IT IS CLEAR FROM THE extensive documentation available to this inquiry that Dr. Koren has played a central role throughout in the L1 controversy. Independently, HSC’s harassment investigator Ms. Humphrey reached this conclusion from her investigation:

Dr. Koren was the most constant individual at the centre or the heart of the L1 trials controversies and most of the issues and conflicts that appeared to have erupted in the wake of the discontinuance of the L1 trials in May of 1996.... All these issues appeared to have involved Dr. Koren in a very direct and personal sense.... [T]here was no other individual... who appeared to have anywhere near the level of detailed knowledge of and direct involvement in the range of post L1 controversies as Dr. Koren.'

(1) Dr. Koren’s involvements in the Naimark and MAC inquiries

The HSC Board of Trustees took action against Dr. Olivieri on receiving the Naimark Report in December 1998, and again on receiving the report of the Medical Advisory Committee (MAC) in April 2000. In each instance, adverse conclusions on Dr. Olivieri’s conduct in the report provided the basis of the Board’s action. These conclusions were based on incorrect information provided by several witnesses, notably Dr. Koren, Dr. O’Brodovich and Dr. Moore. In this subsection we briefly review their involvements, noting the prominence of Dr. Koren (see sections 5K, 5O, 5P and 5Q for details and citations).

Dr. Koren was one of the “primary submitters” of information to the Naimark Review, and he submitted information through Dr. O’Brodovich, as well as directly. In the MAC inquiry he surpassed Dr. O’Brodovich in the extent and detail of his allegations on several matters. Dr. Koren’s testimony may be distinguished from that of Dr. O’Brodovich or Dr. Moore (see below), in that it is documented that he put forward allegations and testimony that he knew to be incorrect. A central instance pertains to the terminations of the two L1 trials. Dr. Koren knew that both had been terminated and neither of them continued or reinstated, and recorded this fact in several letters he wrote between May 1996 and May 1998. He was in a position to advise Dr. O’Brodovich, the Naimark Review, and the MAC that Dr. Moore was mistaken in her contrary statements. It appears that he did not do so. Instead, he himself cited Dr. Moore’s incorrect information to bolster his own testimony to the MAC, although he knew she was mistaken.

Dr. Moore’s testimony both to the Naimark Review and the MAC was that research trial of L1 continued after both trials had been terminated. Yet the fact that both trials had been terminated, and neither continued, was well documented in records available to her. Thus the basis of her misunderstand-
ing is unclear. Dr. O'Brodovich relied on Dr. Moore’s incorrect information in his testimony both to the Naimark Review and the MAC.

Dr. O'Brodovich put forward allegations against Dr. Olivieri in the Naimark Review. The narrative set out in the Naimark Report follows in essential respects the one he put forward in his memo to Dr. Naimark dated September 24, 1998, in which he relied on Dr. Moore’s incorrect testimony. He cooperated with Dr. Koren in putting forward information against Dr. Olivieri during the Naimark Review, and HSC’s harassment investigator Ms. Humphrey “conclude[d] that in all likelihood that the memo [of September 24, 1998] was prepared with input from Dr. Koren.”

Dr. Koren’s false allegations and testimony were believed. This bolstered the mistaken and incorrect information of Dr. Moore and Dr. O'Brodovich. In consequence, very serious adverse actions were taken against Dr. Olivieri and the controversy was widened and prolonged. Dr. Koren’s conduct in these matters has not been addressed, even after he admitted to dishonest actions against Dr. Olivieri in a related context.

(2) Differential treatment

A salient feature of the L1 controversy is the difference between the treatment accorded to Dr. Koren and that accorded to Dr. Olivieri. The following are examples of such differential treatment.

1. The Hospital for Sick Children gave Dr. Koren’s views and conduct full and fair consideration, even when that conduct was improper. When he eventually admitted to misconduct and lying, he was provided with due process, and mitigating factors were taken into account. By contrast, the Hospital did not respect reasoned positions taken by Dr. Olivieri and wrongly cast her proper conduct as misconduct. The Hospital took very serious actions against Dr. Olivieri, in each instance without due process and in some instances precipitously. By contrast, when complaints of misconduct supported by substantial evidence were made against Dr. Koren, lengthy investigations followed. Although action was taken in some instances, in other instances we do not know of any action taken to date, and some complaints against Dr. Koren have not yet been investigated.

2. When in 1996 Dr. Olivieri identified a risk of Apotex’s drug L1 and Apotex attempted to prevent her from communicating on the risk, the Hospital framed this ethical issue as a scientific dispute: “The Hospital took the position that the conflict was a scientific controversy, that the peer-review process was best equipped to decide the issue.” In contrast, when the peer-reviewed medical literature supported a clinical practice of Dr. Olivieri—the use of liver biopsy as a guide to therapy for patients
with thalassemia major—the Hospital ignored this and relied instead on incorrect medical testimony of Dr. Koren, who is not an expert in this field. It consulted no independent experts. (See sections 5P and 5Q.)
3. The Hospital criticized and acted against Dr. Olivieri for an alleged “failure” to promptly report the second unexpected risk of L1 she identified to the Research Ethics Board (REB). Yet although Dr. Koren claimed, in writing, that he both knew of the risk and was the person responsible to report it, and the Hospital said that he told no one about this risk until he was asked about it by Dr. O’Brodovich, there has been no investigation or action regarding his “failure” in this matter. (See section 5O.)

4. The Hospital made public statements in which allegations against the quality of Dr. Olivieri’s work made privately to it by Apotex were repeated. It did this without investigation as to their validity and without first giving her an opportunity to respond. The Hospital’s public statement damaged her professional reputation. In contrast, after Dr. Olivieri and her colleagues provided extensive forensic evidence of serious misconduct by Dr. Koren in May 1999, and still more conclusive forensic evidence in December 1999, the Chair of the Board of Trustees urged them “not to take any unilateral steps which might damage the reputation of one of your colleagues.” (See sections 5L(8) and 5N(16).)

5. In 1997 and 1999 Dr. Koren published findings on the efficacy of Apotex’s drug L1 that were compatible with the position of Apotex, without disclosing the financial support he received from Apotex, and without giving credit to the contributions of Dr. Olivieri and others to generating the data. In a letter criticizing Dr. Olivieri that he submitted to the Naimark Review in 1998, Dr. Koren wrote that the second unexpected risk of L1 constituted “life threatening toxicity,” yet he made no mention of this risk in his 1997 and 1999 publications on L1, all of which were published after he was provided with a full report on that risk. We are not aware of any action taken by either the University or the Hospital in regard to such conduct by Dr. Koren. (See sections 5E, 5H, 5O and 5R(5).)

While the responsibility for some of these instances of differential treatment lies with the Hospital, the University must also bear responsibility for not addressing some of Dr. Koren’s academic and professional conduct, and for not yet holding him to the same standard as other faculty members.
(3) Dr. Koren’s anonymous letters

The anonymous letters and the initial identification of Dr. Koren as the author. During the period mid-October 1998 to mid-May 1999 a series of five anonymous letters against Drs. Olivieri, Durie, Chan and Gallie was sent. The first contained allegations against Dr. Olivieri, and was faxed to the Globe and Mail newspaper on October 20, 1998. Several enclosures were faxed to the newspaper along with the anonymous letter, including several pages from a letter by Apotex Vice-President Dr. Spino to HSC President Mr. Strofolino and several paragraphs from the September 24, 1998 memo by Dr. O’Brodovich to the Naimark Review. The enclosures also contained or implied allegations against Dr. Olivieri. The second letter, dated October 21, was addressed to Dr. Durie. The letter said Dr. Durie had “caused HSC insurmountable damage,” said he “should leave this institution,” and called him “a British version of a foul air balloon [sic].” Dr. Durie was also the recipient of the third letter in the series, sent December 21. It called Drs. Olivieri, Chan and Gallie “unethical” and “a group of pigs.” It asked Dr. Durie, “did you think that their shit won’t touch you?” and suggested he “run as fast as [he] can.” On February 24, 1999 a large number of HSC staff received a letter ridiculing Drs. Gallie and Olivieri. The last of the series was sent to Dr. Durie on May 14, and accused him of “contaminating our air and fabric” and suggested that the Hospital should have “let people like you go long ago.”

Dr. Durie et al. lodged complaints about each of the letters with HSC administrators, with the Board of Trustees and with HSC legal counsel, directly after each letter was received. After the fourth letter in the series, they also complained to Dean Aberman. The HSC administration sent out notices to staff that such letters constituted misconduct, but the author was not discovered and called to account.

Drs. Chan, Durie, Gallie and Olivieri reported to us that they considered these letters to be attempts to discredit them and to intimidate them from continuing in their criticism of the conduct of Apotex, the Hospital and Dr. Koren, thereby infringing their academic freedom. The anonymous author clearly transgressed accepted standards of professional conduct. Dr. Chan et al. reported that they became increasingly concerned about what they felt was a lack of any effective response by the Hospital and the University to their complaints, so in the late winter of 1999 they hired a private detective who gathered information. They engaged forensic experts, a linguist and a documents expert, to review this information. The experts concluded that Dr. Koren was the author of the anonymous letters. The reports of the experts were enclosed with their written complaint against him submitted to the
Hospital and the University on May 17, 1999, and additional material was submitted in June 1999.8

The investigation for HSC by Ms. Humphrey. The Hospital discussed the complaint with Dr. Koren and he denied responsibility for the anonymous letters. The Hospital then hired its own investigator, Ms. Barbara Humphrey. The University left the investigation entirely to the Hospital and made no arrangement to have the Hospital's investigator consider whether Dr. Koren violated any University norms of conduct.9 Ms. Humphrey hired forensic experts who, among other things, essentially duplicated the work of those Dr. Chan et al. had hired. They reached the same conclusion.10

During Ms. Humphrey's investigation, Dr. Koren put forward several accounts about the origin of the anonymous letters, including naming a specific individual as having written them rather than himself. Ms. Humphrey examined these accounts in detail and concluded that "on the balance of probabilities" they were false.11 Many months went by and Ms. Humphrey still had not completed her investigation, due in part, she reported, to Dr. Koren's attempts to "frustrate" her inquiry through lying.12

In early December 1999, seven months after they had submitted the first forensic evidence, Dr. Gallie et al. obtained DNA evidence that Dr. Koren was the author. The matching DNA was from envelopes of two of the anonymous letters, and from the hand-addressed envelope that contained a handwritten letter, in Dr. Koren's handwriting, that he had sent to Dr. Michèle Brill-Edwards (see section 5U(6)).* Dr. Gallie et al. provided this new forensic report to the University and the Hospital on December 8 and Ms. Humphrey received a copy on December 10. Dr. Koren was informed of this development on or about December 10. Subsequently, he admitted to responsibility for the anonymous letters and, by implication, to having lied persistently to cover this up. Following his admission, Ms. Humphrey's report was completed, on December 20. (See also sections 5N(16) and (17).)

Ms. Humphrey did not rely on the DNA evidence provided by Dr. Gallie et al.. She said that it had been put forward by an interested party, and that the DNA evidence "would not, even if we relied on it, alter the conclusion arrived at by this Investigator."13 Ms. Humphrey had earlier asked Dr. Koren for a saliva sample, but he had refused to provide one. Her report found that Dr. Koren had "provided false and misleading information," and that he was "the

*The DNA report, from Helix Biotech of Richmond, B.C., and dated December 7, 1999, identified the author of the three samples (two anonymous, one known) as the same male person, with a frequency of "1 in 385 billion in the North American Caucasian population," with similar frequencies for other North American populations.
individual who drafted and disseminated” all five of the anonymous letters.\textsuperscript{14} She based the latter finding on “strong forensic evidence,” much of which was similar to that already provided by Dr. Gallie \textit{et al.} in May 1999. Her report stated that she also found “compelling motive evidence,” including the fact that Dr. Koren had been criticized by Dr. Gallie \textit{et al.} for his support of the position of Apotex on its drug L1.\textsuperscript{15} Ms. Humphrey noted that the anonymous letters were:

> directed at attacking and impugning the professional status, competency and reputation of Dr. Olivieri, Dr. Durie and to a lesser extent Dr. Gallie and Dr. Chan.\textsuperscript{16}

Ms. Humphrey concluded that Dr. Koren had violated Hospital policy and breached the “trust attending the positions of leadership and direction that Dr. Koren occupies.”\textsuperscript{17} Somewhat surprisingly, the course of action she recommended was that “the HSC give serious consideration to a mediation process”\textsuperscript{18} involving Dr. Koren and the victims of his series of letters. Dr. Gallie \textit{et al.} reported to this Committee that the facts that the Hospital had retained Ms. Humphrey to investigate harassment and provide advice, and that this advice did not treat Dr. Koren’s misconduct and breach of trust as necessitating more than a mediation process, heightened their concerns about the Hospital’s intentions with respect to Dr. Koren, and with respect to themselves. They reported that they were not reassured by the article written by Mr. Alexander Aird, Chair of the Hospital’s Board of Trustees in the \textit{Globe and Mail} on December 31, 1999, in which he said that Dr. Koren “has admitted to authoring unwanted anonymous mail.” This was a curious description for letters in which Dr. Koren called his colleagues “pigs” and “unethical,” where one letter purporting to be from a number of colleagues said, “you cannot overestimate the contempt, appaul [sic] and mistrust we have towards you,” and another suggested that Dr. Durie should have been “let go” by the Hospital “long ago.” Mr. Aird’s article then quoted a passage from Ms. Humphrey’s report in which she suggested that the victims of Dr. Koren’s anonymous harassing mail bore some responsibility for “a web of conflict” in which Dr. Koren had become enmeshed. Mr. Aird’s article omitted mention of the fact that Dr. Koren’s admission was preceded by seven months of lying, and came only after he had been identified by DNA evidence.

Ms. Humphrey’s recommendation of “a mediation process” to address serious misconduct and dishonesty by Dr. Koren, and Mr. Aird’s characterization of the misconduct by Dr. Koren as innocuous, were factors diverting attention away from a process that had been ongoing for several months. The new Dean of Medicine, Dr. Naylor, had brought a complex mediation process between Drs. Chan, Dick, Durie, Gallie and Olivieri, and the Hospital, covering a range of issues, to near completion in early December.
1999. However, as discussed in section 5.N(16), apprehensions that the Hospital would not properly address the serious misconduct and dishonesty to which Dr. Koren had just admitted, resulted in Dr. Chan et al. deciding in December to defer signing the Dean's mediation proposal. Mr. Aird's public statement at the end of December contributed to a decision to defer signing for a longer period. Dr. Olivieri and her colleagues reported to us that they were concerned that failure to address such serious harassment and dishonesty would mean that the benefits to them set out in the mediation document could be nullified by a continuation of abusive conduct by Dr. Koren. If his improper conduct were not properly addressed, they felt it would mean that those in authority had a high level of tolerance for his misconduct. They felt this would provide a context in which Dr. Koren's attempts to create circumstances in which they would "leave this institution" would be more successful.

(4) Disciplinary proceedings against Dr. Koren

On December 21, after Dr. Koren admitted to writing the anonymous letters and the day on which articles in the Globe and Mail and the National Post suggested he was the author, the University and the Hospital both suspended him with pay, pending disciplinary proceedings. The disciplinary panel included senior officers of the University and Hospital, and the proceedings extended over several months. In addition to Ms. Humphrey's recommendation of mediation, the panel had available the submissions of Drs. Chan, Dick, Durie, Gallie and Olivieri, and the University of Toronto Faculty Association (UTFA) to the effect that Dr. Koren's conduct warranted dismissal. In support of their position, Dr. Chan et al. and UTFA presented additional allegations and information on related misconduct. Dr. Koren was accorded due process: he was represented by legal counsel; he was provided with access to the Humphrey report and to the allegations and testimony by Dr. Chan et al. and UTFA; and he had the opportunity to respond.

Disciplinary action was imposed four months later, on April 11, 2000. In a joint letter to Dr. Koren, President Prichard of the University and President Strofolino of the Hospital, listed the actions taken and the reasons. The actions were announced to the press on April 14 and details of the Presidents' letter were later published by the Toronto Star and Nature Medicine. The Presidents cited three types of misconduct: "disseminating anonymous harassing correspondence;" denial of involvement to the Hospital, the University and Ms. Humphrey; and "late admission of responsibility." They noted that he had thrown away a computer and thereby "might have destroyed the
In their disciplinary letter the Presidents wrote to Dr. Koren that:

Academic freedom cannot flourish in an environment in which unwarranted attacks are made on colleague’s personal and professional integrity. Anonymously writing and communicating offensive allegations to colleagues demonstrates a complete disregard for colleagues and for the values which the Hospital and the University seek to foster. The Hospital and the University have the right to expect that their physicians and clinical faculty members will co-operate and be truthful. Your conduct in lying to the Hospital, to the University and to the investigator went beyond a failure to cooperate. You intentionally obstructed the Hospital’s investigation.

You occupy a position of great trust. You have great responsibilities. Your conduct in sending the anonymous letters and in repeatedly lying to Ms. Humphrey demonstrates lack of fair and ethical dealing with colleagues, irresponsibility and reckless dereliction of duty. Your misconduct was hurtful to your colleagues. You did not act in good faith. You only admitted misconduct after incontrovertible evidence was obtained. Your admission was too late. You did not tell the truth when you felt untruth would serve you better. Your lying triggered an expensive investigation. You abused the trust reposed in you and you failed to live up to your responsibilities.

You have provided no acceptable explanation for your misconduct. Your actions constitute gross misconduct and provide sufficient grounds for dismissal.26 (emphasis added)

However, the Presidents did not dismiss Dr. Koren. They took into account several “mitigating factors,” that were outlined in their disciplinary letter. These included: his accomplishments “as a researcher;” his “recent MRC Senior Scientist Award;” that he had no record of previous disciplinary action; and “an outpouring of sympathy for you from your colleagues.” They also noted that he had resigned from two administrative posts. Instead of dismissal, their April 11, 2000 letter imposed: a continuation of Dr. Koren’s suspension until June 1, 2000, the last two months without pay; immediate removal from the CIBC-Wood Gundy Children’s Miracle Foundation Chair in Child Health Research; removal from a University administrative position; and a $35,000 fine “as partial restitution” for the cost of Ms. Humphrey’s investigation.27

Presidents Prichard and Strofolino added that:

This suspension will be on your record. Should there be any other misconduct resulting in discipline to you, your record of discipline will be taken into account in deciding the proper penalty for such other misconduct. In the event that the current research misconduct proceedings result in discipline, or should further information come to light concerning the two letters dated December 18, 1996 and February 8, 1997 that results in a finding of evidence that could have proved or disproved” allegations of further misconduct by him.25
misconduct, any discipline for such misconduct would take into account this suspension.\textsuperscript{28}

It is of note that the two Presidents imposed disciplinary action only for the conduct to which Dr. Koren admitted, "We have based our decision on the admitted misconduct referred to above [writing and sending the anonymous letters, lying about this, and late admission of responsibility].\textsuperscript{29}"

The Hospital and the University did not fully investigate "the two letters" (see section 5R(6)).

At the time this report was completed we had no information on whether any action was taken against Dr. Koren as a result of any investigations into possible "research misconduct," or other possible misconduct by Dr. Koren. In the following subsections we discuss evidence which has led us to conclude that he has committed misconduct for which he has not, to our knowledge, been called to account.

\textbf{(5) Dr. Koren’s 1999 journal article on L1}

In 1999 Dr. Koren published an article on the efficacy of Apotex’s drug deferiprone (L1) in the treatment of iron-loading in thalassemia patients. He was senior author and two Apotex-funded research fellows he supervised, Drs. Orna Diav-Citrin and Gordana Atanackovic, were co-authors, with Dr. Diav-Citrin listed as first author. The article was published in the journal \textit{Therapeutic Drug Monitoring}, and reported data from the long-term trial of L1 (LA-03), that began in 1989 as a pilot study and continued until May 1996 when it was terminated by Apotex. The article was titled "An Investigation Into Variability of the Therapeutic Response to Deferiprone in Patients With Thalassemia Major," and it used data on hepatic iron concentrations (HIC) and on plasma vitamin C (ascorbic acid) concentrations of trial participants, in addition to pharmacokinetic data.\textsuperscript{30}

During the LA-03 trial, the HIC data was generated primarily by Dr. Olivieri in collaboration with Dr. Douglas Templeton (Department of Clinical Biochemistry, University of Toronto), and (from 1992 onward) Dr. Brittenham, some from biopsy specimens, and some from SQUID measurements performed in Dr. Brättenham’s laboratory. Also during the LA-03 trial, Dr. Olivieri collaborated with Dr. Robert Jacob (United States Department of Agriculture) who made determinations of plasma vitamin C concentrations in his laboratory.\textsuperscript{*} (See section 5A.)

\textsuperscript{*}The possible relevance of plasma ascorbic acid concentrations to the study of efficacy of an iron-chelation treatment is outlined in the LA-05 protocol proposal prepared by Dr. Olivieri in September 1995. This proposed a detailed methodology for studying the etiology of the loss of sustained efficacy of L1 observed in some LA-03 participants, and ascorbic acid was included as
The 1999 article by Drs. Diav-Citrin, Atanackovic and Koren stated the conclusion:

This study confirmed the effectiveness of deferiprone in heavily iron-loaded [thalassemia] patients and provided evidence that its effectiveness decreases in proportion to liver iron load.31

A new element of the L1 controversy had developed in the spring of 1997, when it became known that Dr. Koren was senior author of two abstracts on LA-01 and LA-03 data presented at a conference on thalassemia in Malta, of which the first author was an Apotex employee, as discussed in section 5N(5). (Drs. Diav-Citrin and Atanackovic also were co-authors of both these abstracts.) In mid-April 1998 there was further controversy when Dr. Diav-Citrin accessed a patient’s chart in the HSC thalassaemia clinic, and Dr. Olivieri lodged a complaint with Medical Advisory Committee Chair Dr. Becker that the access was unauthorized (see section 5L(6)). Dr. Koren then wrote to Dr. Becker concerning the research activities he and his Apotex-funded research fellows had been conducting after the May 1996 termination of the trials of L1 in thalassemia:

... we have not participated in any effort by Apotex to develop the drug for thalassemia after the trial. All our efforts focus on the use of deferiprone in acute iron poisoning [in an animal model]... The funding we received [from Apotex] after the discontinuation of the trial ... was not dependent on work related to deferiprone in thalassemia.32

However, a month later, on May 11, in another letter written in connection with the controversy over access to clinic charts, Dr. Koren acknowledged in writing that Dr. Diav-Citrin and he had been working on a paper on L1 in thalassemia. In this letter Dr. Koren gave another account of activities “since the termination of the trials,”33 in particular:

The study Dr. Orna Citrin is completing under my supervision pertains to pharmacokinetic data collected on patients between 1989 and Mid 1995...

Our study... has nothing to do with Apotex... ."34

The time period (1989 onward) makes it clear that this was data from the long-term trial (LA-03). In a follow-up note on May 14, 1998 Dr. Koren added:

After May 1996 I switched Orna’s research focus from L1 to other areas of pharmacology and she started writing up the pharmacokinetics aspects of L1. These were presented in 97-98 meetings.35

An abstract published by Drs. Koren, Diav-Citrin and Atanackovic in February 1997 indicates that, in fact, they were working on a broader analysis of the efficacy of L1 based on LA-03 data, using not only one of several factors to be assessed. (See section 5D.) The LA-05 protocol was never approved or implemented because Apotex did not agree to sponsor such a trial of its drug L1.
pharmacokinetics but also HIC and plasma vitamin C data of patients who had been in that trial.\textsuperscript{36}

In a handwritten note written on May 14, 1998, Dr. Koren recorded details of a meeting he and Dr. Diav-Citrin had the day before, May 13, with Drs. Spino and Tricta of Apotex “to discuss Orna’s paper.”\textsuperscript{37} It is reasonable to conclude that this discussion was about the article Drs. Koren, Diav-Citrin and Atanackovic subsequently published in \textit{Therapeutic Drug Monitoring} in 1999, because Dr. Koren’s note referred to “SQUID and biopsy data,”\textsuperscript{38} that is, data on HIC, the principal measure of efficacy in the LA-03 trial and the focus of the 1999 article. (Dr. Koren’s record of the discussion says nothing about any study of acute iron poisoning in an animal model.) The note records a disagreement on a point of methodology between the authors and the Apotex representatives, but it does not record any disagreement on findings or conclusions. The note ends with a comment that Drs. Koren and Diav-Citrin decided to submit the article for publication.

The published article says that it was received by the journal on August 12, 1998 and accepted for publication on October 6, 1998. It reports data of nineteen thalassemia patients who had been enrolled in the LA-03 trial and says:

\textit{For the sake of this analysis, data entry ended in the middle of 1995.}\textsuperscript{39}

Data entry for this trial continued into 1996, but the article does not explain why data points collected later than the middle of 1995 were not included in its analysis of efficacy of the drug. As noted in section 5D, it was in the middle of 1995 that Dr. Olivieri began withdrawing a significant number of these nineteen patients from the trial and transferring them to standard therapy, because their most recent HICS indicated loss of sustained efficacy in their individual cases to an extent that they were at risk from iron overload.

The following facts regarding the 1999 article are clear on reading it:

- The article does not disclose that Apotex funded the work of the three co-authors.
- The article does not acknowledge the contributions of Drs. Olivieri, Brittenham, Jacob, and others to generating the data reported in it.
- The article does not mention the risk of progression of liver fibrosis identified by Dr. Olivieri in data of the same cohort of patients, even though Dr. Olivieri had fully apprised Dr. Koren of this finding in early February 1997 and she had published the finding in 1997 abstracts and in a 1998 article in the \textit{New England Journal of Medicine}. 


The absence of any reference to the previously published finding that L1 poses a risk of progression of liver fibrosis is of particular note, because in Dr. Koren’s testimony to the Naimark Review he characterized the risk as one of “life-threatening toxicity” (his letter is reproduced in full at page 41 of the Naimark Report). After reading the article, we asked each of Dr. Olivieri and Dr. Brittenham whether they had been given any notice of, or opportunity to review or participate in, the publication. Each replied that they had been given no such notice or opportunity.

We conclude that the conduct of Drs. Koren, Diav-Citrin and Atanackovic in this publication, especially the conduct of Dr. Koren, the senior author and research supervisor of the other two authors, was not in conformity with widely accepted standards of conduct in scientific publication, and specifically not in conformity with policies of the University of Toronto.
(6) Dr. Koren’s signed letters against Dr. Olivieri

Dr. Koren put forward to the Naimark Review two letters signed by him and addressed to Dr. Olivieri, dated December 18, 1996 and February 8, 1997. These were taken to be authentic and reproduced in full at page 41 of the Naimark Report. Dr. Olivieri reported that she had never received these two letters and knew nothing of them until the Naimark Report was published. During the disciplinary proceedings against Dr. Koren for his anonymous letters, Drs. Olivieri, Chan, Dick, Durie and Gallie, and the UTFA alleged that these two signed letters constituted additional misconduct by Dr. Koren. In their April 2000 disciplinary letter to Dr. Koren, Presidents Prichard and Strofolino summarized the allegation:

The allegation of misconduct that you deny and that remains troubling to the institutions is that you prepared “two false letters” for submission to Dr. Naimark. These letters are dated December 18, 1996 and February 8, 1997 and are addressed to Dr. Nancy Olivieri and are signed by you.... The allegation is that the letters were prepared at a later date to buttress your submission to the Naimark inquiry and thereby discredit Dr. Olivieri.41

There were two aspects to this allegation: (i) that the dates of the two signed letters were false; (ii) and that their contents were false. The December 20, 1999 report of Ms. Humphrey also raised questions about the authenticity of these letters, which she had considered as comparisons for the anonymous letters. Ms. Humphrey reported that physical examination of the paper on which these letters were typed suggested they may have been typed much later than the dates given on them.42 She also reported that during her inquiry Dr. Koren had alleged that a part-time employee of his had typed certain letters, including these two signed letters. Ms. Humphrey interviewed this person and the person said she had typed both signed letters. After forensic examination, Ms. Humphrey concluded that the testimony by Dr. Koren and the testimony by his part-time employee on these signed letters (and on related matters) were “inconsistent and contradictory,”and “neither credible nor feasible.”43

The presidents’ disciplinary letter did not address the contents of the letters, even though the Naimark Report relied on the contents, as well as on the “dates” of the two letters. As for the “dates;”

The two institutions investigated this allegation to endeavour to determine whether the letters had been prepared on the dates shown and sent to Dr. Olivieri as stated by you. ... In throwing away the computer on which you typed these letters, you might have destroyed the evidence that could have proved or disproved this allegation. As a result of your action, we are unable to make a conclusive determination at this time. Should further evidence come to light concerning the authenticity of these two letters, the matter will be revisited. The case on this allegation is not closed.44
Presidents Prichard and Strofolino did not explain why they did not investigate the contents of the two letters. Unlike the dates, the assessment of the contents was not dependent on retrieval of a discarded computer—copies of the two letters are in the HSC library archives, and the Naimark Review reproduced both of them in their entirety in the main body of its Report. As discussed in section 5.0.2, the contents of these two letters are contradicted by documents written by Dr. Koren himself, as well as by other documents.

(7) Dr. Koren’s incorrect & false testimony

In this subsection, we summarize the main allegations by Dr. Koren against Dr. Olivieri, some put forward both to the Naimark Review and to the MAC inquiry, and others put forward to the MAC inquiry. Documents showing that the allegations were incorrect were included in the collections of documents available to these inquiries, yet they believed his allegations. Dr. Koren also made some of these allegations in Ms. Humphrey’s investigation. The allegations centred on identification and reporting of the risk of progression of liver fibrosis that Dr. Olivieri identified in early February 1997 in data of one group of patients, and on her clinical actions to assess whether patients in another group had experienced this adverse effect.

a) Dr. Koren alleged that he was the practitioner for the post-trial Emergency Drug Release (EDR) use of L1, and that in consequence it was he who had the responsibility to report any adverse drug reactions (ADR) to Health Canada and to Apotex, under the Food and Drugs Act and Regulations. He also alleged that Dr. Olivieri had an obligation to report any ADR to him, so that he could fulfill his alleged reporting obligations. In testimony to the MAC, Dr. O’Brodovich also put forward the allegation that Dr. Olivieri had responsibilities to advise Dr. Koren of adverse effects.

However, Dr. Koren was not the practitioner. The practitioner was Dr. Olivieri, the treating physician of the patients. Even Dr. Koren acknowledged this on page 5 of his December 1998 letter to the MAC, where he wrote that, “Dr. Olivieri refused to give Apotex immediate details of her suspicions and proofs of serious toxicity, despite clear regulations by Health Canada.” In other words, he himself stated in the same letter that the reporting requirements applied to Dr. Olivieri as the practitioner under the Act and Regulations, not to him. He thereby contradicted his allegation made on pages 1 and 2 of that letter. On page 1 he wrote that it was he who had the obligation to “report it [any adverse drug event] to the company and to the government, according to Health Canada Regulations.” On page 2 he wrote, “I was... the individual responsible for Emergency Drug Release... I believe it was her obligation to share the serious suspicion of hepatic
toxicity, so I could report it to Health Canada.” In fact, Dr. Olivieri did report this risk to Apotex and to Health Canada, as she was legally required to do as the practitioner.

b) Dr. Olivieri was not required to report the risk to Dr. Koren, but she nevertheless sent him a copy of the complete report on the risk, on February 5, 1997, one day after she sent it to Apotex. Although he had thus received the full report, Dr. Koren told no one about this risk until two weeks later, when he was asked about it by Dr. O’Brodovich. Thus, Dr. Olivieri did report the risk to Dr. Koren (though she was not obligated to do so), and he, who later alleged that it was he who had the responsibility to report it to Health Canada and others, reported it to no one. Yet he gave testimony to the MAC that he had not been informed of the risk.

c) Dr. Koren gave conflicting accounts of when and how he came to be informed of the risk of progression of liver fibrosis. On February 19, 1997, Dr. Koren told Dr. O’Brodovich that he did have a copy of Dr. Olivieri’s report, but that he had received it from Apotex (as Dr. O’Brodovich related in a letter dated March 3, 1997 to Dr. Olivieri’s CMPA lawyer, Mr. Colangelo). Therefore, Dr. Koren knew that Dr. Olivieri had reported full details of the identification of the risk to Apotex, contrary to his allegation to the MAC that she did not report her “proofs” of the risk to the manufacturer.

Dr. O’Brodovich (in his letter to Mr. Colangelo) implied, and the Naimark Report (p. 134) said that Dr. Olivieri had given Dr. Koren no information “until inquiries were made of her” on February 19, 1997. Dr. Koren told the MAC on January 19, 1999 that he “had not been advised” by Dr. Olivieri.50 This account of Dr. Koren to the MAC is consistent with what Dr. John Dick reported that Dr. Koren told him in September 1997, namely, that “he [Dr. Koren] only found out about it when [on February 19] Hugh [Dr. O’Brodovich] showed him the letter [Dr. Olivieri’s letter to the regulators].”51 However, Dr. Koren’s accounts to Dr. Dick and to Dr. O’Brodovich are inconsistent—to Dr. Dick he said he first obtained the report from Dr. O’Brodovich, but to Dr. O’Brodovich he said he first obtained the report from Apotex. In fact, Dr. Koren actually obtained the report from Dr. Olivieri “in early February,” as he acknowledged to Ms. Humphrey during her investigation.52 One of the signed letters by Dr. Koren reproduced in the Naimark Report (p. 41) indicates that he received the report on the risk on or before February 8, 1997.*

*As discussed above, the fact that Dr. Koren typed the date of “February 8, 1997” on this letter does not establish his claim that he wrote the letter on that date. Rather, it indicates an acknowledgement that on or about that date he did indeed receive Dr. Olivieri’s report on the risk, as he acknowledged to Ms. Humphrey in 1999. Since Dr. Olivieri had sent the report to him through their joint counsel on February 5, 1997, if he had actually written the letter during the
d) In Ms. Humphrey’s investigation, Dr. Koren repeated the claim he had made to the Naimark Review and the MAC that he was the practitioner for the EDR treatment arrangement. Ms. Humphrey reported that he told her that, “he [Dr. Koren] was responsible for those kids and he had promised to let the Company [Apotex] know and let Health Canada know of any adverse effects.”53 However, aside from the facts that he was informed of full details of the identification of the risk (on or shortly after February 5, 1997) and did not let anyone know about it, he wrote letters and memos in 1997 and 1998 confirming that he was not responsible for “those kids.” Indeed he wrote that, after the trials were terminated in May 1996, he had no involvement with the monitoring of any of the patients on L1. There were two groups of patients treated with L1 under EDR, some from the former LA-01 cohort and some from the former LA-03 cohort. With respect to the patients who had been in the LA-01 cohort, Dr. Koren wrote in August 1997 that, after May 1996, “… was not part of the collection, analysis or interpretation of the data” arising from the monitoring of patients.54 With respect to the patients who had been in the former LA-03 cohort, Dr. Koren wrote in May 1998 that after the trial termination, he “was not involved any more in data collection and was not aware that data were continuously collected.”55

e) In May 1998, in connection with the controversy of Dr. Diav-Citrin’s access to charts in the thalassemia clinic, Dr. Koren said that he was unaware that patients who continued on L1 were monitored for hepatic iron concentration (HIC). In a memo to Dr. Buchwald dated May 14, 1998 he outlined Dr. Diav-Citrin’s activities with respect to patients in the former LA-03 trial cohort during the close-out period in 1996, closing with the statement that:

These activities were in the context of compassionate drug administration [EDR] after discontinuation of the [LA-03] trial, and we were not aware that Dr. Olivieri continued to monitor study endpoints, and especially liver iron.56

However, Dr. Koren did know that Dr. Olivieri continued to monitor patients using “study endpoints”—specifically, he knew she continued to monitor liver iron (HIC), the only accurate measure of efficacy of any iron chelation treatment. First, on July 15, 1996 Dr. Koren himself co-signed a letter with her in which they expressly stated that a patient would only be treated with L1 under EDR by Dr. Olivieri if the patient agreed to be monitored by the same safety tests as in the terminated trials, and this letter expressly included “liver biopsy,” the purpose of which was to monitor HIC, as well as histology.57 In this joint letter, Drs. Olivieri and Koren stated that

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53 Naimark Review in 1998 to buttress his submission to that Review, as Dr. Olivieri alleged, choice of the date “February 8, 1997” would help to lend an air of authenticity to the letter.
they remained concerned that L1 “may not have optimal efficacy,” which could expose patients to the risks of iron loading. It was for this reason that “liver biopsy” for HIC and histology was specified in their letter.

Second, Dr. Koren knew that patients who continued on L1 under EDR had in fact been monitored after July 1996, by HIC and other tests. In his May 14, 1998 memo to Dr. Buchwald he acknowledged that “Orna [Dr. Diav-Citrin] indeed continued to see patients to monitor those who received the drug on a compassionate basis [EDR] until the end of November 1996.”

On October 28, 1996 Dr. Olivieri wrote to Dr. Koren about the second stoppage in the L1 supply by Apotex, and in this letter she noted an account she had received that Apotex had taken this action because it objected to her monitoring of the patients and then possibly reporting the results of the monitoring (see section 5J(3)). Dr. Koren was copied on the report of close-out data from both trials that Dr. Olivieri sent to Apotex on November 15, 1996. This report included data points, including HIC, collected until late October 1996.

Dr. Spino wrote to Dr. Koren on October 23, 1997 requesting assistance in obtaining source data of both the LA-03 and LA-01 patient groups. Dr. Spino specifically asked for “histological assessments of the biopsy samples” and “All iron assessments since May 1996, reported by date, and whether the result was obtained by biopsy or SQUID.” Dr. Koren read and understood Dr. Spino’s request in this letter is clear from letter Dr. Koren sent to Dr. O’Brodovich on November 3, 1997, to the effect that he was unable to assist Apotex in gaining access to this data, because he himself had not been involved in the monitoring of patients after May 1996.

Dr. Koren put forward testimony to the MAC that a research trial of L1 had continued after Apotex terminated both trials. Yet documents show very clearly that he knew Apotex had terminated both trials and that there was no trial of L1 after May 1996.* He could have have corrected the misunderstandings of Dr. Moore and Dr. O’Brodovich on this central point. Instead of doing so, he put forward to the MAC in quotes the incorrect statement by Dr. Moore that the long-term trial had continued.

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*Dr. Koren had received the notice from Apotex on May 24, 1996 that both trials had been terminated, and he was present in Dean Aberman’s mediation meeting on June 7, 1996 in which Apotex refused to reinstate any trial (but agreed to the non-trial EDR arrangement). Dr. Koren signed two letters, jointly with Dr. Olivieri, to Dr. Haslam on May 25, 1996 and to Dr. Zlotkin on July 15, 1996, stating that both trials had been terminated. In 1997 and 1998 he wrote several letters confirming that both trials had been terminated. For instance, in a letter to Dr. Buchwald on May 11, 1998, Dr. Koren wrote of “the termination of the trials in May 1996.” (See sections 5K and 5P for citations of this and other letters to the same effect.)
g) Dr. Koren put forward testimony to the MAC that liver biopsies arranged by Dr. Olivieri during February-April 1997 were not clinically indicated. These were on some patients receiving L1 who had biopsies after the risk of progression of liver fibrosis had been identified. In fact these biopsies were clinically indicated (see sections 5K and 5Q), and this was clear from documentation in Dr. Olivieri’s report on the risk, two copies of which Dr. Koren himself said he received. He also alleged that liver biopsy was “a potentially life threatening procedure.” He likely knew that this was not an accurate characterization, because the information and consent forms for patients enrolling in the long-term trial explained that it was a procedure with very low risk. As an investigator for that trial (1989-1996), Dr. Koren was responsible for the accuracy of these information and consent forms. (See section 5Q.)
(8) Conclusions

1 | Dr. Koren put forward incorrect allegations and testimony against Dr. Olivieri to the Naimark Review and the MAC inquiry. His conduct ranged from at best seriously neglectful (for instance, in his allegations and testimony pertaining to liver biopsies), to clearly dishonest (for instance, in the allegation that Dr. Olivieri had not informed him of the risk of progression of liver fibrosis, and in the testimony that a trial of L1 continued after May 1996).

2 | Much of the L1 controversy from late 1998 onward has resulted from the incorrect and false testimony against Dr. Olivieri by Dr. Koren, and the apparently uncritical acceptance of his testimony by the Naimark Review and the Medical Advisory Committee.

3 | Dr. Koren's conduct in publishing the 1999 article on the efficacy of L1 in Therapeutic Drug Monitoring was not in conformity with accepted standards of conduct in regard to scientific publication.

4 | To our knowledge, neither the University of Toronto nor the Hospital for Sick Children has addressed the serious misconduct by Dr. Koren we have reviewed here, other than that pertaining to his authorship of the anonymous letters and his lying to conceal responsibility for them.