PSEUDO-EVIDENCE-BASED MEDICINE: WHEN BIOMEDICAL RESEARCH BECOMES AN ADJUNCT OF PHARMACEUTICAL MARKETING*

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We have made a Faustian bargain. With the best of intentions, we have sold our souls for company gold and, in the process, have put the integrity of our research and the credibility of our universities into serious question.

Prologue: Anatomy of a Scandal

I begin this chapter by anatomizing a research scandal whose aetiology can, in significant ways, be traced to the new entrepreneurial spirit prevailing in our universities. Later, I will argue that, with the ever-growing importance of university-corporate "partnerships," scandals involving the integrity of university research may be expected to multiply in Canada, as they have elsewhere. The resulting loss of public trust is likely to be devastating to our universities and to the wider community that they serve.

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I have chosen the Vioxx scandal to illustrate the ways in which the integrity of university research is threatened by the entrepreneurial university and the new class of entrepreneurial academics who labour in its laboratories and teaching hospitals. The Vioxx story beautifully illustrates the perils that may befall university research when it is funded by for-profit corporations. Sadly, there is no shortage of other examples one could have chosen instead.

The VIGOR Trial: Cox-2 Inhibitors in the Dock

The Vioxx scandal encompassed the world's third-largest drug company, Merck, and the world's most impactful medical journal,[1] the *New England Journal of Medicine* (*NEJM*), as well as its editor Dr. Jeffrey Drazen. It also involved, in the role of first author, a Canadian scientist, Dr. Claire Bombardier, from the University of Toronto's faculty of medicine. Since this is the same faculty and the same university that were earlier implicated in the Nancy Olivieri and David Healy scandals,[2] some readers may infer that the research environment at the University of Toronto is ethically tainted to a degree greater than that which might be found elsewhere in Canada. Whether or not this conclusion is sustainable, it is certainly true that when it comes to attracting massive corporate funding, the University of Toronto is far and away the most successful university in Canada. I shall argue that corporate funding of university research is very close to the heart of virtually all these scandals.

In November of 2000, the *NEJM* published the VIGOR (Vioxx gastrointestinal outcomes research) trial. The trial appeared to demonstrate that those patients who were randomized to Vioxx experienced fewer stomach bleeds than those who received an older and much cheaper drug called naproxen.[3] Publication of the VIGOR trial in the prestigious *NEJM* launched Vioxx on its career as a blockbuster arthritis drug, with annual sales exceeding a billion dollars. The University of Toronto was very proud of the fact that Dr. Bombardier was the lead author of this article.

Vioxx (rofecoxib) belongs to a class of drugs known as COX-2 inhibitors. They are used primarily for the treatment of arthritic pain. When these drugs were first introduced to the marketplace, they were heavily promoted by their respective companies and were widely hailed by the mass media as "miracle aspirin." The miracle was alleged to be the comparative absence of serious adverse effects. Promotional advertising for Vioxx and its main competitor in this class, Celebrex, ran to well over $300 million annually.

Vioxx was not finally withdrawn from the market until September of 2004, when additional clinical trials, such as the ADVANTAGE (Assessment of Differences between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness) trial, provided damaging evidence of the cardiac risks posed to patients taking the drug.[4] The trial that ultimately guaranteed the withdrawal of Vioxx from the marketplace was the APPROVe trial, discussed below. Meanwhile, tens of millions of Americans and millions of Canadians unsuspectingly used Vioxx for arthritic pain before the drug was exposed as being scientifically and ethically suspect.[5] Vioxx was withdrawn from the market in 2004. The demise of Vioxx came about only after it was indisputably shown to carry unacceptable risks of heart attacks and strokes.

The miasma of scandal that surrounds Vioxx did not arise simply because it was found to be much more dangerous than first advertised. Rather, the scandal arose because university (and company) researchers responsible for the conduct and publication of the clinical trial were discovered to have interpreted their data in an intellectually questionable manner and, worse, to have suppressed vital data that would, if disclosed, have enabled doctors and patients to make a better informed choice about whether to recommend or use the drugs.

It is important to note that, as reported by Dr. Bombardier and her colleagues, the research subjects enrolled in the VIGOR trial who took 50 mg of Vioxx per day developed much more serious cardiovascular complications than those taking the comparator drug, naproxen. The VIGOR trial, for example, showed a 400 per cent greater risk of experiencing heart attacks, strokes, and blood clots for subjects who were randomized to Vioxx, compared to those in the naproxen arm of the trial. The study's authors explained, or perhaps one should say "explained away," this elevated risk by claiming that Vioxx was not responsible for the surplus of heart attacks and strokes. Instead, they claimed naproxen was protective. They also claimed, falsely, that the serious heart and stroke complications occurred exclusively in patients with a history of cardiovascular disease. If true, this would suggest that Vioxx might have had a favourable risk-benefit ratio for patients having no previous history of cardiovascular disease.[6]

Given the importance of the issue, one would have expected the VIGOR authors to provide some evidence to support their hypothesis that naproxen was protective against heart attacks and strokes. They provided none. In February of 2001, the United States Federal Drug Administration (FDA) cast serious doubt on the claim that naproxen had been protective, which led, inexorably, to the conclusion that Vioxx was harming many patients.

Curiously (and embarrassingly), the editors of the *NEJM*, when they were refereeing the article prior to publication, somehow failed to challenge the VIGOR authors to justify their sanguine hypothesis. Nor did the editors invite a more skeptical interpretation of the data from independent scientists.

Fortunately, rescue from company "spin" was at hand. Some alert scientists discovered that the VIGOR authors had failed to report several heart attack deaths in their *NEJM* publication even though they had supplied the correct data to the FDA.[7] (As we will see later, it was a similar case of data suppression, in the APPROVe and ADVANTAGE trials, discussed below, that proved to be the final straw for Vioxx.) These additional data showed that patients taking Vioxx were several times more likely to suffer from heart attacks and strokes than patients taking naproxen. Even worse, from the company's point of view, the Vioxx deaths, which had been suppressed from the *NEJM* article, were deaths that occurred in patients with no history of heart disease. This fact kicked the legs out from under the company's specious claim that only those with a history of heart disease were at elevated risk from taking Vioxx.

The investigators did not correct the scientific record. Their failure to do so was compounded when Dr. Jeffrey Drazen, esteemed editor of the *NEJM*, declined an opportunity to publish a letter submitted to the journal by independent scientists. The suppressed letter would have alerted readers to the misleading nature of the data originally published. Years later, when the full extent of the harm done to tens of thousands of patients became undeniably clear, Drazen and his fellow editors at the *NEJM* justified their refusal to publish a timely correction with the intellectually (and morally) feeble excuse that it is the responsibility of authors, not journal editors, to correct data.[8]

Overall, if one considers serious complications—defining "serious complications" as those which lead to hospitalization, permanent disability, or death—the subjects who were given Vioxx had 21 per cent more serious complications (of all kinds: gastrointestinal, cardiovascular, and other) than did those who were given naproxen. Tens of thousands of patients died unnecessarily because this salient fact was not adequately publicized; well over 100,000 suffered heart attacks and strokes.[9]

In sum, if all the data from the VIGOR study had been properly disclosed and properly analyzed, the publication of the trial in *NEJM* would in all likelihood have dealt a death blow to the marketing and sale of Vioxx. Instead, the death blow came several years later—after tens of thousands of unnecessary deaths—with the publication of a second Merck-sponsored Vioxx clinical trial, known as APPROVe.

Merck decide to sponsor the APPROVe clinical trial in the hopes that it would demonstrate that VIOXX was effective as a treatment for patients with colon polyps. The trial involved 2,600 patients. Significantly, all were prescreened to ensure that no one who had any sign of cardiovascular disease was enrolled in the trial. Whether by design or not, this meant that it was less likely that dangerous cardiovascular side effects would be discovered and revealed. Disastrously for Merck, but luckily for arthritis patients who had been unwittingly taking Vioxx, despite the calculated exclusion of high-risk patients, the APPROVe trial demonstrated that 3.5 per cent of the patients assigned to rofecoxib (Vioxx) had myocardial infarction or stroke, as compared with only 1 per cent of the patients assigned to the placebo. This 350 per cent increase in cardiovascular disease experienced by patients randomized to Vioxx led to the discontinuation of the trial and, shortly thereafter, to the permanent withdrawal of Vioxx from the marketplace.[10]

A third clinical trial, the ADVANTAGE trial, also sponsored and funded by Merck, displayed some of the same ethically dubious features as the VIGOR study, but it is worth considering separately, partly because it helps to establish and reinforce the pattern of unethical behaviour in university-industry research partnerships and partly because it introduces some new and disturbing wrinkles to the already toxic mix.

The first point to note is that the ADVANTAGE trial was not a genuine scientific study.[11] Under the guise of science, the marketing department at Merck set up this "study" with the primary purpose of inducing an additional six hundred doctors to prescribe the drug to their patients. In other words, the study was really marketing dressed up as science. (Marketing departments call these pseudo-trials "seeding trials," but to lay people and to many physicians they appear to be scientific research.) Ironically, however, ADVANTAGE demonstrated—what the company had been denying strenuously since its earlier VIGOR trial—that Vioxx carried significant heart attack risks: five ADVANTAGE research subjects taking Vioxx experienced heart attacks, compared with only one in the naproxen arm of the study. Second, although Merck insisted that this number of heart attack deaths did not reach a level of statistical significance, the number of reported deaths was later discovered to have been understated. In an instance of unethical data suppression comparable to that which occurred when the VIGOR study was first published, the ADVANTAGE study authors did not reveal that two additional Vioxx patients died from heart attack. Worse, the number of unreported heart attack deaths was likely three rather than two. Internal

company records reveal that Merck's top scientist, Dr. Edward Scolnick, pressured a colleague to change his views about the cause of one patient's death, which was subsequently recorded as "unknown" rather than cardiac.[12] When all these additional Vioxx cardiac deaths are included in the study's total, they undermine the company's claim that there was no statistical significance to the number of deaths. As if these ethical breaches were not enough, it should also be noted that the lead author of the ADVANTAGE trial, Dr. Jeffrey R. Lisse, an academic rheumatologist from the University of Arizona, later admitted that he was little more than a ghost author: "Merck designed the trial, paid for the trial, ran the trial," Lisse admitted to a *New York Times* reporter. "Merck came to me after the study was completed and said, 'We want your help to work on the paper.'"[13]

When university students put their names to work that they have not done themselves, they are failed for plagiarism. Surprisingly, a significant number of university scientists seem comfortable accepting drug company money in exchange for putting their names to studies that have been designed and carried out by company employees.[14] Prominent academics thus pad their resumes at the same time as they pad their wallets and, in the process, lend their scholarly prestige to the company's products. Frequently, these academic "lead authors" have not even had access to the raw data on which the study's conclusions are based. As a result of the Vioxx scandal and a host of others, many medical journals now require that the lead author take explicit responsibility for the data presented.

Sadly, almost no one emerges with much credit from the VIOXX saga. The drug company, which massively marketed this "miracle" treatment for arthritic pain both to doctors and directly to consumers, made billions of dollars. But, when the facts eventually emerged, the company experienced a serious loss of public trust. Merck now faces a staggering number of expensive lawsuits. The company continues to insist that it took all reasonable measures to determine whether Vioxx carried undue cardiovascular risks and is defending its conduct in all of these lawsuits. Medical journals and their editors, in particular the *NEJM* and its editor Dr. Jeffrey Drazen, were seen by some critics as being incompetent at best, and collusive at worst, in what turned out to be a terrible human tragedy.[15] The medical community allowed itself to be "sold" on these miraculous new drugs, often persuaded of their merits over fine dinners at luxury resorts. The after-dinner talk would generally be delivered by a respected colleague—in drug industry lingo, a key opinion leader (KOL)—who is also a highly paid consultant to the companies. In consequence of such "education," doctors write millions of

prescriptions and their unwitting patients pay a fortune of money for drugs that claim to have a superior safety profile but which are, in fact, inferior to older and much cheaper pain control drugs.

None of this is likely to have enhanced public trust in "evidence-based medicine" or the medical profession that claims to practise it. When the evidence on which evidence-based medicine relies has been massaged or otherwise tainted, then it scarcely provides a reliable tool for medical decision making. In the interests of truth-in-advertising, perhaps the medicine practised in this era of corporate-university partnerships should be referred to as "pseudo-evidence-based medicine."

Finally, and from our point of view most significantly, university scientists, who are professionally obligated to pursue and to publish the truth were instead responsible for withholding data unfavourable to the products of their commercial sponsors. They withheld data and they also misinterpreted the data that they chose to disclose, spinning that data in such a way as to give the impression that their sponsors' drugs had a safety profile superior to older and cheaper drugs.[16] The opposite was true.

Although I have been focusing attention on a single drug manufactured by a single drug company, there is ample evidence that similar problems are to be found with respect to many different drugs and classes of drugs produced and sold by the world's leading drug companies. York University drug researcher Joel Lexchin and colleagues have done a comprehensive meta-analysis of the tendency of drug company sponsorship to produce biased research results. Lexchin concludes, "There is some kind of systematic bias to the outcome of published research funded by the pharmaceutical industry."[17]

Canadian universities, like their American counterparts, tend to measure success by the extent of corporate financial support that their researchers attract. Our universities and teaching hospitals aspire to be world-class research institutions and, in pursuit of this objective, they vigorously solicit money (in support of research but also for new buildings and laboratories) from the world's wealthiest and most powerful drug companies. The pharmaceutical industry has come to be accepted by our research universities as a vital "partner." Handsome new buildings mushroom on campuses across the country, built with funds donated by these companies. However, when one discovers the cost to research integrity that seems to be an inescapable risk of such partnerships, the bargain may come to seem Faustian, with an unacceptable quid pro quo: the loss of research integrity and, eventually, the loss of public trust.

What Are Universities for?

I have been discussing some of the ethically dubious practices in which university scientists have engaged under the aegis of drug industry sponsorship. Now let us go back to basics for a moment to ask: What are universities for?

Universities are places where scholars pursue *knowledge for its own sake*. Hence, the venerable metaphor of the "ivory tower." University research is (primarily) curiosity-driven. Indeed, the intellectual vitality of universities derives from the fact that scholars are largely autonomous—beholden to no one, least of all the wealthy and powerful elites of society. The knowledge gained by university research is then freely disseminated to colleagues, students, and the wider community. For this reason, universities are a vital source of critical perspective on many of the issues that matter most to society. This critical perspective is possible only because universities and the scholars who work in them are fearlessly independent of governmental, church, or corporate control.

Well, this is the story we tell ourselves; or it is the story we used to tell ourselves. The paradigm of the university as a place of independent scholarship derives in some measure from the Enlightenment. We know, of course, that the Enlightenment ideal of the university as a centre for pure scholarship, untainted by the pursuit of wealth, power, and status, was never entirely true. When the Church or other ruling elites/classes controlled universities, there was never a shortage of academics who sought promotion via "scholarship," which told power whatever power wanted to hear. *La trahison des clercs* was a phrase made popular by Julien Benda in 1928 to describe the kind of betrayal intellectuals commit when they advance their self-interest (by providing legitimation to ruling elites) at the expense of the more dangerous enterprise of devoting one's scholarly energies to the disinterested search for truth.[18]

Granting this point, and thereby conceding that there may never have existed a "golden age" of scholarly purity, one might nevertheless insist that there was a time when the percentage of dross mixed in with the gold was less prominent than it is today. It is impossible to deny the claim—and many, within and without the university, want to trumpet rather than to deny it—that we are now living in an era when universities are regarded, perhaps first and foremost, as engines of economic prosperity. We constitute an important part of national "manpower policy." Our graduates, many of them, end up working in the corporate trenches. Our intellectual patents generate wealth for the biotech companies we have formed or with which we

have struck up commercial alliances. Universities themselves often demand and receive an ownership share of these companies, from which arrangement they hope to receive substantial profits. It is now expected, indeed it is demanded, that university research findings should move rapidly from the academic laboratory or teaching hospital to the real world of bottom-line corporate profitability. Arguably, the modern university, in its role as corporate handmaiden, has acted in a way that restricts rather than expands the scope for critical scholarship.

Scientific research in Canadian universities is extensively funded by industry. This is especially true for pharmacological research, which attracts strikingly large sums of money from the drug industry. It is important to remind ourselves, however, that these university-corporate partnerships are a comparatively recent phenomenon. Thirty or forty years ago, most research funds came from governments and from quasi-governmental funding bodies (known as "granting agencies"). Today, although governments continue to invest large sums of money in scientific research (albeit a much smaller percentage of the total than in the past), the marked trend is toward private funding.

Not to put too fine a point on it, this means that academics who seek to pursue a career doing scientific research at a Canadian university had better ensure that their projects will be attractive to potential corporate sponsors. University careers depend heavily upon the ability to attract a continuous stream of research dollars. Pity the naive researcher whose cancer research project involves treating patients with a diet of broccoli sprinkled with lemon juice. Which pharmaceutical corporation would fund such a profit-threatening idea? Which university would give tenure or promotion to a researcher who could not attract corporate funding, however brilliant and socially beneficial her research project might be? Which government agency would support such research in the absence of a legitimating corporate partner? It may be an exaggeration to say that universities have transmogrified into the R&D departments of economically powerful corporations, but the exaggeration, if any, is mild.

The gravamen of my argument is this: we have made a Faustian bargain. With the best of intentions, we have sold our souls for company gold and, in the process, have put the integrity of our research and the credibility of our universities into serious question. Data are fast accumulating that demonstrate that when corporations fund research the results of that research are powerfully biased by the corporate agenda. A worrying series of academic scandals, one of which (the Vioxx saga) has been discussed in some detail above, shows that when universities become closely allied

with the marketplace, their vigilance in the promotion and protection of research integrity may be less than stellar. In other words, when the search for truth turns into the pursuit of profits, the end result is often very far from beneficial to society.

At the outset of this chapter, the Vioxx study was analyzed to illustrate the manner in which powerful drug companies are able, via their funding of university research, successfully to develop and market drugs for which the risk-benefit ratio is known from the outset to be dubious at best. University investigators, whose careers depend on drug company sponsorship, seem to be doing research that often has greater affinities with marketing than with the pursuit of scientific truth. To understand better how this problem arose, it will now be necessary to explore the key concept of "conflict of interest."

Conflicts of Interest

The best short definition of "conflict of interest" is as follows:

> *A person is in a conflict of interest situation if she is in a relationship with another in which she has a moral obligation to exercise her judgment in that other's service and, at the same time, she has an interest tending to interfere with the proper exercise of judgment in that relationship.*[19]

When university researchers accept corporate funding for their research projects, they clearly put themselves in a conflict of interest situation. Drug researchers, for example, have an ethical obligation to put the interests of truth (and patient safety) ahead of the interests of the corporations that are funding their projects. When, however, the researcher's career depends upon the direction of her findings, then there is a worrying danger that the objectivity of the researcher may be biased or skewed. Thus, if a researcher stands to gain monetary and/or career success by demonstrating the safety and efficacy of a sponsor's new drug, but stands to lose research funding and perhaps her job if she finds that the new drug is unsafe or ineffective, then she is in a conflict of interest situation.

The suggestion here is not that researchers who have a conflict of interest will necessarily behave in a (consciously) corrupt fashion. Only a small minority of investigators is likely to be guilty of deliberately skewing their investigations so as to produce dishonest results in an effort to please their corporate sponsors. The real danger is that financial benefit or career

self-interest have a marked (albeit unconscious) tendency to generate biased research findings. There is a deal of social science evidence that demonstrates that "even when individuals try to be objective, their judgments are subject to an *unconscious and unintentional* self-serving bias"[20] (emphasis mine). Moreover, we now have a substantial body of empirical evidence that confirms that when it comes to biomedical research, financial conflicts of interest are associated with significant effects.

The study that first drew wide attention to the issue was published in 1998 by H. T. Stelfox and colleagues.[21] Their goal was to investigate the question of whether industry sponsorship of biomedical research might influence the outcome of that research. To answer this question, they studied published articles on the safety of calcium-channel blockers—a class of drugs used to treat high blood pressure. Stelfox and colleagues first divided authors according to their financial relationship with pharmaceutical companies and then, separately, classified (as "supportive," "critical," or "neutral") their findings on the issue of whether these drugs were safe. What they found was that "96 per cent of supportive authors had financial relationships with the manufacturers of calcium channel antagonists, as compared with 60 per cent of neutral authors and 37 per cent of critical authors."[22] In other words, there was a striking association between the conclusions reached by investigators (with respect to the safety of calcium-channel blockers) and the financial relationship of those investigators with pharmaceutical manufacturers.

More recent studies have repeatedly demonstrated that industry-sponsored studies are significantly more likely to reach conclusions that favour their sponsors' products than studies that are independently funded.[23] To cite Lexchin again,

> *Research sponsored by the drug industry was more likely to produce results favouring the product made by the company sponsoring the research than studies funded by other sources. The results apply across a wide range of disease states, drugs and drug classes, over at least two decades and regardless of the type of research being assessed—pharmacoeconomic studies, clinical trials, or meta-analyses of clinical trials.*[24]

The proliferation of studies pointing to the important impact of funding source on the results of biomedical research should be of serious concern to those who support industry-university partnerships.

It might be helpful to reflect that in fields far removed from biomedical research there is a sharp awareness of the dangers posed by conflicts of

interest. Referees are not permitted to accept benefits or gifts from team owners; police are not allowed to accept benefits or gifts from crime suspects; judges are not permitted to accept benefits or gifts from litigants; professors are not allowed to accept benefits or gifts from students. That is because referees, police officers, judges, and professors are obligated to exercise their judgment impartially according to professional standards. When we hope for future benefits, our self-interest may skew our professional judgment. Moreover, gifts and benefits make the recipient beholden to the gift-giver. The well-established anthropological phenomenon of reciprocity operates powerfully, though (again) often not in a conscious, deliberate manner, to motivate us to return kindness for kindness, gift for gift.

Although most people recognize that the powerful combination of self-interest and reciprocity can bias the judgment of others, often in ways of which the recipient is scarcely aware, few of us are willing to acknowledge that we could ourselves be "bought" in this way. The vehemence with which most researchers deny that their judgment could have be skewed by the acceptance of drug company funding or other financial benefits from these companies reflects a common misunderstanding. Researchers become indignant because they believe that someone is accusing them of deliberate corruption. What many seem not to recognize, however, is that when one allows oneself to be placed in a conflict of interest situation, one tends almost automatically, at a subconscious level, to weigh arguments and evidence in a biased fashion.[25]

At present, the public appears not fully to appreciate that financial and career conflicts of interest have become the norm for university researchers in many different fields, including but not limited to the fields of academic medicine, agriculture, and climate change. Not only is it the case that most of our leading university scientific researchers benefit from sponsorship by industry, it is also the case that the very universities and teaching hospitals in which these scientists work accept substantial amounts of money from the same corporate sources, usually in the form of corporate "donations." Indeed, it is these corporate donations that make possible the proliferation of many fine new research buildings on Canadian university campuses. They also fund the expensive equipment and technical staff without which the buildings would be empty shells.

The connubial relationship between universities and the world of business is seen by many, including a significant portion of university administrators and governing boards, as something to be welcomed and fostered. Revenue generated by such partnerships (in the form of royalties on joint ventures,

funds for salaries, equipment and support staff and the aforementioned donations to erect new buildings) is seen as providing the leverage that universities and teaching hospitals need in order to achieve "excellence" or, even better, to become "world class." The alternative to university-industry partnerships is seen as mediocrity and stagnation. University administrators are persuaded that if they do not aggressively pursue corporate research funds and corporate donations, then their competitor universities/hospitals, both nationally and internationally, will win the race for gold and glory.

University administrators believe sincerely that their strenuous efforts to harness corporate wealth on behalf of university expansion make an important contribution to the promotion of the university's fundamental objective: benefit to humankind through the advancement and dissemination of useful knowledge. It is also true, however, that in their ceaseless quest to raise money, university administrators can easily lose sight of the proper goals of a university. Means and ends are easily confused, with the means (rapid growth) coming to displace the end they were meant to promote (advancement of the public good via the advancement of knowledge).

Conclusions

Many members of the biomedical research community are persuaded that in this era of rapidly escalating costs, industrial sponsorship of university research is the best (and perhaps the only viable) path toward the advancement of science. They see, or claim to see, a synergy between the expansion of corporate profits and the flourishing of scientific creativity. For example, the creation of beneficial new drugs is often cited as evidence to demonstrate that the commercialization of university research is a highly positive development for society as well as for science.

Critics tend to be less sanguine than university administrators about the outcome of increasingly close ties between universities and for-profit corporations. They argue that it was government funding rather than corporate funding that promoted innovative and socially beneficial research. Corporate funding of university research has instead led us to a point where many of the new drugs coming to market are nothing more than "me-too" drugs—invariably more expensive than their predecessors (which have come off patent) but no more efficacious and often more dangerous.[26] Big Pharma's big investment in university research is producing fewer and fewer "new molecular entities."[27] In short, the number of golden eggs produced

by the corporate goose is disappointingly exiguous. Even more worrying, adverse effects from prescription drugs now occupy the number four place on the list of leading causes of death in the United States.[28]

Critics worry about the marked divergence between the fundamental raison d'être of industry, on the one hand, and universities, on the other. If we ask, "What are corporations for?" the simple answer is that corporations are for the maximization of shareholder profits. By contrast, although today's multiversity may aspire to be all things to all people, it nevertheless continues to be the case that the "bottom line" for any university worthy of being so called must continue to be the pursuit of truth.

Corporations owe a fiduciary duty to their shareholders. That duty is to maximize profitability. Realistically, given the competitive global economy in which most corporations now operate, it is short-term rather than long-term profitability that dominates the thinking of corporate officials. If quarterly profits do not satisfy market expectations, then stock values will decrease, sometimes precipitously, and heads may roll. The fundamental commitment of the university, by contrast, is to seek truth even when that truth may have an adverse effect upon the corporate bottom line.

Once it is recognized that our current way of funding biomedical research is both vastly expensive and sadly unproductive of beneficial new molecules, it becomes a matter of some urgency to contemplate alternative funding arrangements. When it is also recognized that corporate funding has drastically undermined the integrity of both our researchers and our research institutions, the urgency is further increased.

Since the fundamental problem arising from university-corporate partnerships is the problem of conflict of interest, and since many of the reforms suggested as tools for "managing" this conflict—reforms such as disclosure of the conflicts—have proven ineffectual, the most promising solution to the problem turns out also to be the most simple: an outright prohibition of corporate funding for university research. The "sequestration thesis," which I propound, insists that university researchers must be entirely sequestered from the process of commercialization.

If we as a society want public science in the public interest, it will have to be funded through public tax dollars.[29] The "partnership" between universities and their researchers, on the one hand, and for-profit corporations, on the other, is almost pre-ordained to produce research findings that promote the interests of the corporations, even when, as not infrequently happens, those interests clash with the best interests of both patients and the wider community.

Hitherto, the community of university researchers has been viewed by society at large as an invaluable source of independent information and critical analysis. University-industry partnerships, as we have seen, threaten seriously to corrode the independence of university research and thereby its integrity. Once the true nature and extent of corporate financial sponsorship becomes widely recognized and understood by the rest of society, the credibility of university research is likely to suffer irreparable harm. Loss of public trust is a heavy price to pay for the short-term benefits that come when universities float on a sea of corporate largesse.

Notes

1 Its impact factor, at 44, is almost double that of its nearest rival. See Richard Smith, "Lapses at the New England Journal of Medicine," *Journal of the Royal Society of Medicine* 99, no. 8 (August 2006): 380–382.

2 Arthur Schafer, "Biomedical Conflicts of Interest: A Defence of the Sequestration Thesis—Learning from the Cases of Nancy Olivieri and David Healy," *Journal of Medical Ethics* 30 (2004): 8–24.

3 C. Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *New England Journal of Medicine* 343 (November 23, 2000): 1520–1528.

4 J. R. Lisse et al., "Gastrointestinal Tolerability and Effectiveness of Rofecoxib versus Naproxen in the Treatment of Osteoarthritis, the ADVANTAGE Study: A Randomized, Controlled Trial," *Annals of Internal Medicine* 139 (2003): 539–564.

5 More than twenty-five million Americans took Vioxx between 1998 and 2004. See Alex Berenson, "Evidence in Vioxx Suits Shows Intervention by Merck Officials," *New York Times*, April 24, 2005; Lisse et al., "Gastrointestinal Tolerability."

6 See an excellent discussion of the cardiovascular risks posed by Vioxx in Chapter 3 of John Abramson, *Overdosed America: The Broken Promise of American Medicine* (New York: Harper Collins, 2004). Abramson also points out that the subjects of the VIGOR trial were quite unrepresentative of the majority of people for whom doctors prescribed Vioxx. More than half of the subjects in the trial were on steroids. This little-noticed fact is of great importance because the study shows significant reductions in risk of serious GI complications only in those patients who were on steroids. For the others (i.e., most of the people who ended up taking Vioxx) there was no statistically significant reduction of GI complications.

7 D. Armstrong, "Bitter Pill: How the *New England Journal* Missed Warning Signs on Vioxx," *Wall Street Journal*, May 15, 2006, A1. See also Smith, "Lapses at the New England Journal of Medicine"; G. D. Curfman, S. Morrissey, and J. M.

Drazen, "Expression of Concern Reaffirmed," *New England Journal of Medicine* 353 (2005): 2813–2814.

8 Armstrong, "Bitter Pill"; Smith, "Lapses at the New England Journal of Medicine"; Curfman, Morrissey, and Drazen, "Expression of Concern Reaffirmed."

9 Abramson, *Overdosed America*.

10 Eric J. Topol, "Failing the Public Health—Rofecoxib, Merck and the FDA," *New England Journal of Medicine* 351 (October 21, 2004): 1707–1709.

11 Theoretically, the ADVANTAGE trial was meant to show that Vioxx caused fewer stomach problems than naproxen, but this had already been demonstrated by the VIGOR study, which had a much larger number of subjects. Dr. Edward M. Scolnick, a top Merck scientist between 1985 and 2002, admitted as much in an internal company memo: "Small marketing studies which are intellectually redundant are extremely dangerous," he wrote. See Berenson, "Evidence in Vioxx Suits."

12 Ibid.

13 Ibid.

14 S. Sismondo, "Ghost Management: How Much of Medical Literature Is Shaped behind the Scenes by the Pharmaceutical Industry?" *PLOS Medicine* 4, no. 9 (September 25, 2007): e286, doi:1374/journal.pmed.0040286.

15 Merck bought nine hundred thousand reprints of the article to use in marketing Vioxx, more than one for every doctor in America. The revenue to the *NEJM* is estimated to be in the range of three-quarters of a million dollars. See Smith, "Lapses at the New England Journal of Medicine."

16 If either the data suppression or the scientifically skewed interpretations were done deliberately, intentionally, or knowingly, then the scientists involved could be seen as corrupt. If these problems arose because of an unconscious desire to please commercial sponsors, then a charge of corruption might not stick. Instead, the researchers would be guilty of unprofessional conduct for allowing themselves to be in the kind of conflict of interest situation that tends to undermine research integrity. The conflicts of interest inherent in corporate sponsorship of academic research are now so pervasive that many now regard them as professionally acceptable because they are unavoidable and because "everyone is doing it."

17 J. Lexchin, K. A. Bero, and B. Djulbegovic, "Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review," *The BMJ* 326 (2003): 1167–1174.

18 J. Benda, *La Trahison des Clercs* (Paris: Editions de la Nouvelle Revue Francaise, 1928).

19 M. Davis, "Conflict of Interest," *Business and Professional Ethics Journal* 1 (1982): 17–27.

20 J. Dana and G. Lowenstein, "A Social Science Perspective on Gifts to Physicians from Industry," *The Journal of the American Medical Association* 290 (2003): 252.

21 H. T. Stelfox et al., "Conflict of Interest in the Debate over Calcium-Channel Antagonists," *New England Journal of Medicine* 338 (1998): 101–106.

22 Ibid.
23 See, for example, J. E. Beckelman, Y. Li, and C. P. Gross, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," *The Journal of the American Medical* Association 289 (2003): 454–465.
24 Lexchin, Bero, and Djulbegovic, "Pharmaceutical Industry Sponsorship."
25 Dana and Lowenstein, "A Social Science Perspective on Gifts."
26 See, for example, M. Angell, *The Truth about the Drug Companies* (New York: Random House, 2004); S. Krimsky, *Science in the Private Interest* (Lanham, MD: Rowman and Littlefield, 2003); J. P. Kassirer, *On the Take* (Oxford, UK: Oxford University Press, 2003); and J. Abramson, *Overdosed America*.
27 Angell, The Truth about the Drug Companies.
28 Arthur Daemmrich, *Pharmacopolitics: Drug Regulation in the US and Germany* (Chapel Hill, NC: University of North Carolina Press, 2004), cited by Philip Mirowski, "Johnny's in the Basement, Mixin' Up the Medicine: Review of Angell, Avorn, and Daemmrich on the Modern Pharmaceutical Predicament," *Social Studies of Science* 37 (2007): 311.
29 For a range of possible answers to the question, "From where will the vast sums of money needed to fund research come?" see Schafer, "Biomedical Conflicts of Interest," 22–24.