

AZT: Attacking AIDS Early and Hard

The witches in Shakespeare's *Macbeth* assured the Scottish monarch that "Macbeth shall never vanquish'd be until, Great Birnam wood to high Dunsinane hill, Shall come against him." Those assurances rang hollow when Macbeth's enemies marched to Dunsinane under cover of the trees they had cut down in Birnam wood.

Literature and legend often require protagonists to survive by resolving such a paradox. Now, two conflicting reports in the Aug. 17 *NEW ENGLAND JOURNAL OF MEDICINE* pose a paradox to physicians about when they should treat patients with drugs that inhibit HIV, the virus that causes AIDS.

Although the studies, one from a U.S. and one from a European team, present apparently contradictory results on whether early treatment with the drug AZT (zidovudine) prolongs life, new understanding of HIV infection suggests that treating patients within months of infection offers the best chance of stymieing the virus.

Early treatment of HIV infection has a checkered past. In 1990, a U.S. team announced that treating asymptomatic HIV-positive individuals with AZT maintained their concentrations of CD4 cells—white blood cells that HIV destroys. Researchers hoped that high CD4 counts would slow the disease.

But in April 1994, the Anglo-French Concorde study indicated that early treatment with AZT neither prolongs survival nor slows the onset of opportunistic infections. Subsequently, some doctors decided to wait for their patients' immune systems to falter before prescribing AZT.

In 1994, however, researchers reported that giving HIV-infected mothers AZT shortly before they gave birth decreased the risk of passing HIV to their newborns (*SN: 2/26/94, p.134*). This finding bolstered the theory that treating HIV with antiviral drugs early on could hold off disease.

The new results seem to reinforce the Concorde findings. The researchers found that people who take AZT after a long disease-free period, when their CD4 counts are still high—around 700—lived no longer than people who initiated therapy when their immune systems began to weaken, as indicated by CD4 counts of less than 500.

The European researchers, on the other hand, treated patients so early in their infection that they had not yet developed antibodies to HIV. Study collaborator Luc Perrin of Geneva University Hospital in Switzerland notes that

most participants suffered from an HIV-associated flulike illness known as anti-retroviral syndrome, which may strike when a person is first infected and often heralds a poor prognosis.

Perrin and his colleagues found that starting AZT within 3 months of infection decreased the number of minor HIV-associated infections and kept CD4 cell counts up. The researchers don't know whether the drug will result in longer survival, but they point out that they are hitting the disease at a vulnerable stage.

"We [need] a very strong antiviral effect early in the infection," says Sabine Kinloch-de Loës of Geneva University Hospital. It won't cure these patients, but "it could change the prognosis."

During the earliest period of infection, HIV replicates rapidly. It mutates fre-

quently as it reproduces, which helps it to evade the immune system and become resistant to retroviral drugs like AZT, 3TC, and protease inhibitors.

Any HIV-infected person carries a swarm of different strains, "but a person is initially infected with [only] a few types of viruses," says Perrin. The limited variety of HIV at this point makes it more susceptible to drugs. The researchers advocate early treatment, preferably with combinations of antiviral drugs.

Steven Schnittman of the National Institute of Allergy and Infectious Diseases in Bethesda, Md., supports the European strategy. "The only way to really know is to look at the patients in the long run," says Schnittman. "But it is the most promising thing we have seen" for early infection. —L. Seachrist

Sometimes a bigger brain isn't better

Researchers have little understanding of the brain malfunctions responsible for autism, a neurological disorder characterized by repetitive behavior, decreased language skills, and an inability to form social relationships. But a new finding—that autistic men have larger-than-average brains—suggests that a problem in early brain development leads to the condition. This points scientists toward possible faults in genes responsible for that development.

Joseph Piven and his colleagues at the University of Iowa College of Medicine in Iowa City used magnetic resonance imaging (MRI) to scan the brains of 22 autistic males ranging in age from 13 to 29. MRI provides snapshot "slices" of the brain at specific depths, and scientists can reassemble these to form a three-dimensional picture.

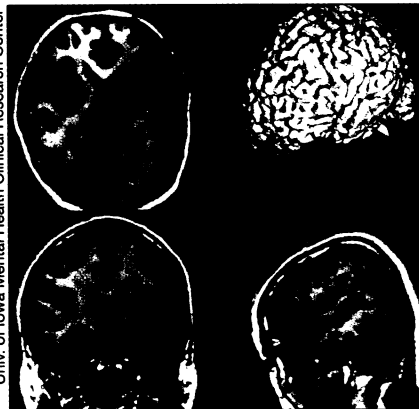
From these reconstructions, the researchers calculated the total volume of the brain, as well as the volume of brain tissue and of the lateral ventricles, structures that contain cerebrospinal fluid. The group reports its findings in the August *AMERICAN JOURNAL OF PSYCHIATRY*.

The large brain volumes indicated by these MRI scans support previous research showing that autistic people have larger head circumferences and heavier brains than average, says Margaret Bauman of Massachusetts General Hospital in Boston.

Piven's group suggests three possible reasons for the increase in brain size during development: more neuron growth, less neuron death, or

more non-neuronal brain tissue.

No one can speculate about the relationship between larger brain size and autism until scientists determine which regions of the brain are enlarged in people with the disorder.



Magnetic resonance images and a full three-dimensional reconstruction of an autistic brain.

Recent studies indicate that as many as 1 in 1,000 people may be autistic, says Fred Volkmar of the Yale University Child Study Center. Studying autism is difficult because people with this condition can have a range of IQs and language skills. Inconsistent diagnosis made other MRI studies contradict each other, he says.

"In this case, the study was very well done, the patients were well characterized, and the important thing now will be to see if other people find it as well," Volkmar says. —C. Wu