typically containing some 32 million particles. With each processor in the Connection Machine taking care of several cells, the system can perform roughly 1 billion cell updates per second. A simulation of 100,000 time steps reportedly takes less than 30 minutes and produces results that compare favorably with those produced by traditional numerical integration.

It must be said that there is still considerable room for skepticism about all this. Massive parallelism is a new and relatively untried concept, and it is not at all clear that the Connection Machine will ever occupy more than a specialized niche. Indeed, it was originally conceived as a device for doing artificial intelligence research; only recently have Hillis and his colleagues begun to explore its potential for more general-purpose scientific computing. Furthermore, as a purely practical matter, anyone who wants to use the Connection Machine for general scientific problems will have to do so without the help of the millions of lines of computer code that have already been written in FORTRAN: Thinking Machines currently offers only LISP and C as programming languages.

On the other hand, it is already clear that massive parallelism allows programmers to tackle problems in ways they never would have contemplated before. And as a purely practical matter, programming code developed for the Connection Machine tends to be short, straightforward, and conceptually transparent. "Not having FORTRAN is a short-term disadvantage," says Hillis, "We debated a lot about whether to offer it. But we think these new languages [LISP and C] offer so much more productivity that people will be won over."

Thinking Machines has accordingly targeted this first version of the Connection Machine at sophisticated users who can explore what its possibilities really are. The first machine has already been delivered to the Defense Advanced Research Projects Agency (DARPA) in return for the agency's $4.7 million of support during the development phase. DARPA has also ordered a second machine, and will be using both in its Strategic Computing project. Two other machines are going to MIT, and one apiece to the Perkin-Elmer Corporation and to Yale University.

"This is among the very best of our computer architecture projects," says Steven Squires, deputy director of the information technology office at DARPA. "It's going to push back the frontiers for years to come. People have had many very good ideas that they couldn't pursue just because the computers have been too slow. Now they can." ■ **M. MITCHELL WALDROP**

AIDS-Related Brain Damage Unexplained

Most AIDS patients develop a variety of neurological problems. The most common is a dementia that seems to be caused by the AIDS virus itself

New results reported at two recent scientific meetings indicate that the retrovirus that causes acquired immune deficiency syndrome (AIDS) not only gets into the brain, but also attacks specific brain regions and cell types. Richard Price and his colleagues have evidence that the AIDS virus is most often in white matter and in gray matter deep within the brain. Anthony Fauci, Scott Koenig, and their coworkers find that most of the virus in brain is in multinucleated giant cells that are derived from macrophages.

Price and Tomas Pumarola, of the Memorial Sloan-Kettering Cancer Center in New York, identify some "process-bearing cells," which may include astrocytes and neurons, as containing a protein made by the AIDS virus. But, like Fauci, they see most of the staining in multinucleated giant cells. Price described a new study of 70 AIDS patients at the recent American Academy of Neurology meeting in New Orleans.*

Fauci, Koenig, and Howard Gendelman, at the National Institute of Allergy and Infectious Diseases, identified cell types infected by the AIDS virus in the brains of three AIDS patients. "By in situ hybridization, the multinucleated giant cell was identified as the predominant cell type containing 95% of the viral RNA," according to Koenig. He described one of these patients at the recent meeting of the Association of American Physicians in Washington, D.C.†

"A very large percentage of AIDS patients have neurological problems," says Richard Johnson, of Johns Hopkins University School of Medicine. "The exact incidence is not known, but as many as 60% will eventually develop dementia. About 10% of AIDS patients present neurological symptoms first, including dementia, neuropathy, or opportunistic infections of the central nervous system. These facts are very important when you are talking about therapies. You could suppress viral replication extraneurally and the patient would continue to dement."

The consequences of AIDS in the brain are devastating. In early stages of the disease, many AIDS patients complain of "forgetfulness, a loss of ability to concentrate, mild confusion, and being mentally slow," says Price. In as little time as a few months later, they may be very confused, unable to speak or function independently, and seemingly unaware of how sick they are.

Accompanying these cognitive changes are motor problems such as leg weakness, an unsteady gait, poor coordination, and trouble with handwriting. Many AIDS patients also become apathetic, withdrawn, agitated, or depressed.

The time course over which AIDS patients manifest different aspects of their disease varies greatly among individuals. The usual sequence of events is as follows: infection by the AIDS virus, seropositivity (having circulating antibodies to the virus), AIDS-related complex (ARC), and full-blown AIDS.

Price estimates that out of all the AIDS patients who develop neurological problems, about 10% have neurological symptoms first, before any signs of ARC. Approximately the next 40% show their neurological symptoms after signs of ARC have appeared, but before they have full-blown AIDS. The remaining 50% develop neurological symptoms after they are diagnosed as having AIDS.

Price, Bradford Navia, also of Sloan-Kettering, Eun-Sook Cho of the University of Medicine and Dentistry of New Jersey, and Carol Petito of Cornell University Medical College, studied 70 AIDS patients, 46 of whom were demented. When Price's group examined the brains of these patients, they found only 5 of the 70 that were histologically normal, and those were from nondemented patients.

Typically, the brain of an AIDS patient is shrunken, a change that can be detected in a living patient by computerized tomography (CT) scans. The ventricles, spaces within the brain that contain cerebrospinal fluid (CSF),

*Annual meeting of the American Academy of Neurology, 27 April–3 May 1986, New Orleans, Louisiana.
†Annual meeting of the Association of American Physicians, 2–5 May 1986, Washington, D.C.

are larger than normal because of the atrophy.

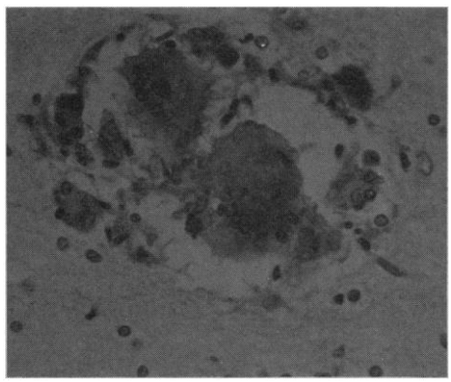
Accompanying the atrophy are "lesions that are confined primarily to white matter of the brain," says Navia. In AIDS-infected brains, white matter, composed of tracts of nerve fibers covered by sheaths of white myelin, does not stain as darkly as it does in a normal brain. The reason for this change is still unknown.

Patients with AIDS often have another white-matter abnormality that affects the spinal cord, called vacuolar myelopathy. "The vacuolization is a bubbly change in myelin tracts in the spinal cord. We think it involves a separation between the layers of the myelin sheath," says Price. This kind of abnormality probably contributes to the leg weakness and other motor disturbances AIDS patients often experience.

Price and his colleagues also find damage to the gray matter deep within the brain, particularly the basal ganglia and thalamus. This is the region in which the Sloan-Kettering group finds a few cells with processes that stain for a core protein made by the AIDS virus. Although Price cannot be completely certain of the identity of these cells, their morphology, size, and the branching pattern of their processes indicate that they may be astrocytes and neurons.

Price's group also finds multinucleated giant cells, abnormal fused clumps of cells, in both gray and white matter. These cellular clumps show most of the staining for AIDS viral protein.

Fauci and his NIH colleagues are able to identify more precisely the cell types in the brain that the AIDS virus infects. They combine a staining procedure, which marks different cell types within a multinucleated giant cell, with in situ hybridization, a technique that detects AIDS viral nucleic acid.



Abnormal cell masses contain the AIDS virus. *Multinucleated giant cells in brain tissue from an AIDS patient. These fused clumps of cells contain the AIDS retrovirus.* [*Courtesy of Anthony Fauci*]

The NIH group reports that 95% of the virus is in multinucleated giant cells, and that most of the cells fused within these clumps are derived from macrophages. This finding contrasts with the localization of AIDS virus in circulating blood, in which the infected cells are T4 lymphocytes.

Even though most of the virus is in multinucleated giant cells, Koenig says "only 5% to 15% of them stain positive for the virus." According to Fauci, the majority of multinucleated giant cells are in the white matter and frontal cortex, whether they contain virus or not.

Price also finds it relatively difficult to find the virus in brain tissue and says that he "can see viral antigen in only about one-third of AIDS patients with neurological problems." Price thinks that this low number of virus-positive brains may reflect the insensitivity of the detection technique rather than a real absence of the virus in patients who clearly have neurological symptoms.

But it does point to one of the major frustrations in research on AIDS dementia. In some patients, the histological changes in the brain that can be seen under a microscope are remarkably subtle, considering the degree of brain atrophy and dementia. As Johnson puts it, "You have a very abnormal brain with only a few histological changes. The brain is losing substance, but you can't tell why."

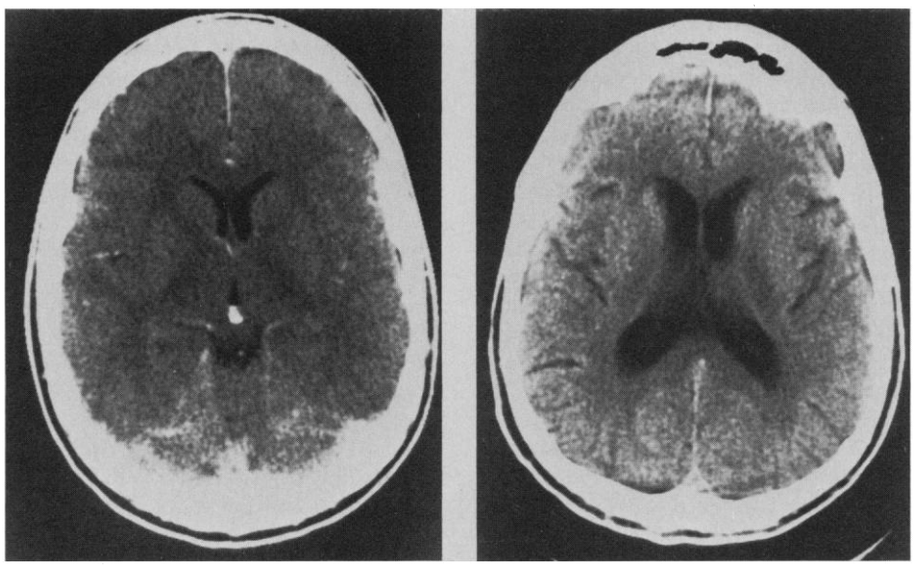
Despite the new studies that correlate changes in the brain with its infection by the AIDS virus, researchers are still at a loss to explain how the virus causes these changes. Johnson raises the possibility that macrophages infected by the retrovirus may secrete a toxic substance that is undetectable in CT scans or in histology sections. The virus does make a protein that causes cell fusion in vitro and in vivo, as evidenced by the presence of multinucleated giant cells.

Finding the mechanism by which the AIDS virus causes dementia will not be easy, even by using animal models. "We are stuck because there is no good animal model for AIDS," says Johnson. "The problem with the AIDS virus is that only chimpanzees get infected. And they do not really get AIDS; they only develop a viremia, at least so far."

The AIDS virus is a lentivirus, a subfamily of the RNA-containing retroviruses that make DNA copies from their own nucleic acid in order to replicate. Ashley Haase of the University of Minnesota says that "another lentivirus, visna virus in sheep, causes central nervous system damage, but in some ways is different from the AIDS virus."

For instance, visna does not infect T4 lymphocytes and suppress the immune system, as the AIDS virus does. Also, the brain damage caused by visna virus appears to be due directly to inflammation, and only indirectly to the virus. "And very, very little of the visna virus is expressed in the brain, even less than the AIDS virus," says Haase.

But there are some obvious parallels between visna and AIDS in brain tissue, making it a potential animal model for studying AIDS infections of the brain. "Visna and AIDS belong to the same subfamily of retroviruses, they are both slow viruses, and both cause a persistent infection of the brain. Furthermore, both infect macrophages that are probably brought into the brain by the bloodstream," says Haase.



CT scans of normal and AIDS brain. *CT scans from the same patient when his brain function seemed normal (left), and 6 months later when he was demented and paraplegic (right). The dark ventricular spaces in the center and the sulci at the rim of the brain enlarge as the brain atrophies.* [*Courtesy of Richard Price*]

Another animal model, mouse leukemia virus, affects the spinal cord without causing much inflammation and causes a vacuolar myelopathy similar to that which occurs with the AIDS virus. But in mice, vacuoles (abnormal spaces) occur in the gray matter, in contrast to the changes in white matter seen with AIDS. Nevertheless, mice may be useful models because, as with the vacuolar myelopathy seen in AIDS, "you see almost a degeneration of the nerve tissue without a lot of specific cell death," says Johnson.

In human AIDS, Price thinks that the localization of virus is "more regional than structure-specific." He does not believe the virus targets one particular area of the brain for attack. Instead, he proposes that, "if the virus comes in through the brain ventricles, then it would be more likely to infect the brain regions around the ventricles," including the deep white and gray matter.

There is no direct evidence that the AIDS virus enters the brain by this route, but the virus can be cultured from CSF. This makes entry through brain ventricles, and the highly vascularized choroid plexus that surrounds them, a possibility. The fact that visna virus in sheep seems to infect ependymal cells in the choroid plexus adds some credibility to this proposal.

Even with the new information, critical questions—how does the AIDS virus enter the brain, exactly what cells does it infect, and how does it cause dementia—are still in very early stages of being answered. Complicating the issue further are the variety of infections to which AIDS patients are susceptible because the virus suppresses their immune response.

A little over a year ago, George Shaw, of the National Cancer Institute (NCI), and his collaborators reported that the brains of 5 out of 15 individuals with AIDS and brain abnormalities had DNA or RNA specific for the AIDS virus. This report indicated that the dementia associated with AIDS may be due to a specific infection of the brain, rather than a secondary effect of other infections that frequently accompany AIDS.

Working independently, Jay Levy and his colleagues at the University of California School of Medicine in San Francisco, and David Ho at Massachusetts General Hospital and his collaborators, cultured the AIDS virus from cerebrospinal fluid and from central and peripheral nervous system tissues of patients with AIDS. These studies added to the evidence that the AIDS retrovirus directly infects the brain.

Lionel Resnick of NIH and his collaborators found that the CSF of 22 of 23 patients with AIDS (21 of whom had neurological symptoms), contained antibodies specific for AIDS virus antigens. Although antibodies from the blood can enter the cerebrospinal fluid, the Resnick group calculated that much of this antibody was made inside the blood-brain barrier, indicating that the virus infected the central nervous system specifically.

It seems likely that researchers will continue to debate whether or not the AIDS virus is neurotropic and attacks brain cells specifically. Price and Johnson think it is neurotropic and Fauci reserves opinion because he has no evidence either way. Perhaps this question can be answered in an animal model or in cell culture.

Price and his colleagues have shown that there is a discernible pattern of neurological symptoms that occurs in most AIDS patients. But the time course of their development varies greatly among individuals and the severity of patients' symptoms does not always correlate well with the extent of detectable abnormalities in their brain tissue. Scientists will continue to wonder if these differences are due to the host, or if the virus itself also varies. ■

DEBORAH M. BARNES

ADDITIONAL READING

B. A. Navia, B. D. Jordan, R. W. Price, "The AIDS dementia complex: I. clinical features," *Ann. Neurol.*, in press.

B. A. Navia, E.-S. Cho, C. K. Petito, R. W. Price, "The AIDS dementia complex: II. neuropathology," *ibid.*, in press.

R. T. Johnson and J. C. McArthur, "AIDS and the brain," *Trends Neurosci.* **9**, 91 (1986).

G. M. Shaw *et al.*, "HTLV-III infection in brains of children and adults with AIDS encephalopathy," *Science* **227**, 177 (1985).

J. Levy *et al.*, "Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms," *Lancet* **1985-II**, 586 (1985).

D. D. Ho *et al.*, "Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome," *N. Eng. J. Med.* **313**, 1493 (1985).

L. Resnick *et al.*, "Intra–blood-brain-barrier synthesis of HTLV-III–specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex," *ibid.*, p. 1498.

The Yin and Yang of Cell Growth Control

There is growing recognition that the development of malignant tumors may owe as much to the loss of growth inhibition as to a surfeit of stimulation

When designing the cell, Nature generally built in a system of checks and balances that allow cellular activities to be closely regulated by opposing stimulatory and inhibitory influences. Investigators who have been trying for the past several years to decipher the mysteries of cancer have concentrated mostly on the forces—such as growth factors and oncogenes—that might actively stimulate the uncontrolled growth of cancer cells. Largely neglected until recently were the inhibitory forces that might check cell division and the development of malignancies.

The increasing interest in research on cell growth inhibition was evident at a meeting, albeit entitled "Growth Factors, Tumor Promoters, and Cancer Genes,"* that was held last month in Steamboat Springs, Colorado. Nearly 20% of the speakers focused on efforts to pin down the factors that might inhibit tumor development. Their results supported what Ruth Sager of Harvard's Dana-Farber Cancer Institute calls the "yin-yang theory of cancer"—meaning that the loss of inhibitory responses may be just as important for unleashing the malignant potential of cells as is activation of the stimulatory forces. In fact, both may be involved, which would be consistent with the view that most cancers develop slowly because several cellular changes are required.

Among the growth-inhibitory substances that are now beginning to attract a good deal of attention is, its name notwithstanding, transforming growth factor, type β (TGFβ). TGFβ, which is a protein, was discovered a few years ago by two groups, one including Harold Moses and his colleagues at the Mayo Clinic in Rochester, Minnesota, and the other including Anita Roberts, Michael Sporn, and their colleagues at the National Cancer Institute

*Some sessions of the growth factor symposium, which was sponsored by Triton Biosciences and the University of California at Los Angeles (UCLA), were held jointly with a concurrent symposium on "Interferons as Cell Growth Inhibitors and Antitumor Factors," which was sponsored by the Schering Corporation and UCLA.