

Dances with the pharmaceutical industry

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In a recent commentary published in this journal, we, along with others, described the relationship of university-based medical researchers with industry as a risky dance with a porcupine.¹ Our focus was the pharmaceutical industry and how its fundamental need to satisfy shareholders could, and at times did, conflict with a researcher's agenda to seek and unveil truth.

Now, for a close-up view of dance partners wildly out of step, we turn to the case of Nancy Olivieri. Her stormy relationship with Apotex Inc., Toronto's Hospital for Sick Children (HSC) and the University of Toronto has been extensively reviewed, not once but twice, in reports that reach diametrically opposite conclusions on some of the major issues at stake. The first, the Naimark Review,² was commissioned by the HSC, where the events took place. It exonerates the Hospital and the University of wrongdoing and places blame on Olivieri. The second, the Thompson Report,³ was commissioned by the Canadian Association of University Teachers (CAUT). It concludes: "The adverse findings against Olivieri in the reports of the Naimark Review and the HSC's Medical Advisory Committee are incorrect and based on incomplete, incorrect and false testimony."⁴ In an official response to the Thompson Report prepared at the request of the HSC,⁵ members of the Naimark Review committee emphatically reject this conclusion.

Readers must decide for themselves which version of events is the more thorough, credible, independent and just. Honourable people may disagree on some points. In our view, the Thompson Report is a must read for anyone concerned with patient safety and the protection of academic freedom in teaching institutions in Canada. If even one third of the findings in this Report are true, it is, as one reviewer has stated, enough to "scare any Canadian witless."⁶ Its implications are distressing not only from a researcher's perspective, but also from the perspective of patients who participate in research.

Olivieri is a specialist in hereditary blood diseases at the HSC, a teaching hospital fully affiliated with the University of Toronto. In the mid-1990s she entered into contracts with a major international pharmaceutical manufacturer, Apotex Inc., to test the experimental iron chelation drug deferiprone on transfusion-dependent thalassemia patients at the HSC. One of the contracts included a confidentiality clause granting Apotex the right to block communication of research data for a year after termination of the trial. During the course of the trials, Olivieri identified an unexpected medical risk in that the experimental drug appeared to lose efficacy with long-term use. She reported her concern to the Hospital's research ethics board (REB). Consistent

with ethical guidelines governing research in Canada,⁷ the REB instructed her to disclose her concern to all research participants. When she moved to comply with the REB's directive, Apotex terminated the 2 trials in progress in Toronto and Olivieri's consulting contract for a third international trial. As well, Apotex threatened legal action against Olivieri should she attempt to inform patients or anyone else of her concerns. Sometime after the trials were terminated, Olivieri identified a second unexpected risk, i.e., that the drug may cause progression of liver fibrosis. Patients receiving the drug and the regulatory authorities were notified directly of this additional risk by Olivieri.

During this period, Apotex and the University of Toronto were negotiating a multimillion-dollar donation toward the construction of a biomedical research centre (\$20 000 000 for the University and \$10 000 000 for its affiliated teaching hospitals). If realized, this would have been the largest corporate donation ever received by the University. While these negotiations were ongoing, then-University of Toronto President Prichard, at the request of Apotex, wrote to Prime Minister Chrétien and 4 other federal ministers regarding proposed drug patent regulations. He wrote that Apotex had:

promised "a very substantial philanthropic commitment" to the university. He went on to say that Apotex "has advised us that the adverse effect of the new regulations would make it impossible for Apotex to make its commitment to us." Prichard urged the Prime Minister and Liberal cabinet members to do what is necessary "to avoid the serious negative consequences to our very important medical sciences initiative."⁸

President Prichard later apologized to the Executive Committee of the University for this action, acknowledging that he had made "a mistake" and that the letter had "placed the University in an inappropriate position of intervening in a matter beyond the legitimate scope of the University's jurisdiction."⁹

Olivieri and a number of other medical scientists at the HSC expressed concerns about the close relationship between Apotex and the University of Toronto and its affiliated hospitals. These concerns were sharpened by the Hospital's and the University's failure to support Olivieri's duty to disclose unanticipated risks to research participants and her right to publish research findings. The Hospital finally responded with the unilateral appointment of Arnold Naimark, former President and Dean of Medicine at the University of Manitoba, to conduct a review of the controversy. Part way through the review, he enlisted the aid of Frederick Lowy, Rector of Concordia University, former Dean of Medicine at the University of Toronto and found-

ing Director of the Joint Centre for Bioethics at the University of Toronto, and Bartha Knoppers, an expert in health law and policy from Université de Montréal. In less than 2 months this team issued a final report that largely exonerated the HSC and criticized Olivieri.²

CAUT then appointed a committee of inquiry. In particular, the committee was to consider whether breaches of medical research ethics, clinical ethics or academic freedom had occurred. Its members were Jon Thompson (chair), Patricia Baird and Jocelyn Downie — respectively, Professor in the Department of Mathematics and Statistics at the University of New Brunswick; University Distinguished Professor at the University of British Columbia; and Associate Professor in the Faculties of Law and Medicine at Dalhousie University. After 2 years they issued a 540-page report that exonerated Olivieri and criticized the HSC, the University of Toronto and others, including CAUT.³

The Thompson Report outlines a series of recommendations for both local and national institutions, including REBs, universities and teaching hospitals, clinical research funding councils and Health Canada. Fundamental to these recommendations is the committee's finding that Canadian clinical research participants are not adequately protected against potential injury. The recommendations aim to increase protections for research participants, to reduce the potential for conflicts of interest and, overall, to safeguard the public interest and foster public trust. For instance, one of the core recommendations is that all contracts, protocols and investigator agreements include a provision expressly identifying the investigator's obligation to advise research participants of risks newly identified during the course of a clinical trial. Although such clauses typically appear in research protocols, contradictory clauses frequently appear in companion documents (including contracts and investigator agreements), and these documents are not typically subjected to REB review. The Thompson Report further recommends that the Association of Universities and Colleges of Canada establish a policy governing university–industry relations, with a focus on the protection of research participants. There are also recommendations addressed to Health Canada to significantly enhance the safety of study subjects. In addition to these broad recommendations, there are specific recommendations to the HSC and the University of Toronto as to measures they should take to redress the wrongs and prevent such a situation from recurring.

The response of the Hospital and the University has been disappointing, to say the least. The HSC has described the matter as “closed” and attempts to revive it as “counter-productive.”¹⁰ The University has stated publicly that the Thompson Report “does not add any substantial information to the case.”¹¹ This stance is troubling in that there are important differences between the Naimark Review and the Thompson Report on a number of key points, including the roles played by senior clinical supervisors, the REB chair and, perhaps most significantly, the Hospital and University themselves. Consider the following contrary findings.

The Naimark Review concludes:

There is no evidence to indicate that any impediment was placed on the free exchange of research information between investigators and senior clinical supervisors, or between the investigators and the REB. There is also no evidence to indicate that there was any impediment to communicating relevant research information to other bodies concerned with patient safety in the hospital, such as the Medical Advisory Committee and its Patient Care Committee. ... There is no evidence that the Hospital did anything to impede or discourage Dr. Olivieri from freely communicating her research findings to the scientific community. In fact, Hospital officials reported that they encouraged Dr. Olivieri to present and publish her research findings.¹²

The Thompson Report concludes:

The Hospital for Sick Children and the University of Toronto did not provide effective support either for Dr. Olivieri and her rights, or for the principles of research and clinical ethics, and of academic freedom, during the first two and a half years of this controversy.¹³

The Hospital for Sick Children took actions that were harmful to Dr. Olivieri's interests and professional reputation, and disrupted her work. In each instance, the adverse actions were taken without providing due process. She was provided neither with the case she was expected to meet, nor a fair opportunity to respond, prior to the actions being taken.¹⁴

In view of the marked differences between the 2 reports, and the importance of this case for the public interest, what justification can there be for the Hospital's and the University's non-response? Although the Naimark Committee's response to the Thompson Report (which disputes several of the Thompson Report's factual findings and exonerates the Hospital from wrongdoing) has been posted on the HSC website and endorsed by the Chair of its Board of Trustees,¹⁵ there has otherwise been virtual silence from both the Hospital and the University. We believe that strong leadership is needed in our public institutions, and most importantly in our universities, to promote scholarship (as contrasted with entrepreneurship) and to protect the integrity and academic freedom of universities from the eroding effects of commercial interests.^{16,17} For the moment, evidence of such leadership appears to be lacking.

In addition to discounting the substance of the Thompson Report, both institutions have sought to dismiss the committee as biased on the grounds that it was sponsored by the CAUT and comprised of university professors. As to the first point, the members of the Thompson committee took steps on appointment to secure their independence from CAUT by obtaining a commitment that they would be free to reach conclusions and make recommendations irrespective of any position taken by CAUT. Further, members did not receive remuneration. They also required that CAUT waive its right both to comment on a draft report and to exercise discretion as to whether or not to publish the final report. CAUT agreed to these stipulations and received the committee's report at the same time as everyone else — Oct. 26, 2001.

As to the second point, it is curious that the fact that all 3

members of the Naimark committee were also university professors did not draw similar criticism. Further, it is worth noting that Patricia Baird — a member of the Thompson committee — had previously been invited to serve on the Naimark committee. She had declined this invitation because she was not satisfied that she would have sufficient independence in stating her own conclusions.¹⁸ Surely if she was suitable for membership on the Naimark committee she was a suitable member of the Thompson committee.

We call on the University of Toronto and the HSC to address the findings of the Thompson Report and to engage meaningfully with its recommendations. We call on them to do so explicitly and on their own behalf, and not simply to rely on the response from members of the Naimark Review committee. A response from both of these institutions is particularly warranted given recent statements regarding the narrow scope of the mandate given to the Naimark Review committee. On their account, their mandate did not include a review of either the context in which the controversy arose, or whether Olivieri was treated fairly as an employee and officer of the U of T and HSC: “the HSC Review was not intended to be a forum for the adjudication of scientific disagreements, of personnel issues and grievances or disputes between Dr. Olivieri and Apotex.”¹⁹ Can the institutions at the centre of this controversy claim to have dealt with a case in all of its ramifications without addressing the substance of personnel, contractual and institutional actions and obligations?

To the broader national community, particularly to anyone engaged in the conduct of clinical research or its ethical review, our message is this: read the Naimark Review, the Thompson Report, the Naimark response to Thompson, and any further instalments in this still-unsettled saga. Given the present climate governing clinical research in Canada, the circumstances that culminated in the Olivieri fiasco are not unique to the University of Toronto or the HSC; indeed, any number of researchers, research participants and institutions throughout the country are similarly vulnerable. We ignore this concern at our peril.

There are many intricate steps in the dance with the pharmaceutical industry. Before accepting an invitation from a prospective partner, one needs a clear idea of the choreography. When the music is unappealing, or the risk of missteps considerable, it is best to announce that one’s dance card is full.

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All 3 authors recently co-authored a commentary on university–industry relations with Patricia Baird and others.

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