Report of the Workgroup on Neuroscience and Behavior

Background and Progress Since Coolfont

The significance of the interaction among the neuroscience, immune, and behavioral factors of human immunodeficiency virus (HIV) infection has only recently been recognized. Thus, the Workgroup on Neuroscience and Behavior of the Second Public Health Service (PHS) AIDS Prevention and Control meeting had an expanded focus.

The workgroup reviewed the neuroscience and behavioral aspects of HIV infection and suggested priorities and recommendations for research and relevant policy applications. Two facts--HIV can be found in the cerebrospinal fluid of many patients early in HIV infection, and some patients develop a devastating dementia or debilitating neuropathy late in illness--underscore the importance of focusing attention on this area.

Although psychiatric and neurologic signs and symptoms of HIV infection were initially believed to be secondary to opportunistic infections and space-occupying lesions of the central nervous system (CNS), a growing number of HIV/AIDS researchers became convinced that these conditions were not sufficient to account for all clinical CNS manifestations. The structural similarity of HIV-1 to neurotropic retroviruses and the observation that the CD4 receptor was present on cells in the brain led to research confirming that HIV-1 directly infects the CNS, producing the cognitive, behavioral, sensory, and motor symptoms now known collectively as HIV-1 encephalopathy.

It is now accepted that HIV enters the CNS early and, directly or indirectly, produces a range of nervous system impairment. Thus, just as previous retrovirologic research contributed substantially to the early identification of HIV-1 as etiologic for AIDS, neuroscientific and behavioral research is proving critical to the understanding of HIV nervous system disease and to the development of effective treatments for the direct and indirect consequences of CNS infection.

Although considerable work remains to be done before the complex neurobiology underlying HIV infection of the nervous system is completely understood, the escalating involvement of neuroscientists and behavioral scientists in AIDS research has greatly advanced our understanding of this condition, as well as ways to treat it. Critical research agendas now under way, not identified at the Coolfont meeting in June 1986 *(1)*, include:

- Collection of data on early neurobehavioral abnormalities in HIV infection and the potential role of HIV in the development of HIV dementia, as well as data demonstrating the shortcomings of clinical neuropsychological instruments in predicting employability/maintenance of independent life style, particularly in relatively less impaired persons.

- Treatment studies, using AZT and a biologic known as Peptide T, that may ameliorate CNS symptomatology in HIV infection.

- Research on the role of the monocyte, the mechanism of transmission of HIV to the CNS, the absence of direct HIV infection of neurons, and the effects of toxic by-products (e.g., gp120) on the CNS.

- Accumulation of evidence that different strains of HIV produce different CNS manifestations, and that some may be more neurotoxic than others--perhaps accounting for some of the variations in CNS symptoms seen in HIV infection.

- Studies of molecular interactions, *in vivo* and *in vitro*, between the HIV genome and factors that are produced in the brain during HIV infection, either by the infected cell or by viruses.

- Research probing the importance of other human retroviruses (such as HTLV-1, which is associated with the clinical syndrome of tropical spastic paraparesis) that may have given rise to neurotropic strains.

This report establishes cross-cutting research agendas relevant to the neuroscientific and behavioral aspects of HIV infection. (It should be noted that the use of the term "behavior" is primarily restricted to those behavioral manifestations that appear subsequent to, and are probably related to, HIV infection. Behavioral research strategies that focus on prevention of HIV infection and transmission are treated elsewhere in the report of the Workgroup on Prevention.)

Current evidence suggests that the risk of neurologic and psychiatric impairment increases as HIV infection advances. However, with respect to seropositive individuals who are otherwise asymptomatic, existing data are insufficient to support policies restricting their employment or other activities solely on the basis of serostatus.

HIV infection presents many problems in balancing the concerns of society. Among the sources of these concerns are issues deriving from the CNS consequences of HIV infection and their influence upon both protection of individual rights and public safety. This paper proposes goals for PHS to address in the near term. While some of these policy-based questions will likely have to be addressed in the absence of conclusive data, this paper offers guidance for balanced consideration in developing policies.

Issues, Goals, and Objectives

This report identifies priority research issues related to the relationships among the neural, immunologic, viral, and behavioral aspects of HIV infection. Clinical manifestations such as cognitive abnormalities in all stages of HIV infection, the full spectrum and natural history of HIV diseases of the nervous system, and risk factors and cofactors for neuropsychiatric diseases, among other areas, will require intensive investigation. Standardized methodology for assessing cognitive, affective, and behavioral sequelae of HIV infection in the full range of at-risk populations must be developed. It will be important to explore the *in vivo* release, by monocyte/macrophages, of HIV-derived toxic substances that may damage the nervous system; the neurovirulence of HIV and related retroviruses; and mechanisms of nervous system dysfunction in both pediatric and adult patients. Another goal is the development of suitable animal models that closely mimic HIV encephalopathy and that can be used to study pathogenesis, behavior, and potential treatments and vaccines. Emphasis must also be placed on human T-lymphotropic virus, type I (HTLV-1) and as yet unrecognized human retroviruses that involve the nervous system. The molecular mechanisms of HIV-induced effects on the CNS must be elucidated as a basis for developing nervous-system-specific drug treatments. More aggressive and strongly supported research in the basic behavioral and neurosciences is also needed.

Issue: Clinical, Neurological, and Neuropsychiatric Manifestations of HIV Infection

Research reports have demonstrated a spectrum of neurological, cognitive, and behavioral changes associated with HIV infection; however, basic questions about the onset, incidence, course, prevalence and extent of these changes remain to be answered.

Goal: Develop a more comprehensive description and taxonomy of the clinical manifestations of HIV nervous system disease. Recent findings from neuroscientific, animal model, and behavioral HIV research should be applied in order to focus the research questions being asked.

Objectives:

- Support longitudinal studies of HIV neuropsychiatric disease to determine the onset, incidence, course and prevalence, risk factors, cofactors, and markers of the various problems.
- Support studies of the clinical spectrum and natural history of HIV nervous system disease.
- Support longitudinal studies of patients with HIV-induced mild cognitive disorders to determine natural history, including any progression to dementia.
- Support studies that correlate clinical manifestations of neuropsychiatric diseases with neuropsychological tests and measures, neurobehavioral measures, neuroimaging, and immunologic and virologic parameters. Variables that can affect neurobehavioral expression, such as head injury or drug abuse, should be used as covariates in these studies.
- Support studies that correlate neuromuscular impairment with electrophysiological, histological, virological, and immunological parameters.
- Support longitudinal studies of patients with early signs of peripheral neuropathy or myopathy to determine the type of neuropathy (i.e., axonal or demyelinating), and assess reversibility or progression.

Issue: Lack of Treatments for HIV-Induced Behavioral and Nervous System Manifestations

No treatments specifically targeted to the neuropsychiatric manifestations of HIV infection and demonstrated to be effective are presently available. Amelioration of these HIV-induced deficits should be a focus in the search for effective therapeutic approaches to HIV infection.

Goal: Develop effective treatments for the behavioral, cognitive, affective and neurological sequelae of HIV infection.

Objectives:

- Identify, evaluate, and develop CNS-specific agents for the treatment of HIV CNS disease through basic and clinical research.

- Identify and develop antiviral agents that will cross the blood-brain barrier. Such agents should be evaluated for their potential toxicity, safety, and efficacy for the treatment of HIV infection.

- Support studies of novel methods of delivering drugs directly to the CNS, which could be used for potentially efficacious anti-HIV drugs that do not cross the blood-brain barrier.

Issue: Include Measures of Nervous System Outcomes in Drug Trials

HIV infection produces clear nervous system manifestations, yet few phase 1 or 2 clinical trials of anti-HIV drugs include measures of nervous system outcome. Such measures need to be incorporated in many more if not all of these trials.

Goal: Incorporate state-of-the-art neurological, neuropsychologic, and psychiatric assessment techniques in clinical trials of anti-HIV therapies to measure neuropsychiatric status and therapeutic changes in trial participants.

Objectives:

- Identify neurological and neuropsychological instruments that demonstrate sensitivity to HIV-related neuropsychiatric manifestations. These instruments should be subcategorized for use in baseline assessment, toxicity and safety evaluation, and efficacy trials.

- Ensure that appropriate neurological, psychiatric, and neuropsychological baseline and outcome measures are incorporated into all relevant studies receiving PHS funds.

- Assure that appropriate neurological and electrophysiological baseline assessments of the peripheral neurological systems are incorporated into all relevant studies receiving PHS funds, and ascertain how HIV causes neurotoxic effects both on the central and on the peripheral nervous systems. Also, examine how an antiretroviral agent can be both beneficial to nervous system function and have deleterious effects on the peripheral nerves.

- Utilize measures of neuropsychologic, psychiatric, and neurologic outcome in patients receiving multiple drug treatments that include neuropsychoactive agents (e.g., antidepressants, anxiolytics, sedatives) in order to measure drug effects, including drug-drug interactions.

Issue: Neuropsychological Assessment Methods

Contemporary methods of neuropsychological assessment have been used to demonstrate the effect of HIV infection on CNS function, but continued progress in this area requires methods that can be shown to be valid in HIV-infected persons and appropriate controls.

Goal: Develop specific, sensitive, reliable, and valid measures to assess the effect of HIV infection on neurological, behavioral, cognitive, and affective function. Repeatable measures that can be used for longitudinal studies need to be emphasized.

Objectives:

- Develop measures of cognitive, emotional, and psychomotor function that are free of cultural or educational bias to assess HIV-related dysfunction across populations with differing cultural and educational backgrounds.

- Develop measures of cognitive function based on animal models of cognitive impairment in order to build a knowledge base of functional systems.

- Develop repeatable, longitudinal measures to assess the impact of HIV related cognitive dysfunction on activities of daily living.

- To complement existing clinical and supervisory assessments, develop valid and reliable neurologic, psychiatric, and neuropsychological tests that predict behavior skills required in defined employment settings.

- Develop neuropsychological instruments sensitive to higher order cognitive functions such as judgment.

- Reanalyze existing large cohort studies with respect to differential thresholds for impairment and cofactors of HIV infection, in order to permit cross-study comparisons.

- Establish reliable neuroimaging modalities that measure early changes in brain function and metabolism. Such methods may include radioactively labeled agents and position emission tomography.

- Establish reliable neurophysiological methods that measure the integrity of the spinal cord and peripheral nervous system. Such methods may include validation of somatosensory evoked responses, and magnetic stimulation.

- Develop valid virologic, immunologic, and electrophysiological tests to establish HIV involvement of the grey or white matter of the brain, the spinal cord, the peripheral nervous system, or muscle.

- Establish histological criteria along with *in situ* hybridization techniques so that biopsies of accessible muscle or nerve tissues can be used to define the spectrum of neuropathies and myelopathies in HIV infection.

- Determine the impact of neurological impairment and of disability related to myelopathy or neuropathy on work performance and fine motor skills.

Issue: Standardization of Research Methods to Promote Comparative Studies

Current investigations of HIV-related changes in the nervous system, behavior, cognition, and affect appropriately use a multiplicity of assessment techniques. However, comparison of results among investigators is hampered by the absence of standard, cross-site methods.

Goal: Encourage all investigators to use comparable assessment methods so that results of research on the neurobehavioral effects of HIV infection can be compared at different research sites.

Objectives:

- Develop a basic set of common measures and norms of affective, cognitive, and neurological function in HIV infection based on recommendations of investigators in the field, and encourage their use. In addition to standardized instruments, guidelines for administering the instruments should be standardized. The recommended neuropsychological assessment measures should consist of a core battery of instruments that measure the domains of attention, memory, motor speed, and verbal skills. Other components of the battery should assess perception, higher cognitive function, and affect.

- Encourage investigators to incorporate new assessment domains that reflect their areas of expertise into neuropsychologic assessment batteries, so that the recommended battery does not restrict the development of innovative approaches to assessment.

- Develop through consensus a battery of tests to assess neurologic, neuropsychologic, and psychiatric function that will more efficiently predict performance in critical jobs.

- Encourage the use of consistent methods for neuropsychological measures, thresholds of abnormality, neuropsychiatric control group selection, and the assessment of neurobehavioral cofactors.

Issue: Neuropsychological Assessment Measures for Drug Abusers

Many drug abusers exhibit neurobehavioral abnormalities that may be mistaken for, mask, or add to HIV-related CNS deficits, and which may decrease compliance with drug and other medical/psychiatric treatment programs.

Goal: Develop neuropsychological assessment measures and norms appropriate for use in drug-abusing populations.

Objective:

- Develop neuropsychological batteries and norms for IV drug abusers that can be used in the context of drug abuse treatment and community outreach/intervention programs. Such batteries should lend themselves to being used in a repeated fashion to follow the degree and sources of neurobehavioral deficits in drug abusers (e.g., depression, fatigue, drug intoxication, withdrawal, head trauma, malnutrition, or substances such as psychotropic agents or methadone used during drug treatment).

Issue: International Comparison of CNS Manifestations Associated with HIV Infection

Because methods are not comparable, it is unclear whether CNS manifestations of HIV infection are the same in developing nations as in industrialized countries.

Goal: Develop methods appropriate for making cross-cultural comparisons of HIV effects on the nervous system, cognition, behavior, and affect.

Objective:

- Work with appropriate international organizations to develop, recommend, and encourage the use of methodology that would allow cross-cultural comparisons of the effects of HIV-related neuropsychiatric disease, and improving comparability of research data.

Issue: Interaction of Psychological, Social, Neurological and Immunologic Factors

HIV infection involves psychosocial and psychoneuroimmunologic factors believed to influence the course of the disease. Investigation integrating the biological, psychological, and social concomitants of HIV infection is needed to bridge otherwise independent areas of study.

Goal: Encourage hypothesis-driven research on psychoneuroimmunologic factors, including behavior change, mood state and preexisting neuropsychiatric disease, and immunologic and endocrinologic status, as they occur over the course of HIV infection.

Objectives:

- Support investigations into the effect of being informed of HIV seropositivity and the effect of being informed of a confirmed diagnosis of AIDS on immunologic, neuropsychological, and social function.

- Support investigation of whether the neurotoxic effects of HIV infection impair judgment, and the subsequent effect of any such impaired judgment on risk-taking behavior.

- Support investigation in HIV infection of the effect, on immunologic, neuropsychological, and social function, of:

  - mood and affect, as well as the interaction of cognitive and affective states;

  - the use of drugs and/or alcohol, including drugs of abuse as well as all types of drug treatments;

  - reactions of others and of social institutions to persons with the disease (stigmatizing reactions);

  - isolation, loneliness, and the lack of social support; and,

  - the interactions between HIV-seropositive individuals and the health care system.

- Support longitudinal studies on interactions between psychological factors and the central and autonomic nervous systems, the neuroendocrine system, and the immune system.

- Support longitudinal studies relating the progression of HIV infection to cultural and gender differences, affective responsivity/lability, and functional differences in neurocognitive capacity and performance.

Issue: Research Needs and Policy Implications of Early Nervous System Impairment in HIV Infection

In some studies, HIV neuropsychiatric manifestations have been observed early in the course of the disease. This has led to the consideration of using HIV serologic status as a surrogate measure of impending neuropsychiatric impairment. Policies using serostatus alone, even without demonstrable neuropsychiatric impairment, to restrict eligibility for jobs, have been discussed.

Goal: Develop adequate scientific information for making policy decisions related to neuropsychiatric impairment associated with HIV infection.

Objectives:

- Determine the nature and degree of impairment, if any, in activities of daily living or job performance in otherwise asymptomatic individuals.

- Determine the nature and degree of impairment, if any, in activities of daily living and job performance in individuals with symptomatic HIV infection.

- Determine whether asymptomatic or symptomatic HIV infection has a predictive effect on the outcome of physiologic and functional tests of performance. This research should include consideration of the costs, benefits, sensitivity, and specificity of HIV antibody testing for this purpose.

- Stimulate the development of new and/or the modification of standard cognitive, neurological and behavioral instruments that are specific to job activities affecting public safety.

- Once methods are established to predict the effect of nervous system impairment on job performance, assess the reliability and validity of these measures in a longitudinal format in HIV seropositive persons and appropriate matched controls.

- Develop a model policy addressing performance of jobs in which complex higher nervous system function is critical, e.g., jobs involving public safety.

Issue: Health Care Service Needs Related to AIDS Dementia

As the number of AIDS cases increases, we can expect an increasing number of individuals to develop dementia. The result will be a need for considerable resources for long-term care.

Goal: Clearly identify specific health care services needed for an increasing population of individuals with AIDS dementia.

Objective:

- Determine the kinds of services, facilities, and health care workers needed to support the increased burden on the health care system.

Issue: Effect of Maternal Behavior on Infant Development

A large percentage of the mothers of seropositive infants are IV drug abusers or the sexual partners of IV drug abusers. There is little information on the effect of woman's behavioral and neuropsychiatric changes on her infant's neurological, cognitive, affective, and behavioral development.

Goal: Develop an understanding of the effect of maternal behavior on the neurobehavioral development of their infants.

Objectives:

- Define relationships among maternal HIV infection, maternal drug abuse patterns, HIV transmission to the infant, and the subsequent course of the infant's neurobehavioral development.

- Elucidate behavioral strategies that would increase the likelihood of women detecting their risk for seropositivity, choosing testing, avoiding pregnancy if seropositive, complying with drug treatment if needed, and getting adequate prenatal care if pregnant.

Issue: Prevention and Control of Neuropsychiatric Disease in Infants with HIV Infection

Virtually all of the infants born to seropositive women initially test as seropositive due to the passive transfer of maternal antibodies. About 30 percent to 50 percent of these babies are actually infected with HIV and go on to develop AIDS. These infants often display CNS manifestations.

Goal: Identify infants at risk for HIV-related neuropsychiatric disease and develop appropriate interventions.

Objectives:

- Develop methods to distinguish between infected and uninfected seropositive infants in order to provide rapid intervention with therapeutic agents such as AZT or still to be developed agents and thus prevent CNS dysfunction or reverse its early development.

- Establish appropriate measures of CNS development-- neuropsychological, psychophysiological, or neurophysiological-- that are capable of differentiating among causes of developmental delay or regression, e.g., trauma, malnutrition, drug exposure, neglect, HIV, and other CNS infection.

- Develop norms for CNS development in infants whose mothers are IV drug abusers or the sexual partners of IV drug abusers.

- Define the role of cofactors such as exposure to drugs of abuse in enhancing vulnerability to prenatal or perinatal infection and to the subsequent development of CNS sequelae.

Issue: Cellular Toxins and Damage to the Nervous System

In vivo release by monocyte/macrophages of HIV-derived "toxic" substances is thought to damage the nervous system secondary to HIV infection.

Goal: Identify relevant neurotoxin(s) produced and released by HIV within the nervous system and demonstrate the relevance of *in vitro* observations to the understanding of the natural history of HIV infection in the nervous system and the development of CNS-specific treatments for HIV infection.

Objectives:

- Isolate, identify, and characterize cellular toxins released in the central and peripheral nervous systems in HIV infection.

- Isolate, identify, and characterize brain-cell receptors for HIV envelope protein (gp120).

- Identify intracellular factors that promote or enhance infection within the nervous system.

- Determine the role of lymphokines and neurokines that mediate cell dysfunction, loss,

and destruction in the nervous system during retrovirus infection.

- Identify "triggering" mechanisms such as stress, drugs, and trauma in the development of overt signs of clinical HIV encephalopathy.

Issue: Neurovirulence of HIV

The neurovirulence of HIV and related retroviruses, and the mechanisms by which they invade and destroy the nervous system in children (prenatally and postnatally) and in adults, are not well understood.

Goal: Define--clinically, physiologically, cytologically, and immunologically--the underlying mechanisms and pathogenesis of HIV encephalopathy, and determine the roles of HIV mutability, strain variations, and infectious or noninfectious cofactors.

Objectives:

- Study the pathogenesis of neurovirulent strains of HIV and related retroviruses.

- Determine the molecular control mechanisms underlying the neurovirulence of HIV by examination of virus-host cell interactions.

- Identify neurally derived cells that serve as targets for infection and their neuroanatomical localization, and elucidate the cellular factors involved in brain cell loss/destruction and/or neurophysiological and behavioral dysfunction.

- Elucidate the role of opportunistic infections in the pathogenesis of retrovirus-induced disease of the nervous system.

- Identify cofactors involved in HIV-induced encephalopathy, dementia, myelopathy, and peripheral neuropathies.

- Determine the significance and mechanisms of demyelination (primary or secondary) in the CNS of patients with HIV encephalopathy.

- Elucidate predisposing influences on HIV dementia that are either immune or viral in nature.

- Study the molecular biology of HIV gene regulation, looking for transcriptional activator/suppressor genes that are expressed in T cells of HIV-positive individuals prior to onset of clinical disease. Expression of these genes may play a role in viral latency and the onset of disease symptoms.

- To identify neurovirulent strains of HIV, compare different isolates for variable expression of CNS manifestations.

- Identify, isolate, and characterize the role and interactions of neuroendocrine and neurotropic factors that influence the development of HIV infections of the nervous system.

Issue: Development of Improved Animal Models

More suitable, economical, and readily available animal models that closely mimic HIV encephalopathy are needed. They should be used to study the pathogenesis, the neurological, neuropsychological, and neurobehavioral aspects, the treatment, and the prevention of HIV infections.

Goal: Develop nonhuman primate models (other than chimpanzees) as well as smaller laboratory animal models for the study of HIV and related human retroviruses.

Objectives:

- To broaden the range of HIV-susceptible hosts, employ transgenic mouse modeling techniques to develop models, in other species, of animals transgenically infected with HIV.

- Study the molecular biology of strains of simian retroviruses that cause nervous system dysfunction.

- Establish retrovirus-infected primate models that can be used for neuropsychological testing of memory, learning, and motor function. Neuropsychiatric testing should occur prior to infection and longitudinally at appropriate intervals following infection.

- Develop animal models for *in vivo* assessment of drugs and other treatments that have been shown to block replication of HIV and related retroviruses *in vitro*.

- Expand the evaluation of animal models to include serial brain imaging and neuropathologic assessment during both the asymptomatic and symptomatic phases of retrovirus infection. Immune, neuroendocrine, and behavioral function should be determined over time.

- Develop suitable animal housing facilities.

Issue: Need for Appropriately Trained Research Scientists

There is a shortage of scientists appropriately trained in research involving the interaction of neuroscience, immunology, virology, and the behavioral sciences.

Goal: Provide funding to train a diverse group of scientists for work at the interface of neuroscience, immunology, virology, and the behavioral sciences relevant to HIV infection.

Objective:

- Increase support for interdisciplinary training of researchers who can work on problems involving the interaction of neuroscience, immunology, virology, and the behavioral sciences. Such training should focus on basic research as well as the clinical and performance manifestations of HIV infection.

Issue: Effects of HTLV-1 and Other Human Retroviruses on CNS

Recent studies of HIV have led to the recognition that the human T-cell lymphotropic virus (HTLV-1) intensifies the severity of disease in HIV-infected persons and, in addition to causing adult T-cell leukemia, is the causative agent of a newly recognized primary demyelinating neurological disease called tropical spastic paraparesis (TSP). TSP is remarkably similar in clinical and pathological lesions to some forms of chronic multiple sclerosis (MS).

Goal: Identify other human retroviruses that affect the central and peripheral nervous systems, and define the clinical, pathological, and immunological parameters of these diseases.

Objectives:

- Assess the immune functions of T cells infected with HTLV-1.
- Determine the modification of virus, virus genetic material, and viral proteins within T cells and their effects on T-cell function *in vivo.*
- Characterize the biological, virological, and molecular biological properties of HTLV-1 isolates from blood, and compare them to isolates from cerebrospinal fluid. These studies should include restriction mapping and sequencing of proviral DNA.
- Identify retroviral sequences in CNS tissues and in lymphocytes in the peripheral blood and the cerebrospinal fluid by *in situ* hybridization and polymerase chain reaction.
- Assess the role of retroviruses in MS, polymyositis, and chronic fatigue syndrome.

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.