

The Olivieri symposium

## Introduction to The Olivieri symposium

A M Viens, J Savulescu

Adrian Viens, Guest Editor of this Olivieri symposium, and Julian Savulescu, the Editor of *JME*, set the scene for the symposium.

In failing...[her] when she needed them most, it is now clear that some members of the University's Faculty of Medicine heard her muffled cries of academic freedom from the back room, yet their response was to serve another round of drinks and turn the music up louder. With the bombshell revelations in the...affair, the plug may have been pulled on this business sponsored party, and hopefully a sober re-examination of the university's neglected role and responsibility toward independent inquiry and academic freedom can begin.<sup>1</sup>

These guys don't get one thing—we're not going away. This isn't a personal vendetta. This is something I want patients to be protected from when I'm dead, fifty years from now.<sup>2</sup>

[The Olivieri affair is] not a mystery novel, but instead the latest skuldugery at Toronto's Hospital for Sick Children.<sup>1</sup>

The legal assaults which you have endured in your battle against the drug company, and in your battle against the medical establishment appear to have been fought with the type of uncommon bravery that is rarely seen. It is for this reason that our trustees have unanimously chosen to recognise you for this most prestigious award.<sup>3</sup>

[The Olivieri affair resulted from] a fundamental misreading of the issue as a mere contractual and scientific dispute...[it is] Canada's worst academic and research scandal in decades...[Since 1998, Olivieri has been] demoted, then restored, then harassed. She has been smeared with allegations attacking her competence, integrity, sanity and personality....<sup>4</sup>

The Olivieri affair is one of the most important events to occur in research ethics. From its dominance

in the Canadian and international news media, to changes in the governance of public health, academic medicine, and biomedical publication that have resulted, to the lives directly touched and altered forever, the Olivieri affair has had a number of wide reaching effects on a number of people. There is much to be learned from this case.

Although there have been articles in the medical and bioethics literature discussing the Olivieri affair, this special symposium represents the first sustained analysis of some of the central ethical issues and lessons that can be learned from such cases. It is hoped that this symposium will provide for those engaged with similar issues and cases a fruitful and informative examination of professional ethics, research ethics, academic freedom, and related considerations.

The Olivieri affair has raised a number of important normative questions concerning the substance and limits of particular theoretical commitments and how ethical judgments and norms are implemented in practice. The issues surrounding the Olivieri case are not novel. Unfortunately, issues of patient safety, conflict of interest, and academic freedom continue to plague many areas of biomedicine. The Olivieri affair has, however, gripped the attention of physicians, researchers, and bioethicists around the world as a prime example of the limitations of ethics review at multiple levels.

In the introduction to this symposium, we shall begin by very briefly explaining the disease and therapy at the centre of this case. We go on to provide a timeline of the most salient events in the Olivieri affair. We conclude by discussing the contributions to this symposium and how they bear on the ethical issues surrounding this case.

### I. THALASSAEMIA AND ITS TREATMENT

Thalassaemia major, also known as Cooley's anaemia or Mediterranean anaemia, is an inherited blood disorder caused by a mutation in the beta chain of the haemoglobin molecule that results in the production of abnormal

haemoglobin. The abnormal haemoglobin that is produced cannot properly bind and release oxygen, and, if left untreated, can result in symptoms such as chronic fatigue, failure to thrive, growth deficiencies, bone deformities, and eventually death.

Consequently, the primary goal of treatment is to provide frequent blood transfusions (approximately every three to six weeks) to maintain a normal haemoglobin level. As a result of the continuous blood transfusions, however, there exists a progressive accumulation of iron in organs such as the liver, heart, and pituitary gland. Haemosiderosis, or iron overload, can lead to hepatic fibrosis & cirrhosis,\* cardiomyopathy, endocrinopathies, and even death.

Thus, the secondary goal of treatment is to remove the iron accumulation using a chelator to bind to excess body iron and promote its excretion from the body. For more information on the thalassaemias (thalassaemia major), see the papers by DJ Weatherall NF Olivieri.<sup>5, 6</sup>

Since the 1980s, Deferoxamine, also called Desferal®, has been the standard of care to treat iron overload for patients with thalassaemia. Deferoxamine is usually administered daily or on alternate days by subcutaneous infusion administered over 10 to 12 hours from a small battery operated pump.<sup>†</sup>

The needle is usually injected in the abdomen, arm, or leg and is very uncomfortable and can leave needle marks, skin irritation, and scar tissue. As a result of the tedious and painful administration and issues of body image, some patients (especially adolescents and teenagers) find it difficult to comply with the demanding regime.

Given this, there was significant interest in finding an iron chelator that could be taken orally to improve compliance. While Deferoxamine had significantly improved the prognosis of thalassaemic patients, the prospect of finding an efficacious alternative therapy for iron overload was seen as a very

\*In addition to the cirrhosis that is caused by iron loading in the liver, as a result of the frequent number of blood transfusions received, there were also a very large number of thalassaemic patients who were more susceptible to contracting Hepatitis C from the tainted blood supply back in the 1980s and 1990s (which causes liver damage).

†It can also be administered intravenously. While intravenous administration avoids side effects such as skin irritation, it also has other side effects associated with it, such as infection or thrombosis of the catheter. Patients are generally advised to use subcutaneous administration, and have intravenous administration as a secondary option.

welcome and promising improvement to the quality of life of thalassaemic patients.

Noted haematologist and researcher at the Hospital for Sick Children and professor of medicine at the University of Toronto, Dr Nancy F Olivieri was a natural choice to investigate the potential safety and efficacy of a new oral iron chelator in thalassaemia. As head of the large and productive Hemoglobinopathy Research Program, Dr Olivieri (and colleagues) had the research experience and expertise, and patient population, to conduct such important research.

## II. TIMELINE OF EVENTS

In the construction of this timeline primarily three documents were used: (i) the Canadian Association of University Teachers' *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*, hereafter referred to as the Olivieri Report; (ii) the report by Arnold Naimark, Bartha M Knoppers, and Frederick H Lowy, *Clinical Trials of L1 (Deferiprone) at the Hospital of Sick Children: a review of the facts and circumstances*, hereafter referred to as the Naimark Report, and (iii) the report of the College of Physicians and Surgeons of Ontario, *Report of the Complaints Committee [complainant: Dr Lawrence Becker, respondent: Dr Nancy Olivieri] December 19, 2001*, hereafter referred to as CPSO.<sup>7-9\*\*</sup> Events not directly referenced are thought to be of a sufficiently public nature and/or uncontroversial as not to require direct referencing.

### ● 1989

- Dr Olivieri (and colleagues) begin to examine the effectiveness of an oral iron chelator, deferiprone (L1), in the treatment of thalassaemia. Research grant by Medical Research Council of Canada (MRC) allows for L1 to be synthesised in capsule form (CPSO,<sup>9</sup> p 3); (Olivieri Report,<sup>7</sup> pp 104–5).

### ● 1991

- MRC renews grant for an additional year (1992–3), but turns down Dr Olivieri's application for funding of short term randomised controlled trial to test clinical effectiveness of L1. MRC suggests that Dr Olivieri seek an industry partner for funding of the clinical trial.

\*\*The report by the College of Physicians and Surgeons of Ontario is on file with the author. It is also available on the website address given in reference 9.

### ● 1992

- Olivieri begins working with Dr Brittenham.<sup>\*\*\*</sup>

### ● 1993

- Food and Drug Administration (FDA) informs Drs Olivieri and Brittenham that completion of three studies—LA-01,<sup>\*\*\*\*</sup> LA-02,<sup>\*\*\*\*\*</sup> LA-03<sup>‡</sup>—would be necessary before commercial licensing of L1 could occur.
- Drs Olivieri and Koren<sup>††</sup> sign contract with Apotex for LA-01 trial (approximately 50% sponsored by MRC, 50% sponsored by Apotex).

### ● 1994

- Planning for LA-02 is commenced.

### ● 1995

- Research contracts are tendered to Drs Olivieri and Brittenham for LA-02 trial. Contained within the contract is a confidentiality provision in which all information concerning the trial is to be kept confidential for three years after the termination of the trial (unless express written consent is given to do otherwise).
- In April 1995, Dr Olivieri *et al* publish a paper in the *New England Journal of Medicine* demonstrating a “favorable effect of deferiprone on iron balance”.<sup>10</sup>
- Around time of publication, Drs Olivieri and Brittenham become concerned about some patients enrolled in the LA-03 trial who display undesirable hepatic iron concentrations. (CPSO,<sup>9</sup> p 5); (Olivieri report,<sup>7</sup> pp 128–9).<sup>†††</sup>
- In July, Drs Olivieri and Brittenham request permission to establish a separate trial protocol for patients in whom L1 appears to be functioning suboptimally. Within this request, it is noted that modification of patient consent forms would be necessary to advise patients of the negative results

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\*\*\*Dr Gary Brittenham, hepatologist at Case Western Reserve University, and one of Olivieri's coinvestigators.

\*\*\*\*Prospective randomised controlled trial to compare effectiveness and safety of L1 to DFO (approximately 65 patients in Toronto and Montreal).

\*\*\*\*\*Safety study to assess particular risks associated with L1 (approximately 200 patients in Canada, Italy, and the United States).

‡Continuation of the compassionate use long term study of L1 (approximately 25 patients).

††Dr Gideon Koren, clinical pharmacologist, HSC, and one of Olivieri's coinvestigators

encountered. Apotex requests to examine the data before consent forms are changed and the Hospital for Sick Children (HSC) Research Ethics Board (REB) or research ethics committee is notified of findings (CPSO,<sup>9</sup> p 5); (Olivieri report,<sup>7</sup> pp 125–33).

- In September, Dr Olivieri submits separate protocol to Apotex investigating patients excluded from LA-03 trial to observe loss of sustained efficacy in L1. Dr Olivieri also informs Apotex of her obligation to communicate her findings of reduced efficacy to HSC REB. (CPSO,<sup>9</sup> p 6); (Olivieri report,<sup>7</sup> §§ entitled “Progress of the Toronto trials [LA-01 and LA-03]” and “Concerns arising in 1995”).
- In October, HSC REB requires a revised protocol for LA-03 study in order for study to continue. Apotex agrees to study patients in which response to L1 was suboptimal, but continues to refuse to agree to inform the REB of suboptimal findings. (CPSO,<sup>9</sup> p 6); (Olivieri report,<sup>7</sup> §§ entitled “Progress of the Toronto trials [LA-01 and LA-03]” and “Concerns arising in 1995”).

### ● February 1996

- Drs Olivieri, Brittenham, and Koren meet with Apotex to review data from long term trial. Upon examination of data, Apotex does not agree with the loss of effectiveness. Apotex restates that the claim that L1 has lost effectiveness in some patients should not be relayed to HSC REB or trial subjects (CPSO,<sup>9</sup> p 6); (Naimark report,<sup>8</sup> § entitled “Scientific disagreement about an unexpected finding”).

### ● March 1996

- Dr Olivieri submits research findings on LA-03 cohort to HSC REB. Findings maintain that a significant proportion of the subjects have liver iron concentrations above clinically desirable levels and Dr Olivieri suggests that further study and observation of these patients is needed to evaluate the balance between risk and

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†††In order to assess and monitor iron loading, thalassaemia major (TM) patients were required to undergo regular liver biopsies to obtain tissue to assess liver histology and to be tested to provide a hepatic iron concentration as a mean of evaluating total body iron stores. Hepatic histology and iron concentration provide the best assessment of the safety and efficacy of iron chelation therapy.

benefit associated with L1 (CPSO,<sup>9</sup> p 6); (Olivieri report,<sup>7</sup> § entitled “Identification of the first risk”).

- Apotex submits documents to the HSC REB representing their interpretation of the data from LA-03 cohort. Dr Zlotkin\*\*\*\*\* responds to Apotex informing them that the REB does not act as an intermediary between researchers and sponsors and directs Apotex to direct further communications to Dr Olivieri for resolution of disagreements. (CPSO,<sup>9</sup> p 7); (Olivieri report,<sup>7</sup> § entitled “Identification of the first risk”); (Naimark report,<sup>8</sup> § entitled “Report to the Research Ethics Board”).
- April 1996
  - HSC REB directs Dr Olivieri to amend patient information and consent forms to reflect findings of decreased sustained efficacy of L1, and to inform other physicians involved with patients receiving L1 and the Department of Health and Welfare (Canada). (CPSO,<sup>9</sup> p 7); (Olivieri report,<sup>7</sup> § “Identification of the first risk”).
  - Application for a clinical trial of L1 for sickle cell anaemia is submitted to the National Institutes for Health (NIH).
- May 1996
  - Dr Olivieri submits revised patient information and consent forms for LA-01 and LA-03 trials to the HSC REB and Apotex. When Dr Olivieri attempts to inform patients of her findings (by directive of the HSC REB chair), Apotex terminates both LA-01 and LA-03 trials (CPSO,<sup>9</sup> p 7); (Olivieri report,<sup>7</sup> § entitled “Trial terminations and legal warnings”).
  - Apotex write to Drs Olivieri and Koren to inform them that their research sponsorship contract has expired and they would not be renewing it. Moreover, Drs Olivieri and Koren are told that all information obtained during the trials are to remain secret and confidential unless Apotex provide a disclosure waiver—otherwise, failure to do so would result in the pursuit of vigorous legal remedies (CPSO,<sup>9</sup> p 7); (Olivieri report,<sup>7</sup> §§ entitled “Ongoing legal warnings” and “Trial terminations and legal warnings”).
  - Dr Spino, pharmacist and vice president at Apotex, Inc, writes to

\*\*\*\*\*Dr Stanley Zlotkin, chair, HSC REB (until July 1996).

- Dr Olivieri giving her notice of termination of the consulting contract between her and Apotex for services related to the LA-02 trial. Letter also refers to the non-disclosure clause in her contract and threatened legal action for breaking that agreement (CPSO,<sup>9</sup> p 7); (Olivieri report,<sup>7</sup> §§ entitled “Ongoing legal warnings” and “Trial terminations and legal warnings”).
- Drs Olivieri and Koren contact the Canadian Medical Protection Branch concerning Apotex’s legal pressures. Dr Olivieri follows Canadian Medical Protection Branch advice to inform Apotex of material she intends to disclose or publish (so that Apotex could exercise legal proceedings to block such disclosure/publication if they so desire).
- June 1996
  - Dr Olivieri contacts Dr Aberman (Dean, Faculty of Medicine, University of Toronto until 1999) to mediate the conflict between Apotex and the investigators. At the meeting, Dr Olivieri requests that L1 trial continue in order to study the effectiveness/loss of effectiveness and to ensure that patients who were responding favourably could continue receiving L1. Apotex did not agree to continue the trial, but did agree to the emergency release of L1, and that Dr Olivieri and Apotex would jointly contact the Health Protection Branch.<sup>††††</sup>
  - In a subsequent meeting with a senior executive at Apotex, Dr Aberman asks Apotex to refrain from threatening legal action against Dr Olivieri (CPSO,<sup>9</sup> p 7); (Naimark report,<sup>8</sup> § entitled “Involvement of the hospital and university administrations”).
- July 1996
  - Dr Spino informs Drs Olivieri and Koren (and HSC REB) of the findings of an expert panel convened by Apotex to review the data at the centre of conflict. The panel did not agree with Dr Olivieri’s conclusions about L1’s efficacy<sup>11</sup> (CPSO,<sup>9</sup> p 8).

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 ††††The Health Protection Branch has since been renamed the Health Products and Food Branch of Health Canada. The Health Protection Branch was a branch of government responsible for managing risks and benefits related to health. The new organisation is responsible for managing risks and benefits related to health products and food.

- August 1996
  - Apotex informs Drs Olivieri and Koren that in the process of closing out subjects enrolled in the trial, the study drug returned by patients appears to be improperly issued. Apotex informs Drs Olivieri and Koren that such an action constitutes a serious violation of the “standard of good clinical practice” (Naimark report,<sup>8</sup> § entitled “Consequences of non-renewal of Apotex sponsorship”).
  - Apotex informs Drs Olivieri and Koren that information was incomplete or missing from data and records of the trial. Dr Olivieri replies to Apotex attributing problems with drug return and records to Apotex’s “abrupt” termination of trials.
  - Drs Aberman, Olivieri, Brittenham, and Apotex meet with a representative of the Health Protection Branch.
  - Dr Spino informs Dr Olivieri that Apotex does not agree with data analysis and interpretation in abstracts submitted to the American Society for Hematology for their annual meeting. Apotex denies consent to submit abstracts. (Naimark report,<sup>8</sup> § entitled “Consequences of non-renewal of Apotex sponsorship”).
- September 1996
  - Drs Olivieri and Brittenham send the report from Apotex’s panel. Both sides reaffirm their original interpretation of data.
  - National Institutes of Health approves clinical trial of L1 for sickle cell anaemia.
- November 1996
  - Dr Spino informs Dr Olivieri that as a result of breaching contractual obligations she is no longer a member of the LA-02 Steering Committee (thus, not entitled to access data or results without Apotex’s consent). Dr Olivieri responds that such action violates regulatory guidelines and previous agreements made with all members of the LA-02 Steering Committee. Apotex disagrees (Naimark report,<sup>8</sup> § entitled “Consequences of non-renewal of Apotex sponsorship”).
- December 1996
  - Dr Olivieri presents research findings from LA-03 at the American Society for Hematology conference in Orlando, Florida.

- Around this time, Dr Brittenham informs Dr Olivieri about potential liver toxicity associated with L1. Dr Olivieri arranges to receive liver biopsy reports in Orlando and finds that some patients in the long term trial did have what appears to be an accelerated progression of fibrosis. Upon her return to Toronto, Dr Olivieri arranges for all biopsies from LA-03 trial to be assembled and analysed (with the help of Dr Cameron<sup>†††††</sup>). (CPSO,<sup>9</sup> p 9); (Olivieri report,<sup>7</sup> § entitled “Identification of the second risk”).
- Dr Koren asks for liver toxicity data presented at the conference. Dr Koren was surprised by the toxicity findings of the drugs and was unhappy that he was being used as a “conduit” for L1 for patients still receiving the drug on emergency release. He informs Dr Olivieri that he will not continue collaborative and data interpretation work with her. (Koren later publishes findings that L1 was effective and safe on a re-analysis of data). (Naimark report,<sup>8</sup> § entitled “The question of toxicity of L1”).
- February 1997
  - Dr Olivieri receives completed assessment of liver histology from Dr Cameron. Dr Olivieri concludes there is evidence of liver toxicity and accelerated progression of liver fibrosis caused by L1. Dr Olivieri recommends to patients that they get new liver biopsies. Dr Olivieri informs all clinical staff involved of evidence regarding accelerated liver fibrosis and the need to inform patients (which is done soon afterwards at a meeting of patients). (CPSO,<sup>9</sup> p 10).
  - Dr Olivieri meets with patients to inform them of the evidence for liver toxicity she has found.
  - Clinical trial protocol for L1 administration in sickle cell anaemia patients is submitted to HSC REB.
  - While some patients in LA-01 and LA-03 studies continue to receive L1, Dr Olivieri stops prescribing L1 to patients (Naimark report,<sup>8</sup> § entitled “The question of the toxicity of L1”).
  - Dr Olivieri meets with Drs O’Brodivich<sup>††††††</sup> and Freedman<sup>†††††††</sup> for briefing of facts and informs them of the new evidence. Reports of liver toxicity are made to HSC REB (CPSO,<sup>9</sup> p 11).
- National Institutes for Health inquiries are made concerning ethics approval of L1 trial for sickle cell anaemia patients. Dr O’Brodivich withdraws support of L1 trial for sickle cell patients (CPSO,<sup>9</sup> p 11).
- March 1997
  - All patients from HSC obtain up to date liver biopsies.
  - Apotex continues to attempt to persuade administrators and patients in Toronto (and the wider scientific and regulatory communities) of L1 safety and efficacy.
- April 1997
  - Apotex offers to provide new treatment arrangements for Toronto patients who did not want to go back to using Deferoxamine (however, the use of liver biopsies would not be part of the monitoring process). Olivieri rejects proposal and continues to phase out use of L1 (Olivieri report,<sup>7</sup> § entitled “Trial close-outs and another stoppage in supply of L1”).
- May 1997
  - Dr Olivieri writes to HSC REB to confirm that L1 is no longer being prescribed to patients (CPSO,<sup>9</sup> p 11).
- September 1997
  - Dr Olivieri expresses concerns about the conflict with Apotex and Dean Aberman’s conduct with University of Toronto’s vice president of research. Dr Olivieri also explores other intra-university complaint/dispute resolution avenues. Nothing comes of it—Dr Olivieri’s complaints are found by the University of Toronto administration to be not specific enough to merit further action (Naimark report,<sup>8</sup> § entitled “The role of the university”).
- November 1997
  - Abstract published in *Blood* by Dr Olivieri *et al.* stating that “... L1 was discontinued in all patients because of safety concerns”. (CPSO,<sup>9</sup> p 12).
- Winter 1997/8
  - Apotex continues repeated communication with HSC REB and with Drs O’Brodivich and Koren to request data on patients who received L1 on compassionate grounds (to meet the requirement of regulatory bodies). A question of whether Dr Olivieri was meeting her obligations—that is, providing data, to regulatory bodies is raised by Apotex. (Naimark report,<sup>8</sup> § entitled “Interaction between Apotex and the hospital”).
- April 1998
  - Dr Olivieri, under increasing workload pressures, indicates to HSC administration that she cannot continue in her position under the prevailing conditions. Dr Olivieri intends to communicate the need for a change in the prevailing conditions. However, her letter is interpreted by HSC as a resignation. Dr Olivieri maintains that this action by HSC was an instance of constructive dismissal. (Naimark report,<sup>8</sup> § entitled “Interaction between Apotex and the hospital”).
- May 1998
  - Intensity of the events surrounding the L1 trials has substantially increased and intensive media attention begins.
- June 1998
  - Apotex continues to attempt to secure data and a review of that data conducted by Dr Aideen Moore, Chair, HSC REB (after July 1996) and Dr Brenda Gallie, ophthalmologist and cancer researcher, HSC.\*\*\*\*\* Drs Olivieri and Brittenham maintain they have no ethical or legal obligation to provide Apotex with any further data (beyond what was already given in 1997). (Naimark report,<sup>8</sup> § entitled “Interaction between Apotex and the hospital”).
- August 1998
  - Dr Olivieri *et al* publish findings in the *New England Journal of Medicine*, detailing findings of liver toxicity in patients receiving L1.<sup>12</sup>
  - Drs Olivieri and Gallie met with Dr Aberman in an attempt to finally resolve issues surrounding L1

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<sup>†††††</sup>Pathologist, Toronto General Hospital (now part of the University Health Network).  
<sup>††††††</sup>Dr Hugh O’Brodivich, Paediatrician in Chief, HSC.

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<sup>†††††††</sup>Dr Melvin Freedman, Head, Division of Haematology/Oncology, HSC

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 \*\*\*\*\*Dr Gallie was also head of the blood and cancer research section where Dr Olivieri’s haemoglobinopathy research program was located.

trials. Among other requests, an independent review of the events which transpired, and an end to her constructive dismissal are sought.

- December 1998
  - The Naimark report is published, reviewing the events surrounding the Olivieri affair. Panel finds that HSC staff and executives did not act improperly.<sup>8††</sup>
- January 1999
  - Dr Olivieri fired/relieved of position as head of Hemoglobinopathy Research Program at HSC. A group of scientists supporting Dr Olivieri are instructed by HSC not to discuss their concerns publicly. (Olivieri report,<sup>7</sup> pp 225–38)<sup>13</sup>
  - Later in the month, an agreement is reached in which Dr Olivieri’s position is restored, her right to academic freedom affirmed, and she is promised financial support in case Apotex pursue legal action. (Olivieri report,<sup>7</sup> pp 265–70, 505–8)
- 1999/2000
  - After the use of forensic evidence, it is found that Dr Koren was the author of a number of anonymous letters and emails disparaging Dr Olivieri’s (and her supporters’) professional and personal integrity. The HSC and University of Toronto discipline Dr Koren for gross misconduct; he receives a suspension, a chair endowed in his name is removed, and he is ordered to make some restitution. Dr Koren is also cautioned by the complaints committee of the College of Physicians and Surgeons of Ontario for his unprofessional conduct. Veracity of Dr Koren’s previous allegations and testimony subsequently called into question—for example, by the Canadian Association of University Teachers.<sup>14 15 16</sup>
  - European Agency for the Evaluation of Medicinal Products approves the use of L1 in limited cases. Dr Olivieri later requests judicial review through European court (on the basis that Apotex misrepresented data).<sup>17 18</sup>
- April 2000
  - HSC (via its board of directors and its medical advisory council)

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 ††Individuals interested in this case are encouraged to read the Naimark report.

announces that it is referring concerns over to the College of Physicians and Surgeons of Ontario regarding Dr Olivieri’s clinical practice involving L1 patients (CPSO,<sup>9</sup> p 2); (Olivieri report,<sup>7</sup> § entitled “The medical advisory committee proceedings”).

- March 2001
  - University of Toronto harmonises its research policies with its affiliated teaching hospitals, in order to make it more difficult for researchers to enter into contracts without them first being scrutinised for conflicts of interest.<sup>19</sup>
- October 2001
  - The Olivieri report is published, report conducted by the Canadian Association of University Teachers reviewing the events surrounding the Olivieri affair. The association finds that Dr Olivieri did not act improperly and that the University of Toronto did not do enough to protect her academic freedom and help Olivieri after it had been alleged that she was constructively dismissed.<sup>7†††</sup>
- December 2001
  - The College of Physicians and Surgeons of Ontario dismisses complaint against Dr Olivieri by HSC.<sup>††††</sup> (CPSO,<sup>9</sup> p 1) The college concludes: “Dr Olivieri ceased to administer L1 in a timely and expedient way, and in a manner which was in the best interest of her patients” (CPSO,<sup>9</sup> p 16).
- 2002/3
  - Dr Olivieri and colleagues reach settlement of dispute with HSC, University of Toronto (and its faculty association). Canadian Association of University Teachers to establish a task force to review policies governing the rights of research to publish their findings and conflict of interest (CAUT press release, “Task force to investigate academic freedom of medical researchers and clinical teachers” 13 June 2002).
  - Series of publications from Apotex sponsored researchers argue that L1 is safe and effective treatment for thalassaemia.

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 †††Individuals interested in this case are encouraged to read the Oliveri report.  
 ††††The complaint was not by HSC itself, but by a member of its staff, Dr Laurence Becker.

- Olivieri and supporters continue to publish articles and letters challenging the validity or accuracy of studies demonstrating efficacy of L1.
- European Court of Justice rules that Olivieri cannot challenge the European drug approval agency’s decision to allow sale of L1. To this point, Dr Olivieri has spent \$300,000 of her own savings to fight approval of L1.<sup>20</sup>

We have attempted to present the most important events concerning the Olivieri affair. We have, necessarily, had to leave out a number of details in the interest of length and readability. Most of the information was obtained from sources in the public domain and every effort was taken to provide accurate dates and an objective accounting of events. Any errors or omissions are entirely unintentional.

### III. ETHICS IN THEORY AND PRACTICE

The Hospital for Sick Children and the University of Toronto initially saw the dispute between Dr Olivieri and Apotex as a scientific dispute best dealt with in the scientific arenas of peer reviewed conferences and journals. It soon became clearly evident, however, that it was much more than a scientific disagreement over the interpretation of data.

There were a number of reasons why the Olivieri affair took the form it did. Some of the failures in this case arose out of simple misjudgments and errors. Others arose out of ignorance of the gravity of what was occurring or an absence of full information that prevented appropriate action. Some, more seriously, arose out of personality conflicts and political considerations. The contributions to this symposium seek to explore and elucidate the issues arising from the Olivieri affair.

Arthur Schafer’s contribution to this symposium provides a detailed examination of the issue and historical context of conflicts of interest in research sponsored by private enterprise. In addition to examining the case of Dr Olivieri, he also examines another case at the University of Toronto—the case of Dr David Healy. By examining both the Olivieri and Healy cases, Schafer elucidates the context and norms governing partnerships between universities and private enterprise in academic medicine. One issue that has been central to the Olivieri affair is the relationship between Apotex and the University of Toronto. In addition to sponsoring research at University of Toronto affiliated hospitals, Apotex was a major contributor to the

University of Toronto—at the time of the Olivieri affair, Apotex was in discussions with the University of Toronto about a multimillion dollar donation.<sup>21 22</sup> In order to be competitive in the academic world, universities often require such donations to fund their research and teaching activities. However, many are rightly concerned with how such relationships could affect public institutions, such as universities and hospitals, and especially about the possibility of conflict of interest. For instance, when it was found out that the president of the University of Toronto had lobbied the Prime Minister of Canada on behalf of Apotex in 1999, there was a major outcry and further talk of distrust of close ties between public institutions and corporate interests.<sup>23</sup> See also report number 317 of the governing council of the University of Toronto.<sup>24</sup>

Schafer goes on to identify two different strategies to prevent results from being biased in corporate funded clinical trials. The first is a regulatory approach that emphasises managing potential risks governing industry sponsored research at public institutions. The second approach advocates sequestering industry from research sponsorship at universities and hospitals. Schafer criticises the regulatory approach and advances a more radical approach, advocating the outright elimination of the close ties currently found in corporate sponsorship.

In another contribution to the symposium, Lorraine Ferris, Peter Singer, and David Naylor have provided an examination of issues regarding the ethics, independence, and integrity of clinical research at public institution sponsored by for profit enterprises. Ferris, Singer, and Naylor elucidate the systemic policy reforms concerning the academic industry interface in the Toronto academic health sciences complex since the Olivieri affair, and how such reforms have sought to strengthen the integrity and effectiveness of human subject research by making ethics a more central focus in the academic complex. The framework outlined here will be of great interest to those involved in ethics governance.

Gordon DuVal's contribution to the symposium provides a very concrete and feasible option available to researchers and research institutions to help protect human subjects and the independence of investigators. Academic research institutions routinely enter into research agreements with sponsors that fail to meet adequate ethical standards. DuVal describes the ethical issues at stake that negatively affect research integrity and academic freedom and how properly structured clinical studies agreements

reviewed by institutional review boards can help to protect research subjects and ethical integrity. A large source of conflict in the Olivieri affair ultimately stemmed from the contract Dr Olivieri signed with Apotex, especially from the confidentially clause attached to the contract. Clinical study agreements that seek to protect patients' and researchers' interests, in addition to the sponsor's interest, need to be primary considerations when public institutions enter into contracts with private enterprise.

Rosamond Rhodes and James Strain's contribution to the symposium highlights the failure of academic medicine to identify and adequately respond to unethical behaviour. Rhodes and Strain maintain that it is the institutional design of academic medicine that systematically ignores serious ethical problems, regards whistleblowers as enemies of the institution and punishes them, and thereby fails to provide an ethical environment. These issues are taken up by Bolsin, Faunce, and Chan.

This is, by most accounts, the experience Dr Olivieri (and her core set of supporters) had.####

After not being supported in her effort to bring forward what she found to be serious ethical problems—for example, the need to inform research subjects of possible increased risk for liver damage associated with the study drug, Dr Olivieri found the need to pursue alternative and more forceful avenues to protect her patients. Arguably, the Hospital for Sick Children and the University of Toronto should have supported Dr Olivieri more in this regard and protected her ability to do what she thought (and had sufficient warrant to believe) was required as a morally responsible researcher. Not only did she feel the need to violate her confidentially agreement at great personal and professional risk, but she also felt obliged to speak out against those who did not support her, and became perceived as an enemy of the institutions to which she belonged. As Rhodes and Strain point out, the environment for whistleblowers is very confrontational and adversarial. Olivieri was allegedly dismissed, sued, received harassing

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####The experience of researchers like Dr Olivieri has even served as fodder for novelists. For instance, in John le Carré's recent novel, *The Constant Gardener*, he writes: "As my journey through the pharmaceutical jungle progressed, I came to realise that, by comparison with reality, my story was as tame as a holiday postcard. ... I drew on several cases, particularly in the North American continent, where highly qualified medical researchers have dared to disagree with their pharmaceutical paymasters and suffered vilification and persecution for their pains".

correspondence, and had her named dragged through the mud—the costs of speaking out against the academic medical complex can be great. Few would have such conviction.

In addition to the Olivieri affair, Rhodes and Strain examine whistleblowing in academic medicine in a number of other cases. They point to the serious and unfortunately repetitive instances of institutions that fail to support individuals and punish those who seek to blow the whistle. Rhodes and Strain advocate for the need to attend to the failures of institutional ethics in academic medicine, and also for the need to create an environment in which individuals feel they can do what they believe is right without the fear of being persecuted or punished. Bolsin, Faunce, and Chan outline practical strategies to train, encourage, and support professionals to follow their conscience and, if necessary, criticise internal regulatory decisions and processes, in both clinical and academic medicine.

Francoise Baylis's contribution to the symposium deals with a topic of paramount importance, which unfortunately receives little attention in the literature—the ethics of bioethics. In addition to the validity of bioethics as field of academic inquiry, the legitimacy of bioethics is often tested in situations like that of the Olivieri affair. In addition to methodological questions concerning the practice of applied ethics, how bioethicists respond to such ethical failings as occurred in the Olivieri affair can also affect the discipline. In a self critical analysis, Baylis contends that bioethicists need to reflect about the meaning and value of their work. Using the Olivieri case as an illustration, Baylis is very critical of the silence of the bioethics community and the countless opportunities for bioethical heroism that were never undertaken.

There are many lessons to be learnt from the Olivieri affair. We hope this symposium will begin a fair and productive examination of these which will lead to better ethical evaluation and regulation of research, not just in North America but globally.

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**Authors' affiliations**  
**A M Viens**, St Anne's College, University of Oxford, Oxford, UK;  
adrian.viens@philosophy.ox.ac.uk  
**J Savulescu**, Department of Philosophy, University of Oxford, Oxford, UK

Correspondence to: Julian Savulescu;  
Julian.savulescu@philosophy.ox.ac.uk

Adrian Viens was one of Dr Olivieri's research assistants in the summer of 1998 and 1999. In addition, Viens and Olivieri collaborated on a journal article (along with six other coauthors) concerning iron overload and iron chelating therapy in Haemoglobin E- $\beta$  thalassemia. This collaboration was not related to the L1 clinical trial (see: Olivieri NF, de Silva S, Premawardena A, et al. Iron overload and iron chelating therapy in haemoglobin E- $\beta$  thalassemia. *Journal of Pediatric Hematology/Oncology* 2000;**22**:593–7).

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## ECHO

## Improved procedures may improve informed consent for neonatal research



Please visit the *Journal of Medical Ethics* website [[www.jmedethics.com](http://www.jmedethics.com)] for a link to the full text of this article.

Obtaining truly informed consent for neonatal research under difficult circumstances may be more achievable with new approaches. These originate from discussions of European neonatologists, ethicists, sociologists, and legal experts—all participants in the Euricon trial.

Urgent or emergency situations when parents are asked to consent to research treatment for their child are especially difficult. Most doctors would probably suspect that here informed consent is compromised by circumstances that hinder parents absorbing and processing complex information.

Alternatives to current process might seek consent in a stepwise or a continuous process—with information initially given by the doctor and later chances to withhold or withdraw consent. Both would allow more time for parents to deal with complex information. A stepwise process would see parents deciding from core information, with more detailed information given later, and a continuous process with them deciding from all information given up front, repeated at later stages, sparing them the realisation that they might have withheld consent at the outset, had they understood the full picture.

Importantly, parents should not assume that responsibility for their child's welfare is theirs alone—it extends to researchers, grant awarding body, senior hospital staff, and research ethics committee. They may be reassured if they know that the research has committee approval, though this should not be allowed to interfere with their decision, and great care must be used to avoid coercive language.

At worst the Helsinki declaration would permit research treatment without parental consent, but this would be a rare event, occasioned by an extreme situation.

▲ *Archives of Disease in Childhood Fetal and Neonatal Edition* 2003;**88**:F166–F167.