

Conflict Over Release of Clinical Research Data

Researchers, editors, and NIH officials debate how to get the word out when a therapy is found to be effective or harmful

LAST WEEK, THE NATIONAL INSTITUTES OF Health took an unusual step: It stopped a clinical trial of a treatment designed to stave off bacterial infections in children harboring the AIDS virus. Though the results of the trial will not be published in the scientific literature for months, NIH decided that the therapy, which involves intravenous injections of immunoglobulin, appears to be so effective that the trial should be terminated early and its findings made public immediately. Within days, a massive mailing went out to 18,000 pediatricians and a news conference was held on 17 January.

The agency's decision to short circuit traditional publication of the data—and the peer review that accompanies acceptance of a paper in a scientific journal—was not taken lightly. In recent months, NIH has been blasted from all directions, in both the popular and scientific press, for the way it has handled early release of clinical trial data.

Some say the agency hasn't done enough to alert doctors and the public about promising—or dangerous—therapies, others argue that NIH has moved too fast, putting out results before they have been adequately reviewed. And there have been allegations that researchers have delayed public release of clinical trial data to avoid prejudicing their publication in prestigious journals.

Indeed, even as NIH officials were scrambling to put out the word about the immunoglobulin therapy, the agency was holding a meeting to consider how to improve the way it informs the medical community and the public about important clinical trials. Clinicians, biostatisticians, journal editors, institute officials, and public information officers spent the entire day of 15 January examining six studies (see box) that reflect the problems presented by the release of information prior to its publication. The discussion proved that there are no easy answers: Journalists argued

for complete disclosure at the earliest possible moment, journal editors warned of the consequences of circumventing peer review, and researchers recounted feeling torn between moving rapidly and being sure they were right in their recommendations.

Even when the results of a clinical trial are clear cut, there is disagreement over how to proceed. Take the case of the Cardiac Arrhythmia Suppressor Trial (CAST). Begun in the summer of 1987, CAST was an attempt to determine whether to use drugs to control arrhythmias—irregular heart beats—in patients who had suffered heart attacks. The therapy was already popular: In 1987, 600,000 prescriptions were filled for flecainide and encainide, two widely used antiarrhythmia drugs, and the following year the number jumped to 800,000. But 2 years into the study, a committee charged with keeping tabs on the data became convinced that heart attack patients receiving those two drugs were at higher risk of dying or suffering cardiac arrest than patients receiving a placebo. The National Heart, Lung, and Blood Institute (NHLBI), which sponsored the study, ordered the part involving flecainide and encainide terminated. The Food and Drug Administration required the drugs' manufacturers to send out "Dear Doctor" letters describing the study's findings, and NHLBI held a news conference to inform the media.

But NHLBI associate director Lawrence Friedman told the panel that physicians were outraged at the way the CAST data were released. They argued that they were not given sufficient information to make informed decisions about the therapy, since the journal article giving a full description of the study was months away. How could they respond intelligently to patients if they didn't have all the facts? Michael Friedman, associate director of the National Cancer Institute (NCI), said such complaints were even more pointed from oncologists who received a Clinical Alert from the NCI in 1988 about the value of adjuvant chemotherapy for node-negative cancer. As Paul Meier, a statistician from the University of Chicago pointed out, the utility of adjuvant chemotherapy was hardly self-evident—subsequent publications showed there were differences of opinion about the interpretation of the results of that study.

Although all the panelists at last week's meeting agreed that it is preferable to have a study's results independently peer reviewed by a journal and in press before they are made public, such reviews can take a long time. Michael B. Bracken, an epidemiologist from Yale University School of Medicine, described his experience with his study of corticosteroids for the treatment of spinal cord injuries. It took *The New England Journal of*

EXAMPLES OF EARLY RELEASE

STUDY	ACTION	PUBLICATION
Cardiac Arrhythmia Suppressor Trial: Showed that two popular antiarrhythmia drugs should not be used for survivors of myocardial infarction with asymptomatic arrhythmia.	Trial stopped – 4/19/89 News conference – 4/25/89	<i>The New England Journal of Medicine</i> – 8/10/89
Adjuvant Chemotherapy for Breast Cancer: Multicenter trial showed improved, disease-free survival when chemotherapy was used in addition to surgery to treat women with node-negative breast cancer.	Results presented to National Cancer Advisory Board – 5/88 Clinical alert – 5/16/88	<i>The New England Journal of Medicine</i> – 2/10/89
Cryotherapy for Retinopathy of Prematurity: Surgical technique shown to be beneficial in preventing a form of blindness unique to premature infants.	Trial stopped – 1/22/88 Clinical alert – 2/12/88 News conference – 3/29/88	<i>Archives of Ophthalmology</i> – 4/88 <i>Pediatrics</i> – 5/5/88
Corticosteroids for Spinal Cord Injury: Methylprednisolone improves neurologic recovery when given within 8 hours of traumatic injury to the spinal cord	Trial concludes – 8/2/89 Journal article submitted – 10/5/89 News conference – 3/30/90	<i>The New England Journal of Medicine</i> – 5/17/90
AZT for Asymptomatic, HIV Infected Patients: Large clinical trial shows treatment with nucleoside analog drug AZT delays onset of AIDS for patients with no symptoms but a deteriorating immune system.	Trial halted – 8/16/90 News conference – 8/17/89	<i>The New England Journal of Medicine</i> – 4/5/90
Corticosteroids for Pneumocystis Pneumonia Consensus panel concludes early use of steroids in treating a form of pneumonia frequently found in persons with AIDS reduces risk of mortality from the pneumonia.	Consensus panel meets – 5/15/90 Consensus statement completed – 8/15/90 "Note to physicians" sent – 10/10/90	<i>The New England Journal of Medicine</i> – 11/22/90

Medicine 4 months to decide that the paper reporting the results needed revisions, and another month to reach a decision on the resubmitted paper. The whole process took nearly 8 months from time of submission until the *Journal* finally gave its nod—and only then did the National Institute of Neurological Disorders and Stroke hold a news conference and send out a clinical alert to acquaint doctors with what everyone agreed were important findings that should change clinical practice. But *Journal* editor-in-chief Arnold S. Relman said Bracken's case was unusual, noting that the *Journal* accepted a consensus statement on the use of corticosteroids in treating AIDS patients with *Pneumocystis carinii* pneumonia in just 4 days. However, the National Institute of Allergy and Infectious Diseases (NIAID), which sponsored the consensus conference, then took more than a month to put out news of the results (*Science*, 30 November 1990, p. 1196).

NIAID director Anthony S. Fauci said federal agencies want approval from medical journals before publicizing an important finding because the journal's review provides an independent check that the conclusions are justified by the data. Researchers, however, have another incentive to wait for publication: editorial policies that forbid prior publicity for a paper before it has been published. But Relman said that authors are wrong to worry about that. He said it is the *Journal's* policy not to interfere with the dissemination of important public health information. Once a paper is accepted, he said, authors are free to discuss it with whomever they wish, so long as they don't refer to their work as about to appear in *The New England Journal of Medicine*. That, Relman said, is permitted only after the final, fully corrected version goes to the printer about 3 weeks before publication. But that still left researchers at the meeting wondering how the *Journal* will treat early release of the results of papers that have not been accepted, or even submitted. In answer, Relman pointed out that both the breast cancer and AZT studies were made public long before they were submitted to the *Journal*.

Though last week's meeting came to no conclusions, the discussion could lead to an NIH-wide policy for handling early release of clinical trial results. John H. Ferguson, director of the office of medical application of research, which sponsored the meeting, says there is a great deal of interest at NIH to come up with such a policy, and individual institutes have already begun to formulate their own procedures. With so many AIDS trials under way, and pressure to get effective therapies rapidly into use, some guidelines are clearly needed. ■ JOSEPH PALCA

Hard Times for San Diego Museum

A funding crisis has hit the San Diego Museum of Natural History, one of the oldest scientific institutions west of the Mississippi, and, as a result, science is being sacrificed to make way for large public exhibitions. Founded in 1874, the museum has been the repository for about 8.5 million rock, fossil, and biological specimens from the southwestern United States, and it has sustained a strong scientific staff with its modest annual budget of \$2 million.

But in the last few years its financial situation has eroded, and the board of trustees decided in December to dismiss roughly 40% of the scientific staff. The exodus included two internationally respected researchers: Frederick Schram, curator of paleontology, known for his research on the evolution of crustaceans, and Amadeo Rea, Jr., curator of ornithology and mammalogy, an expert on endangered coastal bird species.

The last few years have been hard for many public institutions, and particularly tough for museums of natural history. The most conspicuous victim is the British Natural History Museum, which was thrown into turmoil early last year by plans to cut scientific staff and focus research on a few popular areas (*Science*, 11 May 1990, p. 677). What may be a new trend is spreading concern among biologists such as Harvard entomologist Edward O. Wilson, who last week warned the President's Council of Advisors on Science and Technology that it is posing a serious threat to systematic biology. He argues that many academic biology departments have turned a cold shoulder on research involving the evolution of large animal species, and that museums have become by default the most important supporters of this research.

One of the curators at the San Diego museum, speaking on background, agreed wholeheartedly with Wilson. He worries that the San Diego case may become a precedent for other institutions. "If we go under," he says, "it would reflect the failure of our society to recognize the importance of museums not just as repositories...but as a means of educating and informing the public about scientific research."

While the administration of the San Diego museum has trimmed the research budget, it is planning to increase expenditures on public exhibits. In January, it unveiled a new display called the Josephine Scripps Hall of Mineralogy, costing more than \$400,000—half of it financed with a grant from the National Science Foundation. The hall will require another infusion of cash—perhaps as much as \$110,000 according to one source—before it can be completed.

The museum's acting director, Allan Shaw, says the mineralogy hall is one of several projects that have been eating into the museum's financial reserves recently. After taking over in July, Shaw brought in some new accounting procedures and a change in perspective. "When the new comptroller and I got into the books," Shaw says, "we discovered that the revenue projections were not accurate." In fact, he found the museum was running a \$125,000 deficit in its 1989–1990 budget, which is expected to grow even larger this year. Shaw fired half a dozen non-scientific workers and five members of the scientific staff. The library funds were cut to \$6,000, eliminating nearly two-thirds of the journal subscriptions. According to some of the scientific staff, Shaw also put out the word that the museum would try to focus on "blockbuster exhibits" in the future, hoping to draw crowds and raise additional funds by charging admission. Furthermore, the staff has been told that the museum should focus on San Diego County. This prospect is discouraging, one staffer said, since the curators have focused in the past on species found throughout the Pacific region, and "organisms don't respect political boundaries."

After being hit with a spate of negative publicity during the holidays, the museum in January offered to rehire the scientists it had dismissed—but only for 2 months while undertaking an emergency plea for funds. Only one accepted. Says Schram, who is now working at the Scripps Institute of Oceanography as a marine biologist: "I had already packed away 20 years' worth of research and left the building."

In an attempt to rebuild the museum's scientific staff, some trustees have launched an emergency fund-raising campaign. Jackie Hollywood—trustee, wife of a San Diego judge, and an amateur ornithologist—is leading the appeal. She says the first objective is to restore the library's budget and get the science program back on its feet. Over the long term, she hopes the museum will attract a series of endowments, possibly targeted at specific areas such as ornithology, mammalogy, geology, and general science.

■ ELIOT MARSHALL