



Can you believe what you read?

Scientists' financial interests can bias the papers and review articles that they write, studies suggest. But what can editors do to police the issue? Frank van Kolschooten examines journals' policies on conflicts of interest.

Money talks, so they say. But is it whispering covertly through the pages of leading science journals? Too often, the answer is yes, claims a letter sent last month to some 200 journals by the Center for Science in the Public Interest (CSPI), a non-profit organization based in Washington.

The letter urged the journals to strengthen their policies on the disclosure of conflicts of interest — and given that its signatories include former editors of *The New England Journal of Medicine* (NEJM) and *The Journal of the American Medical Association* (JAMA), it cannot simply be dismissed as the blusterings of a fringe element. “Whether the issue is clinical research, cancer clusters or global warming, corporate interests can hide

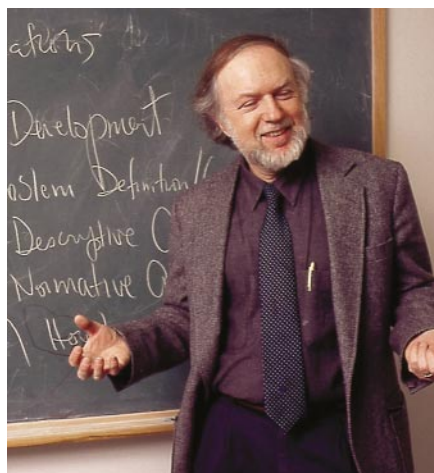
behind the credibility of peer-reviewed journals,” argues Virginia Sharpe, who heads the CSPI’s Integrity in Science project.

As the links between commerce and academia deepen, how to deal with the conflicts of interest that inevitably arise has become an increasingly important issue. Next week sees two meetings devoted to the subject: at Emory University in Atlanta, Georgia, researchers, entrepreneurs and others will meet to debate the ‘Commercialization of the Academy’; meanwhile, Warsaw in Poland will host an international conference on conflicts of interest in science and medicine.

The Warsaw meeting will be addressed by the current editors-in-chief of *JAMA* and *NEJM*. As research agencies, academic institutions and scientific societies all debate

the issue of conflicting interests, journal editors are finding themselves on the front line — the scientific literature is, after all, the main forum for the communication of research results. Some of these editors are thinking hard about strategies to minimize the potential for publications to be biased by commercial pressures, and to draw their readers’ attention to any conflicts of interest that may exist.

Lisa Bero, a pharmacologist at the University of California, San Francisco, who studies how science influences clinical practice, has no doubt that commercial interests are biasing the scientific literature. “Studies that are sponsored by a single company are biased compared with studies with multiple or other sponsors,” argues Bero, who signed the CSPI



Lisa Bero (left) and Sheldon Krinsky worry that vested interests are distorting published science.

letter. "When research is funded by one company that has an interest in the outcome it is much more likely to have a favourable outcome for the sponsor's product."

In 1986, Richard Davidson of the University of Florida College of Medicine in Gainesville reviewed 107 published clinical trials and found that those sponsored by drug firms were more likely to report favourably on the treatment being tested¹. Since then, several studies have provided support for Davidson's conclusion². One famous example reviewed 70 articles commenting on the safety of calcium-channel antagonists, a class of drugs used to treat cardiovascular disease. Among the authors of original research papers, reviews and letters to the editor that were supportive of the drugs' use, 96% had financial relationships with the drugs' manufacturers; for publications deemed neutral or critical the figure was only 60% and 37%, respectively³.

Clinical precision

The factors that underlie such biases remain unclear. "It could be because negative or unfavourable studies aren't published; it could be that companies are not dumb enough to fund a study that is not going to work out; it could be that they are conducted or designed in a poor way," Bero speculates.

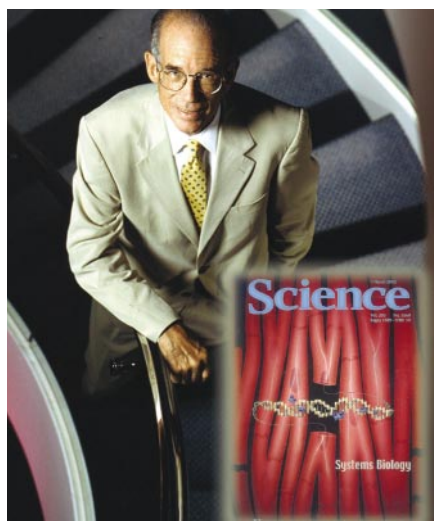
Concerns about commercial conflicts have been most acute in clinical medicine — where human lives may be at stake. Medical journals have led the way in introducing editorial policies to deal with conflicting interests, and they continue to blaze a trail (see 'Who controls the data?', overleaf). At the heart of each policy lies the concept of disclosure: if everyone is made aware of authors' financial interests, goes the argument, the potential for bias can be borne in mind by the reader. But how full that disclosure should be, and how to encourage authors to comply with a stated policy, remain matters for debate.

Leading multidisciplinary journals such as *Nature* and *Science* have also adopted con-

flict-of-interest policies — as have journals in fields such as nutrition, where commercial conflicts have become a serious concern. But in many scientific disciplines the issue is still not on editors' radar screens, despite the best efforts of the CSPI and its supporters. "This is a potential problem in any science in which there is a commercial interest," says Sheldon Krinsky of Tufts University in Medford, Massachusetts, who has studied the conflict-of-interest policies of leading journals and will speak at next week's meeting in Atlanta.

The CSPI's letter was sent to journals in fields including climate research, environmental science and chemistry. Bruce Coull of the University of South Carolina in Columbia was moved to sign the letter by his concerns about commercial conflicts in his own discipline of marine ecology. "Many scientists in our field are sponsored by companies or work as consultants," he says. "I would like to know that when I read their publications in ecotoxicological journals, but most of these journals don't have disclosure policies."

Orrin Pilkey, a coastal geologist at Duke University in Durham, North Carolina, and



another signatory of the CSPI letter, feels the same way. "I see more and more examples of studies with a huge amount of optimism, written by scientists who also work as consultants for companies," he says.

But it seems that the CSPI has some way to go in convincing journal editors to address the issue. "Life is pretty complicated already and this would be another layer of paperwork," says Charles Finkl of Florida Atlantic University in Boca Raton, and editor-in-chief of the *Journal of Coastal Research*. Other editors fear that rigid policies could make researchers send their papers elsewhere. "Every time you put another barrier in the way, people can go to another journal," observes Martin Blume, editor-in-chief of the American Physical Society, which publishes *Physical Reviews*, *Physical Review Letters* and *Reviews of Modern Physics*.

Blurred vision

Even among editors who have embraced the general principle of disclosure, there is considerable divergence over what this should mean (see table, overleaf). One controversial issue, for instance, is whether authors' conflict-of-interest statements should be given to the referees asked to review a manuscript. Donald Kennedy, editor-in-chief of *Science*, explains why his journal does not do this: "That's not part of the referees' job. They are supposed to review the quality of the science; they are not ethicists." *Nature* has the same policy of not disclosing conflict-of-interest statements to reviewers.

But some journals do send the disclosure statements to referees — for good reason, argues Krinsky. "Personal financial interest is a relevant factor in raising the scepticism of peer reviewers," he claims. "There are too many articles that are not sufficiently rigorously reviewed, so the flaws in them are only disclosed after publication."

Another issue that divides the journals is how to deal with the financial interests of the referees themselves. Jeffrey Drazen, editor-in-chief of *NEJM*, says that his journal pays close attention to this potential source of bias. "We ask



In agreement: Donald Kennedy (left) and Philip Campbell back disclosure to readers but not referees.

Who controls the data?

Last September, 11 major medical journals introduced a tough new publication policy. In future, they demanded, authors must sign a statement verifying that they have been involved in the design of the study, and in analysing and interpreting the data. They also must declare that they have seen the raw data and that the sponsor of the research did not have control over whether the results could be published.

"This declaration concerns all kinds of sponsors," says Catherine DeAngelis, editor of *The Journal of the American Medical Association (JAMA)*. "But it was the pharmaceutical companies that forced us to do this. We know several examples of studies where the company and not the sponsored researcher controlled the data."

In several notorious examples, companies have suppressed the publication of clinical trials that reflected poorly on their products. In the 1990s, for instance, a team led by Nancy Olivieri of the Hospital for Sick Children in Toronto, Canada, concluded that deferiprone, used to treat thalassaemia, did not adequately control the build-up of iron in patients' livers. Thanks to a clause in Olivieri's contract with the drug's manufacturer, Apotex, she had to wait three years before publishing her results⁹.

In another case, results suggesting that Synthroid, the leading drug used to treat people with underactive thyroid glands, was no more effective than cheaper alternatives remained unpublished for seven years. During this time, the British company Boots Pharmaceuticals tried to enforce a clause in its contract with Betty Dong of the University of California, San Francisco, that gave the company a veto on publication. After a titanic tussle, Dong eventually published her results in *JAMA*¹⁰.

How many more such papers have never seen the light of day, and how many favourable papers are really the work of drug companies, rather than the scientists named as authors, remains unclear. But Jeffrey Drazen, editor-in-chief of *The New England Journal of Medicine*, says that his experience of researchers who fail to answer questions about their own manuscripts convinces him that the latter does occur. "They don't call you back themselves, but you get the sponsor on the phone, who doesn't want to tell you everything because of his competitive position," says Drazen. "Usually we are forced to reject such a manuscript."

Richard Horton, editor of *The Lancet*, says that the reaction from industry to the new rules has been interesting. "First there was massive condemnation," he says. "But a few months later the reaction was that they were going to comply with all our recommendations because they want to be seen doing the right thing."

In the case of clinical trials, argues Horton, taking the 'right' course of action is not simply an abstract moral issue. "There are too many examples of drugs which had been licensed that had to be withdrawn because the supporting data were inadequate or because the company put too much positive spin on weak data," he says.



Jeffrey Drazen: referees may introduce bias.

negative and positive remarks."

Nature asks referees to disqualify themselves if they think judging a certain manuscript would create a conflict of interest. "But we do realize that it can happen that a referee judges a manuscript he or she should have pushed aside," says *Nature's* editor, Philip Campbell. "We often use three referees, which helps to avoid such problems."

Opinion toll

Other journals that demand disclosure of conflicts by authors have no formal policy for the interests of referees — the *American Heart Journal* is one example, although some of its referees have, on occasion, declined to review a manuscript, citing a conflict of interest.

The authorship of opinion and review articles has also emerged as a contentious issue. Although most journals adopt the same rules as for original research papers, *NEJM* has, since 1990, required authors of such pieces to have had no commercial ties for at least two years with companies whose products they are writing about. But the policy is becoming increasingly difficult to enforce, admits Drazen, and is now under review. "Since the introduction of that rule, the entanglement of scientists and companies has grown," he says. "Therefore we have to exclude a lot of scientists from writing comments. We have collected data to see if that's still the right policy for the journal."



Catherine DeAngelis: no stocks, no conflict.

Editors, too, can have financial interests, and the major medical journals have strict rules on the commercial ties of their staff. Catherine DeAngelis, editor of *JAMA*, had to sign a statement that she had no conflicts of interest when she took up her post in 2000. "I am very careful," she says. "When I received a call that my uncle had left me stocks in the pharmaceutical company Johnson & Johnson, I said immediately that they should be given to my sisters. I don't want stocks."

Drazen, an asthma researcher at Harvard

them to provide information that throws a light on possible commercial and intellectual prejudice. When a referee gives negative advice about a study we liked very much ourselves, we make some calls," he says. "We have seven editors spending all their time reading reviews and judging the relevance of

There are journals where the financial ties of the editor will determine what gets published.



Mildred Cho

University, had to sever his financial ties to 20 drug companies before he took over the helm at *NEJM* in 2000. "The proceeds from stock investments I gave to charity," he says. Drazen also agreed not to deal for two years with manuscripts involving products from companies in which he previously had a financial interest.

Nature requires editorial staff to declare to their managers any interests that might be perceived to influence their editorial judgement. Managers then decide how any potential conflicts should be dealt with.

But move beyond front-line journals, and things become rather murky. "There are journals where the financial ties of the editor will determine what gets published," claims Mildred Cho, a bioethicist at Stanford University in California. She is particularly concerned about journals publishing papers about medical devices. "After publication, those papers are used as marketing tools by the companies that produce the devices," says Cho. "But we don't know the prevalence of editorial staff having commercial ties."

Hidden agendas

Even if a journal has a clear conflict-of-interest policy, it is of limited use if it is widely ignored. Unfortunately, it seems that this is often the case. Last year, Krinsky published a study of articles appearing in 1997 in 1,396 high-impact journals⁴. Only 15.8% of them had an explicit conflict-of-interest policy, of which almost 90% were medical journals. Among the journals with a stated policy, only 0.5% of papers included a disclosure of conflicting interests, and 65.7% of these journals published zero disclosures. In an earlier study, Krinsky unearthed evidence of lead authors with relevant commercial interests in 34% of a sample of 789 papers⁵, so he does not believe that so few authors had conflicts to declare. "Poor compliance is the more likely explanation," says Krinsky.

Nature introduced its conflict-of-interest policy in October 2001. Again, disclosure rates are relatively low: of the first 110 papers accepted under the policy in 2002, only five included a declaration of a financial interest.

Staff at *NEJM* know from bitter experience all about the subtle difficulties of policing a



Richard Smith: sees a rise in declarations.

conflict-of-interest policy. Following revelations in the *Los Angeles Times* that some authors of review articles in *NEJM* had commercial interests in the treatments they were writing about, the journal conducted an internal review. In February 2000, *NEJM* revealed that, since January 1997, 19 of the 40 drug-therapy review articles it had published were written by scientists with industrial links that should have disqualified them under the spirit of the journal's strict policy⁶. The authors had slipped through a loophole that exempted financial support given to their institution, rather than to them as individuals.

Richard Smith, editor of the *British Medical Journal (BMJ)*, agrees that it is hard for journals to enforce their policies. "A lot of researchers still think they are immune to the influences of their sponsor and don't realize

that bias can slip into their research very subtly," he says. "Some see it as an infringement on their freedom. But I must say the numbers of disclosure statements we get are increasing. Maybe the culture has started to change."

Cultural revolution

A recent study by Smith reinforces that view. Counting the disclosures in editorials, original research papers and letters to the editor in five major medical journals — the *BMJ*, *JAMA*, *NEJM*, *The Lancet* and *Annals of Internal Medicine* — in 1989, 1994, 1996 and 1999, Smith found an increase, from two declarations in 1989, eight in 1994 and four in 1996, to 38 in 1999 (ref. 7). But still, the vast majority of the 791 articles published by the journals in 1999 contained no disclosures.

Some researchers who have become embroiled in rows over conflicts of interest agree that disclosure is to everyone's benefit. In October 1997, toxicologist Stephen Safe of Texas A&M University in College Station wrote an editorial for *NEJM* in which he argued that environmental oestrogens such

as polychlorinated biphenyls do not cause breast cancer, and attacked public "chemophobia" fed by "paparazzi science"⁸. When it emerged that Safe had previously received funding of \$150,000 from the Chemical Manufacturers Association, the editorial became mired in controversy.

Safe defends his integrity: "My views on endocrine disrupters have been fairly consistent over the years and based on the scientific data; needless to say, I was upset over the commotion." But in retrospect, he now agrees with the idea of full disclosure of current and prior funding sources.

As to whether well-enforced disclosure policies would reduce commercial biases in the scientific literature, no one can say for sure. "Transparency about conflicts of interests is a bare minimum," argues Bero. "People shouldn't have the idea that everything is OK just because financial conflicts of interest are disclosed."

Krimsky notes that disclosure means different things for different journals — some merely require authors to tick a box indicating whether they have financial interests, whereas others demand a full breakdown of what those interests are. He argues that investigating the effectiveness of different types of conflict-of-interest policy is an important avenue for future research — but says it is difficult to get funding for studies in this area.

Many important questions remain unanswered, agrees Bero. "Do disclosure policies discourage investigators from submitting to journals? How do readers use conflict-of-interest information — do they take it into account when reading an article? Are disclosures that are published in journals accurate?"

Given the increasing number of papers getting bogged down in accusations of commercial bias, perhaps it is time to start searching for some answers. ■

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2. Bodenheimer, T. *N. Engl. J. Med.* **342**, 1539–1544 (2000).
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Table: **Sample policies from leading journals**

	Authors asked to disclose financial interests?	Disclosure statements shown to referees?	Disclosure statements published?	Policy for referees	Policy for editorials/ review articles	Rules for editors
<i>British Medical Journal</i>	Yes	Yes, if received before paper goes to review	Yes	Asked to declare conflicting interests; if editors perceive a conflict, may seek alternative referee	Same as for research papers	Editors asked to declare interests; expected not to make decisions on papers in which they have an interest
<i>Journal of the American Medical Association</i>	Yes	No	Yes	Asked to declare conflicting interests, and to disqualify themselves if these might cause bias	Same as for research papers	Editors and editorial board members must sign financial disclosure statement; expected not to make decisions on papers in which they have an interest
<i>Lancet</i>	Yes	Yes, if statement included in manuscript, as instructions to authors now request	Yes if editors perceive that a conflict may exist	Asked to declare conflicting interests; editors may exclude referees if they perceive a conflict	Same as for research papers, but editors may avoid commissioning from authors with declared interests	Staff invited to declare financial interests to editor-in-chief; editors excluded from papers in which they have an interest
<i>Nature</i>	Yes	No	Yes	Asked to disqualify themselves if they perceive a conflict	No disclosure policy at present; under consideration	Staff must declare financial interests to their managers, who decide how potential conflicts should be dealt with
<i>New England Journal of Medicine</i>	Yes	Sponsorship and author affiliations only	Yes	Asked to declare conflicting interests; this information taken into account by editors	Authors with conflicting interests are excluded	Editors must have no conflicting financial interests
<i>Proceedings of the National Academy of Sciences</i>	Yes	Yes	Yes	Asked to disqualify themselves if a conflict exists	Same as for research papers	Editorial board members asked to disqualify themselves from handling papers if a conflict exists
<i>Science</i>	Yes	No	No, except in rare cases at editors' discretion	Asked to declare conflicting interests; editors may exclude referees if they perceive a conflict	Same as for research papers	Editors expected to follow same guidelines as referees

Integrity in Science project

♦ www.cspinet.org/integrity

Commercialization of the Academy conference

♦ www.emory.edu/PROVOST/SamNunnForum

International Conference on Conflict of Interest and its Significance in Science and Medicine

♦ surfer.iitd.pan.wroc.pl/events/

ConferenceApril2002.html

Nature's policy

♦ www.nature.com/nature/submit/competing/index.html