

Lapses at the *New England Journal of Medicine*

The *New England Journal of Medicine* is the journal to beat. Its impact factor is 44, almost double that of its nearest rivals. Although *JAMA* and the *Lancet* may be snapping at its heels, the most important studies, particularly clinical trials, are published in the *New England Journal of Medicine*. Yet the way that the journal has behaved in the dispute around the VIGOR trial,¹ which was the making of Merck's drug rofecoxib (Vioxx), has raised doubts about its integrity and dovetailed with a growing anxiety about the ethics of medical journals.²⁻⁶

The *New England Journal of Medicine* was made great by Franz Ingelfinger, who banged on every important door in Boston urging researchers to admit their best studies to the journal. The journal assumed the effortless but often genuine superiority of Bostonians so well described—but also ridiculed—by Henry James.⁷ To some this felt like arrogance, and the journal has always been hated as well as admired. Often the motivation for such hatred may have been jealousy or resentment at failure to make it into its hallowed pages.

Ingelfinger was followed by Bud Relman, and the journal grew richer as well as grander. The Massachusetts Medical Society, the owner of the journal, made US\$88m from publishing in 2005. My guess is that the journal accounts for at least US\$75m of that and that its profits are probably at least US\$15m. The society has grown fat on the profits and is keen not only to keep the profits coming but also to exploit the brand. This has led to tensions between the journal and the society, and those tensions were in many ways the undoing of Jerry Kassirer and Marcia Angel, the successors to Relman. Both Angel and Kassirer after leaving the journal published books bemoaning the excessive influence of the drug industry,^{8,9} while the society appointed a new editor, Jeff Drazen, who was depicted by some as a creature of the industry.¹⁰ He had had financial connections with 21 drug companies between 1994 and 2000.

The VIGOR (Vioxx gastrointestinal outcomes research) study, which was published in the *New England Journal of Medicine* in November 2000, was a trial in which over 8000 patients were randomized to receive either naproxen or rofecoxib (Vioxx), a Cox-2 inhibitor that Merck hoped would have fewer gastrointestinal side effects.¹ There were sound theoretical grounds for expecting that this would be the case. The primary endpoint of the trial was gastrointestinal side effects, and sure enough the patients given naproxen experienced 121 side effects compared with 56 in the patients taking rofecoxib. This was a marvellous

result for Merck and contributed to huge sales of rofecoxib. Some 20 million Americans took rofecoxib before it was eventually withdrawn from the market. Merck bought 900 000 reprints of the article from the *New England Journal of Medicine* at a cost estimated to be between US\$700 000 and US\$836 000 to use in promoting the drug. (My estimate is that this must have meant perhaps US\$450 000 of profit for the journal: reprints have a very high profit margin.)

The trial also showed an increase in myocardial infarction in the patients given rofecoxib (0.4%) compared with those given naproxen (0.1%). (It is poor practice to publish only percentages not absolute numbers.) This was an unexpected result and the difference was interpreted by the authors to be caused by naproxen having a protective effect. In September 2004 Merck withdrew the drug from the market when it became clear that rofecoxib did have serious cardiovascular side effects.

In December 2005 the *New England Journal of Medicine* published an expression of concern about the VIGOR study saying that it '... did not accurately represent the safety data available to the authors when the article was being reviewed for publication'.¹¹ These data showed that there were 47 confirmed serious thromboembolic events in the patients given rofecoxib and 20 in those given naproxen—so wiping out the gastrointestinal benefits from rofecoxib. There were also three extra cases of myocardial infarction in the patients on rofecoxib that were not declared, although Merck had reported these cases to the Food and Drug Administration (FDA) in October 2000—before the paper was published. The data were posted on the FDA website soon after. If all of these data had been included in the original report the interpretation that naproxen was protective rather than rofecoxib harmful would have been much less convincing—indeed, it would probably have been untenable.

The *New England Journal of Medicine* reaffirmed its expression of concern in March 2006 after giving the authors a chance to explain themselves.¹² But is the *New England Journal of Medicine* blameless in all this? It published the expression of concern at the end of 2005 because the problems with the study had emerged as evidence was gathered for a court case against Merck brought by patients who allege that they have been damaged by rofecoxib.

It is clear, however, Jeff Drazen knew about these extra deaths long before the end of 2005. Indeed, the *Wall Street Journal* has discovered that Drazen was told about them in August 2001.⁴ Jennifer Hrachovek, a pharmacist who had reviewed the data on the FDA website, told him on a phone-in to a Seattle radio show. She also submitted a letter to the journal, which was rejected. With hindsight the failure of the journal to publish a correction—and probably a reinterpretation of the cause of the excess cardiovascular

side effects—is lamentable. If the journal had corrected the data then the dangers of the drug might have been highlighted much earlier.

But even without hindsight it seems poor practice not to publish a correction. Lots of what medical journals publish turns out to be ‘untrue’ and replaced by new evidence. So not every statement and interpretation can be corrected, but facts surely should be corrected. It is impossible to know which facts will turn out to be important. The journal had reason to suspect that there were three more cases of myocardial infarction than it had published 4 years before it drew attention to the fact.

The journal should probably also have given space to a different interpretation of the data. The FDA cast doubt on the hypothesis that naproxen had been protective—rather than rofecoxib harmful—as early as February 2001. In August 2001 a review of the complete data was published in *JAMA* casting doubt on the hypothesis that naproxen was protective.¹³ Yet in that same month a review article on Cox-2 inhibitors was published in the *New England Journal of Medicine* that repeated the erroneous data and was reassuring on the safety of the drugs.¹⁴

The expression of concern was rushed out at the end of 2005 to avoid bad publicity from presentation in a court case of evidence given on the background to the publication of the VIGOR trial paper by Gregory Curfman, executive editor of the journal. A public relations specialist advised the journal that the publication would divert attention from failings of the journal to the failings of Merck and the authors.⁴

Why was the *New England Journal of Medicine* so slow to correct the record? The editors have suggested that the onus is on the authors to correct data; but it cannot be acceptable for editors to be put on notice that facts are wrong and to leave them unmodified. The editors also point out that the correct data were on the FDA website; but there is a world of difference between data on a website and data included in the world’s leading medical journal and being circulated in nearly a million reprints. The editors must accept responsibility for the accuracy of facts in their own journal: they have a duty to their readers.

This convoluted story has now been made even more complicated by the *New England Journal of Medicine* having to publish a correction to the study it published in 2005 that was the death of rofecoxib.¹⁵ The Adenomatous Polyp Prevention on Vioxx (APPROVe) study established the serious cardiovascular side effects of rofecoxib but also concluded that the increased risk became apparent only after patients had been taking the drug for 18 months.¹⁶ It is this latter conclusion that the journal has had to correct. The study should have included an intention to treat analysis but did not, and Merck submitted the full data of the trial to the FDA a month ago, acknowledging that it had incorrectly

described a statistical method. The original—and incorrect—conclusion was very important for Merck because it made it very difficult for anybody who had suffered an adverse cardiovascular event to sue if they had been taking the drug for less than 18 months.

The journal is no doubt embarrassed by this further twist. It was a failure of peer review, but peer review is an empty gun anyway—as I have argued in this journal before.¹⁷ More worrying is the anxiety that the drug company has used the prominent pulpit of the *New England Journal of Medicine* to advance a message that was very much in its interest—but ultimately incorrect. It fits with the argument that medical journals are an extension of the marketing arm of pharmaceutical companies and that the full data of trials should be published not in medical journals, where an incomplete story is advanced, but on the web.^{6,18}

Whatever the explanation for what has happened around the publication of these trials, the *New England Journal of Medicine*, and journals in general, have been damaged.

Competing interests RS was the editor of the *BMJ* and the chief executive of the BMJ Publishing Group. He is a member of the board of the Public Library of Science, which promotes open access to all scientific research.

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