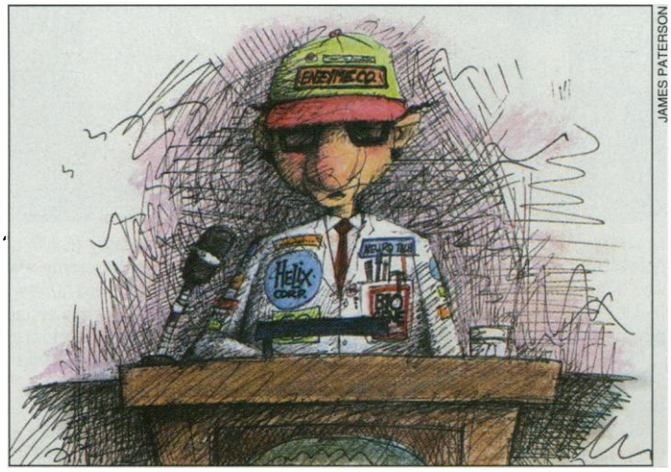
Confusion on the Cutting Edge

In many areas of biology these days it's hard to find a researcher who doesn't hold biotech equity. But there's little agreement on when or how those financial ties should be disclosed



JAMES PATERSON

Consider two cases that epitomize the thorny problems associated with conflicts of interest in today's cutting-edge biology. Harvard neurobiologist Dennis Selkoe is at the top of his field—the biological mechanisms of Alzheimer's disease—and is widely sought after as an author of both scientific and semipopular reviews. Indeed, within 2 recent years, reviews of Alzheimer's research by Selkoe appeared in *Science*, *Neuron*, and *Scientific American*. All three reviews mention work by scientists at Athena Neurosciences, a young biotech company that is doing key research aimed at eventually developing diagnostic tests or treatments. But what readers don't learn from reading any of these reviews is that Selkoe is the scientific founder and one of the largest shareholders in Athena: According to the company's prospectus, when Athena went public last November, Selkoe owned 255,000 shares of Athena stock, worth just over $3 million.

Another angle on the problem is presented by Johns Hopkins University biochemist Paul Miller. Miller is a major player in the field of antisense technology, where a fierce debate is going on over the utility of two different types of synthetic DNA analogs in blocking gene expression. When he wrote a review of one class of compounds for *Bio/Technology* last year and concluded that they "are promising candidates for development as therapeutic agents," readers had no way of knowing that Miller not only holds several patents on the compounds but is a cofounder of Genta, the biotech company to which they are exclusively licensed.

Should Selkoe and Miller have told the editors of those publications about their financial interests? Should that information have been passed on to readers? Selkoe and Miller say the idea of disclosing their affiliations never occurred to them. "I felt I was doing my usual academic job of writing a review," Selkoe says, pointing out that he also wrote about relevant work done at companies other than Athena. He and Miller both say they would have been happy to volunteer the information—if the editors had inquired about their financial ties. Not one editor did.

The reason none of the editors asked is that, like the researchers, they are venturing into uncharted waters, where few rules have yet been formulated. Ten years ago, it was unusual for a basic researcher in biology to have large holdings in a company directly related to his or her field of research. Today, in some fields it's hard to find a researcher who doesn't consult with or have equity in a hot biotech startup. But because the situation is new, there is as yet no consensus about how to handle financial conflicts—or even about whether they are serious enough to bother about.

If scientists are puzzled about ethical responsibilities in this realm, so are two of the main institutions that ultimately will have to provide guidance—journals and universities. With the exceptions of the *New England Journal of Medicine* and the *Journal of the American Medical Association*, which have rules requiring authors to divulge any financial conflicts that may influence their opinions, most major biomedical journals have no formal policies, relying instead on the judgment of their authors (for *Science*'s stand, see the editorial by Daniel E. Koshland Jr. on page 595). Likewise, most universities have not provided strong guidance for their faculty, largely because they've just begun to consider the issue. "This hasn't been the world we've lived in for the last 40 years," says Hal Aaslestad, associate dean for research at Yale Medical School. "We are to some extent all learning our way here."

So those on all sides are learning how to deal with conflicts of interest. To take a closer look at the shape of the learning curve, *Science* interviewed dozens of scientists from several fields that are particularly hot in biotech: neuroscience, antisense techniques, and immunology. Since there is no consensus in the biology community about how to handle such conflicts, we present a variety of anecdotes and a spectrum of responses to those situations. And at the end, to encourage our readers to become directly involved in the debate over conflicts of interest, we offer a fax poll (see page 625).

CONFLICTS OF INTEREST

In this special section *Science* addresses the problem of conflicts of interest in science. Beginning on this page, Marcia Barinaga considers the potential financial conflicts that are now emerging as an important issue in cutting-edge areas of biology—including neuroscience, molecular biology, and genetics—that border on the most lucrative new arenas of biotechnology. Beginning on page 620, Eliot Marshall writes about a much older and more pervasive form of conflict in science: intellectual conflicts of interest. He shows that a researcher's overriding investment in a particular hypothesis can be a great boon, helping scientific intuition cut through a mass of conflicting data, or a disaster, leading the researcher to ignore contradictory evidence on his way down an intellectual blind alley.

Why It Matters

Why would it matter whether a researcher discloses his or her investments in reporting or commenting on research? Surely, if it does matter, the reason is that the information might help a reader evaluate the researcher's perspective and motivations. That may be useful to all readers, but it is particularly important to those who are new to the field. And, among the new readers today is a group who are not even scientists: venture capitalists and investors trying to decide which new biotech company is the most promising. Investors' decisions are complicated by the fact that many biotech companies do not yet have products. "Some of these companies have gone public so early that you don't have any sort of concrete benchmarks" for judging their value, says biotech stock analyst Jacqueline Siegel of the securities firm Hambrecht &

Quist. In these cases, she adds, "the role of scientific publications has taken on a whole new meaning." Indeed, these companies are doing basic research much like the work being done in academic labs, and fortunes may ride on a company's ability to publish in top journals and garner other forms of scientific recognition.

One company that burst on to the stock market last year was Regeneron Pharmaceuticals, which specializes in the study of nerve growth factors as potential therapeutic agents. Regeneron had a wildly successful initial offering; reported by *The New York Times* to be the second largest in biotech history, it netted the company more than $90 million. That stock sale came just 10 days after Regeneron's 21 March 1991 report in *Nature* that the nerve growth factor BDNF may boost the survival of neurons that degenerate in Parkinson's disease. The article was accompanied by a favorable commentary in *Nature*, and was written up in *The New York Times*.

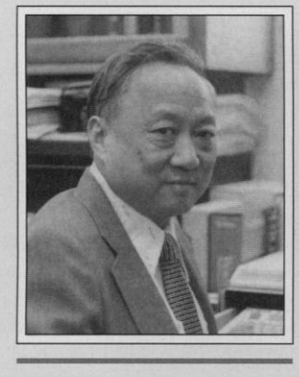
Was there any connection between the favorable scientific and lay press and the high stock price? No one in the business is willing to say how closely coupled these factors are. "Having been around this business for a year now with a public company, I couldn't begin to tell you what influences stock prices," says Stanford University neurobiologist Eric Shooter, one of the scientific founders of Regeneron. Stock analysts are also reluctant to venture a guess as to whether the publication and media attention played a role in Regeneron's successful offering. But Jim McCamant, editor of *Medical Technology Newsletter*, admits that "everything else being equal, you'd love to have scientific publications come out before your deal is done."

But what if the scientists reviewing such a paper for publication happen to own stock in the company or in one of its corporate competitors? It may seem likely that such a person would voluntarily reveal his or her potential bias, but most journals have no way of ensuring that this is so. *Nature* editor John Maddox says he didn't know whether Solomon Snyder, the Johns Hopkins neuroscientist who wrote the favorable commentary on the paper that preceded Regeneron's initial stock offering, had any financial interest in Regeneron. It turns out he doesn't, but it was not *Nature*'s policy to find out. And *Nature* is hardly alone. Editors at *Science* weren't aware of Selkoe's role in founding Athena when he wrote a commentary on several papers, including one from Athena, in 1990; nor did *Science* then have any policy of requesting financial disclosure by authors.

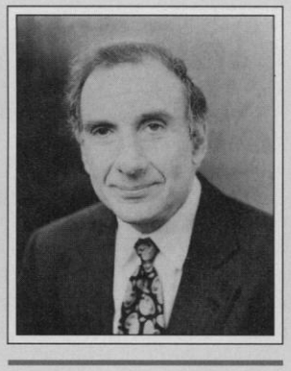
And many researchers who spoke with *Science* don't assume journals need any specific policies for dealing with such situations. In fact, some of those researchers think these situations simply don't raise fundamentally new issues. They argue that scientists have always had to deal with powerful conflicts of interest—conflicts stemming from their intellectual investments in particular theories—and are therefore accustomed to examining their own views for signs of bias (see article on intellectual conflicts of interest on page 620). "I don't perceive that these problems are qualitatively different from the problems we have always had to wrestle with in reviewing people's grants and papers," says neurobiologist Eugene Johnson of Washington University in St. Louis. "It's just a new wrinkle in an old problem."

Ethicists, however, are less inclined to trust individual soul-searching as a way of handling financial conflicts. "All of us have conflicting interests, but to the extent that money comes to bear, it's a much more weighty sort of thing," says ethicist Philip Boyle of the Hastings Center. "All journals should insist on [financial disclosure]," adds biomedical ethicist Arthur Caplan of the University of Minnesota. "It is not up to the individual to decide whether or not their relationships and associations influence their perception of information, or...the weight they give to findings. It is up to the recipient of the information."

That's where the journals come in. Although most journals haven't handled the problem in an explicit manner until now, that could be changing. In at least one instance, *Nature* has already decided to list an author's financial interests. Earlier this year, the journal solicited a commentary on DNA fingerprinting technology from a researcher who also consults for a DNA fingerprinting company. "We agonized about whether we should ask somebody known to be a consultant," says Maddox. The decision was made to go ahead, Maddox says, because, regardless of corporate ties, the editors thought they had found the best person to write the commentary—but they took the unusual additional step of informing the readers about the author's financial ties. The resulting author-identification line—which appeared in the 16 January 1990 issue of *Nature*, read "John Brookfield is in the Department of Genetics, Queens Medical Centre, University of Nottingham...and is a consultant for Cellmark."

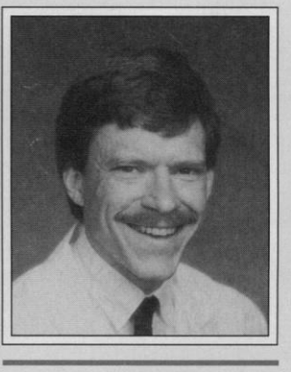


"[Disclosure] makes it seem I am expressing a commercial opinion, and I am not."
—Paul Ts'o



"[Commercial affiliation] is relevant to the intellectual analysis of the work."
—Malcolm Gefter

"I would feel extremely uncomfortable" unless I disclosed my equity holdings.
—Irving Weissman



"If I didn't make it clear that I was not with a company, anything I said would be suspect."
—Arthur Krieg

Not a Commercial Message

But journal editors worry that such tag lines may appear to question the integrity of their authors. And in some cases authors do take it personally. Paul Ts'o, cofounder of the antisense technology company Genta, says that if a journal required such a line on a review article, "I probably wouldn't even

bother to write a review for that journal. It makes it seem I am expressing a commercial opinion, and I am not."

But that position is a bit too simplistic a solution for some. "You cannot presume to say, 'I am reviewing this [field] with only my scientific hat...I'm not reviewing it with my pocketbook.' That would be absurd," says Massachusetts Institute of Technology (MIT) immunologist Malcolm Gefter. Gefter says he discloses his role as a founder of the biotech company ImmuLogic whenever he writes or speaks about topics related to the company's work. "The disclosure should be there," he says, "because it is an affiliation that is relevant to the intellectual analysis of the work."

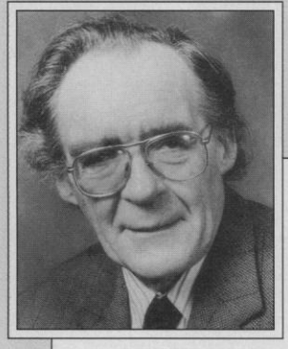
Since few journals and fewer institutions have specific guidelines about public disclosure of financial ties, individual researchers are put in the position of having to draw up personal guidelines about disclosing potential conflicts. And, as a diverse group, they are drawing those lines in very different places. At one end of the spectrum are scientists who never disclose even major equity holdings; at the other end are those who eschew commercial ties altogether. Most scientists, however, find their comfort zone between these extremes. For example, Washington University's Johnson, who works in the commercially active area of nerve growth factors, has decided to consult for several companies but not to hold equity in any company in his field.

But no single personal guideline can remove the need for evaluating individual cases one by one. Johnson acknowledges that recently he had to think carefully about how to proceed when, as associate editor for *The Neurobiology of Aging*, he was asked to handle a paper from one of the companies he consults for. "If [it had been] sent to me for review," says Johnson, "I would not have reviewed it." But he felt that he could be fair in choosing reviewers and making a decision based on their reviews. Johnson says he told the editor-in-chief about his situation and adds that in his choice of reviewers he was even "more circumspect than I would be if it were from any of the 100 or so academic colleagues I know and consider as friends." The editorial decision he had to make when the reviews came back was "not marginal," he says. "I felt comfortable and the editor felt comfortable on this basis."

And section editors aren't the only ones to face such dilemmas. Members of the National Academy of Sciences can sometimes find themselves in a similar position when they are asked to communicate papers to the *Proceedings of the National Academy of Sciences*, a process that involves selecting peer reviewers for the manuscript and evaluating the reviews. Stanford immunologist and academy member Irving Weissman last year drew his own personal line when he was asked to communicate a paper by scientists at SyStemix, an immunology-based company he cofounded. Rather than act as editor himself for the paper, Weissman asked *Proceedings* editor Igor Dawid to take over the communicator's usual responsibilities of choosing reviewers and handling their reviews. But later last year he contributed a second SyStemix

Journal-istic Guidelines

Financial conflicts of interest are only now emerging as a consideration for editors of basic science journals in biology. But in the clinical arena, where researchers' ties to commercial interests are long-standing, journals have been struggling with the issue for years. As a result, they are out front in establishing guidelines. In the mid-1980s, both the *Journal of the American Medical Association* (*JAMA*) and the *New England Journal of Medicine* began asking authors about financial ties and revealing those ties to readers when they found it appropriate. Their reasoning, in the words of *JAMA* deputy editor Drummond Rennie, was that clinical papers are so "close to the prescription pad," that profit-motivated bias could directly affect patient treatment. In 1990 the *New England Journal of Medicine* toughened its rules and stopped accepting editorials or review articles from authors with financial interests in the subject of the review.

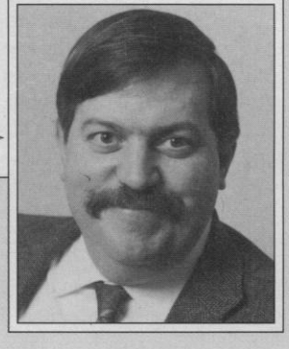


"Disclosure is the simplest and easiest way. We should do it."
—Douglas McCormick

Until now, basic science journals have seen little need to follow the lead of their clinical counterparts—but that is changing. *Science*'s new policy (see page 595), modeled after the policy in place at the National Science Foundation, requires authors and reviewers to inform the journal of any relationships, financial or otherwise, that could be viewed as conflicts of interest. "What we are asking for is anything that will tilt your intellectual opinion," says editor Daniel E. Koshland Jr. "If you have written all your life for the Sierra Club, we ought to know that if you submit an article on the environment. That doesn't necessarily mean we don't want your opinion, we just want to know possible influences on your opinion."

Nature editor John Maddox says he wouldn't rule out establishing a policy but has taken no action yet. Ideally, authors and reviewers would voluntarily reveal any potential conflicts, he says, but most don't consider such disclosure obligatory. "I think the climate of opinion is going to change, and they will," he adds. "If need be, we will do what we can to encourage them."

"I think the climate of opinion is going to change [in favor of disclosure]."
—John Maddox



Cell editor Benjamin Lewin refused to speak with *Science*, or to reveal whether he has considered a financial disclosure policy. But other editors said they are considering the issue. "Disclosure is the simplest and easiest way" to approach the problem, says Douglas McCormick, editor of *Bio/Technology*. "We should do it. We probably will." *Journal of Neuroscience* editor Dale Purves says he has become increasingly convinced that journals such as his may need to adopt disclosure policies. "There is no question that more and more, the potential for conflict exists," he says. "A few years ago, [if I were asked about the need for a policy], I would have said, 'Forget it.' But now I think one has to think about it."

One editor who wasted no time in moving from thought to action is Gavin Swanson, editor of *Trends in Neurosciences*. "It hadn't actually occurred to me to ask people to disclose their associations," he told *Science* several months ago, when interviewing for this story began. But since then, Swanson and Stanford neuroscientist Eric Shooter decided to note Shooter's role as chairman of the scientific advisory board and director of Regeneron Pharmaceuticals on a review article by Shooter that discusses some of the company's work. Swanson says he is curious to see the response to the Shooter article but has no formal policy changes in mind. "It's sort of an experiment with an *n* of one."

–M.B.

paper without those precautions. The reason, he says, is that he was a coauthor on the second paper. "I take responsibility [for the work] if I'm an author," he says.

Weissman's handling of the first paper is hailed by some of the researchers *Science* spoke with as exemplary, but it's an example that isn't being widely followed. Current *Proceedings* editor Lawrence Bogorad of Harvard says that of all the academy members who contribute papers from companies in which they hold stock, Weissman's case is the only one he knows of in which the member delegated the choice of reviewers.

Peer (Review) Pressure

Although the role of author of a hot paper or editor of a leading journal might seem like the most obvious place for difficult choices, there are other roles that may present just as many quandaries, such as that of peer reviewer. Scientists seem uniformly to agree that it's inappropriate to referee papers from companies in which they have financial interests. Many, however, find reviewing papers from commercial competitors of those same companies to be less problematic. "If I felt I could be objective about it, I think I would review it," says neurobiologist and Regeneron consultant Lloyd Greene of Columbia University. What's more, says Greene, if he thought he could be impartial, he wouldn't feel the need to advise the editors of his financial ties. Washington University's Johnson says he would "have no compunction" about reviewing a paper from the competitor of a company he consults for, but adds that, "I would make sure the editors of the journal knew my situation."

As in the case of authorship, it might be easier for referees if journals had clear disclosure policies. But journal editors are as worried about irritating referees as they are about insulting authors. "It's hard enough to get people to referee a paper anyway," says a biologist, demanding anonymity, who acts as section editor for a journal. "If I'm going to ask all my referees for full disclosure, they'd just say, 'Forget it, I'm not going to be bothered and I won't referee it.' "

To make things even trickier, publication isn't the only place scientists are trying to pick their way though unfamiliar obstacles on this subject. In fact, the issue comes up wherever scientific information is being communicated, and that includes conferences and seminars. A few months ago biochemist Arthur Krieg, who does antisense research at the University of Iowa, was speaking at a biotechnology meeting attended by venture capitalists. As he listened to talks by scientists with industry connections, Krieg recalls, he realized his view of their talks depended in part on what he knew about their affiliations. He assumed, he says, that those who had corporate ties were presenting the sunniest possible view of their technologies.

"I was the first speaker for antisense, and I realized that if I didn't make it clear that I was not with a company, anything I said would be automatically suspect," he says. "When I opened my talk, I said...I was at a university and I wasn't affiliated with any companies, and I didn't have any patents, and so I was going to try to tell them what I really, honestly thought the truth was about the antisense field." Krieg says many in the audience found his comment amusing, but that afterward some potential investors thanked him for making his position clear.

Krieg's situation was unusual on two counts. First, he was speaking to investors, not academics; second, he has no commercial ties. More common is the case of a scientist with commercial ties speaking to a university audience. "I get asked to give general lectures on neurotrophic factors around the country," says Stanford's Shooter, cofounder of Regeneron. "The dean here has suggested that when we start off, we should say, 'Please take note that I am involved in this particular company.' I do, when I remember," he adds. "The trouble is, in a university setting, you don't always remember."

Shooter's colleague Weissman says he would have a hard time forgetting his affiliation, no matter where he's speaking. A leader in the study of stem cells (the cells that are the precursors of the immune system), Weissman developed a method for purifying them. SyStemix, the biotech company he cofounded, was bought by Sandoz last December, based on the patents it holds on human stem cells and their purification. Weissman says he discloses his relationship with SyStemix whenever he gives talks on stem cells. "When I move into discussing human stem cells, I say, 'The work I'm going to describe now was carried out at SyStemix, and I want you to know that I have a very significant equity holding in SyStemix.' I get mixed responses to that," he says, "but I would feel extremely uncomfortable talking about it without them knowing."

While scientists like Weissman or Krieg feel uncomfortable not letting audiences know where they stand financially, others are very uncomfortable revealing personal money matters. "Perhaps the best thing is full disclosure," says an antisense researcher who requested anonymity, "but the reason I bristle at that suggestion is that many people consider financial matters confidential." Adds another, also anonymously: "At least some of us are a little bit embarrassed about the [corporate] association." But that embarrassment may be the least powerful factor in the complex situation that journals, universities, and, most of all, individual researchers, are going to have to be navigating their way through in the next few years—as the thicket of connections between commerce and academia grows ever more tangled.

–Marcia Barinaga

Not Merely Academic

Among the major players in the quandaries that arise as a result of conflicts of interest are the research universities. And, indeed, most research universities do have conflict-of-interest guidelines. But in most cases, those guidelines focus on faculty conduct that could directly conflict with university interests. Typical guidelines, for example, limit the time a professor is allowed to spend consulting for industry or prohibit a faculty member from being president or CEO of a company. But few universities provide either guidance or rules on issues such as when, how, or even whether faculty should publicly disclose their corporate ties.

Two institutions, however, have broken new ground by drawing up guidelines that add disclosure of potential financial conflicts to the behavior required of research scientists: the medical schools at Harvard and Johns Hopkins. Two years ago, Harvard plunged into the thicket of financial conflicts by instituting an elaborate set of rules that include a requirement that any faculty member "providing expert commentary on a subject" must make a public disclosure of financial interests relating to the subject. But the presence of a rule doesn't mean the culture of science immediately changes. In fact, says Eleanore Shore, Harvard dean for faculty affairs, the university doesn't actively enforce the public disclosure rule; faculty are left to interpret it on their own.

The Johns Hopkins School of Medicine has instituted a new policy that goes farther than the policy at Harvard, both in its terms and in its mechanism for ensuring compliance. The Hopkins' rules require that any professor with commercial involvements have his or her situation reviewed by a standing committee. If that committee finds the arrangement acceptable, says David Blake, senior associate dean at the Hopkins medical school, the committee "will coauthor with the faculty member a disclosure statement which will have to go on all publications." In public talks, he adds, "we're expecting people to [show] a slide that has this wording or to include it in the abstract."

–M.B.