a way that you're not going to get a reliable answer out of it," she says. "It raises false hopes and you run the risk of telling people that a treatment isn't any good when it is, or telling them it's good when it isn't."

In the case of ddI, a nucleoside analog that blocks HIV replication, nobody knows just how good it is; the drug is only now moving into large-scale clinical trials to find that out. Last week, however, the federal government announced that it would be made available to some AIDS patients even while the clinical trials are taking place.

The idea is that patients who have severe side effects from azidothymidine (AZT)—and thus could not enter the next stage of clinical trials, which will compare ddI and AZT—can be prescribed ddI. Physicians will also be able to give the drug to patients who have failed to improve with AZT treatment. But just how physicians can make an intelligent decision without much information on the drug is an open question (see box).

The statistical group is working out ways to glean information about ddI from those receiving the drug outside the formal clinical trial. Working group chairman Green says it may be possible to design low-tech trials, coordinated through community-based clinics, that can yield important information about a drug's effectiveness. And when more than one antiviral drug becomes available under parallel track, Green speculates that it may be possible to design simple trials to see which drug is working better. The primary advantage of such low-tech trials is that data can be collected rapidly. "The faster we can collect valid data, the better off everybody is," he says.

Parallel tracking poses its own ethical problems. "We have to be realistic and realize that that is going to increase the risk of toxic side effects," says Fauci. "If you want to get the drug earlier to people, they've got to understand that the risk of toxic side effects is going to increase proportionately to the time that you give it earlier." Indeed, ddI phase 2 trials were being redesigned as recently as 2 weeks ago as new toxicity information from the phase 1 trials was evaluated.

While the statistical working group will consider changes in the way trials are conducted, there are some principles that appear inviolable. The integrity of the randomized clinical trial must be maintained because "that's our fastest way of getting reliable knowledge," says NCI's Byar. "No one spoke against that principle. In fact several people said that if the parallel track got in the way by screwing up recruitment, then too bad for the parallel track."

■ JOSEPH PALCA

AZT Reverses AIDS Dementia in Children

Promising, though early, studies in children stimulate ideas about basic research on autism and Alzheimer's dementia

CHILDREN WITH AIDS too often lose their minds. AZT can make them better.

Although it does not cure this ultimately fatal disease, AZT, along with two newer AIDS drugs, has the power to reverse dementia in children. And by blocking replication of the AIDS virus, these drugs occasionally reverse AIDS dementia in adults as well.

These findings drew attention when they were reported at a recent NIH meeting of AIDS experts. They indicate that HIV, the human immunodeficiency virus that causes AIDS, does not necessarily cause irreversible brain damage, as many researchers had supposed. Moreover, researchers are beginning to ask whether these clinical observations mean anything for studies of dementia in general—ranging from autism in children to Alzheimer's in the elderly. "What we're seeing in children may lead us to some very important basic understanding about the way the brain is affected by disease," Philip A. Pizzo, chief of pediatrics at the National Cancer Institute (NCI), said last week in an exclusive interview with *Science*.

The signs of AIDS dementia in children are clear and, Pizzo says, "very painful to watch. Very young children lose words." Words like "mommy" and "daddy" and "bear" are too hard to remember as the AIDS virus multiplies in the young child's body and penetrates the central nervous system.

An 8-year-old boy, once normal, was rendered practically autistic by HIV, Pizzo said. He stopped speaking. Asked to trace a simple outline of an elephant, the boy could not. Painfully, he knew what a simple task it was, and he knew he was failing it. But he could not cry even though his doctors could see tears welling up in his eyes.

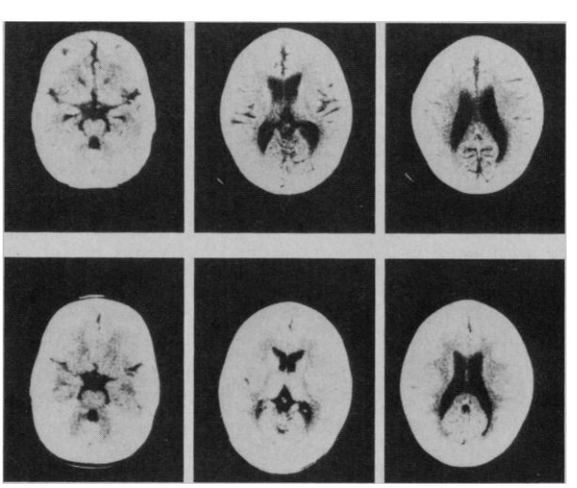
Pizzo has seen children lose IQ points—one boy lost as many as 28—as AIDS ravages their brains. "Kids who used to do well in school really deteriorate," says Pizzo who has "before and after" IQ data from school-age children.

But in a series of remarkable studies, Pizzo has seen AZT (azidothymidine) reverse these symptoms. The child who lost words like "mommy" and "daddy" "got them back," Pizzo says. The boy who lost IQ points is restored to his former capacity. The 8 year old cries. After just a couple of weeks of continuous AZT therapy, the boy who could not trace an elephant is successful at tracing a horse.

NCI director Samuel Broder showed those dramatic tracings to AIDS researchers at Robert C. Gallo's NCI lab meeting a few weeks ago. "You don't have to be a genius to see that this drug works," he said.

Among the audience, thoughts turned immediately to Alzheimer's—the terrible dementia that afflicts more than 2 million elderly Americans. "Why not try AZT in Alzheimer's patients?" asked immunologist David H. Katz, president of the Medical Biology Institute, a biotechnology company in La Jolla. Persuaded that such studies make sense, Katz is already talking with colleagues at the University of California at San Diego about a clinical trial.

"Phil Pizzo's work with kids may be telling us something important about the mechanism behind other kinds of dementia," said NIH AIDS chief Anthony S. Fauci after listening



CAT scans *show abnormal brain metabolism (upper scans) that is improved after AZT therapy (lower panels).*

to Broder's talk. "Maybe this is telling us more clearly than we thought that the virus is damaging the brain because it puts out a toxin of some kind. Maybe dementia is a metabolic problem. These questions are worth exploring."

Pizzo already has thoughts of trying AZT in autistic children and is about to launch a collaborative program with researchers at the National Institute on Aging who have considerable experience studying the dementias of adults.

Pizzo, who is both a pediatric oncologist and infectious disease specialist, has been treating children with cancer for more than 15 years. Neurological examination of the children—including tests of motor and mental function—have been a part of his lab's work. So, when he and his colleagues began studies of children with AIDS, a thorough and ongoing neurological assessment was built into the routine. Evidence of AIDS dementia and its reversal shows up not only on standard neurological measures but also on CAT scans and PET scans which show metabolic abnormalities in the brains of demented patients—both children and adults.

Now, studies often include AZT in combination with one or the other of two newer AIDS drugs—dideoxyinosine (ddI) or dideoxycytidine (ddC). The Pizzo team has evidence not only of obvious improvement that occurs when a child regains the use of words, but also has detected a much subtler, totally unexpected, but nonetheless real effect of the drugs.

"Some children who appeared to be free of neurodevelopmental defects before be-

AIDS Drugs Remain Unavailable for Kids

Even as the Food and Drug Administration breaks precedent by approving promising drugs for use by AIDS patients before the test results are in, one category of patient has been left out in the cold: children. And that's especially heart-rending, considering the preliminary results achieved by Philip A. Pizzo at the National Cancer Institute over the past 2 years.

There, children whose brains had been ravaged by the AIDS virus were returned to near normality for months at a time by taking AZT, which has the capacity to reverse AIDS dementia. But take the same child in, say, an urban ghetto or a small town far from a research center, and AZT is generally not available. Even if a clinician were to prescribe AZT, which can cost up to $4000 a year, no insurance company will pay for it. Why? Because it hasn't been approved by the FDA for use by kids. "The irony now is that an asymptomatic mother can get AZT for herself but she can't get it for her symptomatic child," Pizzo noted.

Recently, physicians at NCI have mounted a campaign to speed AZT through the approval process and maybe change the way the regulatory system deals with pediatric drugs in the process.

Currently, drugs for children must go through their own tests for safety and efficacy; data from tests in adults are not simply extrapolated to the young. One consequence of this is that if a manufacturer does not see a large market in children, the necessary tests for pediatric use may not be done. That, NCI researchers say, is what has happened to AZT. It is also the case with two newer AIDS drugs—ddI (dideoxyinosine) and ddC (dideoxycytidine).

"There is no doubt that these agents are useful in kids," NCI's chief pediatrician Philip A. Pizzo told *Science*. "But they haven't been approved. We get dozens of calls from people who want us to supply them, but we cannot," he said. AZT has been approved not only for adults with AIDS but, just recently, for adults who are infected with the AIDS virus but who have no symptoms.

NCI director Samuel Broder, a pioneer in AZT research, thinks that this may be a good time to make the case that drugs should be available for children sooner. It may be sufficient, he and others now argue, to require safety data alone as the criteria for approving adult-tested drugs for use in children with certain life-threatening diseases.

A spokesman for Burroughs Wellcome, manufacturer of AZT, reports that the company is "working as fast as it can" to get its pediatric data submitted to the FDA. But that claim is disputed by AIDS physicians who are anxious to get the issue resolved.

Burroughs Wellcome is also under attack these days for the high cost of AZT. Until the company announced a 20% price reduction several days ago, a year's worth of AZT therapy came in above $6500 a patient for a standard dose of 12 capsules a day. Because most AIDS patients are neither wealthy nor covered by medical insurance, the federal government has been picking up much of the cost. With the recent decision to give AZT to asymptomatic individuals, the potential cost of AZT to the taxpayers promises to escalate.

In this context, Burroughs Wellcome has been roundly criticized for charging $1.50 a capsule for AZT. One complaint is that because NIH researchers, including Broder, contributed substantially to the development of the drug, the company does not have a valid excuse for setting the price so high.

Burroughs Wellcome clearly resents the accusation that it is milking the public. In a letter to the *New York Times* that ran on 16 September, company president T. E. Haigler, Jr., minimized the NIH's role. Haigler declared that it was Burroughs' scientists who first recognized AZT's potential as an anti-AIDS drug and said that Broder's role was simply to "confirm" that the drug was active. Haigler noted that Burroughs paid for the pivotal clinical trial that NIH conducted and said that, were it not for the company's efforts, "there would have been no treatment for desperate patients" as early as 1986.

Haigler's letter plainly infuriated Broder who fired back a reply that is uncharacteristically blunt for a government servant. In a letter published in the *Times* on 29 September, Broder and coauthors called Haigler's letter "astonishing in both substance and tone." Broder said, "there are few drugs now approved in this country that owe more to government-sponsored research" and proceeded to list a series of things that Burroughs "did not do" along the road to marketing AZT. "Indeed," he charged, "one of the key obstacles to the development of AZT was that Burroughs Wellcome did not work with live AIDS virus nor wish to receive samples from AIDS patients."

Here is a case of an academic (NIH)/industry collaboration gone awry. There are indications that Congress, which after all approves the AIDS budget, may look into the dispute.

Meanwhile, the FDA has just announced approval of ddI, a second-generation AIDS drug, for tests comparing it with AZT and for patients who can no longer tolerate AZT, which is toxic to bone marrow. For now, ddI manufacturer Bristol-Myers will give it free to patients who do not have the resources to buy it. But who will approve ddI for kids who are not enrolled in a study like the one at NCI? The question remains the same. ■ **B.J.C.**

ginning AZT, and whose pretreatment testing placed them in the 'normal' IQ range, also had significant increments in their IQ scores after beginning continuous infusion of AZT," Pizzo reported recently in "AIDS updates."* The findings suggest, he says, that subclinical brain damage may be an early manifestation of AIDS. The catch is one cannot spot the damage until there are signs of its repair.

Why does HIV injure the brain? Many hypotheses have been put forward. Some postulate that HIV stimulates production of toxins, or cytokines, or chemotactic factors that impair neurons and glial cells. Others propose that HIV is able to infect neurons and glial cells directly. The fact that these symptoms can be reversed suggests that "factors other than direct cellular damage by the virus" play a key role, Pizzo has reported.† If true, this is good news clinically. If you can stop a virus from making a product that destroys the brain, you can protect the brain even though the virus may not be completely wiped out.

This is what appears to be going on indirectly with AZT. The drug inhibits the reverse transcriptase enzyme that HIV needs to replicate. Studies have shown that HIV can be found in the brains of children and adults with AIDS dementia, and data from adults support data from children that if you can suppress the virus you can control (or at least modify) the neurological damage. Richard W. Price and his colleagues at the Sloan-Kettering Memorial Hospital in New York published a review of the data from adults last year in *Science*.‡

Although the infecting virus is the same, the course of AIDS is different in children and adults—the onset of dementia being one of the more notable. In adults, dementia is usually a late-stage complication; in children it shows up very early on.

"The way we give AZT or other antiretroviral drugs may be crucial," says Pizzo, who advocates continuous infusion or sustained-release capsules for children and adults because the drug has a short half-life and has to be taken every 4 hours, round-the-clock. A steady state of drug keeps the virus at bay. Low levels of virus mean minimal levels of toxin production, which means maximum protection for the brain. Continuous infusion through an implanted device has long been used for cancer therapy. Sustained-release is common in cold capsules.

But the good news about AZT must be seen in context with the bad. Although AZT can reverse dementia, there is no evidence that it can cure AIDS. Ultimately, the children die. Furthermore, AZT's toxicity puts limits on its use; eventually the dose must be reduced or stopped altogether. The brain again becomes vulnerable to HIV and dementia returns. One of Pizzo's longest success stories is that of a hemophiliac who contracted AIDS from a blood transfusion. For 2 years, AZT kept him intact. At one point so mentally debilitated that he could not go to school, AZT therapy enabled him to resume the life of a normal 12 year old. But when AZT finally took its toll on the patient's bone marrow and the AZT dosage had to be reduced, the boy deteriorated. In the end, he died.

"It leaves you feeling terrible, like you failed," Pizzo says. "But we've learned from parents that even if we cannot save their children, it is crucial that we reverse the dementia at least for a while. Parents tell us that it has given them a chance to say 'goodbye' to their child and that they are grateful for that." ■ **BARBARA J. CULLITON**

ADDITIONAL READING

*"Therapeutic considerations for children with HIV infection," *AIDS Updates* (May/June 1989).

†"Human immunodeficiency virus infection in children," *J Pediatr.* **114**, 1 (January 1989).

‡"The brain in AIDS: Central nervous system HIV-1 infection and AIDS dementia complex," *Science* **239**, 586 (5 February 1988).

Hope for AIDS Vaccines

Yverdon les Bains, Switzerland

Pessimism about the prospects for a vaccine against HIV infection is giving way to guarded optimism. That, at least, is the opinion of Gordon Ada, chairman of the World Health Organization's Programme for Vaccine Development, after listening to a group of leading AIDS researchers discuss their latest results at an international meeting here. The gathering was organized by the Institut de la Vie, a Paris-based foundation.

Although no one approach to vaccine development is yet ready to sweep the field, there are several lines of research that, taken together, are producing the recent optimism. In fact, some new approaches are moving along so well that Ada is worried that older, less fashionable approaches may be overlooked.

A radical idea for a genetically engineered live HIV vaccine is being pursued, but testing might pose a problem.

One of the most welcomed talks at the meeting came from Dino Dina, director of virology at Chiron Corporation in Emeryville, California. Dina presented promising data from a trial in human volunteers of a vaccine consisting of one of the outer proteins of human immunodeficiency virus (HIV) grown in yeast cells.

Tested on people, it produced no side effects other than what Dina described as "mild stinging pain" that generally vanished after a few hours. While he is withholding full details until publication, Dina told *Science* that "results . . . indicated that the vaccine was safe and induced T-cell immunity."

A promising result in animals that had the meeting participants buzzing comes from the New England Regional Primate Center (*Proc. Natl. Acad. Sci. U.S.A.*, 2 August, p. 6353). Trials there tested killed simian immunodeficiency virus. Normally, SIV isolated from African monkeys causes severe illness and death when injected into Asian macaques. But a group of macaques immunized with disrupted SIV and then injected with live virus has not yet come down with simian AIDS.

"So far it looks like delayed disease, not success yet," commented Robert C. Gallo of the U.S. National Cancer Institute. "Maybe next year all the animals will get AIDS." But Dani Bolognesi of Duke University Medical Center reminded Gallo that "some of those experiments with killed virus also protected against infection, and that is something. We don't know what, but we have to find out."

Researchers at the meeting generally agreed that the most exciting animal model for testing candidate human vaccines is the so-called scid-hu mouse. These mice suffer from a genetic disease called severe combined immune deficiency, scid, which leaves them open to opportunistic infection, much like AIDS patients. But by transplanting human immune cells into them, they gain some human immune responses. They become, in effect, a living in vitro system, where the mouse is the test tube with its cargo of human cells.

Gallo, however, remained skeptical: "It's not much different than having a test tube," he said. Other researchers were more supportive. If SyStemix, a California company working with scid-hu mice, can put the complete human immune system into the scid mouse, it will open the door to much more thorough testing of potential vaccines.

Despite the apparent good news from inactivated viruses, Ada pleaded for scientists to focus on live vaccines, pointing out