Legal issues surrounding privately funded research cause furore in Toronto

Miriam Shuchman, MD

In brief

TORONTO PHYSICIAN MIRIAM SHUCHMAN has spent the last 4 months tracking the research issues surrounding a controversial clinical trial conducted in Toronto. Much of the information appearing in this article was gathered while she was preparing a segment for the CBC Radio program *Quirks and Quarks*. Earlier, she had reported on similar issues in the US for the *Annals of Internal Medicine*.

Although research partnerships between medical academics and private companies are proliferating, a case that was widely publicized in Toronto this summer makes clear that these partnerships do not always go smoothly. When the company does not like the research findings, it may try to keep them secret. And if the company is also a major philanthropic force in the community, there is the potential for conflicts of interest for the institutions involved.

The incident itself is relatively simple, but the issues it raises are not. Internist Nancy Olivieri of the Hospital for Sick Children (HSC) and the University of Toronto partnered with a pharmaceutical company, Apotex Inc., to test a drug. Barry Sherman, the head of Apotex, is a generous donor to causes in Toronto and across the country. A dispute developed between Olivieri and Apotex when the company objected to her claims that a drug it had in development was ineffective and possibly dangerous. The company threatened to sue if she made her findings public.

One reason this story has received so much attention is that clinical scientists around the country worry that the dispute at HSC may be the tip of an iceberg. Similar situations have arisen at American universities when companies threatened to sue to prevent publication of negative findings. Now, Canadian researchers fear that similar situations may arise here, and there is concern about the level of support their institutions will provide. Their concerns mean it is worth while to try to understand in some detail what soured the research relationship between Dr. Nancy Olivieri and Apotex.

In August, Olivieri reported on a clinical trial of an experimental iron chelator in patients with transfusion-dependent thalassemia. Her report in the *New England Journal of Medicine* (339:417-23) described the experimental drug as ineffective and toxic to the liver. It was published despite warnings from Apotex, the company developing the drug, that it might bring legal action against Olivieri. The press coverage that followed publication was intense, with Olivieri and her supporters portraying themselves as fighters for the freedom to publish scientific findings.

The players

Olivieri heads HSC's treatment program for patients with sickle cell disease and thalassemia. She is a full professor at the

Tibor Kolley, Globe and Mail

Dr. Nancy Olivieri, patient Patrizia Marmarato

Features

Chroniques

Dr. Miriam Shuchman lives in Toronto and teaches in the Department of Psychiatry at the State University of New York, Buffalo.

CMAJ 1998;159:986-9

See related article page 955

University of Toronto, with more than $1 million in research funds from the Medical Research Council of Canada, the National Institutes of Health and elsewhere. She has published extensively — her August article was her 11th for the *New England Journal* and she is working on her 12th, an invited review.

Apotex, meanwhile, is one of Canada's leading producers of generic drugs. Its owner, Barry Sherman, has a reputation as a successful entrepreneur and he also heads one of Canada's 10 biggest private charitable bodies, the Apotex Foundation. In 1996 he was named Philanthropist of the Year by the Toronto chapter of the National Society of Fund Raising Executives.

Dr. Michael Spino, a pharmacologist from HSC, was brought to Apotex by Sherman to help the company expand from generic drugs into the development of new drugs. In the early 1990s, as he was looking for compounds to develop, Spino heard about the iron chelator deferiprone from colleagues at HSC. He chose it as the company's first venture into new drugs.

Deferiprone would replace a shot with a simple pill. Patients with thalassemia are transfused so frequently that iron overload is a major clinical problem, and the iron chelator deferoxamine has been the only effective means of reducing the iron to nontoxic levels. However, it must be given by injection and infused slowly, over 6 to 8 hours. This means painful, irritating needles every night. If there was an effective pill for iron chelation, it could be used by millions of thalassemia patients worldwide.

The studies

In 1993, Apotex began sponsoring Olivieri's clinical trials of deferiprone. Apotex also asked her to oversee European trials of the drug. By 1995, she had enough data to warrant a favourable report in the *New England Journal* (332:918-22). Within months of that report's appearance, Olivieri began to worry. She thought there had been an increase in hepatic iron in some patients taking the new pill. In them, the drug seemed to become ineffective after prolonged use. A rise in iron puts thalassemia patients at risk of early death.

When these findings first began to emerge, Olivieri wanted to tell the Research Ethics Board (REB) at HSC, but Apotex objected. "We took a look at the data and we said we're sorry . . . we disagree," Spino explained in an interview. "We said, 'Why rush to the ethics board?' This is not the sort of thing that you raise flags over. . . ."

The legal issues

But Olivieri did go to the REB, which suggested a revised consent form be developed for the clinical trial. Instead, the company stopped the trial at HSC and removed Olivieri as head of the European trials. In a letter Spino also reminded Olivieri that she had signed a contract with the company, which meant that all information obtained by investigators was "secret and confidential" and could not be disclosed "except with the prior written consent of Apotex."

He added: "Please be aware that Apotex will take all possible steps to ensure that these obligations of confidentiality are met and will vigorously pursue all legal remedies in the event there is any breach of these obligations."

Dr. Robert Phillips, executive director of the National Cancer Institute of Canada, watched these events unfold. "Apotex was convinced that Dr. Olivieri's view was not valid," he says. "They did not agree with her interpretation, so rather than really debate it in the open scientific community, they tried to stop the debate and prevent that discussion from taking place."

Olivieri admits that she had been naïve to sign a contract obliging her to keep results confidential. She had not shown the contract to a lawyer and no one else at the hospital or the university had signed it. She says she felt the contract could not prevent her from speaking to patients: "I think my ethical obligations to the patients far supersede my contractual obligations to a company. . . ."

Worried patients

One patient who recalls the situation bitterly is Josephine Sirna, who now lives in Ottawa. She says thalassemia patients were "devastated, just blown away" when they had to stop taking the pills and return to nightly injections. Apotex removed the supply of the experimental drug from the HSC pharmacy while Olivieri was out of town, says Sirna, leaving Olivieri's research fellows to face "pleading, angry and frightened patients." When Olivieri returned, recalls Sirna, "her unfortunate reply to her patients' questions was that she couldn't say anything because Apotex had threatened to sue her if she did."

Olivieri hired a lawyer and then alerted Health Canada and the US Food and Drug Administration about her concerns. She also met with patients, but was guarded in what she told them.

Doctors consider themselves obliged to warn patients of the potential dangers of a treatment — the Declaration of Helsinki, which guides physicians conducting research, states that human subjects must be informed of potential hazards. Mary Rowell, an ethicist at HSC, says the patients should have been told about Olivieri's concerns. "Where the risks are serious, even if they are potential [risks], we tell," she says. "That word 'potential' is critical to the informed-consent process."

Apotex responds

By this point Apotex had invested millions of dollars in developing the drug, and it acted aggressively to protect the investment. In addition to stating that it might bring legal action, the company appointed an independent panel to review Olivieri's science. One of the panelists, Dr. Mary Corey of HSC, says "the panel made a strong recommendation that the trial be reinstated because there was nowhere near a clear answer. That recommendation was ignored."

The company also contacted Olivieri's department chair at the hospital: ". . . We went to people that she reports to and pointed out the difficulties that we had with her. . . .," says Spino.

A few months after Apotex stopped the study at the hospital, HSC launched an initiative to move Olivieri's patients with sickle cell disease to another hospital. When she protested this transfer of care, she received a letter from senior administrators telling her that she would be dismissed as director of the hemoglobinopathy program if she did not cooperate.

Olivieri says the company's and hospital's actions upset her. She says she jumped every time her fax machine rang, since many of the legal notices she received arrived by fax. At night she would lie awake, worrying that she couldn't afford her lawyer, that she would lose her job, or that she would be ridiculed in public. She contacted her lawyer as often as 6 times a day, seeking both advice and reassurance.

It would have been even more difficult, she says, had she not been supported by her collaborator, Dr. Gary Brittenham of Columbia University in New York. At one point she told Brittenham that if the company carried out its threats to bring a lawsuit, he might have to sell his house to pay legal expenses. If it came to that, he responded, he would sell his house. That level of support, says Olivieri, kept her from feeling completely isolated.

A toxic drug?

University-based scientists consider themselves obliged to publish their findings. This is especially true when their research concerns matters of public health, such as a drug which might or might not be harmful. As well, without publication scientific discoveries cannot be shared with other scientists or with the public, and scientists' academic careers cannot progress.

Yet Apotex was advising Olivieri not to publish or present. Spino says the company did not want to suppress information but it did want to prevent Olivieri from promulgating misinformation.

After discussions with her lawyer, Olivieri presented her findings at a scientific meeting in Florida in December 1996. While she was there, Brittenham called about a report that a drug similar to deferiprone caused scarring of the liver — hepatic fibrosis — in gerbils. They wondered if the same thing could happen in humans. Back in Toronto, Olivieri pulled the liver biopsy slides of her subjects, and on Christmas Eve she and a pathologist reviewed all of them. Their findings were the most disturbing yet. They thought they saw worsening of hepatic fibrosis in patients taking the experimental drug.

In February 1997, Olivieri and her group submitted a report to Apotex that described the drug as toxic, but Apotex disputed the finding. It had pathologists review the slides and those doctors saw no evidence of toxicity. Today, the toxicity issue remains a subject of scientific debate. Olivieri had 2 British pathologists review all the slides blindly, and they coauthored her August paper. It reported that hepatic fibrosis was seen in more than one-third of patients taking deferiprone. But that paper does not settle the scientific dispute. In an editorial in the same issue of the *New England Journal* (339:468-9), scientists from the University of Washington in Seattle and Tufts University in Boston argued that Olivieri's trial did not include an adequate control group and did not provide ideal liver samples. The pill, they said, required further investigation.

Word gets out

During 1997, word spread about Olivieri's dispute with Apotex. Several scientists urged the hospital and university to support Olivieri and to investigate the company's actions, but no investigation was conducted.

Leaders at the University of Toronto and HSC received letters, phone calls and email from concerned scientists. Dr. David Nathan, a thalassemia expert who heads Harvard's Dana Farber Cancer Institute, called Dr. Arnold Aberman, dean of medicine at the University of Toronto, in support of Olivieri. Closer to home, the National Cancer Institute's Phillips wrote to Aberman and to hospital leaders: "You must make some public statements in support of Nancy and in support of a system that demands collegiality and condemns secret agreements. . . ."

"Scientists have to feel that they aren't going to be exposed to legal action if they perhaps come up with results that aren't as spectacular as perhaps the company selling the drug wants," Phillips said in an interview.

Dr. John Dick of the Hospital for Sick Children also asked Aberman and Dr. Manuel Buchwald, the hospital's director of research, to gather the facts and try to end the legal warnings. Dick says it was "very daunting" to ask for such action. "I'm not a confrontational person," he says. "I'm absolutely consensual, and so it took a huge amount of emotional energy to raise hard issues, issues that you know the person across the desk didn't want to hear."

Dick says Aberman told him that the issue involved a scientific dispute and, therefore, as dean, he did not need to take sides. In an interview, Aberman said: "If there's a contract between 2 parties, a third party doesn't have the right to enter into it and urge 1 of the parties not to abide by it."

In October 1997, 5 of Olivieri's colleagues, including Dr. Stanley Zlotkin, former head of the hospital's REB, and Dr. Peter Durie, head of cystic fibrosis research, met with the dean and hospital leaders, and called for an independent review. They say they were told that no action was needed by either institution.

Buchwald said the hospital thought the company would not sue Olivieri. He added that it would have been wiser for the hospital to have "indicated to Apotex that it viewed their threats as empty and they should stop them."

Olivieri contends that she received little support from the university or hospital. As recently as May 1998 her department chair wrote to accept her resignation, even though she had not tendered it. Olivieri had written to her division chief requesting more resources for her growing clinical and research programs. In her April 1998 letter to the chief of the Division of Hematology, she wrote: "I am unable to discharge my responsibilities as Director of the Haemaglobinopathy Program . . . with the infrastructure presently provided to me." Dr. Hugh O'Brodovich, the department chair, responded in May: "From your letter I understand that in the present circumstances you wish to resign as Director of the Haemaglobinopathy Program. . . . By this letter I accept your resignation as Director."

The potential for conflicts of interest

Drs. Aberman and Buchwald deny that their institutions' decisions about ways to handle the Apotex dispute were influenced by money, and there is no evidence that they were influenced. However, there is the appearance of a potential conflict of interest. At the U of T, the potential conflict involved negotiations with Barry Sherman's Apotex Foundation for a substantial donation that would help the medical school expand its facilities. Sue Bloch-Nevitte, director of communications for the U of T fund-raising campaign, said in an interview that the university has been "hoping that the Shermans would consider making a sizable donation upwards of perhaps $20 million to the facility."

At the hospital, the potential conflict involved a possible donation of $10 million from the Apotex Foundation. Dianne Lister, president of the HSC Foundation, confirmed that the Apotex Foundation had offered the money to one of the city's teaching hospitals; it would accompany its expected donation to the medical school. On Aug. 12, the day the *New England Journal* lifted its embargo on Olivieri's paper, allowing press coverage to begin, HSC President Mike Strofolino announced that the hospital had declined the $10 million. In an interview, Buchwald explained why: "Given the circumstances of the L-1 [deferiprone] trial, we thought it was not in the best interests of this institution to enter into some kind of new venture with them."

Although there is no evidence that these negotiations with the Apotex Foundation affected decisions being made by leaders at the hospital or university about the dispute between Apotex and Olivieri, they are the types of donations that could potentially exert influence. When the appearance of a potential conflict of interest exists, says Dr. Eliot Phillipson, chair of the Department of Medicine at the U of T, the best way to manage the situation is to disclose it to all interested parties. "Conflict of interest is not an act," says Phillipson. "You don't have to do anything. It's a situation or a potential situation [and] in most instances just disclosing the potential is sufficient to remove it as a major issue."

Olivieri, and the scientists who asked the university and hospital to support her, say that the anticipated donations from the Apotex Foundation were not disclosed to them in their meetings with hospital and university leaders.

Support for Olivieri

Two days before Olivieri's paper appeared this August, leaders at Sick Kids received a petition signed by nearly 200 doctors asking the hospital to conduct an inquiry into the issues raised in this dispute. Following extensive press coverage of the dispute, the hospital announced that it would obtain an external review of its policies. Olivieri and other scientists protested that an inquiry into what had happened was required.

They held a press conference to underscore their concerns. Dr. Brenda Gallie, director of cancer and blood research at HSC, announced that she might resign from the hospital if an inquiry did not take place, since she could not be certain that research subjects in ongoing trials would receive adequate protection. In September the hospital announced that there would be an independent inquiry, headed by Dr. Arnold Naimark of the University of Manitoba.

Those findings are expected to be made public next month. ?