AIDS Drug Trials Enter New Age

Although some inviolable rules remain, government biostatisticians have decided it is time to reevaluate conventional wisdom when it comes to testing drugs for AIDS

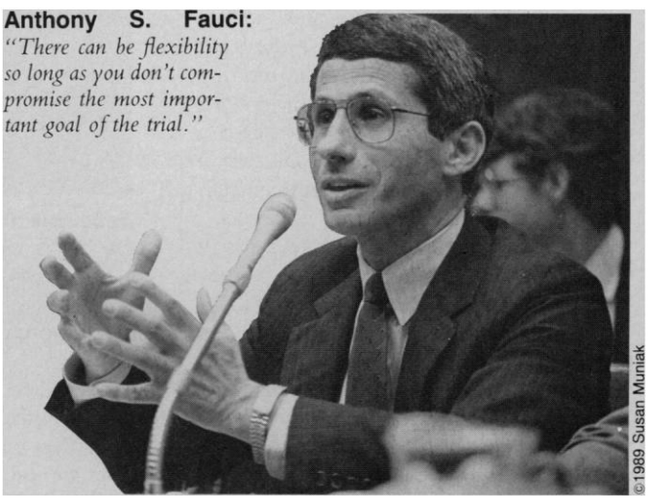
The past few weeks have seen major changes in the regulation of AIDS drugs and promising results in vaccine research. The following five articles describe these events and their implications.

WHEN the Department of Health and Human Services announced last week that the experimental AIDS drug dideoxyinosine (ddI) would be made widely available with less than 100 patients having been evaluated for long-term toxicity, it became clear to the world that AIDS activists had managed to bring about a major change in the way the government approves drugs. But away from the bright lights and television cameras, an alliance has developed between the activists and a small group of statisticians employed in key federal agencies. Together, they are considering changes that cut to the very core of how clinical trials are designed. If they succeed, they will institute a process that could go well beyond the treatment of AIDS, altering the way medical research deals with other life-threatening diseases.

Considering the stakes involved, this work is taking place in a remarkably nonconfrontational way. Says Dan Hoth, director of the division of AIDS at the National Institute of Allergy and Infectious Diseases: "No big government meetings or blue ribbon panels. It's just people at the working level, statisticians and clinicians, working together." Susan Ellenberg, chief of the biostatistics research branch at NIAID, adds: "I certainly have no guarantees that we're going to turn clinical trials inside out, but there may well be better ways to do things."

Ellenberg's comments reflect a consensus among her colleagues that it should be possible to design trials that will produce statistically valid data while providing promising drugs to as many AIDS patients as possible. This unassuming, though revolutionary idea has emerged quietly out of the rhetoric and bombast that grabbed headlines last June in Montreal (see *Science*, 16 June, p. 1255). Ellenberg credits a document called "A National AIDS Treatment Research Agenda," which was released at the international conference on AIDS in Montreal by the AIDS Coalition to Unleash Power (ACT UP), as having opened her mind to new possibilities.

"All I knew about ACT UP at that point were people coming to meetings and yelling and screaming and saying awful things about people who worked for the government," she says. But "I looked at this very detailed, multipage, single-spaced document and I got very excited about it."



Anthony S. Fauci: *"There can be flexibility so long as you don't compromise the most important goal of the trial."*

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The ACT UP agenda spells out principles for conducting clinical trials: involving people with AIDS in trial design, greater emphasis on drugs for opportunistic infections, more flexible protocols, broader entry requirements, avoidance of placebos, and criteria other than body counts for judging whether drugs are effective.

"I thought this document needed to be addressed, and I thought statisticians needed to address it," says Ellenberg.

And this has in turn forced them to face a basic question: What is the purpose of clinical trials? Activists have argued that they should be viewed as a means of delivering experimental therapy to dying patients. But, while researchers want to help patients, that's not the primary goal of a clinical trial.

"It's not to deliver therapy. It's to answer a scientific question so that the drug can be available for everybody once you've established safety and efficacy," says Anthony S. Fauci, director of NIAID. "I think there can be certainly some flexibility in that so long as you don't compromise what really is the most important goal of the trial."

The search for flexibility is being undertaken by a special working group organized by Ellenberg that will consult with the AIDS Clinical Trial Group (ACTG). The ACTG was established by NIAID in 1986 and is a consortium of federally sponsored centers that are carrying out trials of drugs for AIDS and related opportunistic infections. Some 8000 patients have now been enrolled in ACTG-sponsored trials in 46 centers around the country, and next year's budget request stands at $101 million for the program.

The working group has set up two subgroups: One, to be headed by Sylvan B. Green, a senior statistician at the National Cancer Institute (NCI), will focus on trial design issues. The other, which Ellenberg will head, will look at the so-called parallel track program that is to make experimental drugs like ddI available to patients outside of clinical trials.

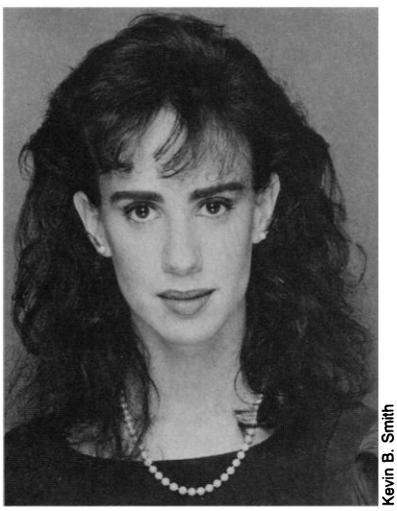
One of the issues most upsetting to activists is how to judge when a treatment designed to prolong life is working. The traditional way to determine this is to compare the rate of some clinically relevant event in a group of patients taking an experimental drug with a control group taking a placebo or a different drug. "Death is the [end point] that ultimately matters" for a drug intended to improve survival, says David P. Byar, chief of the biometry branch of the division of cancer prevention and control at NCI, who chaired the last meeting of the working group on 13 August. "Anytime you're not studying death you're studying a surrogate marker which does not perfectly predict the future."

But activists maintain that this is unethical. "Even if you have a supply of compliant martyrs you have to infuse your trials with some ethical validity," says Rebecca Pringle Smith of New York's Community Research

Initiative who attended the August meeting as a representative of ACT UP. Smith believes that a constellation of so-called surrogate end points—clinical markers of immune state or measures of the presence of virus or viral antigens in the blood—should be used in place of death rates to determine whether a particular drug is working.

Interest in surrogate end points is in fact running quite high among clinical researchers. The Institute of Medicine's round table for the development of drugs and vaccines against AIDS hosted a forum on the topic last month. The consensus at the meeting was that the most promising indicator for predicting the course of the disease in a particular patient is the level of CD4 cells in the blood. CD4 cells are the immune cells that the AIDS virus preferentially targets.

But statisticians like Stephen Lagakos of the Harvard School of Public Health argue that, while surrogate end points such as CD4 levels could play an important role in the design of clinical trials, they should be treated with caution. Lagakos points out, for example, that even if a drug raises a patient's CD4 counts the levels may still be too low to improve chances of survival. Ellenberg agrees, but notes that a surrogate marker might be used in conjunction with a clinical symptom in evaluating the progress of a trial.



Kevin B. Smith

Activist Rebecca Smith: *"Even if you have a supply of compliant martyrs, trials must have some ethical validity."*

If using surrogate end points is still problematic, Byar feels immediate changes can be made in the way patients are deemed eligible to enter clinical trials. "I think there's been too narrow and unimaginative a view about how the trials should be carried out." For example, to avoid skewing the results, patients taking prophylactic treatments for opportunistic infections—such as aerosolized pentamidine to prevent pneumocystis pneumonia—are excluded from many trials. But Byar says that if subjects are randomly assigned to treatments, the trials are still amenable to traditional statistical analyses.

But even if enrollment criteria are broadened, clinical trials for AIDS are still likely to be plagued by a serious problem: many patients fail to comply with the protocols. In some cases patients have had the pills they are taking tested to see which drug they've been given, and if they are getting a placebo or a treatment they consider unsatisfactory, they drop out. Smith says that if trials are designed in a way that patients consider ethical, for example, comparing different doses of a drug already shown to work, or comparing two drugs instead of one versus placebo, then they'll be more willing to comply with them. "Noncompliance can be used as a surrogate marker, if you will, for the extent to which you've been able to infuse your trials with some level of ethics."

But Ellenberg counters that there are many ways to slice the ethics issue. "I've heard people say very strongly that the most unethical thing you can do is to run a trial in

A New Antiviral Drug: Promising or Problematic?

Although making ddI available on an accelerated basis has won approval from AIDS activists, there is now growing concern that there may be a backlash if the drug turns out to be more toxic than expected. To make matters worse, researchers have had a hard time getting what little toxicity data there are on ddI because they have not been published.

"Here's a drug that they're ready to start distributing to everyone in the world, and there's no toxicity data on it," says Howard Liebman of Boston University Medical Center, who conducted phase 1 trials sponsored by ddI's manufacturer Bristol-Myers. "Everybody wants to know what's going on. I'm being asked to speak and I'm trying to contain my data so that I don't threaten its integrity for a peer-reviewed journal."

Margaret Fischl of the University of Miami School of Medicine, who chairs one of the trials on ddI, says a two-page newsletter is being prepared that will go out this week describing some toxic side effects associated with the drug. Fischl says journal editors are aware of the need to get public health information out rapidly and are being flexible about publishing papers with data that have already been sent out to physicians.

So far, the chief side effects seen are pancreatitis and severe pain at the extremities. But these may not appear right away, and this causes Fischl to worry about making ddI widely available. Other toxicities are bound to show up only after wider experience with the drug. She points out the anemia associated with AZT didn't appear until well into phase 2 trials.

"There may only be eight or ten people [enrolled in phase 1 trials] who are receiving doses that will actually be used in phase 2 trials," says Fischl, and only so much information can be gleaned from such a small number.

Things are moving so fast with AIDS drug development that communication of results is becoming a severe problem. This summer, government health officials halted a trial of AZT for symptomatic, HIV-infected patients whose CD4 cell counts had dropped below 500. Patients who had been receiving placebo in the trial were offered AZT as the appropriate therapy.

But a complete report of this trial has still not been published, leaving people to speculate on how the government reached its decision. This is especially a problem for researchers in England and France who are conducting a trial that is extremely similar to the one that was stopped in the United States. Government scientists have not been willing to share their complete data with the European scientists, and according to Stephen Lagakos of Harvard University who analyzed the AZT study, part of the reason is to avoid jeopardizing publication in a journal that has strict rules about prior publication of results.

"I think we're in an impossible situation here," says Ian Weller, chairman of the U.K. working party for the joint British/French study. Weller says U.S. officials have provided some data beyond what was released to the public, but it hasn't been enough to make a decision about whether to halt the trial. A team of U.S. health officials is scheduled to travel to London within the week to give further information to Weller and his colleagues.

But for the moment, Weller can only sit tight. "I think it would be very unwise to either change clinical practice or alter a trial on what is really a press release," he says. ■ **J.P.**

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.

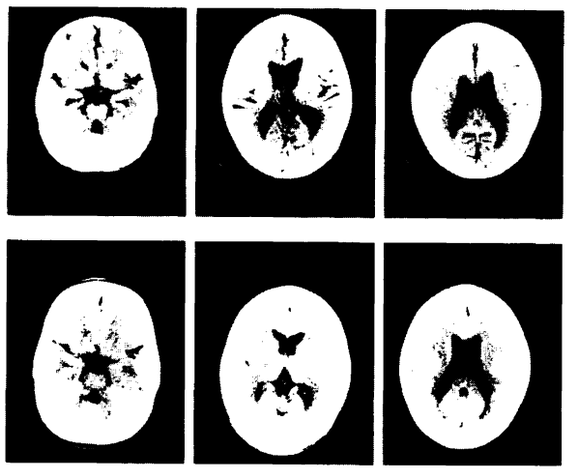
Pizzo has seen children lose IQ points—one boy lost as many as 28—as AIDS ravages their brains. "Kids who used to do well in school really deteriorate," says Pizzo who has "before and after" IQ data from school-age children.

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).*