AIDS must be rethought.

1) A panel must meet to plan out a basic research agenda. Perhaps the most important thing that has to be done right now in basic biomedical research on the disease is the formation of a national panel to map out a plan for AIDS research, listing the questions that need to be answered and areas of inquiry that need to be pursued, as well as deciding upon the allocation of resources. This national basic research agenda, to be revised and updated yearly, should be implemented under the auspices of the NIH. The national basic research panel must be composed of leading scientists in fields such as immunology and virology who may not be involved in AIDS research up until now, in addition to AIDS researchers, clinicians and representatives from affected communities (who would be appropriately advised on scientific matters). The current system of basic research is incapable of dealing with the calamity before us. It provides no battle plan in the war against AIDS. It has no mechanism for providing a broad vision of research needs and prioritizing what needs to be done. It cannot insure that important questions will indeed have someone working on the answers to them. A coordinated and comprehensive research effort is not unprecedented in the history of science. In the 1940's, the U.S. gathered its best scientists together under the Manhattan Project to utilize the recent advances in theoretical physics to create a

weapon of mass destruction during WWII. AIDS, most will agree, is one of the greatest and direst challenges in the history of modern biomedical science, and mandates a similar approach; this time in the interest of saving countless numbers of lives.

2) We cannot rely entirely on investigator initiated research. By and large, the bulk of basic research on AIDS sponsored by the NIH, for example, is derived from unsolicited investigator-initiated grants. This means that what gets studied about AIDS is what individual scientists around the United States are interested in studying. While investigator-initiated research is an important mechanism to foster creativity and independent thinking in science, in the case of basic biomedical research on AIDS, it has kept us from realizing a comprehensive picture of the pathogenesis of the disease. In order to get answers to many of the questions we still have about AIDS, there is going to have to be an increased reliance, in the case of the NIH, on request for applications (RFA's) and requests for proposals (RFP's) on the research topics which while necessary avenues of inquiry are not attractive to investigators.

3) We cannot trust peer review. Another hallowed institution of the world of basic science that has not served us well in the fight against AIDS is the peer review system. The criteria that are used by peer review panels to judge grants on basic AIDS research generally favor work that has a clear molecular approach, that is to say, a strong theoretical basis in molecular biology, over research that takes a more physiologically-driven approach. This tendency retards our progress towards a greater knowledge about AIDS in several ways. First, the championing of "hard" science without regard to its physiological ramifications can often generate results that while examples of beautiful molecular biology have no clinical relevance outside of the test tube. Second, studies that might yield important data, for example, a study of the correlates of immunity in long term HIV + asymptomatics, are often dismissed as "phenomenology" or "a fishing trip." What is clearly needed is a pluralism of approach which will begin to bridge the gap between basic and clinical research on AIDS. While it is not always possible or prudent to do so, peer review committees and other institutions in the scientific community, such as the scientific journals, that have the opportunity to shape the agenda of basic research should encourage investigators to take the physiological ramifications of their work into account and should also push for the rapid application of theoretical issues.

4) The budget for basic biomedical research needs to be increased. Although the point is often made, it bears repeating that only a small portion of the grant applications received by the NIH is actually funded. NIAID for FY 1991 funded under 30% of all the grants, not only those for AIDS research, submitted to them. The budget for biomedical research in this country needs to be increased if we are to successfully vanquish this disease. Although the cry invariably goes up that the resources are just not there to increase funding to the NIH and other institutions, it seems that this lack of money for biomedical research indicates more of a lack of national resolve than anything else. Only a few months ago, the United States was able to mobilize a war on Iraq which cost a billion dollars a day, which is the same amount of money the government has expended on AIDS research in ten years. It is truly horrifying that the lives of millions of Americans and millions of more people worldwide are not considered worthy of a commensurate investment.

5) A forum for open discourse on issues is needed. In the mid-1980's, two related theories of the pathogenesis of AIDS came to dominate scientific discourse. The first theory being the "T-lymphotrophic" theory of HIV's activity which focused much scientific attention and resources on the interactions between the virus and the helper T lymphocyte of the human immune system. The second theory about AIDS widely promulgated and accepted during the end of the last decade was the "Mack-truck" or "killer virus" model of the disease, in which HIV acting on its own was capable of incapacitating the immune system of all those infected with it. Both of these theories have had a profound impact on AIDS research. As a result of the first, a large part of current research on

AIDS still is focused on the interaction between HIV and the CD4 cell, although other cells and tissues of the body are infected with the virus and their infection is implicated in the pathogenesis of the disease. As a result of the second, research on other factors that might contribute to the pathogenesis of AIDS were sidelined or never pursued, although no known other virus kills all those infected with it and various co-factors predispose one to or against survival. The influence of these theories prematurely foreclosed needed scientific debate on the nature of the disease and points to the need for a continuous open discourse on fundamental scientific issues.

6) Stop the virologists' juggernaut. For all that AIDS is a disorder of the immune system, basic and clinical interventions on its pathogenesis have been dominated by virologists. Considering the capers described above, perhaps it is time for the virologists to step aside and allow the immunologists to take center stage.

The original ACTG Biological Response Modifiers (BRM) committee was disbanded in 1989 due to a scientific or political identity crisis. The newly formed Immune-Based Therapies Working Group (IBTWG) is a hybrid of the Immunology and Primary Infection Committees, and cannot conduct trials without the consent of Primary Infection.

The ACTG Immunology Committee should be raised from a resource to a research committee and be allowed to conduct clinical trials without interference from Primary Infection. The only immunologic function mandated for every site in the ACTG Recompensation plan is the ability to phenotype blood cells with flow cytometry. Sites will be able to apply for limited additional funds for "Immunology Developmental Research," but only a handful of \$100,000 grants are likely to be awarded through this mechanism.

In future, as in the past, ACTG immunologists will be forced to scrounge at the interface between basic and clinical research, patching together inadequate funding streams from many sources to conduct desperately needed investigations.

2.0 TREATMENT: Clinical Controversies

2.1 ANTIRETROVIRAL TREATMENTS

"Interpretation begins where perception ends."

-- Thomas S. Kuhn⁵

Nucleoside Analogues. The nucleoside analogues AZT, ddI and ddC remain the most studied therapies, both alone and in combination or alternation with each other, for the underlying "primary infection," in spite of the obvious fact that, alone or in combination with each other, they will never completely stop disease progression or restore the immune system.

Viral resistance to AZT is purported to be a major reason for its inability to halt progression, in spite of evidence that even in the absence of resistance, AZT would not be a cure.

The "newer" nucleosides, ddI and ddC, are likely to be licensed later in 1991 with a tragic paucity of information about their optimal use (which is likely to be in combination, rather than as monotherapy). This reflects the conflict between pharmaceutical-driven research (ddN

⁵ TS Kuhn. The Structure of Scientific Revolutions. 2nd edition. Chicago, 1970, p. 198.

monotherapy) and the ACTG's inability to conduct large-scale, clinical efficacy trials of combinations.

No one knows why CD4 cells rise (briefly) on nucleoside therapy, nor why they then resume their seemingly relentless decline. Recent discussions of surrogate markers have focussed on 1) the putative correlation between CD4 count under 50/mm³ and death; and 2) the putative "X Factor," a mathematical phenomenon which accounts for a non-CD4-mediated clinical improvement caused by ddN therapy. The first phenomenon can be accounted for by the fact that few OIs develop above 50 CD4 cells (from an epidemiological standpoint); the second by either weight gain, by AZT's well-documented anti-microbial activity, or by a statistical overestimation of AZT's efficacy caused by premature termination of the phase II AZT study.

There is a very real danger that the circular methods used to validate CD4 changes as a surrogate marker in evaluating ddN therapy will be prematurely applied to other, non-nucleoside therapies which may not, in fact, manifest the same CD4 response. (Already the FDA has rejected the Treatment IND application of Institut Merieux for Imuthiol on the grounds that the drug had no apparent effect on CD4 counts).

Testing Non-Nucleoside Analogues. Two new classes of antivirals, the new reverse transcriptase inhibitors and protease inhibitors, are finally entering clinical trials. However, we fear that the methodology used to test these drugs will be based on the AZT model rather than on a specific understanding of how these drugs thwart HIV. There has been much talk in the activist community about "home run drugs". If one of these new compounds actually were a home run drug, will we all be staring at our ankles while the ball goes over the fence? We run the risk of missing important new therapies if we do not use surrogate markers that relate to drug mechanism. Basing our clinical trials on surrogate markers poses important methodological and statistical issues. These issues must be tackled at once by the ACTG.

We start with three simple facts that most researchers would agree on:

- 1) A drug that effectively and specifically inhibits the HIV reverse transcriptase would be a good thing.
- 2) A drug that effectively and specifically inhibits the HIV protease would be a good thing.
- 3) No one can say with certainty what clinical effect such drugs would have.

An efficient RT inhibitor might cause T-cells to rise as newly formed T-cells survived HIV's onslaught or it might cause T-cells to transiently fall as a recovering immune system killed off cohorts of HIV-infected cells. One can make equally convincing and contradictory arguments about p24 and other markers.

Does this mean we have to harken back to simpler times when death was our only endpoint? No, it means we have to think about the surrogate markers that we use and only use those appropriate to the proposed mechanism of action of a particular drug. For example, a RT inhibitor might decrease or stabilize the number of infected cells as detected by quantitative PCR.

However, there are too many unanswered questions about techniques such as quantitative PCR. ACT UP has persistently lobbied the CDC and NIH to conduct trials of different markers so that we could assess their prognostic value. This kind of study needs to begin with the L-drug trials and BIRG 587 trials.

We propose that more complete bloodwork be done for a portion of patients in these trials. This

would include newer techniques more appropriate to reverse transcriptase inhibitors such as quantitative PCR. The predictive power of these surrogate markers could then be compared to more accepted methods. Finding these kind of statistical correlations requires creative, top-flight statisticians.

Use of these markers, if validated, would greatly speed up future trials. Once pharmacokinetic work was complete and an optimal dose was determined, it is only necessary to do one phase II trial to demonstrate that a RT inhibitor was indeed inhibiting reverse transcriptase, as measured by quantitative PCR or some other assay, and that the drug was safe and tolerated over some reasonable period of time such as 6 months. While the phase II trial was going on, the drug would be available through expanded access. Of course, if a drug had an unexpected influence on surrogate markers, further mechanistic studies might be required.

Rapid phase II trials and rapid approval mean that drugs can quickly enter large simple trials.

These trials answer questions such as:

- * When do we start antiviral therapy?
- * Which agent(s) do we use?
- * Is it useful to alternate or combine therapy?
- * Do strains resistant to the new RTI's appear? Is there cross resistance?

These questions will not be answered by the trials proposed for the new RTI's.

Similarly, a protease inhibitor might reduce plasma viremia and possibly p24. However, plasma viremia has not been sufficiently examined for it to be an accepted prognosticator of drug efficacy.

Much of the controversy concerning the nucleoside analogues has to do with our lack of faith in the methodology used to test these drugs. We need to use methods that directly assess the viruses activity in the body.

2.2 OPPORTUNISTIC INFECTIONS: 12 Months and Counting

In 1989 and 1990's Treatment Agenda, we called for a rational, coordinated effort to find treatments and prophylaxes for the major opportunistic infections that affect people with immune system disorders. ACT UP updated our goals in 1990 and expanded them, announcing the Countdown 18 Months project in November of 1990. In the Countdown 18 Months plan, we gathered and synthesized all the available information on the proven and potential treatments for opportunistic infections (OI's). We then used this information to prepare a schedule and a strategy to test these drugs by June 1992.

The response to our plan was mixed at best. Tony Fauci, the head of the NIH would not endorse our plan, even though it saved him the work of coming up with one of his own as he had been mandated to by Congress. He was uncomfortable with the idea of deadlines, which is exactly what's wrong with the entire ACTG system. No one displays any sense of urgency. The FDA ignored us as well, not realizing the crucial part they play in developing research strategies and improving access to experimental treatments. Response from the pharmaceutical industry improved over time. Some companies were reluctant to share information, at first. Now, several companies such as Abbott, Pfizer, and Burroughs-Wellcome are accepting some suggestions on protocol design realizing that our suggestions insure that their trials will be inclusive and still answer the questions that PWA's and their physicians want answered. One company even sent a donation. Displaying a less-enlightened point of view, the American Foundation for AIDS Research (AMFAR) did not endorse our plan. We cannot fathom why they would not be in favor of a plan to coordinate and encourage opportunistic infection research. Was it that they were not

in charge? Congress was preoccupied with Iraq and our President and secretary of Health and Human Services don't care about people with AIDS. Once again, a group of volunteer activists had to infuse the AIDS bureaucracy with a sense of urgency and purpose.

Despite this lack of coordination and cooperation, the achievements of CD18 have been substantial; our challenges are even bigger. We summarize our victories and obstacles OI by OI. None of the results we describe pertain to children with HIV as no trials were ever done on children and few appear to be planned.

Pneumocystis Carinii Pneumonia. Even with the availability of various reagents for prophylaxis, PCP is still a leading killer of people with AIDS. The incidence of PCP has not decreased and still accounts for 43 per cent of all opportunistic infections. The large number of cases of PCP are due to breakthrough on partially effective drugs, failure to prophylax because of toxic side effects of existing reagents, failure to prophylax because of the exorbitant prices of these drugs, particularly aerosolized pentamidine, and deficient education for physicians and people with HIV. For example, many people with HIV are not encouraged to use systemic reagents for prophylaxis even though the risk of extrapulmonary PCP is increasing.

A new generation of PCP drugs is finally entering clinical trials. These include 566C80 from Burrough's Wellcome and DMP from Fujisawa. Fujisawa's inane, unproductive secrecy prevents us from saying anything about this potentially important drug. After pressure from CD18M, the trials of 566C80 have evolved to meet the needs of people with HIV. For example, a trial of 566C80 vs. IV-pentamidine has finally started. This trial is explicitly for the many people who cannot tolerate sulfa drugs. This trial is not a substitute for expanded access to 566C80, which is urgently needed. Also, prophylaxis trials must begin as soon as the new oral formulation is available.

Mycobacterium avium Complex (MAC). CD18M had a major victory when it finally got Abbott to agree to expanded access for clarithromycin. The program began the first week of June. Doctors with patients who have documented MAC will be able to call a toll-free number to apply for the drug. Patients who are not geographically or physically capable of enrolling in phase II trials will be randomized to one of two doses of the drug (1000 or 2000 mg/day). This may constitute an important precedent: true expanded access providing useful safety AND efficacy data. We will be monitoring the program closely to make certain it functions properly. Prophylaxis trials are on hold pending further research on clarithromycin-AZT interactions (Phase I trials suggested clarithromycin might lower plasma AZT levels). We are upset by this delay as many people at risk for MAC have already failed AZT. We are concerned about the risk of developing resistant strains, but Abbott asserts that resistance only appears in individuals who interrupt their clarithromycin treatment for a significant period of time. Both Abbott and Pfizer believe that cross-resistance between their respective azalides is likely.

We note that Pfizer will also be providing access to azithromycin when its phase II trial begins. Pfizer also plans to use a novel approach to allow people from all over the country to enter the clinical trial. Also, two of Pfizer's proposed azithromycin protocols allow patients to be on other anti-MAC therapies.

There are also two important prophylaxis trials going on. Adria is studying rifabutin and a community group in San Francisco is studying clofazimine. Both trials should have evaluable data this summer. However, the CC has not been able to secure funding for data analysis. AMFAR has refused to fund the analysis although they underwrote the study. We could know by the end of the summer if a cheap, non-toxic, readily available drug prevented one of the most common and debilitating OI's. AMFAR's failure to respond to community needs is appalling and tragic. If the rifabutin prophylaxis study breaks positive, the drug must become available immediately.

As for the ACTG, they're finally doing a trial originally proposed 3 years ago. It compares a four-oral-drug "cocktail" alone vs. the cocktail plus IV amikacin. In the years that intervened, thousands of people with AIDS died from MAI as their doctors thought MAI was untreatable or didn't know which regimen was best. This trial could have prevented many needless deaths had it been done in a timely fashion. Two major obstacles in MAI research are 1) the long time required for cultures to test positive, and 2) the lack of a common functional definition for MAI. The former issue substantially impedes the standard of care as patients can have symptoms for weeks before their cultures test MAI positive. The latter impedes access to drugs as restrictive definitions of MAI may exclude people from trials or expanded access protocols. The FDA and NIH can provide direction; the latter by devoting resources to new MAI diagnostic procedures, perhaps using PCR and the former by establishing a definition of MAI and appropriate clinical trial endpoints.

Cytomegalovirus Disease (CMV). The situation for CMV is dire. Only one agent is approved for CMV, ganciclovir, which has significant toxicities and must be taken intravenously. Foscarnet, an important salvage therapy, has been trapped at the FDA, which has been procrastinating with the NDA for 9 months, 3 months longer than the statutory maximum. ACT UP finally pressured the FDA to hold an advisory committee meeting (on June 12) that may have set the stage for approval, but that came only after much struggle and many desperate pleas.

Several promising agents are in the pipeline, such as HPMPC and cyclobut, but those in charge of their development betray no sense of urgency. The case of cyclobut is particularly distressing. Three companies are vying over the patent rights to this drug. While this internecine struggle occurs, no research is taking place. A very simple plan would solve this debacle. The three vying manufacturers should have a contract research organization or the NIH start developing the drug while the legal issues are resolved. When the dust cloud settles, the winning manufacturer can reimburse the research organization (plus interest). If this can't happen, Congress should step in. This is a real war and every weapon is needed.

Each year there is new evidence that CMV aggravates HIV infection. Accordingly, many PWA's have been using acyclovir to control CMV as is done in transplant patients. Is the ACTG doing a trial to test this practice. Although PWA's have been asking for this trial for years, it's only just beginning, typical.

Toxoplasmosis. CD18 successfully lobbied for a humane compassionate use protocol for azithromycin in Toxoplasmosis. The dose in this protocol is being reevaluated as some breakthrough is seen after long term treatment. The ACTG is at long last beginning an azithromycin trial. We hope that this trial will be completed quickly so that a supplemental NDA can be filed. However, like most toxoplasmosis trials, it is not being done in the communities hardest hit by toxo such as Brooklyn and Newark. Also, even though clinical trials of 566C80 for toxoplasmosis have begun, this drug needs to be made available through expanded access.

A truly successful toxo program would involve finding new techniques for detection. PCR seems a promising possibility.

Fungal Infections. Work is lagging on the use of triazoles in the treatment of vaginal thrush. We already know that they work. CD18M is actively trying to encourage new trials for these indications. We are also trying to convince the FDA to use European data to speed approval for these indications.

Research needs to progress on fungal infections other than cryptococcal meningitis such as histoplasmosis and aspergillosis. People in regions outside of the coastal United States are at particular risk for these opportunistic infections.

Once again, prophylactic trials are lagging. Many PWA's have already begun to prophylax against fungal infections without adequate information about dosage, long term side effects, and possibilities of resistant strains.

Cryptosporidium. Cryptosporidium is one of the "lost OI's." Despite its prevalence, the ACTG has virtually ignored it, despite the lobbying of prominent researchers. The ACTG has done only two small scale trials, involving reagents whose limited efficacy became apparent. Currently, there are four potentially effective reagents for this dreaded condition: 566C80, azithromycin, paromomycin, and letrozuril. Trials for these agents have either just begun or are slated to begin soon. NONE of them are being done through the ACTG. Once again the ACTG proves itself irrelevant. Maybe the ACTG only knows how to study PCP because they're so familiar with its use as an endpoint.

Education and Access. None of the work that we do will matter unless it translates into therapeutic reality for the millions of people in the world living with HIV. This requires a concerted program to educate physicians, particularly those in inner city hospitals and prisons where patients are routinely denied the latest in treatment and prophylaxis. We also require a commitment from the US government, pharmaceutical industry, and World Health Organization to make treatments and prophylaxes available to anyone. Many approved OI treatments are not even available in Puerto Rico, where some are manufactured. If the US is leading the fight against AIDS, it must bring the fight to the economically disadvantaged. President Bush has just demonstrated that he knows how to fight a war overseas. Let him now mobilize to fight a much more important one.

2.3 OPPORTUNISTIC CANCERS

Kaposi's sarcoma: At last year's AIDS conference, we were all excited by Dr. Gallo's claim that he had a new unidentified agent for KS. Somehow, this compound has failed to materialize over the past year. Similarly, in April 1990, a reporter in Science magazine proclaimed that new KS treatments would soon appear that would involve manipulation of growth factors. Now, over one year later, KS has not been cured, and scientists are still pursuing some of the elusive KS growth factors that they planned to have under control by now. Meanwhile, an entire area of Kaposi's sarcoma research has been ignored, probably because it is not glamorous or high-tech. Despite the accumulating evidence that KS is linked to a transmissible agent, few if any labs are pursuing this mysterious agent. Although it might not be as revolutionary, wouldn't it be simpler to treat KS with an anti-bacterial or an antiviral rather than a complicated regimen using growth factor manipulation? Wouldn't it be better if we could predict which people with HIV were at risk for Kaposi's sarcoma and then prophylax rather than wait until disease develops?

The epidemiology of KS provides an important clue to the nature of the KS agent. If KS were caused by a blood-borne virus, one would predict that the incidence of KS in hemophiliacs would be higher than the incidence of KS in transfusion recipients, simply because hemophiliacs have been exposed to more blood. However, the reverse is the case. This implies that the KS agent is either not bloodborne, which is unlikely in view of its disease properties or that the KS agent is cellular as cellular agents would not be transmitted to hemophiliacs. Does a bacteria cause KS? Bacteria do cause similar infections such as cat-scratch disease, but a bare handful of reports have linked KS to a cellular pathogen. A more likely candidate is a retrovirus spread by cell-to-cell contact such as HTLV-I. We are not saying that HTLV-I causes KS, instead an agent transmitted like HTLV-I causes KS. As there are more than a handful of HTLV-I experts working on AIDS and KS, perhaps they could devote some of their resources to examining if a HTLV-I like agent is responsible for KS.

While, the search is going on, new chemotherapy agents need to be tested against KS. In particular, a trial of liposomal doxorubicin is required. This liposomal formulation of doxorubicin (adriamycin) is manufactured by the Liposome Company and is licensed to Pfizer, Inc. The company posits that the liposomal formulation of the drug is highly specific for sarcomas and similar malignancies, yet does not show the toxicities of ordinary doxorubicin. This could be a promising KS agent, yet no trials are planned. The Liposome company boasts in its annual report that it has worked closely with ACT UP in the design of its trials for liposomal gentamicin. Can we work together on this drug as well?

Aside from KS, HIV-infected patients exhibit a bewildering array of vascular manifestations and exuberant angiogenesis that range from telangiectasia, lymphangiectasia, angiomas, angiofibromas, angiolipomas, pyogenic granulomas, and hepatic peliosis, to nodal vascular transformation, angioimmunoblastic lymphadenopathy (Castleman's disease), thrombophlebitis, vascular sclerosis, generalized purpura, leukoclastic vasculitis, and immune complex vasculitis... Unlike a true primary neoplasm or metastatic malignancy, KS appears to arise as a budding multicentric endothelial proliferation primarily of lymphatics perhaps stimulated by retro- or co-viral infection directly, or indirectly by the host's immune response.⁶

Angiogenesis. Angiogenesis, the processes involved in the formation of new blood vessels, involves the migration, proliferation and maturation of cells that line blood and lymphatic vessels which are called endothelial cells. Certain diseases are characterized by excessive angiogenic activity particularly in lymph nodes. Some of these diseases have features that are similar to some aspects of AIDS. Angioimmunoblastic lymphadenopathy is a disease in which there is an increase in immunoglobulins, a decrease in the T4/T8 ratio, the occurrence of opportunistic infections, autoimmunity and even of Kaposi's sarcoma. Castleman's disease has similar features, including an association with Kaposi's sarcoma both in HIV positive and HIV negative individuals who had inverted T4/T8 ratios. Apart from its role in contributing to some disease states angiogenesis has been studied because it is possible that substances inhibiting it (antiangiogenic factors) may prove useful in the treatment of cancer. This is because tumor growth depends on the development of an adequate blood supply, a process depending on angiogenesis. If angiogenesis is dependent on factors, substances inhibiting these factors should prevent this new vessel formation and provide a basis for treatment. Because of its implications for cancer research the factors that promote new blood vessel formation and agents that inhibit this process have been studied for some years.

As early as 1975 it was proposed that angiogenic factors promoted endothelial cell proliferation in Kaposi's sarcoma. It was also proposed that Kaposi's sarcoma cells could produce factors promoting and perpetuation their own growth. The authors suggested that production of growth factors was stimulated by a chronic immunologic reaction. Despite this early proposal, and the discovery of a series of angiogenic factors there were no reports of research into this aspect of Kaposi's sarcoma until 1988. Very little has been added since. It has now been shown that Kaposi's sarcoma cells do in fact secrete growth factors, as predicted in 1985, and these factors include interleukin 1 beta, basic fibroblast growth factor and interleukin 6.

Research on the factor dependence of Kaposi's sarcoma could have commenced in the early 1980s. Despite difficulties, methodologies to culture Kaposi's sarcoma cells could in all likelihood have been perfected at that time. The empiric systematic screening of compounds with antiangiogenic activity against Kaposi's sarcoma might have produced effective treatments by now. With methods to culture Kaposi's sarcoma now established such screening should be well under way but in all

⁶ ME Witte, CL Witte, DL Way, M Fiala. "AIDS, Kaposi Sarcoma, and the Lymphatic System: Update and Reflections." *Lymphology* 23, 73-80, 1990.

probability is not. An additional approach is the development of monoclonal antibodies against angiogenic growth factors found to be necessary for Kaposi's sarcoma growth. Several antiangiogenic compounds have been described. Fumagillin, protamine, combinations of heparin with certain steroids, shark cartilage extracts and agents that remove copper are some.

The role of angiogenesis in the development of Kaposi's sarcoma represents a potentially fruitful research avenue that might have been pursued as early as 1981 had there been a coherent plan of research on AIDS.

3.0 RESEARCH: The Crumbling Infrastructure

3.1 The ACTG Retrenches

Our criticisms of the ACTG are well known, and need not bear repeating here (see our Treatment Research Agenda 1990, A Critique of the ACTG, and The ACTG One Year Later). In brief, in spite of the opening of the ACTG system to activists and people with HIV, the power structure remains intact, as refractory as ever to demands to alter research priorities, and as intolerant as ever of scientific or activist dissent.

Now comes chilling evidence that the ACTG, already inadequate to its tasks, will be significantly smaller in the years to come. Sometimes, in government, the appearance of effort substitutes for real attempts to solve problems. So it often seems with Federal AIDS research. The appearance of having learned from past mistakes substitutes for the reality. Faced with budget cuts, research administrators meekly plan to make do with less, rather than point out that current funding levels make it impossible to develop new AIDS treatments fast enough.

The National Institute for Allergy and Infectious Diseases (NIAID) recently released its plan for the next 5 years of AIDS treatment research. The plan comes in the form of a request for application (RFA) for the recompetition of the cooperative agreements governing the AIDS Clinical Trials Group (ACTG).⁷

Since 1986, the ACTG has been the major Federally-sponsored mechanism for conducting clinical trials of therapies for AIDS. The ACTG has spent at least \$400 million to fund research at 49 sites (34 adult, 15 pediatric). The ACTG's 129 clinical trials of 36 treatments have enrolled 14,046 participants. By February 1991, 33 protocols had been completed; 45 were closed to enrollment; and 44 were open. Preliminary or final results from at least 20 ACTG trials have been published in the medical literature.

As a result of ACTG work, the FDA lowered the recommended dose of AZT from 1200 mg/day to 600 mg/day, expanded its use to cover people with under 500 T4 cells, and declared it safe for use in children. In addition, ACTG research on the anti-fungal drug Fluconazole contributed to FDA approval in 1990.

For all those accomplishments, there were many disappointments. The ACTG studied several drugs in Phase I trials, among them ddI, ddC, d4T, Ampligen, AL-721, dextran sulfate, and soluble CD4. Other than the first 3 (all nucleoside analogues), none of these agents showed sufficient promise to enter efficacy trials. In AIDS research, a clear "No" is useful, for it allows people with

⁷ NIAID, "Request for Cooperative Agreement Applications: RFA-NIH-NIAID-91-AI-07," May 1991.

HIV to stop taking useless substances (e.g., AL-721, dextran sulfate), and researchers to study new ones. Yet the ACTG long refused to stop pouring research funds after CD4, long after it became clear that this, the first product of "rational" drug design, was as ineffective as it was expensive.

Each of the other significant advances in treating AIDS -- aerosolized pentamidine (AP) for PCP prophylaxis, alpha interferon for KS, DHPG for cytomegalovirus, EPO for anemia -- were brought to approval by pharmaceutical research or, in the case of AP, by community-based research sites. Moreover, with the exception of AZT, the ACTG has been unable to enroll enough people to show whether new antiretrovirals work. Bristol-Myers obtained one third of participants for its ddI trials outside the ACTG. Hoffman-LaRoche found 3/4 of participants for ddC trials outside the ACTG; Pfizer had to get 5/6 of the subjects in its Fluconazole trials outside the system.

It's little wonder so few drug companies submit new drugs for testing within the ACTG. Twice in the last year, the scheduled meetings of the AIDS Clinical Drug Development Committee (ACDDC), which prioritizes drugs for testing by NIAID, has been canceled because no sponsors submitted any new drugs.

A leaner ACTG? According to the recompetition package, NIAID plans to fund only 20-25 ACTUs. This means that between 9 and 14 currently funded sites are likely to be defunded. It's possible that some cities will lose their only AIDS research facilities. New York City has 6 ACTUs (NYU, Albert Einstein, Mt. Sinai/Beth Israel, Cornell, St. Luke's Roosevelt and Memorial Sloan-Kettering). As things now stand, two or more of these New York centers are in danger of being defunded on the basis of poor accrual in the past. NIAID made no provision in its plan for the unique constellation of social pathologies which renders research in New York more difficult than, say, Seattle or Pittsburgh. (Little more than lip service is paid, in the recompetition, to increasing enrollment of people of color, women and IVDUs.)

A meaner ACTG? In future, ACTUs will be funded in two parts. 2/3 (or so) of their funding will come as clinical core grants, awarded on the basis of budgets submitted by the site, which must plan for enrolling a minimum of 60 and a maximum of 150 participants per year in its trials. [This means the ACTG plans to enroll no more than 1200-3750 people in its studies each year.] If the site does not meet its accrual target, its funding will be cut. If a site exceeds accrual targets, or excels otherwise, it may receive extra cash in the form of "incentive funding" from NIAID. This novel formula, perhaps spurred on by long-term activist pressure, means that, for the first time, ACTG funding will be tied to performance.

Research priorities? Each ACTU will have to demonstrate the ability to study drugs for "primary infection" (HIV) and for opportunistic infections. Opportunistic cancers (Kaposi's sarcoma, lymphomas, cervical cancer) are optional, along with neurological conditions. Extra funding can be requested for laboratory virology, pharmacology, immunology or microbiology. Adult sites which conduct pediatric research may apply for support. Pediatric ACTUs will be recompeteted separately.

A cost-conscious ACTG? The ACTG spent \$375 million in 5 years to enroll 14,000 research participants, for a total cost per subject of \$25,050 (industry standard is \$3,000). In five years, no one at the ACTG has ever discussed the cost of their trials, arguing everything "solely on the basis of scientific merit," as they say. Now, for the first time, protocols will be budgeted before trials are approved. Perhaps this will prevent the ACTG from biting off more than it can chew.

Alarminglly, total funding for ACTU sites in the first year of the new plan will amount to \$48 million. Last year's ACTG funding amounted to \$106 million. Is the program being cut by half, or does the other \$58 million represent the cost of the ACTG's other components -- the Statistics center at Harvard, the Operations Office in Bethesda, and other supporting grants?

NIAID funds its own competition. In addition to the ACTG, NIAID has other clinical trial programs. Its Community Programs for Clinical Research on AIDS (CPCRA) funds about 18 sites nationwide to do so-called "community-based" trials, costing about \$17 million a year. So far the CPCRA has conducted several expensive conferences and training sessions, and opened three trials. This fall, NIAID will open its "Division of AIDS Initiative," a \$10-20 million contract program to test drugs that NIAID wants tested fast. This is more or less an admission of the ACTG's inability to accomplish this mission. NIAID also runs six AIDS Vaccine Evaluation Units (AVEUs), which have five trials enrolling 112 participants underway. And NIAID's Intramural Research Program has conducted 12 studies enrolling 200 participants at the NIH Clinical Center in Bethesda.

The first three years of the ACTG can be regarded as the AZT years. 50 of the 101 trials opened before 1990 tested AZT; these enrolled 85% of the total participants. The trials (especially the large ACTG 002, 016 + 019) resulted in 1) lowering the dose of AZT by half (002), 2) expanding the use of AZT for people with early ARC (016) and asymptomatics with T4 cells under 500 (019), and 3) approving AZT for children (003, 043, 049). 1989-91 trials were dominated by ddI. These three phase II efficacy trials (ACTG 116, 117 + 118) opened in fall 1989, completed enrollment in March 1991, and will be analyzed periodically until a difference between AZT and ddI is seen.

This history makes clear that the ACTG can competently study only one anti-HIV drug for efficacy at a single time. Unlike opportunistic infection trials, "endpoints" (disease progression or death) are rare in anti-HIV trials, meaning that they have to be large, expensive and lengthy.

The new ACTG will enroll less than 4,000 persons with HIV each year into its future trials at 20-25 sites around the country. Yet the "drug development pipeline" is full, with scores of new drugs emerging from laboratories and phase I trials ready for efficacy studies. One or more of them could produce major advances in the treatment of HIV infection: Merck's L-drugs, Boehringer Ingelheim's BI-RG-587, Janssen's TIBO derivatives, Roche's tat gene inhibitor, and protease inhibitors from Upjohn, Merck, Roche and SmithKline, to name a few. Where will drug sponsors turn to complete their efficacy trials, if the ACTG is already full? Where, indeed?

Between 1986 and 1991, the ACTG has spent a total of \$375,833,000 to enroll 14,046 participants in its 129 clinical trials, for a cost per participant of \$26,757 -- almost 9 times the industry standard of \$3,000. It is bad enough that ACTG resources are not keeping pace with the exploding pandemic, and worse still that the ACTG cannot manage to conduct cost-effective, rapid, humane or relevant research.

4.0 REGULATION: The Methodologic Quagmire

4.1 FDA PROBLEMS

ACCESS vs. ANSWERS

"There is, to be sure, an incredible irony in all this. Sick gay men, abandoned by a president who refused publicly to acknowledge their disease on all but one occasion, provided the shock troops to move forward his administration's deregulatory drug control program."

-- Harold Edgar + David Rothman⁸

"The ddI expanded access program saved my life."

-- A Person With AIDS

In the past year and a half, more than twenty thousand people have received ddI through expanded access programs. Meanwhile, clinical trials of ddI have enrolled faster than trials for any other comparable antiviral therapy tested by the AIDS Clinical Trials Group (ACTG). This doesn't mean that tensions between the need to adequately characterize a new therapy and the need to provide treatment to people at high risk for severely debilitating disease and death have been resolved. Some activists continue to complain that the ddI expanded access program is overly restrictive and demand the drug's approval before clinical trials have been completed. Many doctors and regulators who have seen Bristol Myers-Squibb's NDA application have expressed doubt about the quality of the application.

This experience has initiated a debate about the importance of "Access vs. Answers," as though there were an essential conflict between allowing people for whom no approved therapy exists to access promising unproven medications and the conduct of sound scientific research on those medications. This is more a sign of the intellectual poverty of regulators, scientists and AIDS activists than an indication of any real dichotomy. The regulation of AIDS drugs, like the treatment of AIDS, must build on its experience; we must incorporate knowledge gained from the ddI experience into future attempts to resolve regulatory and trial design issues.

The need for ethical, well-designed trials that provide clear, quick answers has never been more pressing. Some have suggested that validation of new therapies takes so long as to be virtually useless. However, we cannot allow this crisis to eliminate requirements for sound efficacy evaluation. It is grossly unethical to require PWAs to make treatment decisions in an informational vacuum any longer than is absolutely necessary. While the FDA is often unresponsive and painfully slow, deregulation promises nothing more than a capitulation to life-or-death treatment decisions based on "drug of the month" anecdotes, an unacceptable solution to many of us who are fighting for our lives.

⁸ H. Edgar + D. Rothman. "New Rules for New Drugs: the Challenge of AIDS to the Regulatory Process." The Milbank Quarterly. Volume 68, Supplement 1, 1990

DEMANDS FOR THE FDA

The history of AIDS drug regulation is riddled with evidence of regulatory inadequacy, incompetence, and homicidal negligence. We who are affected (and often infected) by HIV cannot and will not allow any impediment to the development of new, effective therapies for AIDS and its associated opportunistic diseases. The FDA must actively facilitate drug development, encouraging maximum speed and efficiency, and must take into account the realities of living with and treating a potentially terminal illness.

These goals will begin to be met by the following changes:

- 1) **The President and Congress must double the FDA budget.** The recent report of the Edwards Committee describes an FDA that has been crippled in their efforts to meet the scientific and ethical demands of the AIDS crisis. Economic conservatives often complain about the outrageously long time it takes to bring a new therapy to market, while voting against the funding that would allow FDA to act faster. To build a strong, proactive FDA will require new facilities, new information systems, competitive pay and improved scientific equipment. Congress and the President should work together to rectify the current resource crisis at FDA.
- 2) **FDA must develop an open, public process for setting priorities, and all agency activities should reflect these established priorities.** Currently, the Agency is spreading its limited resources too thin, attempting frantically to meet the demands of the next crisis, delaying completion of high-priority tasks and diverting resources to low-priority responsibilities. This process should involve significant input from the affected communities, and all proceedings should be open to the public. The Agency should also consider a cost-recovery scheme for its duties which are necessary but not urgent.
- 3) **The FDA must ensure that potential therapies treating life-threatening or seriously debilitating diseases receive timely review.** FDA has claimed that AIDS drugs receive top priority, however the Foscarnet NDA has languished in the Agency's bowels for more than 10 months now. These delays cost lives, and are completely unacceptable. FDA must give therapies for serious diseases (including the opportunistic diseases associated with AIDS) the highest priority, and must adjust its activities accordingly. If this means that the next over-the-counter cold medication takes twelve instead of eleven years to review, then so be it.
- 4) **FDA must involve all communities affected by AIDS in the process of developing regulatory policies that affect AIDS-related primary care.** A recent meeting of the FDA's Antiviral Drugs Advisory Committee considered data suggesting that early intervention with AZT was less effective in people of color than in white people; despite the extreme implications of this data for communities of color, not a single person of color had been invited to sit on the committee. Socioeconomic factors, including access to health care, must inform FDA's regulatory decisions.
- 5) **The FDA must provide leadership in the development of new models for evaluating experimental therapies.** Recently, FDA convened a workshop of clinicians, statisticians, regulators, and community representatives to consider methods of collecting data outside of the traditional randomized, controlled clinical trial. This innovative workshop began the process of developing parameters for the use of these methodologies. FDA should continue these efforts, and should attempt to define and resolve the regulatory as well as scientific impediments to the use of "alternative" data collection methodologies. Data from randomized expanded access programs should be accepted as one part of an NDA submission.

6) FDA must regulate expanded access programs as they were intended to be administered; little or no proof of efficacy should be required for a drug to be available on expanded access. In denying the Institut Merieux's application for a Treatment IND protocol for Imuthiol, FDA cited the lack of compelling efficacy data. FDA should eliminate efficacy considerations from the evaluation of expanded access protocols; any drug qualifying for Phase 2 trials should also qualify for expanded access.

7) FDA should work with Congress to develop a program modeled on the Orphan Drug Act to encourage companies to research unprofitable new indications for approved therapies and to conduct basic research on alternative and holistic therapies. Currently, many proposed treatments for HIV, including garlic and certain vitamins, provide no profit incentive to corporate research and development. Development of a program providing significant tax reductions to companies researching these therapies could stimulate development of non-toxic inexpensive treatments.

4.2 CRITICAL PATH

4.21 PRELIMINARY TRIALS

Many sponsors of new antiretroviral agents lack a clear picture of appropriate development procedures to ensure comprehensive phase I development which can lead to well-designed phase II trials and expanded access programs. Boehringer Ingelheim, in particular, seems to have chosen a peculiarly slow and irrelevant development program for its new non-nucleoside RT inhibitor, BI-IG-587. Good connections at the ACTG Primary Infection Committee are not now, and never have been, enough to ensure rapid and well-coordinated antiretroviral drug development (if they were, ddC would be approved by now). We refer all the designers of phase I trials to our Treatment Agenda of 1990.

In brief, we proposed 2 stages for phase I, a phase Ia in which people take several doses of the new agent and pharmacokinetic parameters are measured; they then stay on the assigned dose (barring dose-limiting toxicity) for long-term safety and activity assessment. In phase Ib, people are randomized to a series of doses found both safe and active in phase Ia, and followed for changes in surrogate markers (if validated) and "soft" clinical changes, including symptom scores and weight gain/loss. The doses found best in phase Ib are then used to design phase II efficacy trials, and parallel track/expanded access, which, whenever possible, becomes a middle track with randomization to 2 or more doses. Phase Ib and phase II trials can also gather useful information more rapidly by including randomization to monotherapy vs. combination therapy (new agent + ddI or AZT).

Merck's development program for L-661 is a good example of a rapid, well-designed, comprehensive project, in stark contrast to that of Boehringer Ingelheim.

For more details, copies of ACT UP's 1990 Agenda are available from ACT UP, 135 West 29th St. # 10, New York, NY, 10001, USA.

4.22 PIVOTAL TRIALS

"In the case of ddI, we are just starting the trials that are probably going to last 2 years after the last patient is recruited. At the same time, there is expanded access, so that there may be an intelligent and reasonable medical consensus on how and when to use this drug much sooner than that. The question is, from a scientific and medical point of view, aside from the regulatory point of view where it is probably obvious, is that 2 years buying us anything at all?"

-- John James, 11.20.89⁹

AIDS trials to date have failed us in size (too small), in duration (too long), in speed (too slow), in attractiveness (too unresponsive) and in reliability (too inconclusive). We are not keeping pace with the epidemic, especially in the case of treatments for "the underlying condition." Without substantial pressure from statisticians, activists, community clinicians and industry, current programs will continue on their deluded course.

Two suggestions may correct this:

- * The ACTG should focus on phase I trials (getting new drugs out the door) and on classical, data-rich phase II trials using clinical and surrogate endpoints, with intensive immunology, virology and pharmacology when required; simultaneously,
- * Community-based research centers, in conjunction with industry, should conduct phase III trials and expanded access programs, whenever possible in the form of large simple, rapid, ethical + reliable trials.¹⁰

The traditional randomized clinical trial is a reasonable way to validate new therapies for many AIDS-associated opportunistic infections, those which are acute in onset, easy to culture in vitro, and easy in which to monitor a clinical response. There are clear clinical and microbiological endpoints, episodes resolve rapidly, and consequently OI treatment (when it's not ignored) improves relatively rapidly.

HIV treatment research, in contrast, moves at a snail's pace. Disease is chronic and variable, not acute and predictable; virologic and immunologic endpoints are highly controversial, and clinical endpoints rarer (especially in earlier stages of disease). People continue to die of AIDS outside of trials, but ironically, too few die in them, and so answers are slow in coming.

This is an unacceptable way to develop primary therapies in a viral pandemic.

⁹ John S. James, 11.20.89, Jour. Acq. Imm. Def. Synd. 3:82, p. 838, 1990.

¹⁰ Five people deserve thanks for bringing our attention to the great promise of the large simple trial for AIDS drug development: David Byar, who in 1989 first proposed that there should be clinical trials available to every person with HIV who wanted to enroll in one: "a trial for everyone, and everyone in a trial." Dr. Byar has unleashed power among the statistical community just as AIDS activists have empowered ours; he recognized that methodologists are uniquely positioned to help reconcile the needs of people with HIV and those of researchers; secondly to Rebecca Smith, whose principled dissent from the notion of a non-randomized Parallel Track in 1989 foreshadowed our discussions here; Ellen Cooper, who was the first to propose that expanded access mechanisms be transformed, by randomisation, into massive efficacy trials; Paul Haer, who urged us to point out, as we have, the profound differences between LSTs in cardiovascular disease and those in AIDS; and Wendy Strongin, whose FDA symposium on methodology stimulated these reflections. It is encouraging that the FDA Division of Anti-Viral Drug Products recognizes the value of supporting discussions such as these, and their power, hopefully, to stimulate change.

By their nature, traditional randomized clinical trials exclude the population most at risk of death from AIDS. Most usually fit several exclusion criteria (often aclinical lab values) and must take alternatives to what is still, shamefully, the only "standard therapy" for AIDS, AZT, available through the underground, through buyers' clubs, or through uncontrolled expanded access programs.

Over 42,000 Americans were diagnosed with AIDS in 1990. Fewer than 4,000 of them entered ACTG clinical trials.¹¹ No new trials opened for asymptomatics, still the largest population of the HIV-infected. For them too, AZT is still the only available "standard" therapy -- and an inadequate one.

LARGE SIMPLE AIDS TRIALS

To convincingly display which of the new generation of antiretrovirals is safest and most active, trials on a scale, of a simplicity, and of a speed undreamt-of by the principal investigators of the ACTG and by industry must be developed, and fast.

The current ACTG has the capacity to competently develop just one antiretroviral at a time. Each period lasts 2-3 years: AZT from 1987-9 (002, 016, 019); ddI from 1989-91 (116-118).

Smart sponsors will have to turn to mechanisms outside the ACTG to get their drugs tested fast enough. There is only one mechanism available (community-based research units) and they have not yet shown the ability to conduct such multicenter trials. Yet conduct them they must, if we are not to be left with three nucleoside and no other anti-HIV therapy in 5 more years.

What are the goals of AIDS clinical trials?

GOALS OF AIDS TRIALS

1. **When there is no standard of care, or an inadequate one**

- To define the standard of care

2. **When there is a standard of care**

- To optimize the standard of care

(These are the medical goals -- those sought by clinicians and patients both. In reality, many trials, especially in the Reagan-Bush era, are driven by pharmaceutical sponsors' desire to access a bloated, restricted, privileged market.)

To succeed, AIDS clinical trials must be rapid, reliable, efficient, generalizable, ethical and attractive. In order to enroll rapidly, they must use active controls whenever possible, as Jim Eigo stated in 1989:

Another attribute emerges from the activist critique, as formulated by Jim Eigo in 1989:

"I would like to put forth what I feel is both the ethical and practical imperative of designing, even in the face of all the difficulties, active control trials for people with

¹¹ 3,842.

HIV disease at this stage of the epidemic...

My contention has been that if every arm of every trial asked a question of real importance to people with acquired immune suppression, enough of those people would find every arm of every trial a viable treatment option and therefore, if they knew about the trial, could be accrued to that trial... Unless every arm of a clinical trial is a viable treatment option, that trial is fundamentally impractical and unethical."¹²

CURRENT QUESTIONS WHICH COULD BE ANSWERED WITH LARGER, SIMPLER TRIALS

- **Which nucleoside analogue: monotherapy vs combination?**

- AZT vs. ddI vs. ddC
vs.
AZT/ddI vs. AZT/ddC

- **Which non-specific immunomodulator?**

- Imuthiol vs. Isoprinosine

- **Which PCP prophylaxis?**

- AP vs. TMP/SMX vs. Dapsone [a large, simple 081]

- **Which CMV prophylaxis?**

- High-dose Acyclovir vs. oral DHPG

In general, for OI research, where the endpoints are better defined both microbiologically and clinically, traditional RCTs may continue to be the best option, especially for treatment trials. For prophylaxis trials, the LST may be a better option. MAI treatment is an exception, both because MAI is so common, and because optimizing combination regimens may be impossible without an LST approach.

- **Which MAI treatment regimen?**

- Ethambutol + Clofazamine [and possibly Amikacin] for everyone, with randomization to:

- Which rifamycin?** (Rifabutin or Rifampin);

- Which macrolide?** (Azithromycin or Clarithromycin)

N.B.: Abbott appears to have agreed to implement ACT UP's "Middle Track" proposal from 1990, using expanded access for Clarithromycin to answer the question "Which dose is best in an MAI treatment regimen?" by randomizing patients on expanded access to 1 gm/day or 2 gm/day Clarithromycin. This is the latest accomplishment of the **Countdown 18 Months Project**.

¹² James Higo, 11.21.89, JATDE, op. cit., p. 890

Design Features of Large Simple AIDS Trials

LARGE. All AIDS LSTs must have the same inclusion criterion: the uncertainty principle: in the opinion of the physician and the person with HIV, each arm of the trial represents a valid treatment option (the principle of clinical equipoise, amended c/o Jim Eigo), unless an express contraindication exists for one of the treatments (i.e., history of pancreatitis in a ddI trial).

SIMPLE. The endpoints should resemble decision points in HIV primary care: unacceptable toxicity, serious decline in CD4 counts, progression to OI, neoplasm, wasting, encephalopathy or death.

FAST. Enrollment should be complete in a year, with follow-up complete in another year, and data review every 6 months.

ETHICAL. Monitoring must be frequent enough to detect an unacceptable toxicity, and otherwise not so onerous as to prevent primary care physicians from participating. Moreover, for those unable to participate in the LST, expanded access (the original Parallel Track) must still be available. (Hopefully, the LST will be so simple and inclusive, so ethical and attractive, that few will need Parallel Track).

RELIABLE. Each AIDS LST must resolve a high priority clinical controversy in a timely fashion.

4.23 PARALLEL TRACK: the Lessons of ddI

"There is a certain value to doing randomization in the second ['Parallel'] track."

-- Ellen Cooper¹³

20,000 people have now gotten ddI on Parallel Track. This was undoubtedly a life-saving program for many, and a life-prolonging one for others. Yet if Cooper's suggestion had been followed, the drug might be approved already, enabling even more to take ddI, and with a better understanding of its risks and benefits. We might have known by now -- based on irrefutable hard data from a giant randomized exercise -- which dose of ddI was best, and which one had the best impact on AIDS progression and survival.

The ddI experience was a trial run of Parallel Track -- imperfect yet, in its essence, highly successful from the perspective of the community (over 20,000 people with no other treatment options have received ddI on Expanded Access) -- with the hope that these lessons will inform future Parallel Track programs:

1. Clinical trials should be designed and implemented in conjunction with Parallel Track; and both must be designed with extensive community input.
2. Clinical trials should be flexible and attractive enough to survive a change in the regulatory climate. They should be designed regardless of IND or NDA status, for the treatment may move from one to another while the trial is still underway.
3. Clinical trials should debut simultaneously (rather than sequentially, as was the case with ddI) with the Parallel Track program.

¹³ "Remarks on to ACT UP on Parallel Track," Ellen Cooper, MD, June 21, 1989.

4. Data collection from Parallel Track should be minimal (restricted to toxicity and clinical events), as the Parallel Track's primary goal is to provide potential treatment, not pivotal NDA-directed efficacy data. The amount of data demanded on the ddi Expanded Access forms is excessive, given this primarily therapeutic, rather than research-driven goal.
5. Data collection may be more extensive on a "Middle Track," in which the Parallel Track treatment is given on a randomized basis, at various doses, at appropriate sites, including community-based clinical trial (CBCT) centers and in the offices of willing physicians. The Middle Track can provide useful adjunct efficacy data, while still meeting a primarily therapeutic need¹⁴.
6. Most Parallel Track programs (especially those for OI drugs) will be far smaller than were the ddi Expanded Access protocols; some, however (especially those for novel, non-nucleoside anti-HIV agents) may be larger. [This raises the question of economic feasibility, and the suggestion of "conditional approval" recently bruited around Rockville...]

One of the biggest problems in AIDS drug development today is the failure of the pharmaceutical industry to believe, heed and follow the FDA's lead in encouraging an openness to new methodologies which will speed up drug development.

Curiously, Bristol-Myers Squibb, which is virtually the only sponsor to attempt a Two-Phase drug development (of ddi) in accordance with the FDA IND Rewrite of fall 1988¹⁵, seems to be regarded by industry as foolhardy rather than as both brave and compassionate in its development program for ddi.

The unrecognized benefit of Expanded Access programs is that they provide the equivalent of a Phase Four post-marketing study coterminous with the randomized Phase Two efficacy trials -- generating invaluable insights into the patterns of use and real-world toxicities likely to be encountered when the drug is taken by its intended population, with all its diversity and heterogeneity. While the FDA might be understandably reluctant to approve a drug which has only been taken by the small number of people in a controlled Phase Two trial, proof that the drug is safe in a broad swathe of the real-world HIV population would provide significantly greater confidence, thus supporting an NDA.

The key to achieving faster drug development in AIDS lies not in an exclusive focus on Expanded Access or Parallel Tracks, but rather on their integration into an enlightened program of rapid, flexible, humane and attractive clinical trials.

The activists¹⁶, regulators¹⁷, and statisticians¹⁸ have provided the tools. It is up to industry, now, to use these tools to devise not only better treatments and prophylaxes, but a cure for AIDS within this decade.

¹⁴ See AIDS Treatment Research Agenda, ACT UP/New York, 6.90, pp. 22-23.

¹⁵ Federal Register 21 CFR Parts 312 + 314, Docket No. 88N-0359, October 21, 1988.

¹⁶ See ACT UP/NY, A National AIDS Treatment Research Agenda, June 1989; and AIDS Treatment Research Agenda 1990, June 1990.

¹⁷ CFR 21, op. cit., 1988.

¹⁸ DP Byar et al., op. cit., NEJM, 11.8.90.

5.0 U.S. HEALTH CARE: An International Scandal

Progress in treating or preventing the complications of AIDS means nothing if new therapies do not reach the people who need them. Yet, two years after the licensing of aerosolized pentamidine for PCP prophylaxis, and the concurrent PHS recommendations on the use of AP, Bactrim or Dapsone for this purpose, PCP remains the single most common cause of an AIDS diagnosis. Similarly, early intervention with AZT, hailed as a major advance 2 years ago, remains inaccessible to most HIV-infected persons in the USA and almost all worldwide.

The American health care system is in a crisis. Increasingly unaffordable, it provides little or no access to health care for tens of millions of people who live in the US. The quality of the care it does provide no longer meets any decent standard of equity or comprehensiveness. This health care crisis kills thousands of poor people, women, people of color and IV drug users each year, and shortens the lives of millions of others.

The time has come for systemic health care reforms in the USA. Even mainstream groups, such as the American Medical Association, once dedicated foes of any Federal intervention in health care financing and provision, now recognize that without a nationwide, coordinated effort, piecemeal reforms are doomed to fail.

Many schemes for reforming our healthcare system have been suggested in recent years. Some of them would begin from scratch, abandon the present system completely, and establish a national, governmentally-sponsored system that would either provide universal health insurance or would create a complete national health service. Others, less radical in nature, would build on the present system, eliminating many of its worst features by universalizing employer-sponsored insurance, reforming the insurance market, and expanding governmental programs for those who remain outside the system.

We do not, at this point, endorse any particular reform plan, although we are skeptical of those plans that would only extend the flaws of the present system by maintaining its basis in employer-provided insurance. What we desire to do here is to provide a brief outline of the principles upon which a reconstructed American health care system may be based if it is to provide a brief outline of the principles upon which a reconstructed American health care system must be based if it is to be effective and eliminate the worst problems of the current system. At a minimum, these principles are:

1. **Universal Coverage.** All of us must be covered by a single, uniform health care system, regardless of race, gender, sexual orientation, employment status, health status, disability, area of residence, citizenship status, or ability to pay.
2. **Comprehensive Benefits.** Coverage must include all health and health-related social services effective in preventing, diagnosing, and treating disease and disability, including long-term care for chronic illness, prenatal and postnatal care, pharmaceutical therapies, promising experimental treatments, proven alternative therapies, and ambulatory and in-patient care.
3. **Progressive Financing.** Health care must be financed in total by the Federal Government through progressive taxation and the reduction of the military budget. Federal funding for other life-enhancing programs that provide for education, housing, welfare, job training, rebuilding the national infrastructure, and cleaning up the environment -- all programs without which health care becomes ineffective -- must not be sacrificed.

4. **Economic Efficiency.** The proliferation of health care programs has resulted in a quagmire of red tape, waste, and confusion. Under the system now in place, we spend over 12% of our gross national product on health care, more than any other country. Yet a large proportion of our population has inadequate health care coverage or none at all. When more than 20% of the cost of health care is consumed by administrative costs, we are not getting our money's worth. A single, universal system will clearly provide better service and reduced costs.
5. **Proper Allocation of Health Care Resources.** Health resources must be shifted or created to meet the needs of those who require them, especially in poor or rural areas.
6. **Community Input and Control.** Most decisions in our health care system are now made by private parties, employers, insurers and bureaucrats. Our system must become responsive to the people it is meant to serve. Decisions must be made in a democratic fashion with substantial input from the many communities which comprise our nation and from the people who need health care the most.
7. **Substantially Increased Funding for Medical Research.** The development of new drugs and medical procedures must be a major component of a new national priority to improve the quality of health care for all of the people of our nation. This priority must not neglect diseases that disproportionately afflict specific populations, including people of color, lesbians and gay men, women, the young and the aged.

In sum, a restructured health care system must redirect the nation's resources and resolve in a mobilization against disease. It can best do this by providing free, quality health care for everyone through a system subject to democratic control and popular input.

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