The nervous system may be the real target of HIV

Away from the publicity glare of the June 4-9 conference on AIDS in Montreal, startling evidence was presented at a conference of specialists in neurological science. Garance Upham Phau reports.

What if millions of HIV-infected people are fast on their way to profound neurological impairment, including dementia, before developing any evidence of acquired immunodeficiency syndrome (AIDS)? What are the implications of a mass epidemic of brain disease for the continued existence of entire towns, cities, or even countries? What if we don't know how human immunodeficiency virus (HIV) enters the brain, what it does when it gets there, or even how it causes disease? While this may sound like a very bad dream, it accurately describes the situation facing scientists, physicians, and national governments today. In the week prior to the June 4-9 Fifth International Conference on AIDS in Montreal, "The Neurological Manifestations of HIV" was the topic of a gathering of neurological sciences specialists in Quebec City May 31-June 3.

In Quebec City, there were no homosexuals conducting sit-ins and parades, weaving quilts, and aggressively showing off their distinctive intelligence decked out in earrings, lipstick, and miniskirts. In Quebec City, there were no media on the lookout for the "hot stuff" or smut movies and champagne.

In fact, this conference bore the significant title "The Neurological and Neuropsychological Complications of HIV" and purposefully avoided speaking of "AIDS" to emphasize that those neurological manifestations may occur *without the concomitant presence of an immunodeficiency syndrome, e.g., AIDS*.

The conference was the scene of heated polemics. On one side were groups such as the Multicenter AIDS Cohort study group and the U.S. Air Force which claim, along with the World Health Organization, that HIV-infected asymptomatic individuals or patients with AIDS-related complex (ARC) show no signs of increased neurological impairment. On the other side are many neurologists, and some among the most brilliant AIDS researchers, such as Jay Levy of California, who conclusively demonstrate in study after study the neurological effects of the HIV virus, not only in the terminal phases of the AIDS disease, but also among a great many asymptomatic patients who show no immune deficiency.

"New Study Is Easing Fears on AIDS and Mental Illness" wrote Lawrence Altman in the *New York Times* on June 2, from Quebec City. Since there were only three journalists at the conference, it is to be feared that Altman's report will go unchallenged. The WHO's lying claim that, as of March 1988, there was "no evidence for an increase in clinically significant neurological or neuropsychological abnormalities in CDC [Atlanta Centers for Disease Control] groups II or III [HIV-infected individuals]" was retailed by Dr. J. MacArthur, from Johns Hopkins University, who, the *New York Times* gloats, said that neurological disease "affects less than 1% of HIV carriers."

In fact, the list of neurological diseases that have been found to be associated with HIV infection in a number of patients is impressive: Guillain-Barré syndrome, mononeuritis multiplex, sensory neuropathy, autonomic nerve dysfunction, myopathies, progressive multifocal leukoencephalopathy, white matter subcortical brain lesions, and spinal cord diseases such as vacuololar myelopathies.

African studies

All of these various nervous system pathologies can also be found on the African continent, where individuals suffer as much from neurological manifestations of the HIV infec-

tion as from its better-known immunological consequences. For example, a study conducted on 235 HIV seropositive individuals in the Kampala clinic in Rwanda, showed: Paraesthesia, or abnormal sensation, was present in 212 cases (88%); dementia was present in 60 persons (26%); neuropathy (nerve damage) was seen in 47 persons (20%). Five individuals in the group suffered strokes and four of them were paraplegic. Detection of additional findings in patients who had already died was hampered by limited *post mortem* analysis.

"The problem of diagnosis in Africa is acute," said Dr. Katabira of Uganda. "There is inadequate diagnostic equipment and material, poor financial support for research, no standard approach to diagnosis, [and] acute manpower shortages." There are "not enough doctors," he continued. "For example, there are two neurologists in Uganda, and ten psychiatrists."

Robert Levy, neurosurgeon and AIDS researcher at Northwestern University Medical School in Illinois, reported: "Signs or symptoms of neurologic illness were observed in 482, or 37%, of the patients in San Francisco, and 58, or 28%, in Chicago. . . . There were slightly more neurologic complications reported in San Francisco, most probably because patients there were evaluated initially by a neurologist, while in Chicago, a general medical doctor performed the examination," he said. Levy is co-author of the text *AIDS and the Nervous System*. In Quebec City, and later in Montreal, Dr. Levy advocated the practice of stereotaxic brain biopsies as the only definitive diagnostic procedure, which brought him into disagreement with the radiologists, who contend that magnetic resonance imaging (MRI) is adequate for diagnosis.

Dr. L.G. Epstein, of Newark, New Jersey, documented his findings in children with encephalopathies. He emphasized that we don't know how the fetal brain becomes infected or how early in the fetal development. Already, in 1985, HIV-1 was recovered from the brain tissue of a 20-week-old fetus. The identification of HIV in the brain is accomplished by a technique known as *in situ* hybridization, in which a DNA probe binds to complementary virus DNA in the brain.

The following findings were present in 87 children with progressive encephalopathies:

Impaired brain growth	93%
Secondary microcephaly	82%
Cerebral atrophy on CT scan	66%
Loss or plateau of developmental milestones	76%
Seizures	22%

Dr. Epstein commented that "we can't understand this by just looking at molecules."

Three crucial questions

Jay Levy of the University of California at San Francisco, who warned he was going to play the role of "maverick," brilliantly presented the problems and especially the questions facing research into the neuropathology of HIV. Levy's method was to raise such fundamental questions as to whether HIV has a direct effect on neural cells. Does the virus affect the permeability of neural cells? For example, putting the virus surface molecule GP120 in the presence of nerve cells in culture prevents the growth of the cells. In conclusion, he listed the three main questions scientists should debate about and work on today:

1) How does the brain get infected?

Do white blood cells, such as macrophages or T-lymphocytes bring HIV to the brain? Or is the virus transmitted by the cells which line the blood vessels, known as endothelial cells, or by the glial cells, which support and nourish the brain? Or does the free virus enter the brain directly?

2) What is the normal traffic of white blood cells to the brain?

Do white blood cells only go into the brain when the brain is infected? If so, how could the lymphocytes be the first to bring virus to the brain? The virus would have to be there beforehand. Do the cells known as microglia originate from the blood or the brain?

3) How does HIV cause neurological disease?

By direct cell toxicity or by disturbing the blood/brain barrier (endothelial or astrocytes), or by an effect of some virus protein?

During the lively discussion period, one person pointed out that "There is no reason the macrophage would come into the brain unless infection was already there," which brought up a subject first touched upon at last year's international AIDS conference in Stockholm: Are the macrophages in the brain actually removing virus from already-infected neural cells? If the virus enters the brain early, according to Jay Levy, the question becomes "Can free virus cross the blood/brain barrier?"

At this point, Dr. R.N. Boswell, of the U.S. Air Force Wilford Hall Medical Center, intervened to attack Levy, saying that the U.S. Air Force had found no signs of neurological disease in the early stages of HIV infection. In the back of the room, my neighbor chuckled derisively at Boswell's assertion that the Air Force failed to detect neurological impairment in 5,000 patients followed so far. "They obviously don't know how to conduct neurological tests," he concluded.

Even researcher Robert Janssen from the Atlanta Centers for Disease Control, who attempted to stay aloof from the main debate, commented that 14% of people with encephalitis had T-cells greater than 400 per cubic millimeter, that is, did not suffer from AIDS immune depression. At present, the CDC is reserving judgment on the issue of early nervous system involvement in asymptomatic carriers of HIV.

The massive infection of the cells known as oligodendrocytes would imply that the neurons become infected, commented Jay Levy. The evidence is there to indicate that there is "HIV-induced neurological disease even without im-

munological disease."

Jay Levy then discussed the potential reservoirs of the virus. He described experiments in which virus was transferred between T-lymphocytes from the bloodstream and connective tissue cells, known as fibroblasts, which do not possess the so-called CD-4 surface molecule. This is also true of a number of other cells which can be infected by HIV as proven experimentally, including brain tumor cells, such as gliomas and neuroblastomas, osteosarcoma (bone cancer), renal epithelium, and gut epithelium. This shows the existence of other receptors for the virus and indicates that the use of synthetic CD-4 molecules to block infection, as advocated by Dr. Robert Gallo and others, may not prevent infection. The remark was made that there appear to be *no* cells which could *not* be infected with the virus!

One major problem facing researchers is that the virus evolves differently within the same individual, and that some strains are characteristically associated with neurological impairments, while others are more clearly associated with immune dysfunction.

HIV encephalopathy in the U.S.

Robert Janssen presented the CDC survey of HIV encephalopathy in the United States. An HIV encephalopathy case was defined as "a person who was HIV seropositive with disabling cognitive and/or motor dysfunction in the absence of a condition other than HIV infection that could explain the findings. Cases were reported to the CDC from Sept. 1, 1987 when encephalopathy was added to the AIDS case definition, to Dec. 31, 1988."

Over this 16-month period, 1,153 (3%) of the 38,666 adults and 22 (3.3%) of the 666 children (13 years old) were reported to have HIV encephalopathy as their *only* early manifestation of AIDS. Overall, 6.5% of adults and 11.5% of children have HIV. Peaks are among children under 5 and adults over 70 years of age.

Cephalic sensory impairment in neurologically asymptomatic HIV positive patients was presented in posters by Jefferson Katims and DN Taylor, from New York's Cabrini Medical Center, who had the merit of seeking to detect neurological problems in asymptomatic individuals. On the basis of their study, they saw the need for tests to evaluate perception in people with professions in which there was a risk, from pilots and bus drivers, to all operators of heavy machinery. They reported "39 HIV positive individuals (17 asymptomatic, 12 ARC, and 10 AIDS) free of sensory symptoms were tested. . . . Sine wave transcutaneous electrical nerve stimulation was applied biauricalularly to evaluate frequency-dependent noncutaneous perceptions. In addition cutaneous current perception thresholds were obtained from the trigeminal nerve in a painless forced choice procedure of 5 minutes duration. Eighty-two percent of all subjects had measures that differed ($p<0.0001$) from normal. Inability to maintain noncutaneous perception was only observed in the ARC (30%) and AIDS (60%) subgroups."

Summary

What has been known for some time can be summed up as follows:

1) HIV is recovered from the spinal fluid of most patients. HIV strains recovered from spinal fluid and peripheral blood lymphocytes may differ in the same individuals.

2) Ninety percent of AIDS victims suffer neurological damage.

3) Neurological dysfunction increases in severity as the individual progresses from the primary infection to asymptomatic seropositive, to AIDS-related complex, to AIDS; it progress with immunological dysfunction.

4) Pathologies involve the central nervous system as well as the spinal cord and peripheral nerves.

5) These findings are most significant in children, where HIV encephalopathy is more often the first sign of AIDS than in adults.

6) Neurological manifestations of HIV are as common in Africa as they are in the Western industrialized nations.

7) HIV-2 is especially associated with neurological findings.

8) Autoimmune phenomena may be part of the problem.

9) The nature of the relationship between neurological dysfunction and immune dysfunction is as yet unknown.

This should be enough to warrant that fundamental research focus on the neurological pathological effects of HIV, free from homosexual pressure groups trying to pretend that people with severe encephalopathies are "just having normal depressed response to news of HIV infection," or the request that any findings should be correlated with studies on "a blue-eyed homosexual drug addict control cohort," as Dr. Trotot of Pasteur Institute sarcastically commented.

But why are the U.S. Air Force, Dr. MacArthur of Johns Hopkins (whose other colleagues at Johns Hopkins have argued that neurological signs could affect 90% of HIV positives), WHO officials, and the *New York Times* bent on pretending the problem doesn't exist?

As with other aspects of infection by the so-called human immunodeficiency virus, the answer centers around the public health issue of mass testing to detect persons infected with the virus, without which the parameters of the disease—and ability to treat it—cannot possibly be known. In a nutshell, the problem is that if neurological impairment can occur early in the course of infection and can affect psychological and motor performance, then it is essential to know if certain people are affected. Stated more plainly, would you be concerned if the airplane you were on, or the B-1 bomber overhead, was being piloted by someone who was flying with less than a full deck?

If the implications of early nervous system impairment are widely understood, then there is the potential for a groundswell of public pressure which would sweep away the protected status accorded to the virus in the name of "civil rights." It is this which disturbs the cost-conscious bureaucrats at WHO and the *New York Times*.