

# Science Scandal or Ethics Scandal? Olivieri Redux

A Schafer

Published version in : *Bioethics*, Vol. 21 (2) 2007, pp 111-115

Nancy Olivieri is famous for refusing to suppress doubts about an experimental drug with which she was treating thalassemia patients. Her principled stand, and the resulting scandal, led universities to offer researchers some protection against illegitimate drug company pressure. Medical journals changed their publication rules. Research hospitals changed their policies. She became an international icon.

By contrast, Apotex, the drug company which tried to silence her, has attracted international opprobrium. The company repeatedly threatened to sue Olivieri if she publicly revealed her fears about the inadequacy of their drug, deferiprone, and later it publicly questioned her sanity.<sup>i</sup> She sued them for libeling her; they sued her for “slander of goods [their drug]”.<sup>ii</sup> The actions have not yet gone to trial.

Apotex claims still to believe in the virtue of deferiprone, but the company has been heavily criticized for conduct which many interpreted as placing profits ahead of patient safety. Apotex is not alone in the dock of public opinion. Every month seems to bring some new scandal involving drug company suppression of negative data: think Prozac (Eli Lilly)<sup>iii</sup>, Paxil (GlaxoSmithKline)<sup>iv</sup> and Celebrex (Pfizer)<sup>v</sup>. Big Pharma is facing a crisis. Public trust in drug company sponsored research is plummeting.

Olivieri’s hospital, The Hospital for Sick Children, and her university, the University of Toronto, have also taken a public drubbing for failing to provide her with effective support as she struggled with Apotex.<sup>vi</sup> Actually, not only was Olivieri denied effective support, she was fired from her position as the director of the Hospital’s hemoglobinopathy programme, and both she and those colleagues brave enough to support her experienced harassment of many kinds. In the words of the CAUT Report: “Neither HSC nor the University ...took effective action to defend principles of research ethics, clinical ethics and academic freedom.”<sup>vii</sup> When it was discovered that the university was negotiating with Apotex for a huge financial donation, well, some people drew their own conclusions, and these were not flattering to the university.

Miriam Shuchman’s recently published book *The Drug Trial* is the fourth book to be published on the Olivieri affair and the most troubling.<sup>viii</sup> The first was commissioned by the Hospital.<sup>ix</sup> It singled out Olivieri for special criticism but was later shown by two independent inquiries to be based upon misinformation.<sup>x</sup> Next, the Canadian Association of



University Teachers (CAUT) commissioned a report from three eminent academics.<sup>xi</sup> Their extensively documented book exonerates Olivieri, while sharply criticizing the conduct of Apotex, the U of T, and Sick Kids. Then spy novelist John le Carre joined the fray with a murder mystery, *The Constant Gardener*, casting an Olivieri-like character as heroic victim of drug company machinations.<sup>xii</sup>

Shuchman’s book, by contrast with the CAUT Report, pays little attention to the central moral issues of academic freedom and drug company censorship. She concedes that Olivieri was right to go public with her data and that Apotex was wrong to threaten her. Shuchman’s focus, however, is on Olivieri herself, as researcher, physician and person. The book attempts to demonstrate that Olivieri is a bad scientist, a bad doctor and a bad person to boot.

Shuchman, a psychiatrist and medical journalist, goes to great lengths to discredit Olivieri, portraying her as a scientist who is blind to the truth about the drug she once favoured but now criticizes. As Shuchman tells the story, the real scandal is not that a wealthy drug company attempted to suppress negative data but that Olivieri’s scientific doubts about deferiprone are not well-founded. Because of Olivieri’s allegedly irrational opposition to deferiprone and because Olivieri purportedly exercises near-mythical powers

over drug licensing authorities in the United States and Canada, she is blamed for having prevented patients from gaining access to this “life-saving” drug.

In effect, Shuchman accuses Olivieri of personal responsibility for the deaths of many thalassemia patients, deaths which allegedly could have been avoided if Olivieri had not denied them access to deferiprone.<sup>xiii</sup> Perhaps Shuchman is unaware that thousands of requests for unlicensed drugs are granted annually in Canada and the USA and that patients are not being denied access to deferiprone if they seek it.

Relying on quotations from anonymous sources, Shuchman also manages to portray Olivieri as a doctor who is so busy doing medical research and accepting humanitarian awards that she neglects her patient care duties. In case these scientific and moral sins are not deemed sufficiently wicked to warrant banishment to Siberia, Olivieri is also, Shuchman reports, a person who swears frequently at hospital administrators, is tough on colleagues and much too demanding of subordinates.

The veritable cornucopia of discredit which Shuchman heaps on Nancy Olivieri is, I’m sorry to say, standard punishment for those who have the temerity to challenge powerful vested interests. In the popular imagination David bravely slays Goliath. Alas, in the real world, the whistle-blower’s issue of principle is easily re-described as an act of private disloyalty and, worse, as evidence of professional incompetence and psychological disturbance.

For every Erin Brockovitch, rewarded with fame and fortune (when Julia Roberts was cast by Hollywood to portray her brave struggle), there are a dozen other whistle-blowers consigned by employers and colleagues to professional oblivion. Typically, those who challenge authority find that their professional competence, personal lifestyle and mental stability are all brought into question. Most whistle-blowers are also labeled malcontents and publicity seekers, as Shuchman stigmatizes Olivieri. They are duly punished with demotion, suspension, and/or dismissal. The case of Dr. Aubrey Blumsohn, recently suspended from his job by Sheffield University after he blew the whistle on one of that University’s major research funders, Proctor and Gamble, fits the same pattern.<sup>xiv</sup>

Few whistleblowers escape this fate. Olivieri certainly didn’t, though she fought back with admirable tenacity and won some notable victories over the company, the hospital and the university.

To persuade us that Olivieri got the science disastrously wrong, which is the main thesis of her book, Shuchman quotes a large number of Apotex-funded scientists, who claim that deferiprone is safe and effective. However, Shuchman omits to inform readers of her book that the published results upon which she relies have been criticized in the scientific literature, either because the efficacy test used had not been validated, or because the investigators did not report all of their data pertaining to efficacy and safety.<sup>xv</sup> Moreover, Olivieri is far from being the isolated Jeremiah of

Shuchman’s portrait: The world’s leading researchers on genetic blood disorders, David Nathan, former President of the Dana Farber Cancer Institute at Harvard and David Weatherall, Regius Professor of Medicine Emeritus at Oxford, both think that Olivieri got the science right.<sup>xvi</sup> That is, both agree with Olivieri that convincing evidence does not yet exist for the safety and efficacy of deferiprone. Two subsequent studies<sup>xvii</sup>, neither mentioned by Shuchman, have provided support for Olivieri’s published finding that patients being treated with deferiprone are at risk for progressive liver scarring.<sup>xviii</sup>

Although desferol, the current standard treatment for thalassemia patients, requires uncomfortable nightly infusions (unlike deferiprone, which comes as a pill), desferol is both safe and effective. The course of prudence would, therefore, seem to be in the direction favoured by Drs. Nathan, Weatherall and Olivieri. Nathan and Weatherall also agree with Olivieri that it would be imprudent to license deferiprone until better evidence is available. Thus, the reluctance of licensing authorities to give approval to deferiprone would seem to be based upon legitimate scientific concerns rather than, as Shuchman suggests, the malign power of Nancy Olivieri. Indeed the European licensing authority restricts use of deferiprone to “exceptional circumstances” because, to date, “comprehensive information on the safety and efficacy of the medicinal product cannot be provided”.<sup>xix</sup> The licensing authorities in the United States and Canada have not issued even a restricted license for deferiprone.

Since the liver scarring associated with deferiprone is a gradual process, we may not know for years which side of this scientific controversy is correct. Because Apotex cancelled (on 24th May, 1996) the pivotal randomized comparison clinical trial which could have provided the long term data necessary to resolve the scientific dispute – a trial for which Nancy Olivieri was Principal Investigator – the risk-benefit ratio of this drug remains uncertain.<sup>xx</sup>

One of the many relevant features of the controversy not reported by Shuchman is that Apotex tried to discredit not only Dr. Olivieri, but also the monitoring procedure, liver biopsy, essential for assessing the efficacy and safety of iron chelation therapy.<sup>xxi</sup> It was in data derived from this procedure, established in the medical literature and an integral part of the trial protocols (designed by Olivieri, approved by the hospital’s Research Ethics Board and agreed to by Apotex), that the unexpected risks of deferiprone were identified.

To fill out her story, Shuchman compiles a lengthy charge sheet against Olivieri. The most serious accusation is that Olivieri negligently delayed the implementation (at Sick Kids Hospital) of proper guidelines for the treatment of sickle cell patients. Shuchman claims that this delay led directly to the death of a young patient, Sanchia Bulgin. Shuchman is unmoved by the fact that Olivieri was not one of the physicians treating this patient, and that the responsible physicians were found (by two official inquiries) to have violated established guidelines which had been in

place for years. It's a bizarre accusation.<sup>xxii</sup>

**Many of Shuchman's other allegations of ethical misconduct, directed against Olivieri, rely on the testimony of Olivieri's leading foe at Sick Kids, Dr. Gideon Koren.<sup>xxiii</sup> Koren, then a senior scientist and scientific administrator at the Hospital, has been found guilty of and severely disciplined for both professional and research misconduct, first by the hospital and the university, and later by the Ontario medical licensing body. The hospital and the university found that his actions, including persistent "lying" in connection with his efforts to discredit Dr. Olivieri, "constitute gross misconduct and provide sufficient grounds for dismissal."<sup>xxiv</sup>**

**The CAUT Report found that Dr. Koren "attempted to discredit Dr. Olivieri by dishonest means."<sup>xxv</sup> In the words of the Discipline Committee of the College of Physicians and Surgeons of Ontario, Dr. Koren was guilty of "conduct unbecoming a physician". "His actions were childish, vindictive and dishonest", authoring "vicious diatribes" contained in anonymous "poison pen letters" against Dr. Olivieri. <sup>xxvi</sup> Koren was stripped by the University of his Endowed Chair, required to arrange that his ethically suspect research be deleted from the scientific record, publicly reprimanded by the licensing body, and required to pay substantial fines by the hospital, the university and the licensing body.<sup>xxvii</sup>**

**Shuchman has great admiration for Koren and devotes almost a full chapter of her book to trivializing his misconduct and praising his stellar virtues and research accomplishments. Unfortunately, she omits to inform her readers of the full extent of Dr. Koren's publicly reported misconduct.**

Shuchman doesn't admire Olivieri and so, in sharp contrast, spends many pages describing the serious charges of unprofessional conduct which the Hospital made against her, charges that were based on allegations by Koren and persons closely associated with him.<sup>xxviii</sup> Then, almost sotto voce, Shuchman briefly acknowledges that the Ontario College of Physicians and other independent bodies investigated the matter and cleared Olivieri of all the charges brought against her. Indeed, the College found that Olivieri had acted in the best interests of her patients and commended her for "exemplary conduct".<sup>xxix</sup>

The heavily biased manner in which Shuchman assembles her material seriously undermines The Drug Trial's credibility. Credibility is an especially important issue when evaluating the claims made in this book, because most of the hostile quotations are attributed to doctors and patients who are not identified. One of the few clearly identified patients, "Howard", has now gone on record as saying that his words, as quoted in the book, were twisted beyond recognition. He insists that, so far from being critical of Olivieri's patient care or ethics, he considers Dr. Olivieri to be a highly ethical doctor who is utterly dedicated to her patients. A brief

excerpt from Howard's letter of protest to Shuchman, which has now been made public, raises deep ethical concerns about the integrity of Shuchman's journalism: "Dear Miriam: You've used a smoke-and-mirrors approach to spinning my statements to inaccurately portray Nancy by misquoting me, attributing quotes to me that I didn't make, omitting portions of my comments that would alter the effect and taking these comments out of context."<sup>xxx</sup>

My confidence in Shuchman's journalistic reliability, already shaken by numerous factual errors<sup>xxxi</sup> and skewed descriptions of key events was further eroded when I came across a passage in which she "quotes" from a commentary I published in The Globe and Mail.<sup>xxxii</sup> I wrote none of the words she attributes to me.

Reading The Drug Trial I was repeatedly struck by how often Shuchman's account of events is contradicted by the findings of a series of independent inquiries – all public documents, all easily obtainable.<sup>xxxiii</sup> Almost all of the anti-Olivieri "revelations" presented in Shuchman's book are warmed-over versions of allegations already disproven by one or more of these impartial inquiries, and the others are undocumented hearsay. In short, Shuchman's way with well-established facts would have brought a smile to the face of Procrustes.

In the end, what really matters is that once Dr. Olivieri scientifically identified deferiprone's unexpected risks, she was ethically obliged to inform her research subjects, who were also her patients. Every research subject has a fundamental right to give or withhold informed consent to participation in a clinical trial. If information about potential risks is deliberately withheld then the right of informed consent becomes hollow. Put quite simply: patient safety is a value which trumps all others. Olivieri fulfilled her duty to warn her patients of possible risks. She did so in the face of company threats and hospital harassment. For this she is rightly honoured. Her hospital and university saw the battle as a mere "scientific dispute". In consequence, they failed in their obligation to defend her academic freedom and her patients' right to informed consent. They just didn't get it. Shuchman still doesn't.

## Disclosure

The author has not received funds from any party to this dispute. He has appeared at three press conferences with Nancy Olivieri, at which his (unpaid) role was to analyse and evaluate the ethical issues raised by her dispute with Apotex, the Hospital for Sick Children, and the University of Toronto.

## The Author

Arthur Schafer is Professor of Philosophy at the University of Manitoba and Director of the Centre for Professional and Applied Ethics.



## References

- i Transcript of CBS Television program 60 Minutes, broadcast December 19th, 1999.
- ii Actions filed in Ontario Superior Court in 2000, as yet unresolved.
- iii Healy D, Let them eat Prozac. New York: NYU Press 2004; Healy D, Aldred G. Antidepressant drug use and the risk of suicide. *International Review of Psychiatry*, June 2005; 17 (3): 163-172.
- iv Kondro W, Sibbald B. Drug company experts advised staff to withhold data about SSRI use in children. *CMAJ* 2004; 170:783.
- v Okie S. Missing data on Celebrex. *The Washington Post* 2001. August 5: A11.
- vi Thompson J, Baird P, Downie J. The Olivieri Report: Report of the Committee of Inquiry on the case involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto and Apotex Inc. Toronto: James Lorimer, 2001, p.29. Also available on the Canadian Association of University Teachers Web Site: <http://www.caut.ca/en/issues/academicfreedom/olivierireport.asp>
- vii Ibid., p.8, 155-158, 211-280
- viii Shuchman M, *The Drug Trial: Nancy Olivieri and the Science Scandal that Rocked the Hospital for Sick Children*. Random House Canada, 2005, 451 pp.
- ix Naimark A, Knoppers BM, Lowy FH. *Clinical Trials of L1 (deferiprone) at the Hospital for Sick Children: a review of the facts and circumstances*. Toronto: Hospital for Sick Children, 1998.
- x Thompson J, op.cit., p.281-327; and The College of Physicians and Surgeons of Ontario. Complaints committee. decisions and reasons. Claimant Dr. Laurence Becker; respondent Dr. Nancy Olivieri. December 19th, 2001 December 19:No 44410
- xi Thompson J, op. cit.
- xii Le Carre J, *The Constant Gardener*. Toronto : Penguin., 2001.
- xiii Shuchman M, op.cit. p. 370-379.
- xiv Baty P, "Inaction fuels research row", *Times Higher Education Supplement* 2005.
- xv Brittenham GM, Nathan DG, Olivieri NF, Pippard MJ, Weatherall DJ. Deferiprone versus desferrioxamine in thalassemia and T2\* validation and utility. *Lancet* 2003; 361:183. Brittenham GM, Nathan D, Olivieri NF, Porter JB, Pippard M, Vichinsky EP, Weatherall DJ. Deferiprone and hepatic fibrosis. *Blood* 2003; 101:5089-5090.
- xvi Nathan DG, Weatherall DJ. Academic freedom in clinical research. *N Eng J Med* 2002; 347: 1368-70.
- xvii Berdoukas V, Bohane T, Eagle C, Lindeman R, DeSilva K, Tobias V, et al The Sydney Children's Hospital experience with the oral iron chelator deferiprone (I1). *Transfus Sci* 2000; 23(3): 239-240. Maggio A, D'Amico G, Morabito A, Capra M, Ciaccio C, Cianciulli P, et al Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. *Blood Cells, Molecules & Diseases*. I2002; 28(2): 196-208.
- xviii Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, Burt AD, Fleming KA. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998;339: 417-423
- xix European Public Assessment Report, Committee for Proprietary Medicinal Products, European Agency for the Evaluation of Medicinal Products, Commission of the European Communities, August 25th, 1999
- xx Thompson J, op.cit., pp.103-123; 438-447; 452.
- xxi Thompson J, op. cit., 12-13, 373-391
- xxii Report of the Internal Review Committee Investigating the Death of Sanchia Bulgin, Hospital for Sick Children, Toronto. Released October 20, 2000. As the Report makes abundantly clear, the death of this young patient resulted from a failure of communication between the key physicians and surgeons caring for Sanchia. The existing guidelines for pre-operative blood work and other investigations were simply not adhered to by those responsible. Shuchman's baseless suggestion that the guidelines were inadequate and that this was due to failures on the part of Dr. Olivieri is explicitly contradicted by the Committee's Report, and is further disconfirmed by the subsequent Corner's Report.
- xxiii Shuchman M, e.g., at p.332; and pp.393-412.
- xxiv Disciplinary letter from the presidents of the University of Toronto and the Hospital for Sick Children to Dr. Gideon Koren, April 11th, 2000, cited in Thompson J, op. cit., 401
- xxv Thompson J, op. cit., p.30
- xxvi The Discipline Committee of the College of Physicians and Surgeons of Ontario Re: Koren. May 1, 2003. Available from the CPSO. See also: Thompson J, op.cit., p.401, for a description of the penalties against Koren imposed by The University of Toronto Disciplinary Proceedings Against Dr. Gideon Koren for Research Misconduct [Only a brief press release summary of these Proceedings has been made public, but Thompson J quotes from it.]
- xxvii Thompson J, op.cit., p.401-402; *Nature Medicine*,

vol6, no.6 (June 2000), pp.609-610.

xxviii Thompson J, op. cit., 320-321, 336-341, 364-365, 377-385

xxix The College of Physicians and Surgeons of Ontario. Complaints committee decision and reasons. Claimant: Dr. Laurence Becker; respondent: Dr. Nancy Olivieri. 2001 Dec 19:No 44410

xxx Olivieri N, The Toronto Star, Letters, June 9th, 2005.

xxxi Two illustrative examples of factual errors from Shuchman M, op.cit.: (1) p. 14: “They did blood tests and discovered that his liver was near the point of cirrhosis.” Cirrhosis cannot be identified by blood tests; (2) p. 172: “Olivieri was planning to keep studying L1 [deferiprone] surreptitiously”. This incorrect statement, based upon testimony from Drs. Koren and O’Brodivich, has been disproven by two independent inquiries: The College of Physicians and Surgeons of Ontario, op. cit.; and Thompson J, op. cit.

xxxii Schafer A, Medicine, morals and money. Globe and Mail, December 11th, 1998. p A 27.

xxxiii The Hospital for Sick Children Internal Review Committee’s Report on the Death of Sanchia Bulgin; the Coroner’s Inquiry on the death of Sanchia Bulgin; the Hospital for Sick Children and University of Toronto’s disciplinary findings against Dr. Gideon Koren for professional misconduct; the Report of the Committee of Inquiry commissioned by CAUT into the entire dispute; the Ontario College of Physicians and Surgeons report exonerating Dr. Nancy Olivieri of charges brought by the Hospital for Sick Children; the Ontario Health Professions Appeal and Review Board Inquiry into Complaints against Dr. Gideon Koren; the University of Toronto’s disciplinary findings against Dr. Gideon Koren for Research Misconduct; and the Ontario College of Physicians and Surgeons disciplinary findings against Dr. Gideon Koren for Professional and Research Misconduct.