AUTHORSHIP

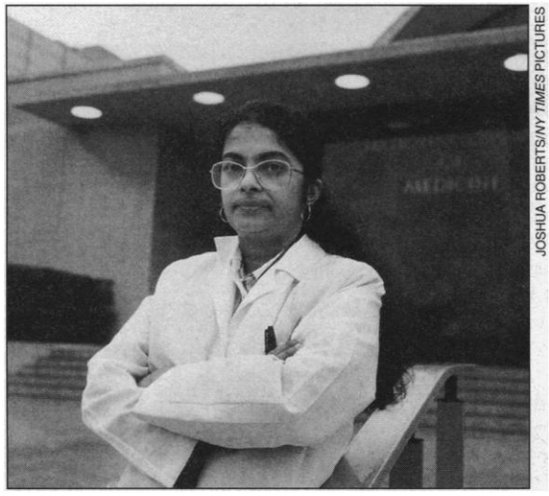
Dispute Slows Paper on "Remarkable" Vaccine

Arturo Casadevall, an expert on infections that prey on people with weakened immune systems, says he has worked with a "wonderful compound" made at the National Institutes of Health (NIH). This candidate vaccine is "remarkable," explains Casadevall, a faculty member at the Albert Einstein College of Medicine in New York, because it mobilizes the immune system to fight a deadly meningitis-causing fungus called *Cryptococcus neoformans*. And that's a boon, because there's no other vaccine or drug that can eradicate this fungus, which infects 8% of people with AIDS, often causing death. Casadevall dreams of the day he will be able to prevent meningitis with such a vaccine. But at the moment, a cloud hangs over NIH's dramatic discovery, because it is caught up in a quarrel over the authorship of scientific papers.

For 3 years, Sarvamangala Devi, the young researcher listed as first inventor of the vaccine on patent documents filed by NIH, has been battling two lab chiefs and her former supervisor at NIH over whose names should appear on a paper about the antifungal preparation. The fight has delayed publication of a report on the vaccine's efficacy in animal tests, and people who might move into this field seem to be hanging back, according to NIH mycology grants officer Dennis Dixon. This situation is "a tragedy," says Stuart Levitz, a researcher at the Boston University Medical Center who works on *C. neoformans*. "Here is a promising vaccine," and "nobody wants to touch it because you've got this dispute."

The battle over the *C. neoformans* vaccine is an extreme example of a phenomenon that is not rare in science: Poised for success, a collaboration disintegrates in bickering over intellectual rights. A junior staff member claims supervisors tried to grab credit for the work, while supervisors claim the junior person's contribution was minimal. Such disputes are the bane of academic publishing, says C. Kristina Gunsalus, chief ethics officer at the University of Illinois, Urbana-Champaign. Gunsalus says the complaint she hears most frequently is from "the student who believes that he or she has been deprived of appropriate authorship or credit for work." Quite often, Gunsalus reports, the student is the "victim of a misunderstanding" or an exaggerated sense of importance. But in many cases, she says, the grievance is justified.

Most cases of this kind attract little notice beyond a small circle of peers. But this one could have broad consequences, because in the United States, many thousands of AIDS patients are infected each year with *C. neoformans*. The scene for this dispute was set in 1989, when Devi, an Indian-born U.S. citizen, began working on vaccine development at NIH as a training fellow under bacteriologist-pediatrician Rachel Schneerson in John Robbins's lab at the National Institute for Child Health and Human Development (NICHD).



JOSHUA ROBERTS/*NY TIMES* PICTURES

Tough stance. Sarvamangala Devi filed misconduct and discrimination charges, claiming NIH colleagues took credit for her vaccine research.

Robbins's lab was well known for having developed a childhood vaccine to fight *Haemophilus influenzae* type B, a vaccine NIH officials credit with protecting thousands of children against mental retardation and death from meningitis each year. Devi's major task at the lab was to formulate a new vaccine using a bacterium (*Escherichia coli* K92) to generate antibodies to protect against bacterial meningitis. She performed the K92 work successfully, winning a place as lead author with Robbins and Schneerson on a paper in the August 1991 *Proceedings of the National Academy of Sciences (PNAS)*.

The first flare-up between Devi and her colleagues took place soon after the *PNAS* paper appeared, according to documents in a complaint filed with the Department of Health and Human Services (HHS) by Devi and obtained by *Science*. Rancor surfaced when the *Washington Post* ran a report on 15 August 1991 telling how "researchers led by John Robbins and Rachel Schneerson" solved a technical problem in manufacturing the bacterial vaccine. It described in detail how "the two researchers" manipulated a surface protein but failed to mention Devi's name. After Devi complained to Schneerson and Robbins, they notified the *Post*, which published Devi's name in a "clarification."

Soon afterward, even more contentious issues arose involving Devi's work on the vaccine against *C. neoformans*. This yeast-like fungus infects both healthy and sick people, but Casadevall estimates that 95% of cases are among AIDS patients. Researchers had come to believe antibodies could not be effectively mobilized against this or any other fungus. The consensus was that only another part of the immune system, its "cellular" arm, might be useful against fungi. The "existing paradigm," says NIH mycologist Dixon, held that a vaccine wouldn't work.

The NIH project challenged that paradigm. Devi became a link between the vaccine-making skills of the Robbins lab at NICHD and the expertise in fungi lodged at the clinical mycology section headed by John Bennett at the National Institute of Allergy and Infectious Disease (NIAID). It was Devi who conceived a plan to use NIH's vaccine technology to attack *C. neoformans*, Bennett acknowledged in a lecture he gave before the Infectious Diseases Society of America on 12 October 1992. And, according to an internal NIH memo, Bennett was initially skeptical of the plan.

Devi's strategy, she wrote in a statement filed with NIH, was to use a concept originated by the chemist Meir Wilchek of the Weizmann Institute in Rehovot, Israel, and adapted for bacterial vaccines by Robbins and Schneerson. Devi chemically joined a part of the fungal polysaccharide capsule to a known antibody stimulator—tetanus toxoid—and injected the compound into test animals. In 1991 she met with success: Mice treated with the vaccine showed a dramatic antibody response. Later studies, including those by Casadevall with NIH material, showed that the antibodies helped fight infection.

NIH quickly filed a patent application for a *C. neoformans* vaccine, dated 16 September 1991. Under the heading "first or sole inventor" is Devi's name. Schneerson, Bennett, and Robbins appear as second, third, and fourth inventors. *Infection and Immunity* published a paper in October 1991 describing how the vaccine promoted an antibody response in mice. Devi was the first of seven authors; Robbins and Bennett as lab and section chief took senior rank as last authors.

In the months following this publication, the collaboration came apart. Devi's term as a training fellow was ending, and NIH didn't offer to extend it. NIH officials refuse to

comment officially on why NIH was reluctant to extend her fellowship, but one observed that Devi and her colleagues "weren't getting along." With Schneerson's help, Devi applied for a fellowship at a bacteriology lab at the Food and Drug Administration (FDA) and was hired there. In February 1992, she moved to FDA, where she now works. Devi declined to respond directly to *Science*'s questions about her time at NIH, saying that NIH had instructed her to keep her case confidential. But she filed narrative and supporting documents for use in NIH and HHS investigations, which *Science* has obtained.

According to Devi's narrative, she left her original NIH data and lab notes with Schneerson in February 1992. However, she did try to retain some lab materials even after she left the Robbins lab. Negotiations over who would control these materials became tense, then angry. In a note to Devi on 7 May 1992, Bennett, Robbins, and Schneerson informed Devi they were accepting her resignation from the group and demanded that she return the materials. Devi responded the following day by letter that she was not resigning. In later memos, Devi contended that former male fellows had been treated as "guest workers," allowing them to extend their stay at the Robbins lab for as long as 3 years beyond an initial term.

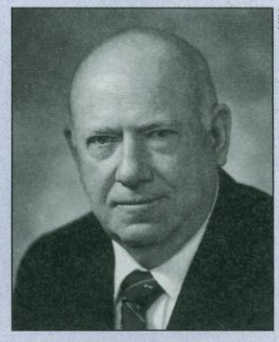
Arthur Levine, NICHD scientific director, intervened, writing to Devi on 11 May that "relationships have deteriorated beyond the point of salvage" and urging her to "go your separate way." On 13 May, Levine demanded Devi relinquish the research materials. She complied, but sought to publish a study on the vaccine's efficacy in mice and to remain involved in clinical trials of the specific lots of vaccine she had made. The NIH team declined.

Rather than having Devi work on further vaccine trials, Robbins and Bennett called on a medical fellow at NIAID, physician Peter Williamson. In May 1993, at a meeting of the American Society of Microbiology, Williamson presented data on the vaccine's efficacy. According to documents Devi presented to NIH to back up her complaints, she was in the audience for Williamson's presentation. She complained through the chain of command at NIH that Williamson was taking credit for her work. On 24 June 1993, Devi met with several top NIH officials, including then–Deputy Director for Intramural Research Lance Liotta. According to Devi's account, she was told her accusations were unfair and that she had been "divorced" from the project.

On 1 July 1993, Bennett wrote Devi that he had scoured the lab for her research notebooks that afternoon and hadn't been able to find them. Devi replied by letter on 15 July that she was "appalled" by the loss and by the fact that Bennett had not looked for the

"Better Relationships" the Stadtman Way

It's easy to spot Earl Stadtman in the National Institutes of Health (NIH) dining room. He's the older fellow who comes in with a gaggle of young scientists, talks through lunch, then departs with his pack, debating all the way back to the lab. Stadtman has been carrying on this way ever since 1950, when he joined the staff of the National Heart, Lung, and Blood Institute (NHLBI). His students—many now famous—describe him as a lab chief who fosters intellectual growth and self-confidence in juniors. A distinguishing feature of Stadtman's practice, say those who have worked with him, is his liberal awarding of authorship credit.


NIH

Mentor. Earl Stadtman is revered for giving junior colleagues responsibility and authorship early in their careers.

It's not that Stadtman is merely a mentor, sacrificing himself to speed younger researchers on their way. His own list of publications on enzyme regulation is very impressive. He's been elected by his peers to the National Academy of Sciences—along with his wife Thressa, also a senior NHLBI scientist. But former trainees interviewed by *Science* say Stadtman has a special touch with younger researchers on the way up.

Among those who have had the "Stadtman experience" are some of the best-known figures in biology: Roy Vagelos, chief of research and chief executive officer of Merck & Co. until his retirement last year; Michael Brown, an expert on genes and heart disease at the University of Texas, Dallas, who won a Nobel Prize in 1985; and Stanley Prusiner, of the University of California, San Francisco, who discovered the mysterious brain-damaging proteins known as prions. In different words each told the same story: Stadtman let them author papers and assume responsibility at a surprisingly early stage.

Vagelos recalls that in the beginning, Stadtman was "hesitant to take me on because I was the first MD-postdoc to work with him for an extended period." Vagelos concedes that "I was pretty much a novice in research." A recent medical school graduate, Vagelos spent 2 years as a clinical associate at NIH devoting half his official hours to patients and half to Stadtman's lab and his "spare" time to learning biochemistry. When Vagelos moved to the lab full-time, he says, Stadtman "handed me the project he was working on and started something else himself. ... He essentially pulled out of the research." Vagelos says this exemplifies Stadtman's "tremendous self-confidence."

In Stadtman's lab, Vagelos recalls no fights over authorship. But he does remember being put into a position of authority—and then being challenged to defend every assertion in a paper five or six different ways. Stadtman, he says, "was willing to get down there and argue with a person who was 6 months into science. ... The veins stick out on his forehead. ... He gets right into it with beginners."

Prusiner says he learned the same rigor from Stadtman. The lesson: "When you find something new, you need to prove it five or six independent ways," says Prusiner. In addition, Stadtman is starkly honest—"never afraid to say what he doesn't know," notes Prusiner. It's important for a young scientist to realize that "it's OK not to understand everything." As for authorship fights, there were none. Prusiner says Stadtman was generous with credit, "but I must say that when he didn't want to put his name on one of my papers, I felt a little uneasy."

For Brown, moving from med school to Stadtman's lab was "like walking from a murky, foggy world and suddenly entering this crystal-clear light of science." The most important thing he learned from Stadtman was an obligation "to think of every way possible to shoot down your own idea before you can begin to accept it."

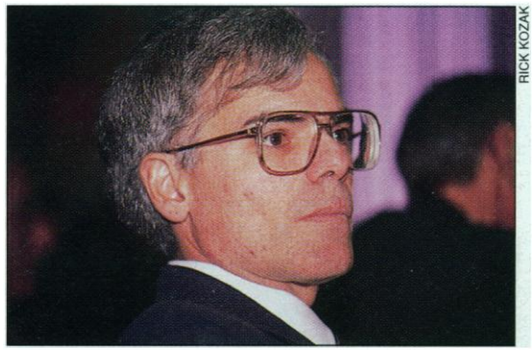
Questioned about how he handles authorship issues today, Stadtman told *Science* he has a simple rule: "In the case of postdocs, they do research and are senior authors on any publications that come out of their work. After the first year of study, my name will go on the paper as the last author; thereafter, they can publish independently anything that they do." Stadtman says that he would prefer not to put his name on such papers at all. But he found that if he didn't, "it led people to think I didn't believe the work was creditable." In general, he only signs papers for which he has done experiments or contributed directly in some way. In giving credit, he errs on the side of generosity because "it makes for better relationships all round."

–E.M.

notebooks sooner. Bennett and his colleagues decline to discuss the loss of the notebooks; NIH Deputy Director Michael Gottesman, who has been working to mediate the case, says the loss remains a mystery.

In the 1 July letter to Devi, Bennett wrote that because Devi's original data were lost, and because the copies Devi had made before leaving the lab were likely to be incomplete, he, Robbins, Schneerson, and Williamson had agreed that "neither you nor we have sufficient data to publish" the original mouse studies. He added, however, that with Williamson's help, the NIH team had "extended the mouse protection experiments which we began after you left the laboratory." Bennett added that the four team members would be publishing the mouse studies "with an acknowledgment for your assistance in vaccine preparation."

But NIH documents reveal that in May 1993, before Bennett's letter was written, Bennett and his NIH colleagues had already submitted a manuscript on a mouse study of the vaccine to *Science*. According to an administrative memo signed by Gottesman on 7 April 1994, Devi's contribution was "not clearly acknowledged" in that manuscript, nor had the manuscript been submitted to NIH for prepublication review. The authors withdrew the paper.



RICK KOZAK

Mediator. NIH's Michael Gottesman says the arrangement he has worked out leaves Devi free to publish.

In August 1993, Bennett and his colleagues submitted a revised paper on the mouse studies to *Science*, inviting Devi to be the second of five authors, with Williamson as first author. Devi balked at taking second place to Williamson, noting in a letter to Bennett that "I designed and performed experiments very similar" to those attributed to Williamson "well in advance of Dr. Williamson's involvement in the project." She added that she hadn't even seen the manuscript she was being asked to sign. She refused to collaborate under these conditions. That manuscript was

McGill: Analyzing the Data

While John Bailar was a statistical consultant for the *New England Journal of Medicine*, a position he held for a decade, he read "enormous numbers of manuscripts," a fair share of which he says seemed to be deceptive—whether consciously or unconsciously. The deception rarely involved fabrication, falsification, or plagiarism, says Bailar. Instead, the authors were "misleading readers and users about the strength of their evidence—trying to tell a pretty story when the story isn't pretty, trying to find a statistically significant result when there may not be anything there."

Bailar, now chair of the epidemiology department at McGill University in Montreal, says the papers he reviewed got him thinking about responsible science. He began teaching a course on the topic after he won a MacArthur Fellowship in 1990. Bailar started the course against the advice of colleagues who suggested students didn't need it: "They know it all, won't be interested; they'll be tied up with other concerns." But Bailar says "Students gobble it up; they're eager to learn what is acceptable conduct."

The course meets once a week for 3 hours during the month-long summer session at McGill. Bailar has about a dozen students, all at least graduate students. He likes to say he teaches a course on scientific conduct, with "misconduct and bad practice used only to cast light on good conduct." The reading material for Bailar's course consists of documents on both the good and not-so-good faces of science. On the one hand, his students must read the 1989 book by the National Academy of Sciences *On Being a Scientist* and the 1994 American Association of Medical Colleges pamphlet on "Maintenance of High Ethical Standards and Conduct of Research," along with McGill's own statement on integrity of research and scholarship. Then they are given reports of examples of purported scientific misconduct, with specific questions they have to answer "to make sure they really do think and don't just read them on the bus on the way in to class."

MCGILL UNIVERSITY

... and statistics. Epidemiologist John Bailar focuses his ethics course on how data are used to support a conclusion.

What sets Bailar's course apart from other ethics courses is that these assignments and the discussions that follow are as much about the scientific and statistical methods scientists use to draw inferences from their data as they are about what would ordinarily be considered good conduct or misconduct. As Margaret Somerville, director of McGill's Center for Medicine, Ethics, and Law, puts it, "Good ethics depends on good science. If you're not doing good science, you're not even in the ballpark of doing good ethics. So you have to know is this good science; is this statistically valid what you're proposing to do."

In one assignment, for example, Bailar's students read a 1993 *American Scientist* article by Judith Swazey and colleagues from the Arcadia Institute in Maine reporting on a survey of scientific misconduct at American universities. Swazey "surveyed graduate students and faculty members about what they knew regarding instances of misconduct," says Bailar. "It was a mail survey: shipped them out, dropped them back, did an analysis, and published." Rather than just discussing the results and assuming they are meaningful, Bailar asks his students to study the report's strengths and weaknesses, asking whether the data support the conclusions. Only then does he have them write on their own knowledge of misconduct.

An assignment that hits closer to home is analyzing the case of Montreal surgeon Roger Poisson, who admitted last year to falsifying data in research studies on the treatment of breast cancer. Bailar spends a short time in the classroom going over the details of the case, then tries to stimulate the most lively discussion possible. In the case of the breast cancer study, at least, Bailar certainly succeeded. "One of the seminar participants was a physician from one of the French hospitals here in town," says Charles Weiger, a postdoctoral fellow at McGill who is studying experimental medicine and took Bailar's course. "And there was quite a bit of argument over whether Dr. Poisson had been treated fairly, how serious in fact was the fraud, and so on." The discussion, recalls Weiger, was "memorable" and "loud."

–G.T.

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.

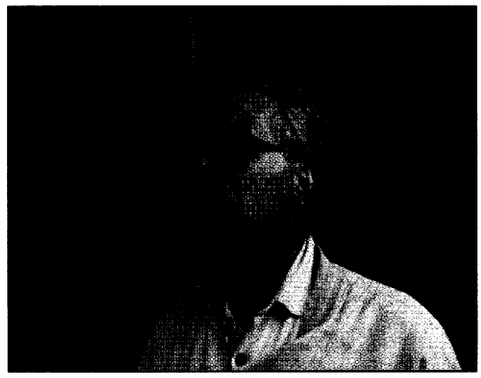
Perhaps Gottesman's action means this matter is on the verge of resolution. Yet even if the dispute ends tomorrow, this case has already slowed publication of results that many researchers would love to see published so that they can get on with research.

–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."



INSTITUTE FOR GENETICS, UNIVERSITY OF COLOGNE

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

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 after 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."