A Bitter Battle Over Error (II)

Two researchers' post-publication "audit" of a scientific paper has led to allegations of error and a debate about the role of unofficial watchdogs in assuring accuracy in the literature

This is the second in a series of occasional articles on conduct in science.

"ERROR is the stuff of science," says David Baltimore of the Whitehead Institute. His nemesis Walter Stewart of the National Institutes of Health thoroughly agrees. "The only way to avoid error in science is to avoid work," Stewart said recently.

Agreement ends there.

Baltimore hews to the tradition that the scientific literature is self-correcting—that as researchers try to repeat or extend each others work, they may find new interpretations of the data and that through a normal, even necessary, course of backing and filling, progress is made and answers are found.

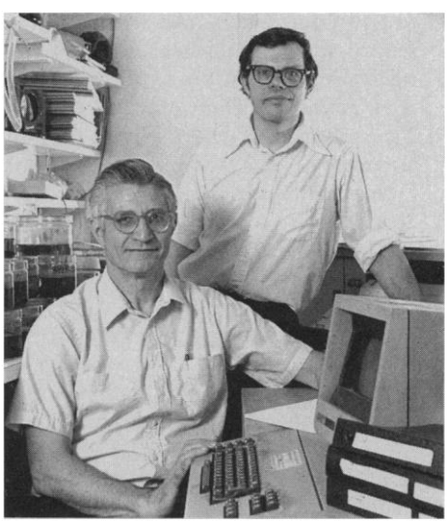
Stewart maintains that error (including minor error), once known, should be explicitly corrected. Further, he believes that examining the published literature for error is an appropriate pursuit. In particular, he thinks that alleged errors in a *Cell** paper coauthored by Baltimore in 1986 demands correction. In April, Stewart and his NIH colleague Ned Feder told two separate committees of the United States Congress that they had analyzed data from 17 pages of laboratory records and "concluded that the published paper contained a number of serious misrepresentations of scientific fact . . . " (*Science*, 24 June, p. 1720).

Neither Baltimore, nor the other coauthors, nor the reviewers were invited to refute the statements against them.

But then, as aides to Representative John Dingell (D–MI), who chaired one of the hearings, have said, the purpose of the hearing was not to reveal the truth but to focus on how the system reacts to whistle-blowers (*Science*, 22 April, p. 386).

Stewart and Feder's congressional testimony has contributed to the transformation of a dispute about a complex paper in immunology and serology into a very public fight that has contributed to talk in Congress of legislation that would shift responsibility for reviewing scientific disputes from researchers to an outside auditing or watchdog agency.

Dingell noted at the opening of his hearing that "This subcommittee has spent 4 years investigating defense contractors and we have been critical of apparent conflicts of interest. In the health industry [read biomedical research], they do not even recognize conflict of interest."



Ned Feder and Walter Stewart: *Inspecting the scientific literature.*

On Capitol Hill Stewart and Feder have made a favorable impression as scientists who are willing to publicly examine the dark side of science. Around NIH, their recognition on the Hill as self-appointed guardians of scientific purity is referred to as the "lionization of the turkeys."

Through circulation of their manuscript and Hill testimony, Stewart and Feder's opinions have become well known. In May, Baltimore sent a letter to more than 1000 colleagues, stating his side of the story, and signaling an intention to fight back.

"I believe that it is of critical importance that I set the record straight, not just to clear my own name and the names of other authors who have been compromised by this attack, but for another, more compelling reason:

A small group of outsiders, in the name of redressing an imagined wrong, would use this once small, normal scientific dispute to catalyze the introduction of new laws and regulations that I believe could cripple American science.

This story has as many shades of gray as it does of black and white. The role that Walter Stewart and Ned Feder have assigned themselves as actors in this drama is, itself, an important part of the story.

For the past 4 years, Stewart and Feder have been examining certain published papers they suspect are inaccurate. Entirely on their own initiative, they conducted a post hoc "audit" of scientific papers coauthored by John Darsee, a young cardiologist who was caught fabricating data at Harvard (*Science*, 1 April 1983, p. 31). Subsequent to testifying before Congress that they could not get their manuscript published because there were threats of a libel suit, *Nature* published a version that had been edited by lawyers in its 15 January 1987 issue (*Science*, 23 January 1987, p. 422).

Stewart and Feder's analysis of the April 1986 *Cell* paper, whose principal author is Thereza Imanishi-Kari, is their second well-publicized effort to police the scientific literature.

Stewart and Feder may be self-appointed guardians of scientific accuracy, but they have managed to get NIH's approval to spend 20% of their time on investigations of published papers. In fact, they have been spending closer to 100%, according to their supervisors. However, they are not in any way part of the NIH fraud office. "We're not investigators *for* NIH," Stewart told *Science*. "We look into facts as scientists."

According to Stewart and Feder's congressional testimony, they first heard about a dispute over the Imanishi-Kari *Cell* paper from Charles Maplethorpe, a former graduate student in Imanishi-Kari's lab at MIT. Maplethorpe reported that a postdoc named Margot O'Toole had challenged Imanishi-Kari's data on the basis of 17 pages of laboratory records which, she claims, contradict the published findings (*Science*, 24 June, p. 1720). Stewart and Feder persuaded a reluctant O'Toole to send them Xerox copies of those 17 pages long after she had decided to drop the matter entirely.

Thus armed, Stewart and Feder wrote a

*"Altered repertoire of endogenous immunoglobulin gene expression in transgenic mice containing a rearranged Mu heavy chain gene," *Cell* 45, 247 (1986). The principal author of the *Cell* paper is Thereza Imanishi-Kari who was at MIT when the research was done and who is now at Tufts University. Informal post-publication reviews of the paper have been conducted by Herman Eisen at MIT and a committee formed by Henry Wortis at Tufts.

long, critical analysis of the Imanishi-Kari paper. In accordance with usual procedure they gave their manuscript to NIH superiors for review before formally submitting it to a journal for publication. It was bucked directly to Joseph E. Rall, NIH deputy director for intramural research who sent it out to three reviewers. Each said it was impossible to judge the manuscript without knowing whether the 17 notebook pages on which Stewart and Feder rest their case were the whole of the data.

Stewart and Feder had not contacted the paper's original authors.

Reviewer number 3 had this to say: Stewart and Feder "state at the outset that it represents an 'internal audit,' but they never state where they obtained the 'internal' information. . . . In this regard, the reader is placed in the same position as the receiver of an anonymous phone call!"

"If the data [in the Stewart manuscript] are authentic and correct, they indicate that mistakes were made . . . ," reviewer number 3 continued. But "I would hesitate to evaluate any of them without first hearing the explanation offered by the original authors."

So, Stewart and Feder were told to ascertain more facts before resubmitting their manuscript for clearance.

In a letter to all six coauthors dated 18 December 1986, Stewart and Feder said, "We are writing to ask for your help on an important and possibly difficult matter," and proceeded to ask for access to *all* of the original data. "We would like to have access to the original laboratory data extant at the time the manuscript was submitted for publication. . . . "

"If you are willing to let us have access to your laboratory records, we could arrange to meet with you, at a mutually convenient time," they wrote, emphasizing that they were not acting in any way as official NIH investigators but merely as researchers with an "interest in studying the accuracy of the scientific literature." However, they said "We should add that we have talked about our preliminary observations with some NIH administrators."

In fact, after reading their draft manuscript, NIH authorities brought the matter to the attention of the institutes' office of research fraud to investigate the possibility that Stewart and Feder had spotted a case of misconduct, not just error.

When Baltimore got Stewart and Feder's letter he was outraged, as his reply a couple of weeks later made clear. On 21 January 1987, Baltimore told Stewart and Feder that he would have nothing to do with them.

"Your notion of doing an 'internal audit' of the data is not one I can accept," he said, arguing that it would establish a precedent by which outsiders would "tie up the scientific community in continuous wrangles. . . . External reviews of data are only relevant when probable causes of fraud have been established. In this case, a number of respected immunologists not involved in the work examined the situation and did not find probable cause."

Baltimore stated that he considered the dispute a "dead issue" and declared "I do not recognize your right to set yourselves up as guardians of scientific purity." Period.

It was but the beginning of months of correspondence on the matter. No data would be forthcoming, Baltimore decided as a matter of principle because Stewart and Feder have no official standing and, furthermore, are not working in the field. But he did agree to let them have copies of the two informal reviews that had been done in response to O'Toole's challenges. "If they remain unsatisfied [as they did], I see no other solution than to have a further review of the data," Baltimore wrote Rall, asking that NIH "appoint a couple of immunologists to examine Stewart and Feder's charges." Baltimore also demanded an apology from the two if the review concluded that "the norms of scientific research were not transgressed." and an agreement to drop the subject.

"These are difficult times for those of us who pursue knowledge in the biological sciences. I see this affair as symptomatic, warning us to be vigilant to such threats, because our research community is fragile, easily attacked, difficult to defend, easily undermined. What is now my problem could easily become anyone else's if circumstances present themselves."
David Baltimore

For a variety of reasons, Stewart and Feder rejected Baltimore's proposal. "It contains novel and strict sanctions against free and open scientific debate," Stewart wrote.

(NIH has just recently appointed three scientists to review the data as an official examining committee. They met at Tufts for the first time on 23 June.)

By the time Rall got Baltimore's letter, a number of NIH officials had met to think about what to do. Stewart and Feder apparently would settle for nothing less than access to the data. They weren't going to get it. Besides, the NIH fraud office was now conducting its own preliminary inquiry. It was late March 1987.

Rall decided not to clear Stewart and Feder's manuscript for submission to a journal until he had more information.

On 9 April, Stewart and Feder sent Rall an eight-page memo asking him to reconsider. They argued that "actual harm will almost surely result from suppression of our study." On 20 April Rall again said no. "It is clear that a resolution among scientists would be preferable to airing what may not be a correct analysis of the data in the public press"—something that surely would result from publication of the manuscript.

Stewart and Feder sought help from outside. They prepared a ten-page, single-spaced appeal outlining their view of the circumstances surrounding the *Cell* paper, Margot O'Toole's allegations of error and her version of the way they were handled, and a chronology of their own involvement. They stated that "NIH has ordered us to commit what we believe is a serious departure from generally accepted standards of research." And, striking a theme that runs throughout much of their correspondence, they said "If we do not comply with NIH's directive, we doubtless further jeopardize our jobs."

Stewart and Feder attached a copy of their manuscript to this appeal and sent it out to some 100 prominent researchers, including members of the National Academy of Sciences (NAS) and heads of scientific institutions. "We have been forbidden by NIH to communicate our findings to a journal, even as private citizens. . . . We would like to have your advice. . . . "

Thus, what started out as a debate at MIT, and then moved to official channels at NIH, became a matter of widespread public knowledge within the biomedical research community.

It was not the first time Stewart and Feder have taken their problems to their "scientific colleagues" at large. One previous instance occurred in November of the previous

Update. Last week, *Science* reported that Baltimore had declined to send original data to Dingell's subcommittee in the House. Within the past several days, Baltimore and some of the coauthors have, in fact, submitted their data to the subcommittee. Stewart is now assisting the subcommittee at Dingell's request, on loan from NIH.

"Internal Audit" a Challenge

Walter Stewart and Ned Feder of NIH have prepared a manuscript that sharply questions the validity of data in a paper published by David Baltimore, Thereza Imanishi-Kari, and others in a 1986 issue of *Cell*. Stewart and Feder, in a 30 September 1987 draft of their as yet unpublished critique open with this statement: "Experimental records from the laboratory of the authors of a recent paper fail to support, and in certain cases contradict, assertions central to the main conclusions of the paper."

The paper, which describes a complex experiment in immunology and serology, reports evidence that a gene from one strain of mouse, when transplanted into a second strain, affects the expression of immunoglobulin molecules native to the second mouse. If true, it is a potentially important observation.

Stewart and Feder's criticisms of the manuscript, whose principal author is Imanishi-Kari, are based on an analysis of 17 handwritten pages of notebook records—some of them in Portuguese—that they requested from a graduate student who has challenged the data. Imanishi-Kari has told *Science* that the 17 pages do not tell the whole story.

Researchers who have reviewed Stewart and Feder's manuscript for NIH or for this reporter agree that there are discrepancies between certain data in the *Cell* paper and data in the 17 notebook pages that have yet to be explained. One issue among those that remain unresolved concerns data in two of the tables. Critiquing table 2, Stewart and Feder's draft manuscript suggests that the authors' procedures for data analysis "were not appropriate," that the "data were almost certainly scrambled," and that the laboratory records contradict some of the scientific claims stated in the table.

The observation that there may be problems with the tables is confirmed by a comment made by one of the NIH reviewers back in the fall of 1986. Referring to the *Cell* paper, the reviewer noted, "For example, Tables 1 and 2 in this manuscript are said to represent the published and the raw data versions of the same experiment, but are clearly discrepant."

Without access to all of the original data, it is impossible to fully evaluate Stewart and Feder's analysis. An official committee appointed by NIH is conducting a full evaluation now. The three committee members—Joseph M. Davie of Searle, Hugh McDevitt of Stanford, and Ursula Storb of the University of Chicago—held their first meeting in Boston on 23 June. A report of their findings, which NIH will make public, is expected within weeks.

Meanwhile, Stewart and Feder have submitted their manuscript to *Nature*. Stewart declines to discuss the paper, saying that he considers it confidential and had expected each of the 100 or so scientists to whom he has sent copies to treat it that way. Furthermore, he avers, "This is a scientific debate and should be handled through the normal channels of publication in the scientific literature." ■ **B.J.C.**

year—1986—at the time their manuscript was first going through internal NIH review.

Feder had recently received an unsatisfactory "performance assessment" from his superiors in the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). For example, his assessment, which Stewart and Feder distributed unsolicited, said that Feder had only "partially met" a requirement to define significant areas of research for the two-man lab of which he is chief, and that he "failed to meet" a requirement that he "maintain a creative environment conducive to good research." (On appeal the latter rating was changed to "partially met.")

Stewart and Feder have stated that the institute is using their lack of research productivity as an excuse for punishing them for their work in revealing scientific misconduct.

In a 21 November 1986 memo sent to prominent scientists outside of NIH, Stewart and Feder aired their grievances against their NIH superiors and asked for letters of support.

Feder, 60, is a 1953 Harvard Medical School graduate who went to NIH in 1955, was back at Harvard from 1958 to 1967 where he was an assistant professor and lecturer. In 1967 he returned to NIH. His bibliography lists 22 research papers in scientific journals, the last published in 1976.

Walter Stewart, 43, is also a Harvard man. He graduated from Harvard College in 1967 and came to Feder's lab at NIH in 1968. His title is "research physicist." He is known for a paper he published several years ago that describes a Lucifer yellow dye that has become a valuable, widely used tool for nerve cell research.

Since Stewart's Lucifer dye paper, neither he nor Feder has published any original research papers. Nor is their ongoing research, using snails as a model in which they use synthetic chemicals to study the shape of nerve cells, ready for publication. One scientist says of their work during the past 5 years, "They have violated the basic demand of science that you collate and write up your data."

NIH officials admonished them about productivity as early as June of 1983, when Jesse Roth became scientific director of their institute and conducted a review of all intramural NIADDK staff. At one point, Stewart and Feder were granted time off from research in order to complete work on their first evaluation of the literature—their paper on the Darsee affair. The agreement was that they would then go back to laboratory research—with 20% time allocated to investigating the accuracy of other people's papers. But that has not happened.

By Stewart and Feder's own admission, their research is somewhat on hold and misconduct studies occupy most of their time. They say it is because NIH has so cut back their research resources that they can no longer do science.

NIH officials do not buy that. It is true that during the course of the past 3 or 4 years, Stewart and Feder's lab space has been cut back. It is true that when they (and many other NIADDK researchers were moved to a new building) Stewart and Feder were among those who ended up with space in the basement. They accuse NIH officials of retribution. In off-the-record interviews with *Science*, NIH sources argue that when space is tight, as it is all over the campus, you do not assign large amounts of space to unproductive workers. Furthermore, they say, someone has to occupy the basement labs which—minus a window—are like many NIH labs. Other scientists on the same floor, including a distinguished member of the Academy, apparently do not share Stewart and Feder's sense of persecution about it.

NIH officials are uneasy about Stewart and Feder's new role as watchdogs. But they have explicitly affirmed that it is important for NIH to honor the tenets of academic freedom; therefore, they believe it is right to allow Stewart and Feder some scope. And they do not refute Stewart and Feder's contention that studying the accuracy of the literature is a legitimate pursuit.

And now—perhaps most important—they acknowledge that it would be political

suicide to go after Stewart and Feder, whose public status as whistle-blowers has gained them the protection of powerful members of Congress—Representative Dingell in particular.

"It costs NIH perhaps a couple of hundred thousand dollars to keep Stewart and Feder," one source told *Science*. "The political costs of dumping them would be too high."

Eventually, NIH granted Stewart and Feder permission to submit their manuscript for publication. The editors of *Cell* and *Science* rejected it†. They have very recently submitted a revised version to *Nature*.

And Stewart and Feder continue their work as an unofficial fraud squad. The phones in their laboratory ring constantly with calls from people reportedly alerting them to cases of scientific error or misconduct. "About 100 allegations are brought a year that appear to be meritorious, or at least not delusional," Stewart told *Science*. He also said that he keeps no log of these calls. "I wouldn't want to keep records or have that minute an accounting," he said.

■ BARBARA J. CULLITON

Science *will report further developments in subsequent issues.*

†Reporters on the news staff of *Science* received copies of the Stewart and Feder manuscript from persons who were sent it by the authors prior to its formal submission to either *Cell* or *Science*. In fact, Stewart and Feder have circulated two draft manuscripts—one dated 1 May 1987 and the other 30 September 1987.

USDA Grants Program Threatened

In 1977 Congress established a competitive research grant program at the Department of Agriculture (USDA) to bolster basic research and enable more investigators from outside land-grant agricultural schools to participate in the field. While the funding for this program has varied over the years, Congress has always supported its competitive thrust—that is, until this year.

In a break with tradition, the House and Senate Appropriations Committees have both directed USDA's Cooperative State Research Service (CSRS) to fund up to $10.75 million in specific "research" projects in fiscal year 1989, which begins on 1 October. In the past, Congress appropriated funds for broad categories of research but never designated where the money was to be spent. Grants have only been distributed on the basis of competitive proposals that undergo peer review.

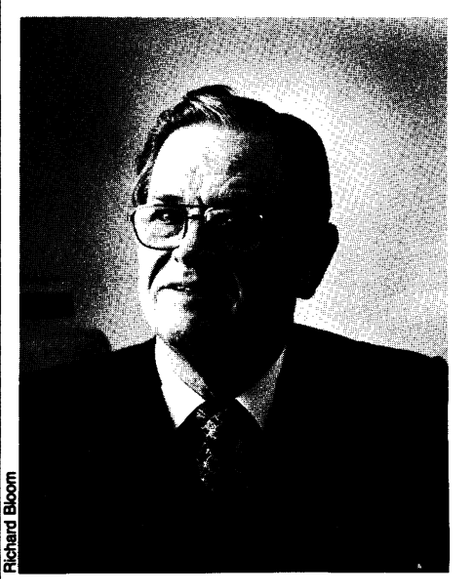
"We have had a fundamental breach of the program and its basic charter," says Pat Jordon, administrator of CSRS. "It will destroy the program. If they earmark 20% of the program this year, you can look for 75% of it to be earmarked next year."

Even without the pork-barrel projects, the competitive grants program could be savaged, depending on how a conference committee resolves differences between the bills passed by the House and Senate. The Reagan Administration recommended $54.5 million for the competitive grant program in 1989, a $12-million increase. The House, however, chopped the program to $29.4 million, while the Senate trimmed the budget by $1.5 million, to $40.8 million. In either case, says Jordon, there will be substantially less research funded next year because congressional "earmarks," the legislators' term for pork-barrel projects, will probably have to be funded.

Jamie Whitten (D–MS), chairman of the House Appropriations Committee, makes no apologies for the insertion of pet projects in the competitive grant program. He says the members were "performing a public service" by finding a way to go forward with these projects in the face of tight budget ceilings.

The biotechnology industry does not share Whitten's view. "ABC would be very concerned if Congress took on the responsibility of a granting agency in the absence of a peer review system," says Bruce Mackler, general council for the Association of Biotechnology Companies. "Those decisions are better made by the department."

One beneficiary of the House and Senate action is the Midwest Plant Biotechnology Consortium, which is composed of 16 universities and 37 companies, including the University of Chicago, University of Michigan, University of Iowa, Eli Lilly, General Mills, Quaker Oats, and Pioneer Hi-Bred International. The effort to organize the consortium first began in 1984 and has been led by Harvey Drucker, associate director for energy, environmental, and biological research at Argonne National Laboratory. The purpose of the consortium is to conduct basic research on key midwestern crops such as wheat, corn, oats, and soybeans. All research proposals would be subject to a peer review process.



Richard Bloom

Jamie Whitten *says members of Congress are "providing a public service" by finding a way to fund their pet projects.*

"Basically I think projects should stand on their own merit," says Alan Schriesheim, director of Argonne National Laboratory, a consortium member. The Midwest consortium, he contends, will pass that test. Schriesheim said, however, that he was not prepared to comment on the merits of funding the consortium at the expense of USDA's competitive grants research program. Drucker is away on travel and could not be reached for comment.

Dorin Schumacher, executive director of the consortium, told *Science* that she was concerned about the decisions of the appropriations committees to tap USDA's competitive grant funds. She hopes the department and the appropriations committees can work something out. But Schumacher could not say whether the organization's members would refuse to accept the funds if they are to be extracted from the department's competitive grants program.

Robert Haselkorn, director of the center for photochemistry and photobiology at the University of Chicago, says the consortium should decline the money if USDA's competitive research grant budget is going to be adversely affected. Haselkorn contends that the USDA competitive grants program should be much larger than it is now. The program could use $400 million, he says.

In addition to the Midwest consortium money, the House wants another $2.5 million in grant funds for the Michigan Biotechnology Institute, which would be charged with developing "new products and chemicals from agricultural raw materials." The Senate also has earmarked $2 million to create a national center for alternative pest control at the University of Arkansas. Still another $2 million of animal science grant funds would go to a food safety consortium composed of the universities of Arkansas, Kansas State, and Iowa State. Finally, $1.75 million more in biotechnology funds would go for waste treatment equipment to benefit Iowa State University and the city of Cedar Rapids.

■ MARK CRAWFORD