Report of the Workgroup on Clinical Manifestations and Pathogenesis

Background and Progress Since Coolfont

As noted in the 1986 Coolfont Report (1), infection with the virus that causes AIDS--now known as HIV--results in a broad spectrum of manifestations. These range from asymptomatic disease, an acute retroviral syndrome, and chronic lymphadenopathy to more serious disease entities such as opportunistic infections, Kaposi's sarcoma and other malignant neoplasms, and neuropsychiatric disorders.

Since the Coolfont Report was issued, advances have been made in a number of important areas. Clinical and epidemiologic studies, along with growing practical experience, have helped to define certain features of the natural history and clinical presentations of HIV infection.

The types of immune dysfunction that occur in HIV-infected persons, trends in the progression of immune defects over time, the broad range of opportunistic infections, the neoplasms that can develop, and the many syndromes directly related to HIV infection have been extensively studied over the past 2 years. This has facilitated efforts to determine where and how intervention attempts should be directed to limit progression of disease. It should be emphasized that the advances that have been made in the early diagnosis and treatment of opportunistic infections and other clinical manifestations have improved both the quality and duration of survival for AIDS patients.

Equally extraordinary advances in understanding the virology and pathogenesis of HIV have been made over the past 2 years. Variants of HIV-1 have been identified, the structure and function of HIV genes have been delineated, and important insights into the mechanisms of immunopathogenesis have been achieved. A distinct but related human immunodeficiency virus, HIV-2, has been identified, and its virology, epidemiology, natural history, and cytopathogenicity are being actively studied. Although the precise nature of protective immunity to HIV infection is not fully understood, the scope of humoral and cellular immune responses to the virus is unfolding. A number of animal models for related retroviruses have been established and are providing further insight into pathogenic mechanisms that might be applicable to HIV. The role of cofactors in the initiation and propagation of HIV infection is an area of active investigation.

The Federal Government has a longstanding commitment to the support of biomedical research. Much of what has been learned thus far about the pathogenesis and clinical manifestations of HIV infection derives from the support of investigator-initiated research project grants funded by agencies of the PHS, particularly the National Institutes of Health.

Clinical Manifestations

Opportunistic infections and other manifestations

The past 2 years have seen substantial improvements in the diagnosis and treatment of opportunistic infections and certain other manifestations of HIV infection. Earlier diagnosis has led to earlier, more targeted treatment. This is affecting the natural history of HIV disease and has resulted in at least modest improvements in the quality and duration of life for infected persons.

Over time, it has become evident that subsets of HIV-infected individuals exhibit differing clinical manifestations and susceptibilities to disease progression. It has long been noted that, among people with AIDS, Kaposi's sarcoma (KS) occurs almost exclusively in homosexual men, and there are indications that other subpopulations, too, display characteristic patterns of opportunistic infections and other features of HIV infection. Why such differences exist and what factors may play a role in them remain unclear. Furthermore, the pattern of disease manifestations appears to be shifting in some cases without adequate explanation. Apparent reductions in the incidence of *Pneumocystis carinii* pneumonia (PCP) may reflect the increased use of prophylactic measures or changes in reporting procedures.

Another important area of progress concerns the nature and role of simultaneous infections in the expression and progression of HIV. Basic science studies indicate that other viruses may provide activation signals that stimulate HIV. Research suggests the possibility that HIV-infected individuals progress to disease faster when they are infected concomitantly or sequentially with other organisms. Combined infection by HIV and other viruses such as human T-lymphotropic virus, type 1 (HTLV-1), herpes simplex virus (HSV), or cytomegalovirus (CMV) may prove to have particular relevance.

There is growing evidence that certain important clinical features associated with HIV infection--including thrombocytopenia and other hematologic abnormalities, arthritis, pneumonitis, nephritis, certain diarrheal syndromes, wasting syndromes, and neuropsychiatric manifestations--may represent direct viral effects, rather than secondary consequences of virus-related immune dysfunction.

Kaposi's sarcoma

Among those infected with HIV, KS occurs with disproportionate frequency in the male homosexual population, although no clear risk factors have been associated with this phenomenon. Lifestyle, genetic susceptibility, and co-infection have been suggested as risk factors but remain undocumented. Results from several studies indicate that the incidence of HIV-related KS is decreasing. The reasons for this decline remain speculative, but it may be linked to alterations in as yet unidentified infectious or environmental cofactors.

Another interesting aspect of KS is reflected in survival patterns. Some patients who present with KS alone survive longer than patients who present initially with opportunistic infections. The reasons for this are unclear; it may be that patients who present with KS are not as immunosuppressed as patients presenting with opportunistic infections.

Prior to the identification of AIDS, KS was seen in association with certain immunodeficiency conditions. Decreased cell-mediated immunity is recognized as a component of non-HIV related KS; however, KS has been reported in HIV-positive individuals in the absence of any recognizable immune defect.

The pathogenic cell of origin for KS has been thought to be the endothelial cell; however, recent studies raise questions whether KS is truly an endothelial cell disorder, a mixed cellular response, or a clonal malignancy. Of interest, KS tumor cultures infected with different HTLVs produced high levels of autocrine factors that may play a role in the abnormal cellular proliferation seen in KS.

Non-Kaposi's neoplasms

Over the past few years, evidence has grown that HIV-infection may be associated with a range of neoplastic processes, including lymphoid, hematologic, and epithelial tumors. The majority of non-KS neoplasms are B cell lymphomas, including both non-Burkitt and Burkitt-type lymphomas.

Non-Hodgkin's lymphoma (NHL) appears to be rising in incidence among HIV-infected individuals. It is estimated that half of the NHLs in HIV-infected individuals appear after the diagnosis of AIDS has been made. The remainder appear before AIDS diagnosis, with no clear signs of accompanying immunosuppression.

An altered natural history of NHL, often marked by an unusually aggressive course, has been noted in persons with HIV infection. In addition, AIDS patients with NHL often have tumors at atypical sites, with an unusually large proportion of them occurring in the brain, rectum, mouth, skin, and parotid glands. Direct infection of B lymphocytes with HIV may be one potential cause of NHL in this population, although other viruses that might stimulate B cell proliferation, such as Epstein-Barr virus (EBV), HTLV-1, human B-lymphotropic virus, type 1 (HBLV-1), and CMV, may play a role.

Anogenital tumors in homosexual AIDS patients are being reported with increasing frequency. These tumors already occur more frequently in seronegative male homosexuals than in the general population.

A number of other nonmalignant proliferative and premalignant neoplastic syndromes--for example, hairy leukoplakia, psoriasis, and angiotumors of the skin--may occur in HIV infection. Their etiology remains unexplained.

Neuropsychiatric manifestations

The neurologic complications of HIV infection include a variety of opportunistic infections, neoplasms, and several syndromes that are thought to be related to HIV infection of the nervous system. A great deal has been learned in recent years about the nature and scope of HIV infection in the nervous system and its relationship to neuropsychiatric manifestations.

Neuropsychiatric abnormalities of varying degree occur in at least 60 percent of AIDS patients. The most common HIV-associated neuropsychiatric abnormality is dementia, often referred to as AIDS dementia complex (ADC) or HIV encephalopathy. This is a heterogeneous neurologic syndrome characterized by varying degrees of cognitive, motor, and behavioral abnormalities. Patterns of progression are variable, but the syndrome generally appears to parallel the overall disease process. A

variety of neuromuscular disorders, including peripheral neuropathies, have also been observed in AIDS patients. Pathologic findings in the central nervous system of AIDS patients include multinucleated giant cells, white matter pallor, perivascular infiltrates, and vacuolar myelopathy.

The monocyte/macrophage appears to be the cell most often infected in the central nervous system (CNS). There is no clearcut evidence that HIV directly infects nerve tissue; however, the mechanisms of damage to nerve tissues are an active area of study.

Pediatric AIDS

AIDS in children is predominantly a perinatal disease; nearly 80 percent of reported cases have occurred as a result of HIV infection acquired at or near the time of birth. The precise time of transmission of HIV from mother to infant during the intrauterine and perinatal period is not known. HIV transmission via breast milk has been reported, but only rarely.

It has been estimated that approximately 30 to 50 percent of children born to HIV-infected women are infected with the virus; however, it is difficult to obtain accurate estimates because many obstacles complicate the diagnosis of HIV infection in children under 15 months of age. Anti-HIV IgM antibody levels have not been validated as an indicator of infection. Virus isolation, though useful in detecting infection, is not always successful, nor do all institutions have the necessary resources to perform this procedure.

In contrast to adults with AIDS, children with AIDS frequently develop severe bacterial infections. A large proportion of HIV-infected infants have mental and/or motor retardation.

Children with hemophilia represent the other pediatric population severely affected by HIV infection. The development of techniques to avoid HIV contamination of blood products needed for these patients should dramatically reduce the incidence of new infections in this population.

The full spectrum of clinical manifestations and pathogenic mechanisms of HIV infection in pediatric cases is still being elucidated.

Pathogenesis

Virology and molecular biology of HIV-1

Two areas of study of the virology and molecular biology of HIV-1 were stressed during the Coolfont meeting in 1986: (1) assessment of target cell susceptibility and (2) assessment of the function of viral gene products, as well as the meaning and mechanisms of genetic heterogeneity. Over the past 2 years, significant progress has been made in both these areas.

Scientists have learned that certain classes of cells in addition to the CD4-positive T lymphocyte can be infected by HIV-1. These include monocyte/macrophages, Langerhans cells, dendritic cells, and microglial cells.

The structural and replicative proteins of HIV-1 are now more thoroughly understood, and additional genes of the virus have been identified. The *tat* gene has been shown to play an important role in augmenting viral replication by encoding a protein that functions as a potent transactivator of HIV-1 gene expression. In addition, the *rev* gene product has been shown to be required for efficient synthesis of proteins. In contrast, the *nef* gene product is a negative regulator of viral synthesis. The *vif* gene is critical to the efficient generation of infectious HIV-1 virions. The function of an immunogenic protein encoded by the *vpt* gene remains unknown. Further characterization of the long terminal repeat (LTR) sequences has demonstrated the presence of several regulatory elements for HIV-1 replication. Most recently, a ninth regulatory gene, *vpu*, has been identified.

With respect to the genetic heterogeneity of HIV-1, scientists have confirmed that HIV-1, like some other retroviruses, can readily mutate. The virus can even mutate within an infected person over time. The biological significance of these variations is unclear at present.

HIV-2 and related viruses

A second human retrovirus that causes an acquired immunodeficiency syndrome, HIV-2, has been isolated and characterized. Seroepidemiologic studies indicate that HIV-2 is not currently a problem in the United States. To date, only one case of HIV-2 infection has been documented in this country. This case occurred in a patient from West Africa who had been infected before arrival in the United States.

An impressive array of molecular biological studies has shown that HIV-1 and HIV-2 are distinct but related retroviruses that produce similar disease patterns. In fact, the two viruses use the same receptor for gaining entry into host cells, namely the CD4 molecule. Even though the envelopes of HIV-1 and HIV-2 are quite dissimilar, the CD4-binding sites of these two viruses are presumably the same.

The genome of HIV-2 appears to be closely related to that of a simian immunodeficiency virus (SIV) that causes an AIDS-like disease in macaques. Unlike HIV-1, HIV-2 and SIV contain an additional gene (*vax*), as well as a stop codon in the transmembrane envelope gene that codes for a truncated protein.

Development of HIV infection

Although much remains to be learned, great strides have been made in understanding the pathogenesis of HIV infection. It is clear that the foundation of basic research in virology and immunology that existed before the AIDS epidemic was instrumental for building this knowledge.

The precise mechanisms of HIV's cytopathic effect in CD4-positive cells is the subject of intense investigation. Many theories about HIV-induced cell killing have been proposed; these include a massive increase in the permeability of the cell membrane due to large amounts of budding virus, formation of syncytia between infected cells and uninfected CD4-positive cells, the accumulation of unintegrated DNA; intracellular complexing of CD4 and HIV envelope glycoproteins; and autoimmune phenomena.

It is possible that HIV plays an indirect role in T4 cell cytopathicity via a number of mechanisms, including infection of a T4 cell precursor; infection and selective depletion of a subset of T4 cells, or even CD4-positive nonlymphoid cells, that are critical to the propagation of the entire T cell pool; and the induction by HIV, or the secretion by HIV-infected cells, of soluble factors that are toxic to T4 lymphocytes.

New information on the role of the CD4 molecule in normal human immune responses has shed light on the mechanisms by which HIV may impair T4 cell function. Since the HIV envelope binds avidly to the CD4 molecule, exposure of CD4-positive cells to HIV or its products might block the interaction of CD4 with its natural ligand, the class II major histocompatibility complex (MHC) molecule, during T cell interaction with monocytes and macrophages. HIV infection also causes CD4-positive cells to express fewer CD4 molecules.

Evidence has been accumulating to support the concept that monocytes and macrophages play a major role in the propagation and pathogenesis of HIV infection, as they do in lentiviral infections of sheep and goats. Clearly, cells of the monocyte/macrophage lineage can be infected by HIV. Virus particles have been shown to bud intracellularly within monocyte/macrophages, where the virus is sheltered from immune response. *In vitro* data suggest that virus can survive and actually replicate in this cell without substantial cytopathic effects. If these observations hold true *in vivo*, it may be that cells of the monocyte/macrophage lineage serve as a reservoir of HIV, contribute significantly to the viral burden in an infected host, and transport the virus to various organs in the body such as the brain.

Research into the mechanisms by which a latent or low-level HIV infection can be converted into full-blown disease has demonstrated that *in vitro* HIV expression can be activated by exposing cells to mitogens, antigens, transfected heterologous viral genes, and physiologic cellular inductive signals that might be encountered as part of the normal immune response. It has been shown that activation of HIV expression occurs via a transactivating mechanism and involves the binding of proteins to the regulatory elements in the LTR sequences in the HIV genes.

Immune response to the virus

The scope of host immune responses to HIV infection has become clearer over the last 2 years. Scientists have demonstrated that HIV is the target for neutralizing antibodies, antibody-dependent cellular cytotoxicity, natural killer cells, and cytotoxic T cells directed against HIV.

It has been shown that antibodies against specific regions of the envelope glycoprotein can neutralize the virus; however, most of the neutralizing antibody responses that have been generated in animal models by immunization with envelope protein appear to be strain-specific. To date, the presence or absence of neutralizing antibodies does not appear to be correlated with disease progression.

In HIV-infected patients, the humoral immune responses that develop appear to be group specific. Cytotoxic T cell responses appear to be broadly reactive as well. It has been reported that antibodies to the core protein, p24, appear to decline as p24 antigen levels rise and disease progresses.

In contrast, anti-envelope antibodies appear to remain relatively constant throughout the course of infection.

Animal models

Having an animal model for HIV infection would clearly facilitate the acquisition of a wide range of information on the pathogenesis and natural history of infection. A number of viruses that can be studied by utilizing animal model systems are in various stages of development. They include: 1) retroviruses other than lentiviruses, e.g., murine leukemia virus (MuLV), feline leukemia virus (FeLV), and type D retroviruses; (2) ungulate and other lentiviruses, e.g., Maedi-Visna, caprine arthritis encephalitis virus (CAEV), equine infectious anemia virus (EIAV), feline immunodeficiency virus (FIV), and bovine immunodeficiency virus (BIV); (3) HIV-related lentiviruses of nonhuman primates, e.g., SIVs; 4) HIV infection of chimpanzees; and (5) HIV in transgenic mice and mice with severe combined immunodeficiency (SCID).

At present, animal retroviruses in general and simian retroviruses in particular are ideally suited to address AIDS research issues requiring *in vivo* infection. SIV mimics HIV-1 and HIV-2 in that it has similar cell tropism, cytopathology, and genomic organization, and SIV-infected monkeys die from AIDS-like complications. The SIV system can be used to understand the origins of HIV infection, pathogenesis, treatment, and vaccine approaches.

Cofactors

Cofactors appear to play an important role in HIV infection, enhancing transmissibility by increasing either infectiousness or susceptibility. Cofactors may also accelerate the progression of HIV infection by augmenting viral replication and/or lymphocyte destruction.

There is increasing evidence that sexually transmitted diseases (STDs) accompanied by genital ulcerations (chancroid, syphilis, herpes, and condyloma acuminatum) increase the risk for HIV infection independent of other risk factors. These epidemiologic associations suggest that damage to genital skin and mucous membranes may facilitate HIV transmission.

Epidemiologic studies in the United States have implicated herpes simplex virus as a cofactor for infection. *In vitro* data showing that HIV expression can be activated by transfection of heterologous viral genes, including those of the herpes simplex virus, are consistent with the model of these viruses as cofactors. Researchers have also determined that HTLV-1 can augment HIV expression. Since HTLV-1 and HIV can simultaneously infect individuals, HTLV-1 and HIV interactions may be important in disease progression.

Issues, Goals, and Objectives

Issue: Opportunistic Infections and Miscellaneous Clinical Manifestations

While much has been learned about the natural history of HIV infection, significant gaps in our knowledge demand further study. For example, a number of HIV-related syndromes cannot be fully explained. The precise pathogenic mechanisms of clinical features sometimes associated with HIV infection--for example, thrombocytopenia and other hematological abnormalities, arthritis, pneumonitis, nephritis, certain diarrheal syndromes, wasting syndromes, and neuropsychiatric manifestations -- are not now understood. It would appear that certain clinical manifestations of HIV infection represent direct viral effects, rather than consequences of virus-related immune dysfunction.

Another area requiring investigation concerns differences in the clinical manifestations of opportunistic infections among differing subsets of the HIV-infected population. The characteristics of these differences need to be further delineated. Why these differences exist and what factors may play a role in them remain unclear. In addition, the pattern of disease manifestations appears to be shifting in some cases without adequate explanation.

The basis of the morbidity and mortality associated with HIV infection and AIDS is not well understood. The clinical features most obvious to the treating physician--for example, fever, severe diarrhea, neurologic problems--are not always directly correlated with biopsy or autopsy findings.

Animal models for the study of opportunistic infections associated with HIV remain inadequate.

Goal: Continue studies of the natural history of HIV infection and associated opportunistic diseases in groups at risk, particularly in cohorts of women and children.

Objectives:

- Conduct studies to delineate the role of direct cytopathic effects of HIV on target tissue versus secondary manifestations of HIV infection such as immune defects or opportunistic infections.

- Conduct studies to define the effects of HIV infection on various organ systems, such as muscle, bone, and skin.

- Conduct studies to determine how earlier diagnosis and treatment of HIV infection and its complications have influenced survival.

Goal: Pursue further studies of the epidemiology, pathophysiology, diagnosis, and treatment of common opportunistic infections (such as PCP and CMV) as well as less common opportunistic infections (such as *Cryptosporidia* sp. and *Isospora belli)* that can be associated with AIDS.

Objective:

- Initiate studies of the natural history of these infections in patients with and without HIV infection.

Goal: Expand studies of the basic biology and pathogenic mechanisms of the full spectrum of opportunistic infections, together with their interactions.

Objective:

- Apply the techniques of molecular biology to gain understanding of the life cycle, pathogenesis, and diagnosis of opportunistic infections.

Goal: Clarify the role of co-infection, as well as other possible exogenous or endogenous cofactors, in relation to both the natural history and the clinical manifestations of HIV-associated disease.

Objective:

- Perform intensive prospective cooperative trials.

Goal: Place renewed emphasis on obtaining autopsies and pathological specimens.

Goal: Continue efforts to develop animal models for HIV infection, transgenic mice, SCID mice, and simian AIDS.

Issue: Kaposi's Sarcoma

Although much descriptive data about KS have been collected and advances have been made in diagnosis and treatment, little progress has been made in understanding the disease process.

The nature and role of immunodeficiency in the appearance of KS in AIDS patients remains an enigma. Decreased cell-mediated immunity is recognized as a component of non-HIV KS. However, KS has been reported in HIV-positive persons in the absence of any recognizable immune defect.

Results from several studies indicate that the incidence of KS is decreasing. The reasons for this decline remain speculative but may be linked to alterations in as yet unidentified infectious or environmental cofactors.

Understanding the natural history and pathogenesis of KS will involve careful basic science, epidemiologic, and clinical studies.

Goal: Direct studies to define the epidemiology of KS.

Objectives:

- Define the subpopulations at risk for KS.

- Fully examine the shifting patterns of disease.

Goal: Direct studies to define the etiology and pathogenesis of KS.

Objectives:

- Clarify the patterns of HIV expression and progression of disease in AIDS patients with KS.

- Determine the role of cofactors.

Issue: Non-Kaposi's Neoplasms

To a large degree, the basis of the relationship between AIDS-associated neoplasms and HIV infection remains to be clarified.

Most non-KS neoplasms are B cell lymphomas and may occur in HIV-infected individuals who manifest no clear signs of accompanying immunosuppression. The nature and role of immunodeficiency in the appearance of neoplasms in HIV-infected individuals is an important area for further study.

The incidence of non-Hodgkin's lymphoma (NHL) appears to be rising among HIV-infected individuals, but the reasons remain unclear. An altered natural history of NHL has been noted in the AIDS population.

Investigations into the mechanisms triggering B cell proliferation, the nature of proliferation (polyclonal, oligoclonal, monoclonal), and the control of continued stimulation and altered growth are important.

Studies in these and other areas--including anogenital tumors in homosexual men and other nonmalignant proliferative and premalignant neoplastic syndromes--will offer insights not only into the etiology and pathogenesis of HIV-related disease but also into malignant neoplasms and immunological disorders not associated with HIV infection.

As earlier diagnosis and improved treatment of serious opportunistic infections allow HIV-infected patients to live longer, an increasing number of malignant neoplasms may be observed. This would have important implications for treatment and care.

Goal: Conduct studies at the population, patient, and cellular levels to gain better understanding of the expression and progression of malignant neoplasms in HIV-infected individuals.

Goal: Direct epidemiologic studies to identify the subpopulations at increased risk for non-KS neoplasms and the cofactors involved.

Objectives:

- Define the populations at risk.
- Examine fully the patterns of disease.

Goal: Obtain information regarding the growth and regulation of proliferative/neoplastic processes.

Objective:

- Perform serial histopathologic examinations of lymph nodes in HIV-infected persons with lymphadenopathy.

Goal: Examine the range of factors that might stimulate and/or regulate the neoplastic process at the cellular level.

Objective:

- Examine the complex interrelationships of other viral infections, immune function, and the development and progression of neoplastic processes.

Issue: Neuropsychiatric Manifestations

Although much progress has been made in characterizing and understanding the neuropsychiatric manifestations of HIV infection, important issues still need to be clarified.

Much more information on the viral pathogenic mechanisms underlying HIV in the nervous system is required. Critical basic science questions need to be answered about the timing and mode of viral entry, activation of latent infection, recruitment of infected macrophages, and amplification of infection in macrophages. Factors controlling or influencing the spread of HIV infection in the brain should be investigated. These include immunosuppression, local CNS factors such as other infections or substances elaborated by cells, and neuropathic viral variants. The cause and mode of CNS dysfunction should be studied to determine the relative roles of direct and indirect virus-induced pathogenesis.

Clinical-pathologic correlates also need to be carefully studied and delineated. It will be important to better define and understand the presence, distribution, expression, and role of HIV in the nervous system throughout the range of clinical neuropsychiatric conditions, extending from infected but neurologically asymptomatic individuals to persons with full-blown disease.

A fuller understanding of the broad spectrum of HIV-associated neuropsychiatric disorders and their natural history is needed, along with clearer diagnostic criteria.

Goal: More precisely define the full spectrum of HIV-associated neuropsychiatric disorders.

Goal: Establish clinical and epidemiologic studies to better stage and define the natural history of these HIV-associated neurologic disorders, including the early manifestations.

Goal: Identify both laboratory and clinical predictors of disease development, progression, and therapeutic response.

Goal: Elucidate the presence, distribution, expression, and role of HIV in the associated nervous system disorders.

Objectives:

- Determine the timing and mode of viral entry into the CNS.
- Elucidate the mechanisms of activation of latent virus.
- Examine the patterns of migration of infected macrophages into the CNS.
- Study the mechanisms of viral replication in macrophages.
- Determine the relative roles of direct and indirect virus-induced pathogenesis.

Goal: Study and delineate the clinical-pathologic correlates of neuropsychiatric disorders in HIV infection.

Goal: Investigate factors controlling or influencing the spread of HIV infection in the brain, including immunosuppression, local CNS factors such as other infections or substances elaborated by cells, and neuropathic HIV variants.

Issue: Pediatric AIDS

The spectrum of clinical manifestations and pathogenic mechanisms of HIV infection in pediatric cases is still evolving. Little is known about the progression of the disease in children, particularly with regard to the role of immune suppression.

The precise time of transmission of HIV from mother to the infant during the intrauterine and perinatal periods is not known. HIV transmission via breast milk has been reported, though rarely. Little is known about the effects of HIV infection on pregnancy or about the effects of pregnancy on disease progression in an infected mother.

Many problems in the diagnosis of HIV infection in children under 15 months of age can make it difficult to obtain accurate estimates. There is also little current knowledge about the clinical manifestations of AIDS in adolescents.

Goal: Further research into the modes and timing of transmission of HIV from mother to fetus and/or infant.

Objectives:

- Examine fetal and placental tissues of HIV-infected women to learn when transmission occurs.
- Examine the potential role of breast milk in HIV transmission.

Goal: Initiate further studies of the potential embryopathic effects of HIV infection.

Goal: Examine the nature and scope of illnesses in pediatric HIV infection, including neurologic, kidney, and cardiac manifestations.

Goal: Develop a more precise clinical classification system for HIV infection in children.

Goal: Develop better prognostic indicators for the development of AIDS in children.

Goal: Improve diagnosis of HIV infection in infants.

Objectives:

- Examine cord blood samples to identify at birth those children at risk of developing clinical disease.
- Adapt gene amplification techniques to large-scale screening.

Goal: Conduct studies of the natural history of HIV infection in pregnant and postpartum women.

Goal: Begin studies on rates of seroprevalence and the natural history of HIV disease in adolescents.

Issue: AIDS-Related Complex

The term AIDS-related complex (ARC) has been used to refer to a variety of nonspecific symptoms that could reflect undiagnosed opportunistic infections and malignancies. Some manifestations such as lymphadenopathy and herpes zoster can occur at any point in HIV infection. No consistent, universally agreed upon definition of ARC exists, and it is questionable whether the term has any epidemiologic, prognostic, or clinical value. The Centers for Disease Control now categorizes as AIDS patients persons who have HIV infection and wasting syndromes characterized by fever or diarrhea of 30 days' duration or involuntary loss of 10 percent or more of body weight. These persons previously would have been said to have ARC.

Goal: Reevaluate the current ARC classification.

Objective:

- Delete ARC from the HIV categorization scheme, as indicated.

Issue: Virology and Molecular Biology of HIV-1

The structural and replicative proteins of HIV-1 are better understood, and new viral genes have been identified. However, specific functions for parts of the HIV-1 genome and the mechanisms of regulation have yet to be fully determined.

Variants of HIV can develop within an individual, and in the population at large over time, but the biological significance of these variations is unclear. Although HIV infection is persistent in the host, the mechanisms of this persistence remain unknown.

Goal: Emphasize multidisciplinary approaches, incorporating disciplines such as chemistry, biochemistry, and structural biology, in HIV research.

Objectives:

- Establish programs to develop and distribute reagents. The NIAID AIDS Reagent Repository (described in the report of the Workgroup on Therapeutics) is an example of such a program.

- Coordinate research on the virology and molecular biology of HIV with research on diagnosis, treatment, and vaccine development efforts.

Goal: Conduct further research into the genetic heterogeneity of the virus.

Objectives:

- Examine the correlations between those HIV variants that develop *in vitro* and those that develop *in vivo*.

- Examine the role of genetically defective viruses in acute versus chronic infections.

- Identify immunologic and other host responses associated with genetic change in the virus.

- Study virus isolates from patients in whom disease progression is abnormally rapid or virus transmission is abnormally efficient.

- Conduct microepidemiologic analyses--for example between sexual partners--to determine the presence of genetic alterations in HIV.

Goal: Expand studies of genetic variability and disease susceptibility in the host.

Goal: Elucidate the mechanisms of viral persistence.

Objectives:

- Examine the chain of events that follows the infection of resting T cells.

- Determine whether a true latent state, similar to that seen in herpes virus infections, exists *in vivo*.

Goal: Delineate the natural history of HIV infection.

Objectives:

- Use animal models to investigate HIV's initial portals of entry and to determine the cells that are initially infected.

- Explore the extraordinary complexity inherent in HIV infection through studies of the natural history of the virus *in vivo*.

Issue: HIV-2 and Related Viruses

An impressive array of molecular biological studies has shown that HIV-1 and HIV-2 are distinct but related retroviruses that produce similar disease patterns. Further study of HIV-2, as well as other potentially related viruses, is needed.

Goal: Expand studies of the natural history, epidemiology, and clinical manifestations of HIV-2 infection.

Objectives:

- Investigate the transmissibility of HIV-2, the length of the asymptomatic period, the proportion of people developing disease, and the severity of disease.

- Perform further seroepidemiologic studies, both in the United States and abroad, to monitor the potential spread of HIV-2 infection.

- Conduct further virologic studies, using molecular technology, to examine the cause of differential reactivity to HIV-1 and HIV-2 and its clinical consequences.

Goal: Expand virologic studies to address the apparent difference in cytopathicity between HIV-2 and HIV-1, and the ability of HIV-2 to infect and induce disease in monkeys.

Objectives:

- Analyze potential recombinant viruses that may arise as a result of simultaneous infection of cells by HIV-1 and HIV-2.
- Conduct additional molecular biological studies of HIV-2 genes to understand the similarities and differences between HIV-1 and HIV-2.

Goal: Continue surveillance of the blood supply for evidence of HIV-2 infection.

Objectives:

- Evaluate the accuracy of current anti-HIV-1 tests in detecting HIV-2 infection.
- Assess the role of gene amplification techniques in detecting HIV-1 as well as HIV-2 sequences.

Issue: Pathogenesis of HIV Infection

Although we have learned much about the pathogenesis of HIV infection, there are significant gaps in our understanding of pathogenic mechanisms both *in vitro* and *in vivo*. A great deal more needs to be learned about the direct cytopathic effect of HIV in T4 cells. HIV may potentially also play an indirect role in T4 cell cytopathicity. The precise mechanisms of these effects should be carefully studied and delineated.

In addition, further understanding of the mechanisms by which latent or low-level HIV infection can be converted into full-blown disease will be critical to the development of strategies to prevent and control AIDS.

Goal: Conduct research on a suitable animal model to delineate precisely the pathogenic mechanisms of HIV infection.

Objectives:

- Identify the cells that are initially infected at the virus' portal of entry.
- Define the viral antigens that are recognized by the immune system.
- Determine why the immune system fails to contain the infection.

Goal: Continue support of basic research in order to advance our understanding of the pathogenesis of HIV infection.

Issue: Immune Response to the Virus

Knowledge of the nature and role of the immune system has major importance for understanding the body's natural defenses against HIV infection, as well as for designing and evaluating vaccines. The complex relationships among antigen levels, antibody development, and disease progression need to be further studied.

It is clear that cell-mediated immunity must play a major role in protection against HIV, given the fact that the virus can be transmitted not only as cell-free virus but also through cell-to-cell contact. Yet the specificity of these cellular responses, as well as the role of major histocompatibility complex (MHC) restriction, are yet to be fully characterized.

Another important area for investigation concerns possible correlations between the demonstration of cell-mediated cytotoxic T-cell responses and the stage of clinical disease, and whether or not cell-mediated cytotoxicity protects against disease progression.

Goal: Elucidate the precise relationship of antigen levels, quantitative antibody levels to specific viral proteins, and isotypes to disease progression.

Objectives:

- Establish multidisciplinary efforts to determine the correlates of an effective immune response.
- Identify immunogenic viral epitopes that elicit protective humoral and cell-mediated responses or, alternatively, immune responses that enhance viral activity.
- Utilize animal models to investigate the role of the immune system in protection or in enhancement of infection, as well as its capacity to recognize diverse viral isolates.

Goal: Initiate further studies to determine the precise role of neutralizing antibodies that have been defined *in vitro* and also the role of mucosal immunity in protection against HIV.

Goal: Conduct studies of cell-mediated responses to HIV that address the characteristics of cytotoxic effector cells and the role of MHC antigen restriction of cytotoxic T cell responses.

Goal: Launch an examination of the role the immune system plays in acute HIV infection.

Issue: Animal Models of HIV Infection

Establishment of an animal model is of central importance to the acquisition of a wide range of information on the pathogenesis and natural history of HIV infection.

Considerations of humane animal treatment, appropriate facilities, cost, and feasibility are all important issues, in addition to scientific needs and goals.

Goal: Extend existing animal models and develop new ones.

Objectives:

- Establish facilities for animal models of HIV infection.
- Establish resource repositories for animal model reagents.
- Expand knowledge about normal immune function in animals, particularly monkeys and cats.
- Systematically screen for other retrovirus infections in feral animals, particularly mice.
- Make animal models more accessible to researchers, so that work in this area can be expanded.

Goal: Broaden the use of animal models to study issues such as natural history of opportunistic infections and neoplastic processes as well as mechanisms of virus transmission.

Goal: Develop effective public education regarding the importance of the use of animals in research on the pathogenesis, diagnosis, and treatment of HIV infection.

Issue: Cofactors

More research is needed to elucidate the role of cofactors in the acquisition and progression of HIV infection. Influences on transmissibility and susceptibility need to be carefully examined at the cellular, individual, and population levels.

Goal: Continue to evaluate environmental cofactors and behavioral determinants in the acquisition, transmission, and progression of HIV infection.

Goal: Delineate the role of cofactors in disease progression using animal and cellular models.

Objectives:

- Clarify the role of possible cofactors, such as the cytokines secreted by body cells.
- Clarify the role of other viruses, such as herpes viruses and HTLV-1, as potential cofactors.

Goal: Conduct prospective studies of HIV-infected individuals to determine the levels of virus expression before and after the occurrence of other infections, including opportunistic infections.

Goal: Continue and expand basic research on STDs and their control.

Objectives:

- Determine, in prospective studies, the impact of other STDs, particularly those that cause genital ulcers, on HIV transmission.
- Carry out intensive immunologic and virologic studies of the effect of STDs on the natural history of HIV infection.
- Monitor the effects of STD control efforts on HIV and STD incidence rates.

Cross-Cutting Issues

Issue: Classification of HIV Infection

A broad issue that should be addressed at the outset is the clinical definition of AIDS. Concern exists regarding the full applicability of the neuropsychiatric, pediatric, and ARC case definitions. As more is learned about the natural history and clinical manifestations of HIV infection, diagnostic criteria may require modifications, as has occurred in the recent past. From a research perspective, changing definitions may complicate ongoing studies, but excessively rigid definitions may distort perceptions of the actual disease patterns. From a clinical perspective, clear and usable definitions are critical for diagnosis, prognosis, and treatment.

Goal: Develop approaches to the classification of HIV infection that would reflect the spectrum of disease, ranging from asymptomatic infection to symptomatic infection and illness.

Objective:

- Convene a broad-based group, including representatives of the World Health Organization, to recommend classification schemes suitable for all countries and ages.

Issue: Interdisciplinary Collaborative Studies

Interdisciplinary collaborative studies would greatly enhance knowledge of the natural history of perinatal transmission, pediatric and adolescent AIDS, neuropsychiatric disorders, the acute retroviral syndrome, opportunistic infections, and KS and other malignant neoplasms. This approach would facilitate better understanding of HIV infection especially in subpopulations at increased risk. Important correlations between laboratory indicators and clinical state--for example, p24 antigenemia and disease progression, or the clinical correlates of protective immunity--could most effectively be studied in this setting.

Goal: Establish interdisciplinary collaborative studies, including international initiatives, that offer the necessary research setting in which to address important questions about HIV-related disease.

Issue: Autopsy/Biopsy Collection

A dearth of pathologic specimens, the result of a low rate of autopsies on persons with HIV disease, has proven to be an obstacle to the comprehensive study of the clinical and pathologic consequences of HIV infection.

Goal: Heighten efforts to educate the public about this problem, increase training of health care personnel, and provide adequate facilities to perform autopsies.

Issue: Standardization of Assays and Measurements

In the clinical setting, important problems center on the need for laboratory quality control for virus culture, diagnostic assays, and hematologic and immune function measurements. In addition, there is a need for standardized approaches to key measurements, particularly those that are often used in a comparative manner over time and between laboratories, such as T4 cell counts. There is also a need to standardize such materials as reagents and neutralizing antibody assays.

Goal: Convene a series of advisory groups in key areas to evaluate standardization of laboratory/diagnostic tests and to offer specific recommendations.

Issue: Technology Development and Transfer

In many areas of basic and clinical research, progress is limited by a need to develop or gain access to certain research tools and techniques. These tools and techniques include reagents, molecular probes, diagnostic strategies, quantitative indicators of infection and immune dysfunction, pharmacologic agents, and animal models.

Goal: Support ongoing activities in technology development and transfer, and foster collaboration in sharing materials and information.

Issue: Safe Handling of HIV

Studies of the basic virology, immunology, and molecular biology of HIV require the use of suitable containment facilities by personnel trained in the safe handling of human pathogens.

Goal: Encourage the provision of state-of-the-art equipment and techniques to ensure safety in handling HIV and specimens infected with the virus.

Objectives:

- Assist in the construction, renovation, and upgrading of clinical and basic research laboratories working with HIV.
- Ensure that state-of-the-art laboratory equipment is available for work with HIV and other pathogens.
- Encourage the training and periodic retraining of persons working with live virus.
- Develop techniques to minimize exposure to live virus.
- Establish consistent criteria and monitoring for laboratory safety.
- Perform surveillance of persons handling HIV and related viruses.
- Ensure the availability of proper containment facilities for working with animals infected with HIV and related viruses.

Issue: Availability of HIV Researchers and Health Care Providers

At present, there are too few trained basic researchers, research and clinical laboratory person-

nel, and health care providers to combat the HIV epidemic. It is essential to increase the numbers of such persons available to the research and clinical care pool.

Goal: Increase the number of researchers and clinical care providers involved in the AIDS effort.

Objectives:

- Increase the numbers and level of training of researchers carrying out HIV-related studies.
- Increase the numbers and level of training of health care providers and clinical laboratory personnel working in the HIV area.

Issue: Basic Research

Since much of the progress in HIV research derives from basic research funded prior to the HIV epidemic, expansion of HIV-related activities should not be carried out at the expense of other areas of basic research.

Goal: Increase support of undifferentiated basic biomedical research in areas such as molecular biology, immunology, and microbiology.

Objective:

- Increase support for investigator-initiated research in basic biomedical disciplines.

References

1. Coolfont report: A PHS plan for prevention and control of AIDS and the AIDS virus. Public Health Rep 101:341-348, July-August 1986.