A Storm Over Steroid Therapy

Health officials are fuming about a news story that drew attention to their 5-month delay in publicizing a new treatment for AIDS-related pneumonia

WHEN RICHARD CHAISSON, DIRECTOR OF AIDS patient care at Johns Hopkins Hospital in Baltimore, visited a small hospital in rural Massachusetts in September, the infectious disease specialist there asked him what was new in treating opportunistic infections associated with AIDS. Chaisson, who stays abreast of AIDS research, told his host that the hottest news in the last year was that steroid treatment was gaining widespread acceptance for AIDS patients with *Pneumocystis carinii* pneumonia (PCP). But this wasn't news to his small-town colleague. "We know about that already," replied the physician.

So for Chaisson and many other AIDS researchers the headline on the front page of *The New York Times* on Wednesday, 14 November must have seemed a bit odd: "News of AIDS Therapy Gain Delayed 5 Months by Agency." To federal health officials the steroid therapy story was more than odd, though; it was infuriating. "Most of the people who read that [headline] are going to conclude that for some diabolical reason the agencies of health in this country deliberately and with malice aforethought delayed a therapy that might help someone," says an outraged Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID). "That's patently nonsense."

NIAID

Outraged. *Anthony Fauci, director of NIAID, said allegations of delay were "patently nonsense."*

The article went on to describe how NIAID officials had waited 5 months before notifying doctors that a panel of experts had judged steroids to be a valuable adjuvant therapy for treating PCP. The article quoted an AIDS activist who called those responsible for the delay "murderers."

These words ignited a controversy that illustrates how difficult it is for AIDS researchers and workers to find a way of releasing new information that will satisfy everyone in the field. When should new research results be put into general clinical practice? How should doctors be informed of these results? What role, if any, should peer-reviewed journals play in determining public health policy? The story of how steroids came to be used as a therapy for PCP is a real-time case history of an attempt to proceed with caution into new territory and the backlash it produced.

On one level, the newspaper headline was absolutely accurate. On 15 May, a panel of 17 clinical researchers and biostatisticians met in San Diego, California, to discuss five recently completed clinical trials designed to judge the effectiveness of corticosteroids in addition to other anti-pneumonia drugs in treating PCP. Yet not until 10 October did NIAID take specific steps to notify doctors about the panel's conclusions. The *Times* article implied that people had died in the interim because officials delayed releasing the conclusions for petty bureaucratic or professional reasons. But according to AIDS experts contacted by *Science*—including a leader of an AIDS activist group—the story just isn't that simple.

At the end of the day-long meeting in May, the panelists agreed that taken together the five studies showed that steroids could be beneficial in moderate-to-severe cases of PCP. This wasn't an insignificant finding considering the fact that although the frequency of PCP cases has dropped considerably with the advent of effective prophylactic treatments, officials estimate that 40,000 cases of PCP will appear among AIDS patients in the next decade, and between 5% and 30% will suffer respiratory failure and die as a result of the illness. In the largest of the five studies, conducted by Samuel A. Bozzette of the University of California at San Diego and his colleagues in the California Collaborative Treatment Group, mortality from PCP declined from 22% with standard therapy alone to 11% with standard therapy plus steroids.

And yet NIAID chose not to call a press conference the next day to announce this good news to the world. Why? For several reasons: Although they agreed on the broad general endorsement of adjuvant steroid therapy, the panel came to no consensus on specifically for whom it should be used, says Henry Masur, chairman of the panel and chief of clinical care medicine at the Warren Grant Magnuson Clinical Center at the National Institutes of Health. For example, patients suffering from PCP begin to lose lung function, as measured by the amount of oxygen entering their blood. Panelists had questions about what level of oxygenation should make a patient eligible for steroids. Then there was the issue of when to begin treatment. In one of the five studies, steroids were used without measurable benefit after patients had begun to experience respiratory failure. In the others, patients received steroids either 1, 2, or 3 days after starting other therapies. In two studies the drug was given orally; in the three others, intravenously.

"Everybody felt it would be very irresponsible to say steroids seem like a good thing, without being able to say for which patients, or what were the appropriate doses, or when ought it to be given, or what are some of the problems," says Susan Ellenberg, chief of the biostatistics research branch at NIAID's division of AIDS and one of the panelists. "There was a concern about doing something that would do more harm than good."

Panelists were also acutely aware of the poor track record of steroids as therapeutic agents. "Steroids are probably the most sleazy of modern day medications," says John Mills, professor of medicine at the University of California, San Francisco, and chief of infectious diseases at San Francisco General Hospital. In several cases, steroids gained widespread acceptance in treating diseases—such as septic shock and adult respiratory distress syndrome—only to be rejected after large, carefully controlled clinical trials showed that they were of no benefit or, in some cases, actually caused harmful side effects.

Then, too, there is the paradoxical nature of using steroid therapy in AIDS patients. One of the well-known side effects of steroid treatment is a suppression of the immune response. Researchers have also shown that adding steroids and certain growth factors to cells that have been infected with the AIDS virus causes them to start producing more virus particles. Giving steroids to AIDS patients certainly has a risky element to it. "I've seen [AIDS patients] who were given steroids mistakenly, and their Kaposi's Sarcoma progressed aggressively," says Jerome Groopman, an AIDS researcher from Harvard University. "People also get fungal infections on steroids, so it's not a therapy that one uses lightly or indiscriminately at all."

So, there were many scientific reasons to go slow with news of the steroid "breakthrough." The *Times* article conceded some of these points, but added one that enraged researchers. According to the *Times*, at least one reason for the delay was that researchers feared that early release of the consensus statement might jeopardize publication of their research results in a prestigious medical journal. This reluctance may have been critical in this case, considering where they intended to publish: in *The New England Journal of Medicine*, notorious for its Ingelfinger rule, which forbids researchers from speaking about their work before it appears in print. In fact, Paul Meier, a statistician from the University of Chicago who was vice chairman of the consensus panel, was quoted in the *Times* article saying that several scientists insisted that the consensus letter not appear before their research papers were published.

But panelists contacted by *Science* insisted that publication concerns did not hold up the consensus report. "That's demonstrably false," says an angry Bozzette, whose paper was in fact submitted to *The New England Journal of Medicine* in mid-August. "It's so demonstrably false that I think it raises the specter of malicious intent on the part of the author [of the *Times* article], rather than us." Indeed, the day after the article appeared Meier was anxious to clarify the statements he made in the newspaper, telling *Science* that although the issue of publication status came up, it did not "contribute in any appreciable degree to the delay in producing the consensus report."

In an interview with *Science*, *Journal* editor-in-chief Arnold Relman says he does not know what went through the scientists' minds, but they should know that there are two conditions that allow the Ingelfinger rule to be waived. First, if the paper deals with AIDS and has already been reviewed by the *Journal*, then the authors may publicize it any way they wish. Second, if a government agency reviews a study and decides that it is so important that it should be released before being published, the *Journal* has no objection. But Relman certainly didn't think

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the second waiver applied in the steroid case: "This was not brand new information bursting on an unaware, uninformed world. This was simply a refinement of what was already out there."

If scientific and professional qualms slowed the process, so too did the fact that most panelists thought the steroid therapy was already well known. "You could argue persuasively that if you had locked all the people in the consensus conference in a room and said, 'Listen guys, there's no food until we see a consensus report,' it would have appeared sooner," says Mills. "But no one felt there was a tremendous degree of urgency here because everyone felt it was already in the public domain." Bozzette's study had ended in the summer of 1989, and he began presenting preliminary findings at the November 1989 meetings of the Interscience Conference on Antimicrobial Agents and Chemotherapy. It was also presented at several AIDS Clinical Trials Group meetings, the first time in late 1989. In addition, even as the panel met, one of the five studies—by Julio S. G. Montaner of the University of British Columbia in Vancouver, Canada—was already in press in *Annals of Internal Medicine*. That study, which looked only at lung function and showed that it improved with adjuvant steroid treatment, appeared on 1 July, accompanied by an editorial from Masur discussing the therapy's value. Results from several of the individual studies, including Montaner's, Bozzette's and a smaller, double blind placebo-controlled study conducted at Jackson Memorial Medical Center in Miami, Florida, by Suzanne Gagnon (now at the University of Kansas School of Medicine) were presented in June at a session on opportunistic infections at the 6th International Conference on AIDS.

Finally, after a summer of drafts and redrafts, the panel reached a consensus on 15 August. But even then NIAID officials decided not to publicize it. Instead, they sent the statement to *The New England Journal of Medicine* for peer review. According to Fauci, the agency sought independent review of the panel's conclusions for several reasons. First, because of steroid therapy's checkered history, NIAID was anxious not to endorse it prematurely. Second, the agency was still smarting from criticism heaped on it for an earlier decision in which it didn't seek peer review. In that case, NIAID officials recommended the use of the antiviral drug AZT for asymptomatic individuals infected with the AIDS virus long before the studies supporting the recommendations appeared in print. The agency got angry complaints from clinicians who resented being told to change established practice just because the government assured them it was the correct thing to do.

Even some of NIAID's harshest critics agree with Fauci that it was prudent to seek peer review before expanding the use of steroids. "Many of the people who are screaming at NIAID about this [delay] would scream at NIAID about anything," says Mark Harrington of the group ACT-UP. "But they would have screamed just as much if NIAID rushed out a recommendation to use steroids."

There are disadvantages as well as advantages in asking a scientific or medical journal to play a role in setting federal health policy. On the positive side, Fauci explains, it prevents the charge of cronyism—the suggestion that agency officials have pre-selected favorable reviewers. But on the other hand, says Relman, outsiders like himself cannot issue recommendations with as much

authority as the government, because they cannot "vouch for the truth" of a publication. "All we do is we say it has been critically reviewed by the best brains available."

On 11 September, NIAID got word that the *Journal* would accept the consensus statement for publication, along with the papers by Bozzette and Gagnon. But the agency still had to decide how to let doctors know. Although at least one member of the panel felt that a press conference was appropriate, NIAID decided on the more conservative route of sending a letter with news of the results to the 2600 physicians on a mailing list maintained by LyphoMed, the company that sells a commonly used prophylactic therapy for PCP. The agency also informed all members of its AIDS Clinical Trials Group by electronic mail, and sent an "Update" to a list of AIDS constituency newsletters. Why no press conference? Insiders say the agency was confident the news had already reached the people who needed to hear it and was reluctant to make a big splash with a potentially controversial therapy before it was published.

The consensus statement appeared in its completed form as a special report in the 22 November issue of *The New England Journal of Medicine*, along with reports of the studies by Bozzette and Gagnon. J. Allen McCutchan, an infectious disease specialist at the University of California at San Diego and one of the conveners of the consensus conference, expects some physicians will change their practice in light of the panel's recommendations, but "it's a matter of opinion on how to get clinicians to change," he says. Mills agrees, adding that researchers must take an active role in keeping abreast of new information, especially when dealing with the fast-changing world of AIDS treatment.

"I don't think there was substantially more that could or should have been done," says Fauci. "This furor obviously makes one say maybe we should have done more. But this is a furor that was fueled by the placement of an article on the front page of *The New York Times*."

Nicholas Wade, science editor of the *Times*, thinks his paper made the right decision: "I can't think of anything that would suggest we should have played the story differently. It definitely deserved the front page."

On 15 January NIAID will hold a conference that was scheduled long before the *Times* article, but one with a remarkably prescient topic: When should research results be made public, to whom, and after what kind of scientific scrutiny? The example of steroids will still be fresh in the participants' minds. ■ JOSEPH PALCA

NIH Readies Plan for Cost Containment

In response to a congressional directive, the agency is working on a long-term strategy for funding grants

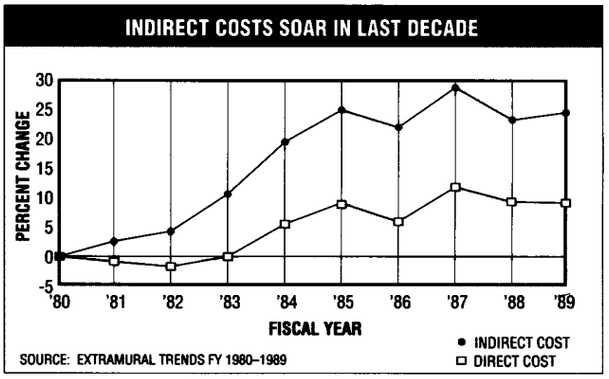
"WE ARE ENTERING A TIME WHEN WE NO longer can conduct business as usual," says John Diggs, the man in charge of developing a "cost management" plan for the National Institutes of Health. The plan was mandated by Congress in response to a chorus of alarums from biomedical scientists who perceive a "crisis" in research funding as the fraction of grants approved by NIH has sunk to an all-time low.

With Representative William H. Natcher (D–KY), chairman of the House appropriations subcommittee for NIH, taking the lead, Congress gave NIH nearly $1 billion more for fiscal year 1991 than the Administration requested. But, in return, Natcher directed NIH officials to respond to a 10-point plan of his own for ways of redistributing and controlling research costs. Included in Natcher's formula were suggestions that NIH reduce the average length of awards and consider the total cost of individual grants—including indirect costs—in deciding which proposals to fund (*Science*, 28 September, p. 1496).

NIH's response will be debated at a public meeting on 17 December, but already elements of the scientific community are taking sides. Although some details of the plan have yet to be worked out, *Science* has learned that NIH leaders have agreed on key points.

As *Science* goes to press, these points seem likely to be incorporated in the final draft:

■ The plan will adhere to congressional advice to contain the cost of grants overall by setting the average length of grants at 4 years. During the past decade, the cost of individual grants has been rising and the average length of grants in NIH's portfolio has inched up to 4.3 years. In addition, the indirect cost rate per grant has risen substantially. After much debate about how to achieve a 4-year average, NIH officials are leaning toward giving individual institutes discretion on the matter. Some institutes may develop a portfolio that mixes 5-year, 4-year, and 3-year awards to get a 4-year average. One is thinking of cutting its support of indirect costs by 10% across the board. Another is considering a "sliding scale" by which only the most meritorious grants would get full funding; other grants would be funded in somewhat smaller amounts, with the total portfolio equalling the equivalent of a 4-year grant average.



■ At Congress's insistence, NIH will either eliminate or put strict controls on the current process of "downward negotiation" for funding grants once they have been awarded. Instead of cutting grants across the board by 15% to 18%, which has become common practice, cuts will be limited to 3% to 4% at most—a figure that is now called the "historic norm" because it was an unstated limit at the beginning of the 1980s.

■ NIH may scrap the system by which grant applications are given a designation of "approved" if there is little chance that they will actually be funded.

■ In order to simulta-

Taskmaster. *William Natcher asked NIH for a plan.*