Conference Report

Should 'AIDS' be renamed 'CNSD,' 'Central Nervous System Disease'?

by Our Special Correspondent

We continue our coverage from last week of the World Health Organization's Fourth International AIDS Conference held in Stockholm, Sweden. As the world statistics on AIDS continue to climb, WHO offers nothing more than "control strategy" to stem a pandemic it insists is caused by "sex and dirty needles." Our report this week discusses in depth the startling new research indicating that HIV infection is primarily a neurological disorder which causes *the immunological dysfunction. While much of the material may be highly technical for the average reader, we think it is important to make it available to the public at this time.*

Among the stars speaking at the World Health Organization AIDS conference plenary sessions in Stockholm June 19, three honest remarks were made: Harvard's William Haseltine said, "This is a progressive degenerative disease of the immune and central nervous system." The Pasteur Institute's Luc Montagnier admitted that we do not at present understand the action of the HIV virus on the lymphocytes of the immune system, "a central problem which remains to be solved," in contrast to the U.S. National Institutes of Health's Robert Gallo's line that the molecule says it all. And finally, Professor Ada reflected that our mastery of immune system functions may not be at the level necessary to envision a cure or a vaccine.

That WHO's definition is wholly inadequate to characterize the disease is underscored by the ceaseless fight, waged especially—but not solely—by tropical medicine specialists, to have this or that "opportunistic" disease added to the "accepted" list of AIDS Opportunistic Diseases—the Western World list, and the more restrictive African list (the "Bangui" definition), which WHO AIDS director Jonathan Mann seems to have conceived of for the "natives," because, he rationalizes, African physicians are too poorly equipped to identify other diseases, such as neurological ones.

The problem with WHO's definition of what we call Acquired Immune Deficiency Syndrome (AIDS) is even more serious than statistical juggling. As the astute Irishman Dr. William Howlett, a clinical neurologist in Tanzania, remarked to this author, "It is the first time in the history of modern medicine that a disease is defined by peripheral secondary clinical manifestations, instead of by the 'primary complex.' "

What is the "primary complex" in HIV infection? A small but active minority at the congress sought to identify the disease associated with human immunodeficiency virus infection as *primarily a disease of the central nervous system (CNS).*

American and European findings concur that at autopsy, at least 90% of patients have detectable lesions of the brain. Clinical evaluation, however, only "officially" detects neurological abnormalities in 5-15% of patients, depending on the study. Those clinicians who can detect neurological disease syndromes in 90% of patients are a minority. Dr. William Howlett is one of these.

There are two types of physicians who seek to identify AIDS as a primary disease of the CNS, as a *neurological disease* whose immune deficiency aspects are only secondary, and may or may not exist in the patient. Clinicians who rely exclusively on their intelligence as practitioners, often lacking equipment because they operate in developing countries, have degrees of astuteness rarely matched by the routine practitioner in the industrialized sector. The second category is the specialists using nuclear magnetic resonance (NMR) imaging, Simple Photon Emission Computed Tomography, and other high-performance medical techniques of recent years.

Dr. Howlett has sought abnormalities in patient reflexes indicating neurological damage, in a study of 200 patients done in Kilimanjaro. He can detect characteristic HIV neurological damage with simple clinical tests (see **Table 1**). His findings, and how to conduct those tests, so far remain "hush-hush," and he was not permitted to present them publicly in Stockholm. His studies will only be made public in the AIDS in Africa conference this September in Tanzania. At least privately, the best-known neurologists working on AIDS research at Johns Hopkins University (the leading U.S. AIDS reasearch facility today), are very interested in those find-

ings, as are the Pasteur Institute African AIDS researchers.

That the mechanism of the disease would be changes in brain performance leading to subsequent immune damage, is the firm conviction of the best AIDS research teams in France. These teams will never appear on your television, and equally abhor media hype and "AIDS education programs" with their associated socio-anthropological rhetoric. These scientists are convinced that we need new advances in our understanding of the interactions between the brain and immune systems, and we need to focus attention on HIV-induced changes on the brain, which will help us understand the consequent immune disorder.

It is the impression of this writer that if Gallo and so many others seek to preserve the image of the T4 lymphocyte/HIV molecular interaction as a primary disease mechanism, and keep focusing on "opportunistic" diseases as true definitions of AIDS, it is only to satisfy certain pharmaceutical interests who attend these congresses, and to preserve the radical beliefs of the most reductionist tenets of molecular biology.

A wealth of research

From the public workshops, from the posters (graphic presentations of material not included in the speeches), and from participants strolling in the corridors, this writer was able to uncover a wealth of interesting research which begins to document and give us leads, on the nature of AIDS "primary complex."

Dr. Renée Malouf of Harlem Hospital in New York City, shared with Howlett some of that passionate quest for the truth and liking of people which makes for a good scientist and a good physician. Dr. Malouf, a small woman with a feisty spirit, is a neurologist who has carried out a study on 190 HIV-infected drug users with either AIDS (129) or ARC (61), of whom 151 were parenteral drug abusers. Of the total, 166 patients (87%) had neurological symptoms or signs (see **Table 2**). She also privately remarked that she had found five psychotic patients—two homicidal and three suicidal—who were admitted to the psychiatric ward, to be HIV positive. They subsequently developed AIDS.

Her observations are corroborated by a Milan study by Dr. Zamperetti who, testing for HIV in a psychiatric ward, found a high 7.2% HIV positive, contrasting with the 0.1% positive found among Milan's blood donors. He advocated systematic testing in psychiatric hospitals (with the prior informed consent required by law for all European countries).

Renée Malouf was appalled at the threat the spread of drugs in the U.S. ghettoes poses in relation to HIV infection. She expressed fear, based on her own experience, that the free distribution of needles is encouraging more youth to try out hard drugs; meantime, drug abusers, who are usually prostitutes, are impervious to "safe sex and clean needles" propaganda. In fact the "educational" approach, as far as she could tell, would probably increase "crack" consumption, because the cocaine derivative, crack, does not require needles; increased consumption of crack, moreover, not to mention increased incidence of crack's effects: paralysis, brain damage, and often death, as lethal as AIDS itself!

The debate as to whether neurological diseases are just "opportunistic" diseases of immunodeficiency, is foregone. There is too much direct evidence for HIV neurological effects, and last year the Atlanta Centers for Disease Control were forced to include *dementia* among the list of AIDS symptoms. The debate has now shifted to focus on whether

TABLE 1

Neurological findings in HIV-positive patients

(total 100 cases)

Frontal lobe reflexes (snout/palmomental)	59
Dementia confusion	49
Pyramidal tract signs	16
Tremor	8
Incoordination	8
Absent reflexes	5
Depressed myotonic reflexes	5
Cranial nerve palsy	4
Seizure	3
Paraparesis	2
Hemiparesis (complete)	2
Hemianopia	1

Source: Dr. William Howlett.

TABLE 2

Neurological disease in HIV-infected drug abusers

(Total 190 patients: 129 AIDS and 61 ARC)

	AIDS		ARC	
Altered mental status	83	(44%)	23	(38%)
Focal cerebral lesions	30	(16%)	9	(15%)
Myelopathy/neuropathy	29	(15%)	9	(15%)
Seizures	13	(7%)	5	(8%)
Herpes zoster	6	(3%)	6	(10%)
Meningitis	5	(3%)	1	(2%)
Cerebral ataxia	4	(2%)	0	(0%)
Cranial neuropathy	2	(1%)	2	(3%)
Normal	18	(9%)	6	(10%)

The study conducted by Dr. Renée Malouf of New York City's Harlem Hospital concludes:
"1) Neurologic disease in HIV infection is more common than previously reported. 2) The prevalence of different neurologic symptoms and signs is similar in drug abusers and non-drug abusers, and in patients with either AIDS or ARC."
Source: Dr. Renée Malouf.

there is a "subclinical" neurological AIDS: how early the HIV carrier demonstrates signs of neurological damage; what type of damage, how to identify it, and how extensive it is; and whether HIV can directly infect neurons and related cells, in addition to the traditionally accepted view of macrophage infection in the brain.

Finally there are the interesting findings (Kansas team 1577) that HIV isolates from the brain, exhibit different biological and serological properties from that of peripheral blood.

- "Subclinical cerebral dysfunction" was identified by a team from Australia, led by Dr. I.H. Frazer (Lions Immunology Labs), which concluded that HIV was "neurotropic and capable of directly inducing brain damage even in immunologically normal subjects, early in the course of HIV infection."

Also from Australia, a team with Dr. Michael Perdices (NHMRC epidemiological unit) emphasized that HIV-infected patients show impairment of information-processing abilities on *complex,* but not on simple, tasks, which is related to disease progression. The only study of its kind, this finding is interesting, because it highlights the deficiency in the typical U.S. reductionist mental test, which may not detect damage to higher cognitive functions.

- Irina Elovaara, University of Helsinki, Finland, presented NMR and/or CT findings of 47 HIV-infected patients related to neurological dysfunction and intrathecal HIV antibody synthesis. "The results show that central and cortical brain atrophy as well as brainstem atrophy are frequently found in HIV-infected patients with cognitive/and or behavioral abnormalities. However, intrathecal HIV antibody synthesis found earlier than neuroradiological alterations may indicate subclinical HIV disease of the brain."
- Researchers at Ludwig Max. University, found that, "examining the CNS, [cerebrospinal fluid] findings suggestive of an inflammatory CNS disease, were found in 77% of HIV-positive, clinically and immunologically healthy persons."
- Igor Grant, in studies done in London, reported, "MR scans rated by a neuroradiologist blinded to group membership showed 3 ARC/AIDS patients had some atrophy and two-thirds had scattered high-intensity lesions. Among HIV positive, 10 out of 14 had mild atrophy and 5 out of 14 had parenchymal lesions." His team concluded that this was "confirmation of earlier studies showing early brain involvment in HIV infection."
- Ann Collier (Washington University): "In HIV-positive [patients], MRI scan showed white matter disease in 11 out of 18 cases, ventricular enlargement in 3 out of 18, sinus disease in 9 out of 17." The conclusion is that "CSF abnormalities, white matter lesions on MRI scan, and subclinical neurological and neuropsychological abnormalities are common in homosexual men that are asymptomatic or have clinically mild HIV infections." Some researchers find "subclinical functional impairment of CNS affecting predominantly the cortical structure" (Landi, Milan), this as explanations of minor alterations in Brainstem Acoustic Potential, (7 out of 23 patients) *and* abnormal Pattern Reverse Visual Potential (7 out of 23) but no change in subcortical sensory conducting time.

(Some researchers emphasize subcortical lesions, others emphasize cortical ones.)

Studies on AIDS dementia

In workshops, the most interesting presentation was made by Dr. Price (Memorial-Sloan Kettering), on a study done to "further characterize brain HIV infection associated with pallidonigral degeneration noted in two patients aith AIDS Dementia Complex (ADC):

"In both brains there was severe neuronal loss in the globus pallidus (GP) and substantia nigra (SN) with axonal spheroids and marked regional iron deposition." HIV infection could not be detected in neurons and other glial elements. The conclusion was most interesting. "Two contrasting, but not mutually exclusive, hypotheses are offered: 1) Productive HIV infection of macrophages and microglia releases products toxic to certain neurons; or 2) selective HIV targeting of particular neurons explains the localization of infection, and the neighboring infected macrophages and microglia are 'indicator cells' that have 'rescued' and amplified low-grade or latent neuronal infection."

While the toxin hypothesis has already been formulated, notably by Montagnier, the other hypothesis is bolder and more intriguing: What if the infected macrophages were *indirect* evidence of neuronal infestations? This dispenses with the common attitude which says "we know" that macrophages are both the transporter of HIV to the brain and the reservoir of infection, which "fact" may be a secondary feature of a primary infection of neurons.

That neural tissues *are* a target for HIV, was demonstrated by another experiment conducted by W.D. Lyman (Albert Einstein College of Medicine) who tested the hypothesis that HIV can infect neural tissues during gestation. "Sections of fetal cortex obtained from seronegative women were harvested and the culture was incubated with HIV. The culture done without HIV developed and differentiated normally, the culture with HIV, for at least seven days, showed significant pathological and cellular infection with HIV." The conclusion of the team was that "HIV can infect neural cells and cause pathologic changes *in vitro* similar to those observed *in vivo*."

Another presentation by Price stated that "clinically detectable eye movement abnormalities" could be a useful means of detecting neurological damage in HIV-infected patients. Rates of Corrective Saccade frequencies in eyes of seropositives are clinically detectable and seem usable markers of early HIV neurological disease.

Simple Photon Emission Computed Tomography

(SPECT) was used by F.W. Schaef (Johns Hopkins University) to indicate that HIV infection is associated with diffuse brain involvment, disrupting *both* the cortical and subcortical area. "Individuals may demonstrate SPECT abnormalities early in infection, before showing up on neuropsychological test performance."

The importance of MRI studies

A. Sonnerborg (Karolinska Institut, Stockholm) in a study using Magnetic Resonance Imaging, found himself is close agreement with Tanzania's Dr. William Howlett in an interesting meeting of minds from both sides of the planet using totally dissimilar techniques, from advanced technology to astute clinical observation.

He studied 64 patients in different stages of HIV infection. "Brain pathologies were detected and characterized from MR scans using a recently developed procedure of computer-assisted classification. Detected aberrations exhibited a significant relation to the stage of HIV infection. Focal pathologies, e.g., abcesses, cortical atrophy, and enlargement of the ventricles were most pronounced in patients with advanced immunodeficiencies. More subtle changes such as demyelinization of the white matter was detected in all groups. The conclusion was that tissue characterization by ultralow-field MRI in combination with computer-assisted classification was a useful method of the study of brain lesions in HIV-infected patients." Another Karolinska researcher used low-field MRI to non-invasively detect white matter demyelinization in AIDS patients.

- Lionel Resnick (Mount Sinai Medical Center study supported by the U.S. Army Med. Res.) presented studies on early markers for HIV infection of CNS, which concluded that "elevated intra BBB IgG synthesis and abnormal serum IgG bands are indicative of early CNS infection by HIV."
- Peter Pohl (University of Innsbruck, Austria) used SPECT to show "pathological changes even in the early phase of the disease." The data indicated both disturbances of cerebral amine metabolism and alteration of local perfusion share in the pathophysiology of AIDS Dementia Complex.

'Slim disease' in Africa

Margareta Larsson (University of Gothenburg, Sweden) showed how HIV's metabolic effect could be at the origin of the "slim disease" so often seen in Africa in correlation with HIV infection. "Significant changes in the indolamine turnover in the blood and brain compartment were seen at an early stage of HIV infection and found to be most pronounced in patients with AIDS." This may lead to effects in the production of the enzyme nicotinamide adenosine dinucleotide (NAD) as well as on the transmitter serotonin thereby inducing the "slim disease" and affecting the brain function.

The director of the Bangui Pasteur Institute, M. Georges, argued for the Bangui definition to be revised to include neurological manifestations in African HIV-positive patients, based on his own experience. He was snubbed by the WHO gurus moderating the workshop.

Zairean neuropsychiatrists met recently at a medical congress told this writer that they were worried about the HIV-associated dementias, which are fast becoming epidemic in their country.

- Dr. Guillermo Garcia (neurology service of the Instituto Nacional de la Nutrición "Salvador Zubiran"), in a study in Mexico, identified neurologic illness as manifest in 33.2% of AIDS patients.

HIV as a neuromuscular disease

David J. Eilbott (Walter Reed Army Institute of Research) presented his studies showing that "HIV RNA is detected by *in situ* hybridization in the spinal cord of AIDS patients with myelopathy and the close correlation of HIV RNA localization with histopathological findings, suggest direct role of HIV in pathogenesis of myelopathy in AIDS and AIDS-related conditions."

Al Belman (State University of New York at Stony Brook) observed loss of myelin and axon in children with symptomatic HIV infection. Clinically corticospinal tract (CST) signs had been a prominent feature in 14 out of 15 patients. *Post mortem,* 10 had lateral CST degeneration, in three, the anterior was also affected. Tract degeneration in four children was characterized by loss of myelin and axon. "CST degeneration in some children may represent an axonopathy that is tract specific, and in some there was evidence of developmentally delayed myelination."

Other studies show the entire neuromuscular system appears to be involved.

Ron Kletter (BAART-FACET, Department of Pediatrics, University of California at San Francisco) reported the findings of a most worrisome study on the children born of seropositive women, where the children appear both infected and not infected. The study showed the developmental pattern of seronegative children of HIV-positive mothers resembles that of seropositive children: 66% had a patttern of declining mental development index with age. This could indicate either that the children are infected though seronegative, or an effect of the HIV-positive mother on the child during gestation which would be some form of hidden brain damage.

Also to be noted is that, Robert Gallo's assertion to the contrary notwithstanding, HIV-2 is as lethal as HIV-1 and has already been found to induce neurological damage. "HIV-2 should be suspected in patients with only neurological symptoms even if they have never been to West Africa" says Dr. Sicard, Cochin Hospital, Paris.

We do not as yet, screen blood for HIV-2. Yet, while most African countries have not even one Nuclear Magnetic Resonance scanner, WHO is offering new projects to study "sex behavior" in Africa (Gagnon of Princeton, during the plenary).