

also withdrawn from *Science* and since then has been entangled in the wrangling at NIH. The result is that neither Devi's original mouse study nor Williamson's confirmation has yet been published in a peer-reviewed journal.

In July 1993, Devi filed a sexual and ethnic discrimination complaint against her former NIH colleagues. In September, she filed a scientific misconduct charge as well. With the help of NIH's self-appointed misconduct police, Walter Stewart and Ned Feder, she accused the four NIH scientists of "theft of research and professional credit." On 18 December 1993, the *New York Times* ran a story on the allegations.

Starting in 1993, NIH and HHS investigated Devi's charges, including the charge that scientific data were plagiarized. Although NIH and HHS decline to comment for the record, officials say privately that the misconduct charge was dismissed in April in a precedent-setting decision by HHS's Office of Research Integrity (ORI). According to an NIH official, ORI ruled that disputes over credit among collaborators on a joint project are not to be treated as scientific misconduct. Devi's discrimination complaint, however, is still under review at HHS.

Through an attorney, most of the NIH team declined comment. Schneerson declined to respond except to say that "there is no truth to any of [Devi's] allegations." Yet 4 years ago, in a letter of recommendation for the FDA job, Schneerson wrote: "Dr. Devi ... suggested and successfully carried out the development of a conjugate vaccine against *Cryptococcus neoformans*. ... Dr. Devi's contributions to this work were both original and consistent. She has shown independence of thought and great interest in her work, which she carried out skillfully and carefully." Asked to comment on that letter, Schneerson says: "Mea culpa. I was too generous."

As far as publication of the disputed research goes, Gottesman says that last October he proposed an administrative settlement that asked Williamson and Devi to publish their work in a joint paper. Devi refused, according to letters she sent Gottesman. Although Gottesman believes his action freed Devi to publish in November, he says Devi apparently didn't realize she had won this right until the spring of 1995. She submitted a paper to NIH for clearance; Gottesman cleared it on 15 May 1995. Meanwhile, NIH researchers have tested the vaccine in Phase I clinical trials that are not yet ready for publication.

Perhaps Gottesman's action means this matter is on the verge of resolution. Yet even if the dispute ends tomorrow, this case has already slowed publication of results that many researchers would love to see published so that they can get on with research.

—Eliot Marshall

RESEARCH MATERIALS

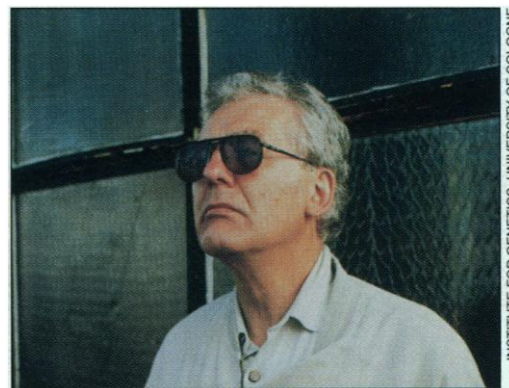
Share and Share Alike Isn't Always the Rule in Science

At one of the prestigious Keystone meetings last year, Klaus Rajewsky of the University of Cologne in Germany added something extra to his talk on B cells, the immune system's antibody-makers. The bonus was a slide listing knockout mice made in Rajewsky's lab that are available to other researchers. Knockouts, mice with a specific gene deleted, are key to much of what's hottest in immunology today—and naturally they are in demand. But many researchers say they have trouble getting knockouts from their colleagues, with requests being turned down, ignored, or put on hold for years. Rajewsky's slide threw down the gauntlet by showing his own generous policy. "It raised a lot of discussion," recalls Rajewsky. "Many people realized the situation should be made easier."

Science's investigation reveals that although most researchers who make knockout mice share them freely, some knockout-makers have developed a reputation for being less than completely openhanded. And problems in materials sharing aren't limited to mice. They crop up in cell-line repositories, crystallographic databases—indeed wherever competitors would like to share research materials. And these problems stir passions in the scientific community. "Typically, over coffee or beer at night, this is what our colleagues are talking about," says one researcher at the University of California, Berkeley, who insisted on anonymity.

Scattered indicators suggest that sharing problems may be getting worse. "We're finding more reluctance, more people wanting to hold on to their material for longer and longer periods of time," says Richard Mulivor, who runs the Coriell Cell Repository in New Jersey, a National Institutes of Health (NIH) contractor. A National Research Council (NRC) report last year on problems with sharing genetically engineered mice such as knockouts concluded that "increased cost and competition ... appear to be challenging the tradition of sharing in some branches of biological research."

These problems won't be resolved easily. For a start, as the NRC report stresses, sharing is hampered by increasing links between industry and academia. And on a personal level, sharing can be a volatile subject. Colleagues are wary of confronting each other: Dozens of researchers interviewed for this article would speak only if they were not named. Yet official bodies rarely intervene. NIH, for example, requires grantees to share freely af-



Dark views. Klaus Rajewsky says the sharing of knockout mice is more difficult than it should be.

ter publishing, but *Science* has found that this policy is rarely enforced. The combination of contentiousness and no clear institutional authority makes materials sharing one of the toughest areas of scientific conduct.

Pulling the knockout punch. As Klaus Rajewsky's Keystone gesture suggests, sharing is a particularly hot issue when it comes to knockouts and "transgenic" mice (which have novel genes added to the usual repertoire). These mice are a precious resource to immunologists, cancer researchers, and geneticists alike, and investigators have long complained that they are not shared freely (*Science*, 2 April 1993, p. 23).

Last year's NRC report, stemming from a 1993 workshop, focused on researchers who patent mice and license them to companies, which in turn sell them for exorbitant prices. This problem has since been addressed by NIH, the Howard Hughes Medical Institute (HHMI), and several volunteer organizations, which pooled funds to set up the Induced Mutant Resource repository at Maine's Jackson Laboratory to breed and distribute genetically altered mice for a modest fee.

But setting up the mouse repository at Jackson doesn't mean that everyone who makes knockouts embraces the ideal laid down in NIH policy, which all NIH grantees agree to abide by when receiving an award. NIH policy states that "unique research resources" such as knockouts must be made "readily available" to colleagues after they are published so as not to "impede the advancement of research and the delivery of medical care."

NIH Director Harold Varmus, who chaired the NRC meeting about sharing genetically altered mice, says the principle that applies to sharing is clear: "Once something's published, in my view, it should be accessible."

Oncogene researcher Robert Weinberg of the Massachusetts Institute of Technology (MIT) shares this view. "The public did not invest in making these things to accelerate my career but in order to move the field forward," says Weinberg, who says he distributes all reagents, mice included, no strings attached as soon as they are published.

Science's investigation, however, reveals that while no makers of knockouts simply refuse to share them, some researchers substitute their own policies for those of NIH: not sharing mice until long after publication, or sharing mice selectively. Insiders in the field—none of whom would allow them-

selves to be named—repeatedly mentioned Nobel Prize-winning immunologist Susumu Tonegawa as someone whose mice are not freely available immediately after publication. Tonegawa is an HHMI investigator at MIT who receives substantial NIH funding. He currently has three multiyear NIH grants, totaling \$1.2 million (65% of which is for direct costs); all three grants are for work involving genetically altered mice.

A number of researchers interviewed by *Science* cited a knockout called TAP1 as an example of a mouse made by Tonegawa that they had trouble obtaining from him. The TAP1 molecule (for "transporter associated

with antigen processing") plays a key role in the immune response against invaders such as viruses. Tonegawa's lab published the knockout in *Cell* in December 1992.

Interviews by *Science* turned up several researchers who had tried to get the TAP1 mouse from Tonegawa and been refused. One researcher says Tonegawa refused to provide the mouse for an experiment in an area outside Tonegawa's interest. "He said 'No way,'" this researcher says.

When *Science* contacted Tonegawa, he provided a list of 30 researchers whom he said had received the TAP1 mouse from his lab or the labs of his associates. *Science* at-

IIT: Serving Up Ethics for Lunch

Vivian Weil is a philosopher, not a chef. Yet she serves up one of the more provocative campus dining experiences: Bring your own lunch, and she'll provide ethical dilemmas for table talk. Welcome to the Illinois Institute of Technology's (IIT's) Research Ethics Sack Lunch program, which meets on the first Monday of every month at the Center for Study of Ethics in the Professions, which Weil directs. She started the sack lunches 4 years ago after a year-long stint at the National Science Foundation (NSF) studying ethics and values. Twenty showed up for the first lunch in February 1992; the numbers have stayed pretty much the same since.

Weil's sack lunch is only one element of IIT's multifaceted approach to raising awareness of research ethics among both students and faculty. For 4 years running, with funding from an NSF grant, Michael Davis, a research associate at Weil's center, organized and ran a week-long workshop to help faculty members teach ethics, called the Ethics Across the Curriculum Program. That program in turn led IIT faculty members to work ethics into their other courses.

The IIT workshops, says Weil, were sparked by young faculty members who felt an obligation to teach ethics but realized their training hadn't prepared them. "They felt that it was not legitimate for them to teach it," she says, "but with the right preparation they could and would."

The faculty members, selected from a pool of applicants, receive stipends for participating. Over the 4 years the program ran in the summer session, some 50 IIT faculty members attended. Attendees at the workshop are given readings from classical texts in ethics and moral philosophy, as well as articles and clippings on business, engineering, and research ethics—on the Challenger o-ring seal incident, for example.

Three weeks later, the participants return for a half-day session in which they present and discuss problems that they'll either put in homework assignments or exams or discuss in class. A week later, they come back for another half day to discuss how they will grade the problems, what weight they'll give them, and why. "The idea," says Weil, "was how to get them over the hump on how

they're going to do it." And the participants aren't finished until the end of the next semester, she says, "when they turn in a report that gives their student evaluations and describes what they did in class and evaluates it."

Based on these experiences, the IIT faculty is working ethics into courses ranging from mathematics to bioengineering to thermodynamics. Mukund Acharya, for example, who teaches a lab course on measuring systems, says he now devotes one of his sessions to a discussion of the ramifications of decisions taken about measurements in an industrial setting using a fictitious case study.

"We look at a small company that's manufacturing load cells which are going to be used in weighing machines," says Acharya. "One of the young engineers discovers a small flaw that can be corrected in one of the prototypes they're developing. He brings this to the attention of his boss, who says 'We'll take care of it in due course. There's no need to alarm our customers by discussing it. For the prototypes we're sending out, it won't be a big deal anyway.'"

Acharya presents the scenario, then has students discuss the issues from the point of view of the young engineer, the boss, the company, and the customers. "We look at all the different perspectives," he says; "try to figure out what's right. If the boss tells you to keep quiet, do you? Do you go to someone else in the company? ... It invariably ends up with the students having a fairly lively discussion."

Ethics Across the Curriculum serves to make students more aware of ethical issues; Weil's sack lunches serve the same purpose for the faculty. Participants spend the lunches discussing cases they've come across, and the lunches serve to expose faculty members to ethics issues and perspectives from fields outside their own. Few of the discussions, says Weil, are about classical scientific misconduct. "We're much more interested," she says, "in the ordinary kinds of problem that never rise to public scandals but can be damaging nonetheless. ... Of course, we know that misconduct occurs. But ... we think it's much more important to look at what supports responsible research and produces an atmosphere of trust."

—G.T.



Table talk. In Vivian Weil's Research Ethics Sack Lunch Program, the conversation focuses on issues of conduct in daily lab life.

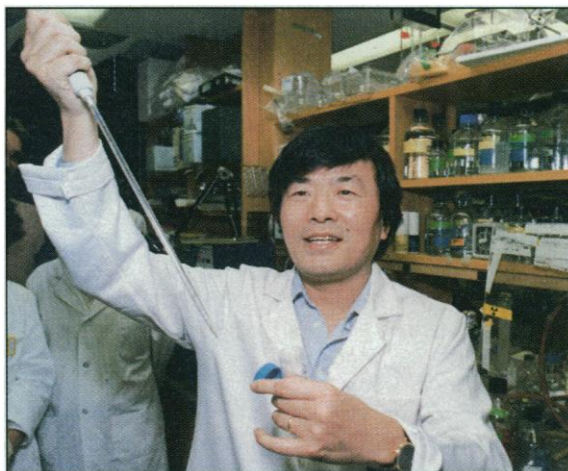
tempted to contact every researcher on Tonegawa's list who works in the United States; 15 of the 30 were interviewed.

Of the 15, three told *Science* they had requested the mice from Tonegawa but received no reply. More than a year later, each of the three says, they received the mice from Luc Van Kaer of Vanderbilt University, the former Tonegawa postdoc who made the TAP1 mouse. Of the 12 other researchers contacted, one says Van Kaer, at Tonegawa's urging, initially turned down his request because he was a direct competitor; that researcher was later given the mouse for a specific experiment in an area unrelated to Tonegawa's or Van Kaer's work. Four researchers say they received the mice as part of direct collaborations, in some cases initiated by Tonegawa's lab. Six other researchers said they requested the mice from Van Kaer after he left the Tonegawa lab; some said they hadn't bothered to ask Tonegawa because of a perception that he was reluctant to share.

Researchers are divided as to whether Tonegawa should be credited for sharing mice his former postdoc gave out. "It's not fair for Tonegawa to take credit for Luc's generosity," says one TAP1 recipient. Others, including Van Kaer, feel differently. "I was allowed to send the mice to whomever as long as they were not competitors," says Van Kaer. "That was generous of Susumu."

Tonegawa has not yet put the TAP1 mouse into the Jackson repository, where it would be freely available to all in the community who want it. Indeed, oncogene researcher Anton Berns of the Netherlands Cancer Institute actually went to the trouble of making a TAP1 knockout after hearing complaints from his colleagues that Tonegawa's TAP1 was not freely available. Berns, whose lab had earlier abandoned its TAP1 project because Tonegawa's lab was clearly ahead, says that when he heard the complaints, he began breeding mice and giving them away. "I was just pissed that they were not available," says Berns.

In response to questions from *Science*, Tonegawa provided a written statement regarding his distribution of knockout mice. The statement notes that he has made five of his immunological mutant mice available through the Jackson repository. It also says he is now willing to put TAP1 in the repository as well. He did not do so initially, he writes, because two postdocs in his lab had invested almost 18 months in making that strain. To protect those junior colleagues, he writes, requests for TAP1 mice "have been handled case by case depending whether the requester's project is directly in competition



Holding back? Colleagues have criticized Nobel Prize-winning immunologist Susumu Tonegawa for being less than completely openhanded in sharing knockout mice.

with the project of the postdoctoral fellows." Giving mice to direct competitors "would not only dismay and discourage young investigators but also can potentially jeopardize their careers," Tonegawa writes.

Tonegawa writes that he supports distribution of genetically altered mice through repositories such as the Jackson Labs. "What is much needed," he writes, "is a formulation of internationally acceptable and consistent guidelines for the distribution of these mice. I believe that, in light of the specific situation regarding the generation of these mice, a period of controlled distribution should be permitted even after publication of initial results." His statement concludes by saying that "if and when a reasonable and internationally applicable guideline which takes these issues into account is developed, we will be second to none in following it."

Tonegawa's sharing practices have their critics. But he also has stout defenders, some of whom join him in criticizing Varmus's position regarding sharing immediately after publication. Princeton University immunologist Martin Weigert, for example, calls Varmus's attitude "nonsense." He adds: "This ideal of communal science risks diminishing the importance of ideas." Weigert, himself a maker of engineered mice, says he "was the beneficiary of a very generous gift of probes very, very early" from Tonegawa. Columbia University neurobiologist Eric Kandel says

he has also benefited from Tonegawa's generosity, specifically with knockout mice made to study neurobiology, a field Tonegawa has recently been working in. "I find him to be perfectly reasonable, and I don't think in the neurobiology community there's been any trouble with him," says Kandel.

Tonegawa isn't the only one of the top knockout-makers whose sharing practices have generated heat. Another is Tak Mak, an immunologist at Canada's Ontario Cancer Institute. At the Keystone session where Rajewsky announced his sharing policy, Mak announced during his own presentation that his mice are also available. "There was sort of this giggle that ran through the room," says one critic who was there. Another critic complains: "He has said yes to me, but by the time I got the mice, the question I was interested in was unimportant."

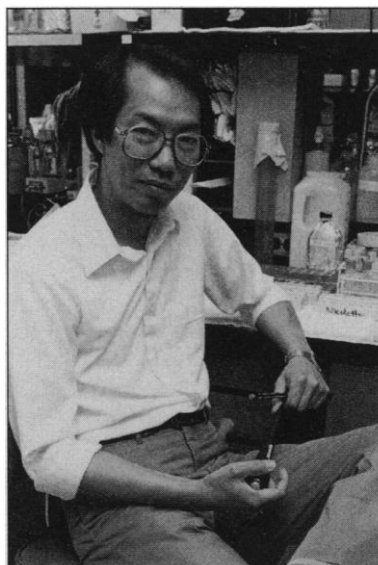
Mak says he knows some colleagues have trouble with his sharing practices, but he argues that they simply don't understand the problems that arise when a researcher makes many knockouts others want. "If I had made one mouse, I wouldn't get a bad reputation," says Mak. "But I've made 25 mice and published about a dozen. ... Everybody and their brother would like to get my mice, and if they don't get it within 3 months, they badmouth me."

Mak provided *Science* with a list of 116 researchers he has sent mice to during the past 2 years. Many, he says, are competitors; he told *Science* he has a full-time technician devoted to distributing mice. "There is not a single individual we have refused to send mice," says Mak, who does not charge for the mice. "We're just swamped. We receive two to three requests a week."

Unlike Tonegawa, Mak does not receive NIH funds. In addition, he has links to indus-

try that he says tie his hands where sharing is concerned. Mak says Jackson cannot distribute his mice because his institute is funded by Amgen, the California biotech company. Although he says the company has "allowed us to send mice out to everybody" who signs an agreement saying the recipient is using the mice only for research, Amgen lawyers review each transaction. Mak says he doubts Jackson would allow Amgen to have that level of oversight.

John Sharp, supervisor of Jackson's mouse repository, thinks he may be able to work something out with Amgen, but he has not yet approached



Tied hands? Immunologist Tak Mak says his ties to a commercial company, Amgen, make it difficult for him to deposit his knockouts in a repository.

Mak or Amgen. "If a mouse is held by a commercial company, it can turn into heavy negotiations," explains Sharp. Although Mak "has very important mutants," he adds, until recently Jackson has been flooded with mice sent in unsolicited and therefore didn't need to solicit others.

The problem of sharing knockouts isn't going away overnight. Indeed, even Rajewsky, whom immunologist Ronald Schwartz, who runs a mouse repository at NIH, calls the "saint" of the knockout-sharing enterprise, says that "it's a very difficult problem when you look at it in detail." Diane Mathis of the IGBMC in Strasbourg, France, concedes that "it hurts" to give out mice to competitors immediately after publishing them. But, says Mathis, the principles of scientific cooperation imply that "you're obliged to overcome the hurt."

Crystal clear. The knockout-makers aren't the only scientific community where some members seem to formulate their own rules. Take crystallographic data. Six years ago, the x-ray crystallography community confronted stubborn issues similar to those connected with mouse mutants. Like genetically altered mice, x-ray images and the accompanying data that reveal the structure of a macromolecule can take years to produce. And it can hurt to turn them over to a rival as soon as they're published. Not long ago, researchers discovered that those feelings were translat-

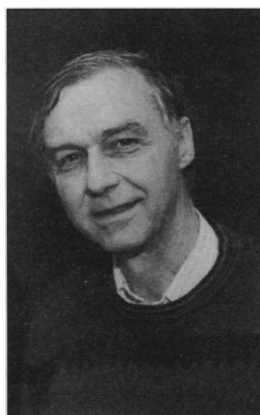
announcing the crystal structure is published, although researchers can put the coordinates on "hold" for up to 1 year after publication. "It's been remarkable how cooperative people have been," says Brookhaven head Joel Sussman.

But not everyone cooperates in precisely the same way. One who follows the Brookhaven guidelines without question is Brian Matthews, an HHMI investigator at the University of Oregon. Matthews is the database's biggest contributor, having deposited more than 200 structures, three times as many as his nearest competitor. "Experience has shown that science has been well served by the sharing of data—period," says Matthews. Matthews says he has never lost by being generous. "To the contrary," he says. "It's promoted other labs to use our data."

But other researchers appear to operate by their own rules. Brookhaven records obtained by *Science* reveal that the database's second biggest contributor, Nobel laureate Robert Huber, director of the Max Planck Institute for Biochemistry in Martinsried, Germany, routinely requests that structures be held for 2 years. The 1-year limit "may be an American standard, but it's not mine," says Huber. "It's not Europe's." Indeed, the British journal *Nature* has no rules regarding depositing coordinates; the journal merely "requests" that authors deposit coordinates. Yet Huber also publishes in *Science*, which does endorse the 1-year rule. *Science*, he says bluntly, does "not enforce the 1-year policy."

Huber says one motivation for his 2-year policy is that a shorter lag would give unfair advantage to commercial companies, which are under no compunction to share their data. "There is a strong competition with commercial companies," he says. "They of course hold their data back. I see no reason why we should give them our structures." Huber also says he thinks science benefits if he retains control of coordinates, because his contacts with colleagues who want to share his data lead to new collaborations. "I have no example," he says, "of where any collaboration begins when people get data freely from the database."

Science's investigation found other researchers who disagree with the 1-year rule but take an approach less direct than Huber's:



MAX PLANCK INSTITUTE FOR BIOCHEMISTRY

Different viewpoint. Robert Huber says Brookhaven's standards aren't his.

submitting partial data. The typical strategy is to submit only the central carbons, or "alpha" coordinates, of a structure's amino acids, but not the critical side chains. "It's a kind of compromise that I thoroughly disapprove of," says Harvard University's William Lipscomb, Brookhaven's fourth most frequent contributor. Disapproved or not, it's a stratagem some researchers adopt to meet the letter of the law while continuing to frustrate competitors.

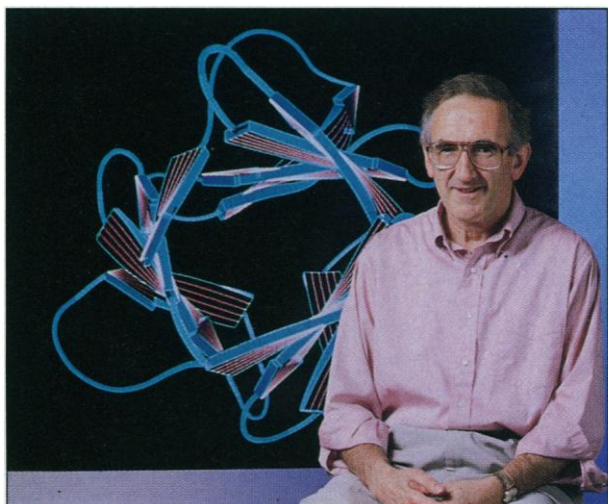
Carrots and sticks. Because the policies of journals, funders, and databases aren't resolving the sticky issues in materials

sharing, some researchers say a more active stance is needed. The National Center for Human Genome Research (NCHGR) offers one model of a funding agency taking the lead. "If you get a grant from NCHGR, any data you generate have to be in the public domain within 6 months," says NCHGR Director Francis Collins. "Now it's very much a part of the culture. It's a badge: I'm a genome scientist, and I have to be open." When those positive reinforcements don't work, says Collins, NCHGR takes action against rule-breakers, as it has done in a few cases.

As for other solutions, several researchers endorsed the idea of the National Academy of Sciences, NIH, HHMI, and leading journal editors getting together to issue a tough declaration about sharing. HHMI President Purnell Choppin notes that a Hughes committee is now drafting a report about sharing. The report, says Choppin, "comes under the heading of 'moral suasion' rather than a formal edict." Varmus says he would "prefer things be worked out in other ways" than asking NIH to be the enforcers, but he says if complaints are brought to NIH's attention, "we'll step in." As for other solutions, Brookhaven's Sussman argues that journal editors could do more, because editors can now easily check via the Internet whether a crystallographer is playing by the rules.

In the absence of institutional sanctions, the most powerful motivations are rewards and punishments from peers. "In a small community, shame is almost more powerful than any other type of sanction," says Richard E. Dickerson, a University of California, Los Angeles, crystallographer. On the up side, Harvey Lodish of the Whitehead Institute for Biomedical Research argues that "the system ultimately rewards people who are generous." Immunologist David Sachs of Harvard Medical School, widely respected for being generous with reagents, agrees. "'Do unto others as you want them to do unto you' works in science, too," says Sachs.

—Jon Cohen



KENT PETERSON

Win-win. Chemist Brian Matthews, Brookhaven's biggest contributor, says he's never lost by sharing data and materials freely.

ing into a reluctance to share.

Since 1971, a database for crystallographic coordinates has existed at Brookhaven National Laboratory. But in the late 1980s, it became clear that many important published macromolecules were not being deposited there (*Science*, 13 September 1989, p. 1179). As a result, the International Union of Crystallographers set a formal policy that NIH and several journals, including *Science*, adopted: Coordinates must be deposited when a paper