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THE COLLEGE OF PHYSICIANS AND SURGEONS OF ONTARIO

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**PRIVATE AND CONFIDENTIAL**

December 19, 2001

Dr. Nancy Olivieri
The Hospital For Sick Children
Division of Haematology/Oncology
555 University Avenue
TORONTO, Ontario M5G 1X8

Dear Dr. Olivieri:

Re: Dr. Laurence Becker

I am writing to advise you that the Complaints Committee has now considered the complaint referenced above. A copy of the Committee's written decision and reasons is enclosed.

This letter is your notice, pursuant to subsection 27(c) of the Health Professions Procedural Code, that you may, in accordance with subsection 29(2) of the code, request the Health Professions Appeal and Review Board to review the decision. Should you wish to request such a review, you must do so within 30 days of receipt of this letter. A request for a review must be directed to the Registrar of the Board, whose address and telephone number are:

Abby Katz Starr
Registrar
The Health Professions Appeal and Review Board
151 Bloor Street West, 9th Floor
Toronto, ON M5S 2T5
Tel: (416) 327-8512 or Fax: (416) 327-8524

The Complaints Committee, having rendered its decision, is not able to consider the matter again, unless directed to do so by the Board.

Yours truly,

James Cranton
Acting Manager
Complaints Committee Support Area

JFC:ss/Enclosure

cc: Mr. Michael Mitchell,
Sack Goldblatt Mitchell

THE COLLEGE OF PHYSICIANS AND SURGEONS OF ONTARIO

# COMPLAINTS COMMITTEE DECISION AND REASONS

**COMPLAINANT:** Dr. Laurence Becker

**RESPONDENT:** Dr. Nancy F. Olivieri

## BACKGROUND[1] AND AREAS OF CONCERN

In the early 1980s, deferoxamine (Desferal) became the standard of care to treat patients with Thalassemia major (a condition which results in the progressive accumulation of iron in body organs). Desferal was administered by subcutaneous infusion, and worked to bind iron and promote its excretion. Some patients, however, find it difficult to comply with the therapy regimen for Desferal on a daily basis, and so there is considerable interest in finding a safe and effective orally active chelating agent. The issues surrounding this case relate to finding an alternative treatment for iron-chelating therapy in patients with Thalassemia major.

In the 1980s, Deferiprone (L1) showed potential as an orally active chelating agent. Prior to consideration of the commercial licensing of Deferiprone (L1) by the Food and Drug Administration (FDA),[2] however, the following studies were necessary:

- a prospective randomized trial to compare effectiveness and safety of L1 to deferoxamine, termed LA-01

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[1] The background information contained in this section was compiled from the materials obtained by the Committee in the course of its investigation into this complaint.

[2] A number of abbreviations will be used throughout this decision, including the following:

| | |
|---|---|
| FDA | Food and Drug Administration |
| HSC | Hospital for Sick Children |
| MAC | Medical Advisory Committee |
| L1 | Deferiprone |
| MRC | Medical Research Council |
| REB | Research Ethics Board |
| CMPA | Canadian Medical Protective Association |
| ASH | American Society of Hematology |
| NIH | National Institute of Health |

- a one year, 200 patient international safety study to assess particular risks associated with L1, in particular its effect on bone marrow function and joint disease, termed LA-02
- continuation of the compassionate use long-term study of 25 patients, termed LA-03

Dr. Nancy Olivieri, Haematologist, was the principal investigator in the LA-03 study. In 1999, the Board of Trustees of the HSC referred questions relating to Dr. Olivieri's involvement in the study to HSC's MAC. These questions arose out of a report by Dr. Arnold Naimark in December 1998 which stemmed from events surrounding an article published in *The New England Journal of Medicine* in August of that year, of which Dr. Olivieri was the first author. The article outlined findings with respect to the loss of effectiveness of L1, and concerns regarding toxicity. The MAC undertook an investigation into the matter, and eventually Dr. Becker, the Chairman of the MAC, filed a complaint with the College outlining the concerns raised by the Board of Trustees[3].

The members of the MAC are concerned that:

- Dr. Olivieri continued to administer L1 to her patients after drafting a letter to the FDA on January 22, 1997 indicating that L1 may cause liver toxicity;

- the liver biopsies for patients ordered by Dr. Olivieri may not have been clinically indicated and were performed for the purpose of research;

- Dr. Olivieri should have advised her Department Chief and co-workers about her concerns about L1 toxicity.

## INVESTIGATION

The materials obtained by the Committee in its investigation of this matter included the following:

- letter of complaint from Dr. Becker, with enclosures

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[3] In her response to the complaint, Dr. Olivieri took the position that the referral of the matter to the College was an irresponsible act on the part of the HSC. She maintained that the HSC had improperly abdicated its responsibilities, and that the College should not agree to investigate what was essentially a political battle within the hospital. She pointed out that the MAC investigation into the matter was flawed, and that she was not provided with the opportunity to review all of the relevant material before it and properly respond to the allegations being made against her. Dr. Olivieri also indicated that the MAC and the HSC acted improperly in holding a national news conference to advise that it had referred the matter to the College, without ever having advised her or her counsel of its decision.

- response from Dr. Olivieri
- further correspondence and information received from Dr. Olivieri
- independent expert medical opinion

## CHRONOLOGY OF EVENTS

The following provides a synopsis of the chronology of pertinent events, as described by the parties to this complaint.

| **Dr. Becker/MAC's Submissions:** | **Dr. Olivieri's Submissions:** |
|---|---|
| 1988<br>Start of LA-03 study (open design, 25 patients). | September 1988<br>Dr. Olivieri applied as principal applicant and principal investigator to MRC for funding of pilot study of use of L1, termed LA-03. Dr. G. Koren was included in application as co-applicant. |
| | 1989<br>Dr. Olivieri received two year MRC grant. Dr. R. McClelland of Department of Chemistry at University of Toronto synthesized drug which was then encapsulated for patients by Novopharm, a generic drug company. |
| 1991<br>Application to MRC for funding for randomized trial. (Not funded, so industry sponsorship sought). | 1991<br>Dr. Olivieri received one year renewal from MRC, and applied for MRC grant to do randomized trial of drug based on success of short-term results. MRC turned down application and suggested that Dr. Olivieri find industry partner for randomized trial, but granted one year terminal grant for 1992 - 1993. |
| | 1992<br>Dr. Olivieri began working with Dr. Brittenham (expert on iron metabolism in Cleveland). Dr. Brittenham developed SQUID (superconducting quantum interference device) technology for non-invasive measurement of liver iron burden. |

**Dr. Becker/MAC's Submissions:**

1993
Apotex agrees to fund LA-01 (randomized trial).

**Dr. Olivieri's Submissions:**

1993
Dr. Fredd of FDA told Dr. Olivieri and Dr. Brittenham that three studies would be necessary to complete before L1 could be considered for commercial licencing by FDA (LA-01, LA-02 and LA-03). For these trials, Dr. Fredd noted that investigators would have to persuade pharmaceutical manufacturer to synthesize drug under good laboratory practices.

Dr. Koren introduced Dr. Olivieri to Dr. Spino (VP of Apotex). In March, letter of agreement was sent to Dr. Koren setting out that, in exchange for providing L1 for patients and some financial support to continue long-term compassionate use trial begun in 1989, Apotex would obtain use of information produced by study to support regulatory submissions on drug.

In April, formal contract was signed with Apotex by Dr. Olivieri and Dr. Koren, in which Apotex agreed to partly fund LA-01. Balance of cost of trial (approximately 50%) was funded by MRC under MRC/Industry grant.

April 1995
Initial results from LA-03, which included all data generated up to June 1994 through support of MRC, were published in *The New England Journal of Medicine*, with the conclusions that L1 had favourable short-term effect on iron balance. Around publication time, Drs. Brittenham and Olivieri became concerned that a few patients in LA-03 were beginning to demonstrate potential reduction in long-term effectiveness and increases, or unacceptably high stabilizations, in hepatic iron concentrations.

| **Dr. Becker/MAC's Submissions:** | **Dr. Olivieri's Submissions:** |
|---|---|
| | 1994<br>Planning for LA-02 commenced. The LA-02 protocol was designed and co-authored by Drs. Brittenham and Olivieri. Study required enrollment of approximately 200 thalassemia patients. |
| | 1995<br>Drs. Brittenham and Olivieri received final contracts from Apotex pertaining to LA-02. Within contract was provision that required all information to be kept confidential for three years after termination of contract. The contracts relating to LA-01 and LA-03 contained no such provision. The contracts contained a licence to use the information for regulatory purposes and the LA-01 had a one year post termination ban while LA-03 contained no such publication ban. |
| April 1995<br>*New England Journal of Medicine* article re: LA-03 trial (favourable effect of deferiprone on iron balance). | July 1995<br>Drs. Brittenham and Olivieri informed Apotex of results and requested permission and funding to set up separate protocol to study those in whom L1 appeared less than optimally effective. They advised Apotex that it would be necessary to change the consent forms for the patients involved in the trials to advise them of these negative results in some patients. Apotex requested data prior to agreeing to changes and notifying the HSC REB. |
| | April 1995<br>Initial results from LA-03, which included all data generated up to June 1994 through support of MRC, were published in *The New England Journal of Medicine*, with the conclusions that L1 had favourable short-term effect on iron balance. Around publication time, Drs. Brittenham and Olivieri became concerned that a few patients in LA-03 were beginning to demonstrate potential reduction in long-term effectiveness and increases, or unacceptably high stabilizations, in hepatic iron concentrations. |

**Dr. Becker/MAC's Submissions**:

August 1995

Dr. Olivieri was going to report concern re: alleged loss of efficacy to REB; suggests single new L1 protocol to Apotex to explore this. Correspondence back and forth with Apotex about validity of conclusion re: loss of efficacy.

March 1996

Dr. Olivieri submits report re: concern re: lack of sustained efficacy to REB (consent forms revised).

**Dr. Olivieri's Submissions:**

October 1995

Revised protocol for LA-03 required the HSC's REB's approval for study to continue. Apotex signed contract committing to studying those patients in whom L1 appeared to be less than optimally effective in separate protocol. Apotex continued to refuse to agree to informing REB of the findings.

February 1996

Drs. Brittenham, Koren and Olivieri met with Apotex representatives to review data from long-term trial. Following the meeting, Apotex determined that it did not agree that there was loss of effectiveness of L1. Apotex stated that it did not want investigators to inform patients of their concerns. Apotex indicated that their concerns represented incorrect interpretation of the data.

Late February 1996

Dr. Olivieri forwarded to Apotex a draft letter to REB, signed by Drs. Koren and Olivieri. The draft letter outlined concerns about the loss of effectiveness in some patients.

Early March 1996

Dr. Olivieri forwarded the letter to the REB.

| **Dr. Becker/MAC's Submissions:** | **Dr. Olivieri's Submissions:** |
|---|---|
| Spring 1996<br>NIH application re: L1 for Sickle Cell. | April 1996<br>REB directed Dr. Olivieri to submit revised patient information and consent forms, incorporating the concerns about inadequate effectiveness to the REB for approval. |
| May 1996<br>Apotex discontinues LA-01 and LA-03 at HSC. | May 21, 1996<br>Dr. Olivieri submitted revised forms with copies to Apotex. |
| | May 24, 1996<br>Apotex terminated LA-01 and LA-03 trials and invoked post termination clauses to prevent Dr. Olivieri from informing her patients about concerns, even though there was no such clause in LA-03 contract. Drs. Koren and Olivieri contacted CMPA for advice pertaining to Apotex's legal threats. CMPA counsel advised Dr. Olivieri to follow process of staged disclosure giving Apotex notice of material which she proposed to disclose or publish so that they would have opportunity to bring legal proceedings if they wished to prevent disclosures. Dr. Olivieri followed advice of counsel and CMPA. |
| | June 7, 1996<br>Drs. Olivieri and Brittenham met with University's Dean of Medicine, Dr. Arnold Aberman. Dr. Aberman mediated agreement with Apotex to ensure company would continue to supply L1 to those of Dr. Olivieri's patients who, in Dr. Brittenham's and Dr. Olivieri's opinion, were continuing to benefit from drug. These patients were no longer in a research trial and so were no longer under the jurisdiction of the REB. It was agreed that Dr. Koren would serve as conduit for communications about drug between Dr. Olivieri and Apotex. Apotex continued substantial research funding to Dr. Koren (Dr. Koren re-analysed data and later published findings that L1 was effective and safe). |

| **Dr. Becker/MAC's Submissions:** | **Dr. Olivieri's Submissions:** |
|---|---|
| July 1996<br>Emergency release of L1 begins. | July 20 or 21, 1996<br>Dr. Olivieri notified REB of premature termination of LA-01 and LA-03 trials<br><br>July 29, 1996<br>Drs. Brittenham and Olivieri prepared summary of data and submitted this to Dr. Spino, requesting that he forward data to an Apotex-appointed advisory panel to review and confirm company's decision to terminate trial. (Paul Taylor in "A Doctor Takes on A Drug Company"[the Globe and Mail, 13 August 1998], states that the data was never shown to at least one of the four panel members, Dr. Mary Corey). Two members of the panel (whose centres were and are supported by Apotex), constructed a post hoc analysis of the data which supported Apotex's position that there was no basis for concerns. |

| **Dr. Becker/MAC's Submissions:** | **Dr. Olivieri's Submissions:** |
|---|---|
| August 1996<br>Reports made regarding lack of efficacy in LA-03. | |
| September 1996<br>NIH approval of L1 for Sickle Cell. | |
| December 1996<br>Presentation to ASH re: liver toxicity. | Around December 5, 1996<br>Dr. Olivieri attended ASH conference in Orlando. Dr. Brittenham contacted and first alerted Dr. Olivieri to potential liver toxicity associated with L1. Dr. Brittenham discussed published studies of administration of a closely related chelator to gerbils. Dr. Olivieri arranged for whatever liver biopsy reports were readily accessible to be sent to her in Orlando. Upon preliminary review of small number of biopsies relating to some of patients enrolled in long-term study, Dr. Olivieri noted some suggestion of accelerated progression to fibrosis. She was unable to draw any inferences due to the limited sample. Upon Dr. Olivieri's return to Toronto, she arranged for all biopsy reports on LA-03 patients to be assembled. |
| December 18, 1996<br>Dr. Koren wrote to Dr. Olivieri asking for information about her presentation re: liver toxicity at ASH. | Late December 1996<br>Dr. Olivieri arranged with Dr. Ross Cameron from Toronto Hospital to analyse the liver histology, which he began in late December. |

**Dr. Becker/MAC's Submissions**:

January 1997

- Abstracts on toxicity (eg. Biomedicine 1997, which was withdrawn).
- Sickle Cell submitted to REB.
- Letter to FDA (dated January 22, 1997) re: exacerbation of hepatic fibrosis in LA-03 patients.

**Dr. Olivieri's Submissions:**

Early to mid-January 1997
Dr. Cameron completed his initial assessment of the liver histology. Dr. Olivieri shared the report with Dr. Brittenham and her CMPA counsel.

January 22, 1997
Over one to two week period, Drs. Olivieri and Brittenham prepared draft letter to FDA, addressed to Dr. Fredd. Dr. Olivieri shared draft letter with Dr. Cameron, who asked that she delay sending letter to FDA as he wished to reassess slides and confirm scores.

End of January 1997
Dr. Cameron completed his reassessment and reported his conclusions to Dr. Olivieri.

Beginning of February 1997
Dr. Olivieri concluded there was evidence of liver toxicity caused by L1. She became concerned that her patients in receipt of L1 might be experiencing accelerated progression to fibrosis, which would have serious implications for their overall medical care. She recommended to her patients that if they had not recently had their annual liver biopsy, they have it early in order to determine their state of health and to decide on appropriate health care plan for them. She notified all clinic staff including Dr. Massicotte (clinical associate of Haemoglobinopathy program at HSC) regarding evidence of accelerated progression of liver fibrosis and need to notify patients.

**Dr. Becker/MAC's Submissions:**

February 4, 1997

- Dr. Olivieri's counsel sends letter to Apotex prior to submission to FDA.
- Apotex sends copies to Drs. O'Brodovich (Pediatrician-in-Chief at HSC) and Koren.
- Dr. Olivieri holds information session for her patients.

February 19, 1997

- Dr. O'Brodovich meets with Drs. Olivieri and Freedman (Head of Division of Haematology/Oncology at HSC) to discuss FDA letter, and he undertakes to report the liver toxicity to REB.

February 1997

- Dr. Olivieri requests more L1 from Apotex.
- NIH inquires about ethics approval for L1 in Sickle Cell.

February 26, 1997

Dr. O'Brodovich withdraws approval for L1 in Sickle Cell.

February 18 or 27?, 1997

- NOTE: not clear when HSC patients no longer received L1

**Dr. Olivieri's Submissions:**

February 4, 1997

Dr. Olivieri met with patients. There were poor weather conditions. Many patients attended. Dr. Massicotte did not attend but was informed of concerns and meeting.

Through her counsel, Dr. Olivieri forwarded her draft letter to Dr. Fredd to Apotex for review, giving them until February 10 to respond. Apotex sought and was granted extensions until February 20.

February 18, 1997

Dr. Olivieri stopped prescribing L1 to her patients.

February 19, 1997

Dr. Olivieri met with Dr. O'Bradovich, at his request, and gave him briefing of all relevant facts.

February 20, 1997

Dr. Olivieri met with Dr. Aideen Moore, chair of REB, and made full disclosure of situation.

Around February 20, 1997

Dr. Olivieri contacted her HSC patients and families to attempt to persuade them to discontinue L1 therapy.

February 24, 1997

Letter was sent to Dr. Fredd.

| Dr. Becker/MAC's Submissions: | Dr. Olivieri's Submissions: |
|---|---|
| • no prescriptions filled through HSC Pharmacy after February 18, 1997. | |
| March 1997<br>• Dr. Olivieri replies to NIH; no mention of liver toxicity<br>• Dr. Olivieri writes to REB; no mention of toxicity.<br>• Dr. Olivieri holds information session for her patients. | End of March 1997<br>All patients from the HSC had undergone liver biopsies. |
| May 1, 1997<br>Dr. Olivieri writes to REB confirming that L1 had been discontinued for HSC patients. | |
| November 15, 1997<br>Abstract #1161 in *Blood* (journal of ASH) states "in Toronto,...iron concentration....was monitored up to May 1997, when L1 was discontinued in all patients because of safety concerns." | |

## REVIEW OF INFORMATION RELATING TO COMPLAINTS

***Continued Administration of L1***

During its investigation into Dr. Olivieri's involvement in the LA-03 study, the MAC became concerned that the documentation provided by Dr. Olivieri indicated that she continued to administer L1 to her patients after she had advised the FDA of her concerns regarding the toxicity of the drug.

In her response to this complaint, Dr. Olivieri noted that Dr. Naimark's report had criticized her for not advising HSC of her concerns regarding L1 toxicity prior to February 1997, but pointed out that in coming to that conclusion, Dr. Naimark had relied upon two documents from Dr. Koren, which were subsequently established by forensic evidence to be fabrications created for the purpose of discrediting her and harming her professional reputation. She indicated that it was also established that Dr. Koren had sent anonymous hate mail to her supporters between October 1998 and May 1999, designed to harm her reputation and to impair her relationships with her colleagues at HSC, and she advised that Dr. Koren had been disciplined[4] for gross misconduct in relation to that course of events.

Dr. Olivieri stated that she first became aware of the possible toxicity of L1 when speaking with Dr. Brittenham on December 5, 1996, regarding previous animal studies involving a closely related chelator. She indicated that she immediately reviewed the available patient records, and reported her preliminary, very narrow and tentative observations carefully at the ASH Conference. She advised that she then conducted a full review, and within three months reported the results and her conclusions to her patients, the regulatory authorities and her professional colleagues who required the information.

Dr. Olivieri reported that upon her receipt of Dr. Cameron's final assessment, around the end of January 1997, she scheduled an initial meeting with her patients and their families, to take place on February 4, 1997. She advised that the purpose of the meeting was to apprise her patients of her findings, and to recommend that patients have liver biopsies if they had not had one recently, in order to determine whether there was evidence of progression of fibrosis. Dr. Olivieri stated that she shared her concerns about liver toxicity with clinic staff, and instructed them to assist her in contacting the patients and their families, asking them to attend the scheduled meeting.

According to Dr. Olivieri, she and her staff contacted her patients as expeditiously as possible, once she had a reliable, scientific basis upon which to act. She pointed out that not all patients immediately elected to discontinue L1 therapy. She explained that in order for Desferal to be put in place, new pumps had to be ordered, and the order could not be filled immediately by the manufacturer. Given that liver fibrosis progresses slowly (over a median of 3.2 years in L1 treated patients), and given that the risk of toxicity and premature death in transfusion-dependent thalassemia patients in the absence of alternative chelation therapy may be much faster than this, especially in heavily iron-loaded patients, Dr. Olivieri advised that there was a balanced risk between continuing and stopping L1. She indicated that her opinion was that in light of the unavailability of

[4] The HSC, jointly with the University of Toronto, conducted a formal investigation into the matter of this anonymous correspondence. As a result of this investigation, Dr. Koren was suspended from HSC, the chair endowed in his name was removed, and he was ordered to make some restitution.

other treatments in the short term, and the long period which it normally takes for fibrosis to develop, there was a balanced risk in taking the drug for a very short period of time, while those risks (real and/or anticipated) were sorted out, and while other chelator therapy was arranged. She stated that some patients initially chose to continue on L1 until Desferal treatment could be arranged, or until biopsy results were obtained, and that therefore, in the first half of February, some patients continued on L1.

Dr. Olivieri reported that after Dr. O'Brodovich became aware of the potential adverse effects of L1, on his insistence, on or about February 20, she called her HSC patient families to attempt to persuade them to discontinue L1 therapy. She indicated that Dr. O'Brodovich insisted on withdrawing L1, despite her explanation of the potential for iron toxicity in the absence of a chelator. She reported that, to the best of her knowledge, by the end of February 1997 all of her HSC patients were off L1. She pointed out that all documentation confirms that no L1 was dispensed at HSC after February 18, and that all patients were off L1 by the end of February 1997, regardless of whether Desferal treatment was in place.

According to Dr. Olivieri, L1 continued to be administered to some of her adult patients at the University Health Network (Toronto Hospital site) after February 1997. She pointed out that there was never any concern raised by the UHN about the continuation of the L1 administration, despite its full knowledge of Dr. O'Brodovich's concern over the continuation. She questioned how there could be medical misconduct to prescribe and administer the drug at HSC, when the very same drug was being prescribed and administered at UHN with full knowledge of all the circumstances.

Dr. Olivieri pointed out that she had previously been threatened with litigation by Apotex for disclosing her concerns over the loss of effectiveness of L1, and that she therefore had to proceed with her disclosure of her concerns regarding toxicity of L1 in light of those threats. She explained that throughout May 27, 1996 to June 21, 1997, she was represented by CMPA counsel, and that she followed their advice with regard to the need for staged disclosure of her concerns.

Dr. Olivieri maintained that her conduct in administering L1 was consistent with or exceeded accepted standards. She feels that there is no evidence of any impropriety which would warrant any investigation.

***Liver Biopsies***

In responding to this aspect of the complaint, Dr. Olivieri indicated that she assumed that the concern regarding this issue was in reference to the biopsies she recommended to patients in February/March of 1997, following receipt of Dr. Cameron's assessment of liver histology data. Dr. Olivieri reported that regular liver biopsies have been part of the standard of care in patients with thalassemia and

other transfusion-dependent patients in the HSC program since the early 1990s, and pointed out that she has frequently spoken and written on this subject (as in, for example, *Blood*, Vol. 89, No 3 1997: pages 739-761 Authors: Olivieri, N.F. & Brittenham, G.M.). She explained that liver biopsies are the only quantitative method for measuring body iron burden, and noted that the most commonly used screening blood test, serum ferritin concentration, is an imprecise estimate of body iron burden resulting in serious over or under treatment which can lead to serious toxicity and inadequate treatment ending in death. Dr. Olivieri stated that the SQUID machine is only available at one site in the U.S., and does not provide information about tissue histology. She indicated that if fibrosis or cirrhosis is suspected, a liver biopsy is the only method of diagnostic assessment for patient care in this population of patients.

Dr. Olivieri stated that from the beginning of February 1997, when she concluded that there was evidence of liver toxicity caused by L1, she became concerned that her patients in receipt of L1 might be experiencing accelerated progression to fibrosis, which would have serious implications for their overall medical care. She indicated that she recommended that her patients undergo a liver biopsy if they had not already had their annual biopsy recently. She explained that the liver biopsy would determine their state of health and assist to decide on an appropriate health care plan for them. Dr. Olivieri reported that at HSC, all patients had undergone biopsies by the end of March 1997, authorized by usual patient consent to biopsies.

Dr. Olivieri maintained that there was a clear responsibility to investigate whether patients who had been taking an experimental drug, for which there is an established effective and safe alternative, had suffered toxicity from the drug. She noted that all patients that underwent these biopsies consented to the procedure. She also pointed out that following the termination of the L1 clinical trials on May 24, 1996, she continued to recommend regular biopsies to the patients who had been enrolled in those trials, whether or not they were receiving L1, just as she had done to her transfusion-dependent patients who had never taken L1.

***Information to Department Chief and Co-workers***

In her response to the complaint, Dr. Olivieri stated there was no dispute that the first people informed about her concerns regarding liver toxicity were the clinic staff and the patients, as outlined above.

Regarding notification of her Department Chair and colleagues, Dr. Olivieri indicated that she was not aware of any obligation that would require her to notify the chair or her colleagues at large (ie. other than those involved in treating the patients) about her concerns. She reported that from 1995 to 1996, she followed a process of disclosure of her concerns regarding the loss of effectiveness of L1, which appeared to be consistently acceptable at the time to her Department Chair, Dr. Robert

Haslam, and his successor, Dr. O'Brodovich. She indicated that, consistent with the advice of CMPA counsel, she followed the same procedure in 1997 with respect to dissemination of her concerns regarding toxicity.

## COMMITTEE'S CONCLUSIONS

Having carefully reviewed the record in this matter, the Committee concludes, for the reasons set out below, that no further action is warranted against Dr. Olivieri.

The Committee was assisted in its review of this matter by an independent opinion provided by a panel of physicians holding senior academic positions, with expertise in paediatrics and thalassemia, liver pathology, clinical trials methodology, and bioethics. The panel thoroughly reviewed the College's investigative file, including correspondence from the MAC, Dr. Olivieri, other concerned parties, and all records and reports submitted in connection with this matter. In reaching its decision in this complaint, the Committee has relied on the analysis and conclusions arrived at by this highly qualified and experienced panel, which concluded that Dr. Olivieri did not fall below a reasonable standard of care in any of the areas of concern raised in this complaint.

### *Continued Administration of L1*

The panel concluded that Dr. Olivieri ceased to administer L1 in a timely and expedient way, and in a manner which was in the best interests of her patients. The panel based its conclusion on the following:

- Dr. Olivieri promptly set up meetings with her patients and informed clinical personnel;
- L1 was likely a better alternative than no treatment for many patients (alternative therapy arrangements could not be made immediately due to logistics);
- the L1 toxicity concern was liver fibrosis, which progresses slowly;
- the number of patients on L1 after January 22, 1997 was small; and
- the patients' parents made informed decisions regarding remaining on the drug.

The Committee concurs with the panel in finding that use of the drug was terminated in a timely and expedient fashion, in the best interests of Dr. Olivieri's patients. The Committee notes that even in the presence of the potential for slowly developing hepatic fibrosis, the risk of no treatment was likely as great. It would appear that the risk that the patients were facing from continued use of L1 was not one of acute toxicity, and that there was therefore time to co-ordinate a safe and orderly transition to the standard treatment.

In short, the Committee is of the opinion that Dr. Olivieri acted reasonably and appropriately in the manner in which she terminated the use of L1 in her patients after learning of the potential toxicity of the drug.

***Liver Biopsies***

The panel felt that the concern that Dr. Olivieri failed to meet a reasonable standard of practice in ordering liver biopsies was also not supported, for the following reasons:

- frequent liver biopsies were consistent with Dr. Olivieri's practice and are becoming more the standard of care;
- if she had not performed the biopsies, the parents would have questioned why she had not done so, due to her established practice and the concerns of hepatic toxicity/lack of efficacy that had been raised regarding L1;
- if disease progression was noted, additional therapy in the form of more aggressive forms of deferoxamine was available; and
- the risks associated with liver biopsies were very low.

Once again, the Committee concurs with the conclusion of the panel in this regard. The Committee notes specifically that frequent biopsies are the standard in monitoring patients suffering from conditions such as Thalassemia. And, as also pointed out by the panel, the current risks associated with biopsies of this sort are relatively low.

The Committee is of the opinion that Dr. Olivieri's judgment in advising patients to undergo biopsies was not only reasonable, but commendable in the circumstances.

***Information to Department Chief and Co-workers***

The panel concluded that Dr. Olivieri appeared very concerned about notifying all of the appropriate people, and was diligent in communicating and publishing her data. Its conclusion was based upon the following:

- Dr. Olivieri adequately and appropriately informed the clinical staff and her co-workers of her concerns informally;
- the time frame for communicating the toxicity concerns was very compressed;
- her staged disclosure was appropriate in view of her legal advice;
- formal notification of her chief of staff would not have been the usual standard of practice in most medical departments, and there was no evidence that the University of Toronto had a policy demanding such notification; and

- given the highly charged environment, it would be difficult to assign her responsibility for poor communication.

The Committee agrees with the conclusion reached by the panel on this issue. The Committee is of the opinion that staged disclosure was appropriate in this case, and that Dr. Olivieri communicated diligently with those who required information regarding her concerns.

## DISPOSITION

For the reasons set out above, no action will be taken with respect to this matter.

PANEL MEMBERS: November 2001

MR. G. DEMERY - Public Member - Chair, Complaints Committee
G. H. BOND, MD
O.S. KOFMAN, MD
O.J. MANDEL, MD
D.M.C. WALKER, MD
MR. J. MARTEL - Public Member