The deferiprone controversy: time to move on

C. David Naylor

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The Editor has asked me to comment on the report[1] issued by the Canadian Association of University Teachers (CAUT) on the controversy surrounding the trials of the iron-chelation drug deferiprone (L1) at the Hospital for Sick Children (HSC).

The CAUT Inquiry report is yet another in a series of reports and commentaries on what has been an exceedingly protracted and difficult dispute. Authored by Jon Thompson, Patricia Baird and Jocelyn Downie, it revisits some of the ground covered in an earlier review commissioned by the HSC in late 1998 from Arnold Naimark, Frederick Lowy and Bartha Maria Knoppers.[2] The CAUT report is highly critical of both certain conclusions drawn by Naimark and colleagues and the actions of a number of individuals. Responding to the CAUT Inquiry in December 2001, Naimark, Knoppers and Lowy characterize it as "in large measure, a grievance investigation designed to find fault, lay blame and call for redress" as contrasted with the "prospective and constructive purposes" of the HSC Review.[3]

The self-characterization of the original HSC Review as "prospective and constructive" will be contested by those who see that report as underpinning a decision by the Medical Advisory Committee (MAC) of the HSC to investigate Nancy Olivieri's conduct during the L1 trials. In the spring of 2000 the MAC referred its unresolved concerns to the College of Physicians and Surgeons of Ontario (CPSO). Similar concerns were referred to the Faculty of Medicine for investigation as potential research misconduct. The HSC and MAC widely publicized both referrals, ignoring the Faculty's policy that referrals about misconduct should be made confidentially to protect the scientific and scholarly reputations of our colleagues. The CPSO has now investigated and dismissed those concerns, and the Faculty of Medicine has dismissed the parallel allegations pursuant to the CPSO decision.

The CAUT Inquiry faults the HSC Review for proceeding without the involvement of Olivieri and her supporters, who refused to participate in its work. In turn, Naimark and colleagues "take particular note of the fact that the CAUT Inquiry Committee did not invite any of the Review Panel members to meet with it to provide clarification or other assistance about matters concerning the HSC Review that seem to have perplexed the Inquiry Committee."[3] Indeed, virtually none of the individuals who are criticized in the report or others identified with the administrations of the HSC and the University participated in any way with the CAUT Inquiry report.

This non-participation reflected a reasonable apprehension of bias, given the sponsorship and composition of the panel. CAUT represents faculty unions and the dwindling number of non-unionized faculty associations in Canadian universities. Among its affiliates is the University of Toronto Faculty Association (UTFA). UTFA has legally and financially supported Olivieri and her local allies in litigation against HSC officials and grievances against the University administration. Hence, as Naimark and colleagues put it, "The Inquiry Committee was no more independent than the Review Committee. Both were constituted unilaterally and both were limited because of non-participation of key individuals."[3]

Some matters covered in the CAUT report relate to confidential proceedings, and University officials cannot comment on them. Others are the subject of grievances before University tribunals. For reasons given above, the University views the report as representing primarily the perspective of the grievors and will comment on the relevant facts and issues as appropriate in the setting of University grievance proceedings.

For context, it is perhaps helpful to observe that iron-chelating compounds such as deferiprone are primitive and palliative "half-way technologies"[4] in the management of thalassemia major — a genetic disease of global importance and impact. Incalculable amounts of time and money have now been spent on repeated cycles of public relations gamesmanship, media manoeuvres, lawsuits, misconduct proceedings and academic tribunal activities related to a dispute about a single drug that has, at best, uneven efficacy and uncertain toxicity. It is surely time for some positive process of settlement that may, if good sense prevails, close those local issues that remain unresolved, and allow energy to be redirected to research that might someday yield more definitive gene-based treatments for thalassemia.

In the meantime, the University and hospitals have moved on. The general lessons of the L1 dispute regarding the ethical and independent conduct of industry-sponsored research have been drawn in the original HSC Review by Naimark and colleagues, and amplified both in a related 1999 HSC Research Policy Review Task Force report[5] and the CAUT Inquiry report. As I report elsewhere in this issue,[6] the University and all the Toronto teaching hospitals are making steady progress in implementing various of those recommendations. We look forward to exchanging ideas and experiences with other Canadian universities and hospitals taking similar steps.

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Competing interests: Dr. Naylor was based at the Institute for Clinical Evaluative Sciences and Sunnybrook and Women's College Health Sciences Centre until the summer of 1999. He was not involved in the matters discussed in this commentary, nor had he worked directly with any of the principal disputants, until his appointment as Dean of the Faculty of Medicine at the University of Toronto in August 1999. He was not involved in the 1998 HSC Review report nor in the subsequent response by that group to the CAUT Inquiry in 2001, nor did he meet with the CAUT Inquiry panel.

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Early Toronto experience with new standards for industry-sponsored clinical research: a progress report

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Industry-sponsored biomedical research has grown substantially over the past few decades and generated innovations that have materially and positively affected the diagnosis and treatment of myriad human diseases. Much of this research has been done collaboratively with academic investigators. Given the accelerated pace of therapeutic innovation arising from post-genomic biotechnology, the interface between industry and academe is likely to expand and become more complex in the years ahead.

On the other hand, industry's potential steering effects on the clinical literature have become a source of serious concern. Pharmaceutical review articles appear to be skewed in favour of specific drugs when authors have financial relationships with the relevant companies.[1] As Montaner and colleagues have noted,[2] the "epidemiology" of industry-sponsored clinical research differs from that of research sponsored by peer-reviewed agencies. This appears to reflect not inferior scientific quality but pre-selection of interventions and designs,[3–5] probably reinforced by delayed publication of unfavourable results. Delayed publication in general could have as much to do with a misguided culture of "positive publication bias" as with actual sponsor interference. However, study contracts may carry clauses that allow sponsors to suppress studies,[6] and there have now been several highly publicized incidents wherein industrial sponsors have litigated or otherwise attempted to interfere with the dissemination of findings that might be construed as adverse to their corporate interests.[7–10] Such actions can intrude on researchers' clear-cut ethical obligations regarding the safety of patients enrolled in clinical studies. Furthermore, whether defined in terms of their scientific integrity, academic freedom, professional autonomy or duties to subjects who may have volunteered in hopes of advancing medical knowledge, researchers also have well-established rights and responsibilities to publish findings deemed valid after peer review.

These tensions at the academic–industry interface recently led the editors of major medical journals to issue guidelines designed to ensure the independence and integrity of clinical research studies sponsored by for-profit enterprises or co-authored by industry scientists or both.[11] In Toronto, recognition of this trend and an intense local controversy led the Hospital for Sick Children in 1999–2000 to review and enhance its approach to management of clinical research involving industrial sponsors.[12] Similarly, in early 2001, the University of Toronto Faculty of Medicine and all 8 University-affiliated teaching hospitals agreed on a set of principles governing clinical research contracts with third parties, as the first step in ensuring the independence and integrity of industry-sponsored research. Only by harmonizing standards across all hospitals in the