Trials and Tribulations of AIDS Drug Testing

Reports of excess deaths among patients taking an experimental drug and new testing of Compound Q have raised a furor

THE SWITCHBOARD at the AIDS program office of the National Institute of Allergy and Infectious Diseases was jammed last week with calls from terrified AIDS patients. A front-page article in *The New York Times* on 12 March proclaimed that people taking dideoxyinosine (ddI), an experimental new AIDS treatment, were dying at an alarming rate. AIDS program officials spent hours on the phone calming callers' fears. True, they explained, the death rate was high, but not unexpectedly so, given the fact that most of the patients taking the new drug were already desperately ill before they began the treatment.

The flap over ddI, and another that erupted a few days earlier over the experimental therapy known colloquially as Compound Q, were pointed reminders of how efforts to make experimental AIDS therapies quickly available can create new sets of problems.

Take the decision to make ddI widely available outside controlled clinical trials. Last fall, when clinical trials of ddI began, federal health officials announced that the drug would be made accessible to people who either could not get into the trials or whose condition could not be helped by azidothimodine (AZT), the only antiviral drug currently approved for treating AIDS. Like AZT, ddI interrupts a key step in the AIDS virus's genetic machinery, but it has been touted as having far fewer side effects (see *Science*, 28 July 1989, pp. 353 and 412). By broadening access to the drug, officials were hoping, in part, to head off a stampede for participation in the trials.

There certainly was no stampede. According to data from ddI's manufacturer, Bristol-Myers, more than 8000 patients are receiving the drug through the expanded access program, while only about 700 are taking it as part of a clinical trial protocol. One likely explanation: Patients want to be certain to receive ddI, rather than enter a trial and risk getting AZT, the drug against which ddI's performance is being compared.

Critics of the expanded access program have warned that not enough was known about ddI's safety to make it widely available, and the news about the death rate appeared to confirm their fears. The rate from all causes was much higher among patients receiving ddI through the expanded access program than in clinical trials. As of 23 February, 290 patients had died in the expanded access program compared with 15 who had enrolled in clinical trials, according to Bristol-Myers.

Put like that, expanded access looks like a disastrous mistake. So why aren't officials rushing in to stop the program? Because, as Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, puts it, they knew all along there could be problems with the drug, so they made explicit rules for who could get it outside clinical trials: "Expanded access is for people who do not have standard therapy available for them and cannot be in the clinical trial, either because of inconvenience, undue hardship, or inability to fulfill the criteria for entering the clinical trial." In other words, expanded access was for patients in extremis who had few, if any, options. "All early indications are that the vast majority of those cases are due to the severity of the illness itself," says Fauci.

Six people taking ddI did apparently die from one of the drug's toxic side effects. The deaths were related to pancreatitis, a previously discovered problem with ddI. Five of the deaths were among patients getting the drug outside the clinical trials. For now, the trials and the expanded access will proceed, until it becomes clearer that ddI is truly effective—or truly dangerous.

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—Sandoz V.P. David Winter

The painful history of the AIDS therapy known as Compound Q, a protein extracted from the root of an Asian tuber, is another example of the difficulties of testing new AIDS drugs. A study presented in the *Proceedings of the National Academy of Sciences* (April 1989, p. 2844) last year reported that in laboratory experiments, the purified plant protein tricosanthin, dubbed GLQ223, inhibited viral replication in two kinds of infected immune cells, T cells and macrophages. Last spring the FDA gave Genelabs, the maker of GLQ223, permission to begin a phase I toxicity trial in patients.

But at the same time, Project Inform, a consortium of local physicians in the San Francisco area, was conducting an unauthorized trial of Compound Q. Since Project Inform conducted its trial without FDA approval, the agency took steps to halt it. Project Inform said they had finished anyway and suspended the trial last summer. But earlier this month, the agency announced it was giving Project Inform permission to resume the trial. And Sandoz, the Swiss pharmaceutical company that holds a license from Genelabs to market GLQ223, will provide $250,000 to pay for the testing. "It's clear that we're going about this in a somewhat unorthodox way," says Sandoz vice president David Winter, "but the enormity of the problem is such that more innovative approaches are quite justified."

But critics of Compound Q and Project Inform voiced disapproval of the FDA's action. By not reprimanding Project Inform for conducting an unauthorized trial, FDA is sending a message saying "anybody can do whatever they want to people with HIV infection and AIDS," says Donald Abrams of San Francisco General Hospital and a member of an FDA advisory committee on new antiviral drugs. In addition, Abrams and others say the data supporting compound Q are weak. Indeed, the AIDS clinical drug development committee of NIAID decided late last year not to recommend starting an NIAID-sponsored trial of GLQ223 until the in vitro work had been replicated and there was evidence that it was possible to reach adequate concentrations of the drug in vivo.

Winter is not especially concerned about the failure to replicate the laboratory findings: "One hallmark of work in this field has been the capriciousness of a number of in vitro tests. Unless conditions are exactly right, it is not at all unlikely for difficulties to be found in reproducing results."

And Martin Delaney, head of Project Inform, says his group's interest in Compound Q is based not solely on the drug's possible effectiveness, but also on the fact that people in the AIDS community were already using it. "When drugs come into common use in the community, something faster than the standard clinical trials process needs to look at the safety of what people are doing," he says.

Right now, what's moving fastest of all is the deadly progress of the disease. Until a cure is found, health officials will have to continue their delicate balancing act between speed and safety. ■ JOSEPH PALCA