Sounding Board

Academic Freedom in Clinical Research

"Is the university–industrial complex out of control?" The editorial that appeared under this eye-catching title in *Nature* in January 2001 came to the conclusion that links between academia and industry are of increasing concern to academics and to society at large and that the sectors involved must review and revise their policies in order to sustain the public accountability and academic freedom of universities.[1] It ended with a list of New Year's resolutions for actions that would be required to maintain public trust in higher education and publicly funded research. But with the notable exception of the decision of many leading medical and scientific journals to tighten up regulations regarding conflicts of interest among their authors,[2] these resolutions seem to have gone the way of most New Year's resolutions.

A recently published independent review sponsored by the Canadian Association of University Teachers (CAUT) of a long-standing dispute involving Nancy Olivieri, a clinical researcher at the Hospital for Sick Children (Toronto) and the University of Toronto, provides an impetus to revisit this issue.[3] Since the remarkable advances in the biomedical sciences stemming from the human genome project are likely to reach their potential for clinical application only through an increasingly effective partnership between academia and industry that preserves academic freedom, ensuring such freedom is a matter of great urgency.

The Dispute

The Olivieri case involves the search for a safe and effective orally active iron chelator. This quest has dominated clinical research on thalassemia and other conditions characterized by iron overload for decades.[4,5] Of many compounds that have been considered, only one, a hydroxypyridin-4-one with the generic name deferiprone, has entered clinical trials. The events surrounding clinical trials of this drug at the Hospital for Sick Children and the University of Toronto represent a modern nadir in the relations among academic investigators, their institutions, and the pharmaceutical industry.

Deferiprone, a bivalent iron chelator, was initially synthesized by Robert Hider and his colleagues.[6] It was briefly licensed to Ciba–Geigy (now Novartis) but was abandoned by the company in 1993 because of its low therapeutic index in animals without iron overload,[7] its poor stoichiometry (three molecules of drug are required for binding of each iron atom[7]), and its rapid removal from the circulation.[8,9] The efficacy of the drug is therefore critically dependent on its poorly maintained concentration in body fluids.

Deferiprone was first investigated in uncontrolled clinical trials by a group at the Royal Free Hospital in London.[10] After reading the report of these trials, Olivieri and her colleagues produced enough of the drug to initiate clinical studies. Encouraged by her preliminary results, she and Gideon Koren, a former colleague of hers at the Hospital for Sick Children, entered a collaboration with Apotex, a Canadian manufacturer of generic drugs. Apotex produced the drug, and Olivieri, who is the director of the largest hemoglobinopathy clinic in North America, began a relatively short-term, uncontrolled clinical trial of deferiprone in patients with thalassemia who had iron overload. The trial was sponsored by a grant from Apotex to the Hospital for Sick Children. To obtain the grant, Olivieri and Koren (then the associate director of the Hospital for Sick Children Research Institute) signed a confidentiality agreement that was compatible at that time with the policy at both the University of Toronto and the hospital, and the hospital accepted the grant.

The initial results were published in 1995 and were encouraging.[11] The drug appeared to reduce or maintain liver iron levels in patients with thalassemia who had undergone multiple transfusions. Although an editorial accompanying the report warned that much more time would be required to determine the efficacy of deferiprone,[12] there was high expectation among researchers and physicians who treat patients with thalassemia that the drug would prove useful in the management of the iron overload associated with long-term transfusion. In the process of trying to gather the data to answer this important question, Olivieri, Apotex, the Hospital for Sick Children, Koren, and the University of Toronto became embroiled in a nasty controversy.

Olivieri started a second prospective trial (for which she did not sign a confidentiality agreement) in which deferiprone treatment was compared with therapy with the standard drug, deferoxamine. Patients who take deferoxamine regularly have a steady decline in hepatic iron levels. In a substantial proportion of patients in Olivieri's second study, deferiprone either failed to reduce hepatic iron levels below their starting points or actually increased them to a value that was substantially above their starting points.[13] In addition, in some of the patients who received deferiprone but in none of those who received deferoxamine (who had much lower liver iron levels, on average), increased hepatic fibrosis appeared to have developed, as judged by four independent pathologists who were blinded to the treatment-group assignments. An editorial[14] ac-

companying the published report stated that deferiprone might be ineffective or even toxic in some patients and that further trials were required. The question of whether deferiprone induces hepatic fibrosis remains unresolved.

When she became aware of the findings, Olivieri thought it was her responsibility to report these adverse events to her institutional review board, present them to a scientific meeting, and submit them for publication. In response, Apotex stopped all clinical trials involving Olivieri and threatened to take legal action for her violation of the confidentiality agreement that she had signed before the first trial if she released to the public the information gained in the second trial. Within a few years, two lawsuits totaling $20 million were formally lodged against her. Olivieri defied Apotex by submitting the material for publication and presenting it at a scientific meeting.[15]

CURRENT STATUS OF DEFERIPRONE

It takes years to demonstrate whether an iron chelator is clinically effective. In the case of deferoxamine, for example, more than two decades of observation were required to show that the incidence of cardiac disease, the most common cause of death in patients with thalassemia, could be reduced by the drug.[16-19] As of this writing, the safety and efficacy of deferiprone have not been established; it is beyond the scope of this article to review the scientific data concerning the use of the drug in any detail. Published papers suggest that deferiprone does a poor job of removing iron from hepatic stores in a substantial proportion of treated patients.[20-23] The issue of its safety with respect to hepatic fibrosis has not been resolved. Suffice it to say, when the dispute began, Olivieri had good reason to believe that deferiprone was neither safe nor effective.

THE ETHICAL STRUGGLE

The series of events that followed the disagreement between Olivieri and Apotex and the company's attempt to prevent the investigator from publishing her results are described in the CAUT report, an exhaustively researched and annotated 540-page document.[3] The report describes years of harassment and the generation of misinformation about Olivieri, as well as providing even more worrisome accounts of a large donation that the University of Toronto was negotiating with Apotex.[3] The report makes clear that Olivieri's academic freedom to present her concerns to her peers was abridged. More important, although the Hospital for Sick Children and the University of Toronto knew that this freedom was under attack, Olivieri received harassment instead of support from the hospital and ineffectual support from the university in her legal stand against Apotex.

The CAUT report is not the only one that has been produced on this subject. About two years ago a panel sponsored by the Hospital for Sick Children found fault with Olivieri's handling of events after the termination of the trial.[24] The CAUT report provides strong evidence that the panel's conclusion was based at least in part on incorrect information that was fed to it by Koren, who, the panel knew, was in the midst of his own bitter dispute with Olivieri.[3] Subsequent to the release of the panel's report, which is now known to be flawed, the hospital's medical advisory committee inquired further into Olivieri's conduct — a process that culminated in her being referred for research misconduct to the College of Physicians and Surgeons of Ontario,[3] the medical licensing board of the province. Information about the humiliating referral was made widely available to the public by both the Hospital for Sick Children and the University of Toronto, even though release of such confidential information was in violation of the then-current policy of the university. Recently, the College of Physicians and Surgeons issued a statement concluding that none of the allegations have any basis and completely vindicating Olivieri on all scores.[25]

CONCLUSIONS

Although the Olivieri debacle is complicated by personal animosity, poor administrative judgment, and bad behavior among academic colleagues, the case report raises a number of fundamental questions about the research interface among teaching hospitals, academic clinical departments of universities, and industry. As the authors of the CAUT report state in their summary, these are issues that affect the entire biologic-research community.

What is central to this particular case is the principle of academic freedom. It does not matter whether, in the end, Olivieri was right or wrong in her assessment of the efficacy and safety of deferiprone or whether she is a pleasant or difficult colleague. What matters is that, at the time of the dispute, Olivieri was concerned enough about the safety of the drug to convey her doubts to a scientific meeting and to a peer-reviewed journal so that members of the medical community could judge the issue for themselves.

But the CAUT report also underscores the inadequacies of the University of Toronto and the Hospital for Sick Children in resolving this vexing problem at the interface among the university, industry, and the investigator. In our opinion, the hospital had an inadequate control mechanism for clinical research, and its leadership managed the case poorly. At the same time, administrators at the university were unable or unwilling to persuade the hospital or Apotex to provide more effective and stable management for what became a public crisis. In part, the university's response

might have been influenced by the prospect of a large gift from Apotex, but in our opinion, most of the failure was due to excessive legalism and an unwillingness to force a high-stakes and very public confrontation with the Hospital for Sick Children or Apotex.

The Toronto episode probably represents an extreme case, engendered in part by deep hostilities within the ranks of the faculty at the Hospital for Sick Children and the determination of Apotex to win at any cost. We would like to believe that most universities would support faculty members who were exerting their right to academic freedom in the face of angry and disappointed industrial sponsors of trials that did not go their way. Apotex is probably an unusual company. Few pharmaceutical companies, even those with severe hubris, would so zealously pursue a drug like this one — recently described by the dean of the University of Toronto as an agent with "uneven efficacy and uncertain toxicity"[26] — to the point of litigation and adverse publicity.

But as unusual as this case may be, it is not unique. There are other examples of serious failure of institutional support in similar circumstances.[27-29] There can be no useful interactions between industry and academic physicians if lawsuits are to result from publication of data that may not suit the business plans of the sponsor. Institutions must protect the right and duty of their faculty members to publish their research. No sponsor can be permitted to stand in the way of that right and duty, because they represent the central ethos of university life.

What lessons can be learned from the recent events in Toronto and the growing evidence that things may not be much better, albeit less bizarre, elsewhere? It appears that at the time when Olivieri entered into her contractual agreement with Apotex, neither the Hospital for Sick Children nor the University of Toronto had adequate procedures for arrangements of this kind with industry — a situation that has since been corrected.[3,26] Most contracts now allow investigators to publish information arising from joint studies of this type after a fixed period, although the specifics vary widely among contracts. But is this provision sufficient? The enormous legal and financial power of the pharmaceutical industry puts clinical investigators in a very difficult position if there is a major controversy about the outcome of a particular study. Clinical scientists and, incidentally, industry itself need a fail-safe mechanism for cases of this kind in order to protect academic freedom, the safety of patients, and the rights of industrial sponsors. Such a mechanism could be created if, as part of the original contract, an independent external review panel were established, with members who were acceptable to both parties, to mediate in cases of scientific disagreement about the outcome of a particular study. Indeed, this approach might be more effective if a national panel were established by a respected body such as the National Institutes of Health, the Institute of Medicine, or equivalent national research councils in other countries in order to deal with problems of this kind. It would be hoped that such a standing committee would rarely need to be activated, but its very existence might serve as a deterrent against events like those that occurred in Toronto.

Universities will have to decide on the extent to which they wish to become commercialized and will have to monitor the effect that such commercialization has on the pattern of their research, on public confidence in research, and on academic freedom.[30] They need to reexamine every aspect of their contracts with industry, ways of preventing dangerous relationships between faculty members and industry, and ways of evolving standards for research practice that will protect scientists when difficulties arise. Universities must develop much clearer understandings with their teaching hospitals about the standing of academic clinicians; in the Toronto affair, neither party seemed to know what the other was doing and no one was in overall control.[3]

We now have the potential to enter one of the most productive periods in biomedical research, the success of which will depend to no small degree on an increasingly close partnership between universities and industry. It is vital, therefore, that the problems of this interface be recognized and corrected. No doubt, leaders of medical schools and teaching hospitals, or their equivalents, who read the CAUT report about events in Toronto — and they should read it — will want to tell themselves that such things could never happen in their universities. Unfortunately, they are happening, although they generally take milder and less public forms. All of us in academic medicine must look carefully at our own houses and set standards that protect the rights of faculty members to express their opinions in scholarly settings and journals. The Olivieri case represents an important warning that academic freedom can disappear if we do not protect it. How tempting and comforting it would be to believe that the case is unique. And how much wiser it would be to conclude instead that there, but for the grace of God, go we.

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Collaborating with Industry — Choices for the Academic Medical Center

THE relationships between academic institutions and private companies are strengthening. The decision of several large pharmaceutical companies, and many biotechnology companies, to build major new laboratories near U.S., European, and Asian universities is just one example of the growing commercial value of academic innovation in biomedicine and the talent that produces it. Individual faculty members and universities in the United States and other countries have increasingly strong financial and nonfinancial incentives to start new companies and to participate directly in the development of drugs, devices, and diagnostic tests.[1]

Many negative implications of this trend have been recognized. Articles in the popular and scientific press have discussed concerns about patient safety in clinical trials, issues related to privacy, conflicts of interest on the part of researchers and their institutions, a shift of priorities in academic research from the public good to private commercial gain, and the potential for disruption of the historical compact between physicians and their patients.[2]

These changes have not gone unnoticed. The Association of American Universities, in collaboration with the Business–Higher Education Forum,[3] and the Association of American Medical Colleges (AAMC)[4] have recommended general safeguards and institutional procedures for the management of academic–commercial ties, with special attention to the need to avoid conflicts of interest that may compromise the safety of patients in clinical trials. Several specialty societies have issued recommendations that address particular issues of concern in their fields. Yet these guidelines serve only as starting points for defining what is desirable: they leave many questions unanswered, and they do not address nonclinical research.

THE FORCES CHANGING BIOMEDICAL RESEARCH

Academic biomedical research and industrial biomedical research have similar needs. Both require ready access to specialized talent, from senior investigators