Commentary

On selected aspects of the Report of the Canadian Association of University Teachers Committee of Inquiry on the Case Involving Dr.Nancy Olivieri, the Hospital for Sick Children, The University of Toronto and Apotex Inc.

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December, 2001

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December 19, 2001

Mr. Alexander Aird
Chair, Board of Trustees
The Hospital for Sick Children
Toronto, Ontario

Dear Mr. Aird:

We submit herewith a commentary on selected aspects of the recent report of the Committee of Inquiry established by the Canadian Association of University Teachers to look into the case involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto and Apotex Inc.

In our December 1998 report arising from the review we conducted on behalf of the Board of Trustees of the HSC pertaining to the controversy involving Dr. Olivieri, the HSC and Apotex Inc., we made the following undertaking:

If at any time we come into possession of evidence which contradicts any material aspect of our Report we feel honor-bound to report that to the Board of Trustees and to make that report public.

This commentary, and the agreement of the Board to make the commentary public by posting it on the HSC web-site, is intended to fulfill that undertaking, insofar as the CAUT Report is concerned, and is also intended to take up certain general matters concerning the development of sound policies and procedures for the regulation of clinical investigation.

For present purposes we define the phrase "evidence which contradicts any material aspect of our Report" as meaning findings in the HSC Report that are contradicted by corroborated evidence brought to light by the CAUT Inquiry, that are relevant to the nature and purpose of the HSC Review and Report and that warrant an alteration of the conclusions or recommendations contained in that Report. We found only one such item of evidence.

The Board should note that the commentary does not cover matters in the CAUT Report that were considered to be contextual from the perspective of the HSC Review (e.g. personnel actions and grievances arising from them, disputes between the University and Dr. Olivieri, disputes between Apotex and Dr. Olvieri about the details of trial management and data provision, etc.). We express no opinion on the CAUT Report's representations of fact or conclusions related to

these issues at this time. The commentary also does not address those aspects of the CAUT Report dealing with issues arising from events that took place after the HSC Review was completed except where, as in the case of Dr. Koren, they have a bearing on the evaluation of facts and circumstances antedating the completion of our Report.

Please let us know if there are any aspects of the commentary about which the Board wishes to have clarification or further information.

Dr. Arnold Naimark
University of Manitoba

Prof. Bartha Maria Knoppers
Université de Montréal

Dr. Frederick H. Lowy
Concordia University

Commentary on the Report of the CAUT Committee of Inquiry on the Case of Dr. Olivieri et al.

Biographical Sketches of Reviewers

Professor Bartha Maria Knoppers
BA, MA, PhD, LLB, DEA, BCL, DLS, LLD

Professor Knoppers is Professor at the Faculté de droit, Université de Montréal, Senior Researcher at the Centre de recherche en doit public and counsel to the firm of Borden, Ladner, Gervais. Her current research and teaching concentrates on genetics, law and ethics, children and the law, pharmacogenomic research and consent and DNA/tissue banking.. Prof. Knoppers is the Chair, International Ethics Committee of the Human Genome Project, and a member of the International Bioethics Committee of UNESCO that drafted the *Universal Declaration on the Human Genome and Human Rights.* She was a member of the standing Committee on Ethics, Medical Research Council of Canada. She is recipient of The Medal of the Quebec Bar, the Heritage Visiting Scientist Award of the Alberta Heritage Foundation for Medical Research and was named Scientist of the Year by Radio Canada. Prof. Knoppers has published extensively and serves on a wide range of boards, institutes and associations in Canada and abroad, and currently holds a Canada Research Chair

Dr. Frederick H. Lowy
BA, MD, CM, LLD (Toronto), FACP, FRCP (C)

Dr. Lowy is currently Rector of Concordia University. He is a former Dean of the University of Toronto's Faculty of Medicine and the founder and former Director of the University of Toronto's Centre for Bioethics. Dr. Lowy was a Professor of Psychiatry and Department Chair at the University and Director and Psychiatrist-in-Chief of Toronto's Clarke Institute of Psychiatry. Dr. Lowy served as the first Chair of Canada's Tri-Council Working Group on Ethics of Research with Human Subjects and on the Royal College of Physicians and Surgeons Committee on Ethics, the Medical Research Council of Canada's Standing Committee on Ethics, and the National Council on Bioethics in Human Research. Dr. Lowy has served as a hospital trustee, Vice-Chair of the Metro Toronto District health Council Restructuring Committee and as chair of an Ontario government inquiry into the pharmaceutical industry.

Dr. Arnold Naimark
OC, BSc (Med), MSc, MD, LLD (Mt. All, Toronto), FRCP (C), FRSC

Dr..Naimark is Professor of Medicine and Physiology at the University of Manitoba and Director of the Centre for the Advancement of Medicine. He is a former Chair of the Department of Physiology, Dean of the Faculty of Medicine and President and Vice-Chancellor of the University of Manitoba. Dr. Naimark has served as President of the Canadian Physiological Society, the Canadian Society for Clinical Investigation, the Association of Canadian Medical Colleges, the Association of Universities and Colleges of Canada and as Chairman of the Association of Commonwealth Universities. Dr. Naimark is Founding Chairman of the Canadian Health Services Research Foundation and of the Canadian Biotechnology Advisory Committee, a Director of the Health Sciences Centre, Winnipeg, and the Research Council of Canadian Institute for Advanced Research. He is recipient of the G. Malcolm Brown Award of the Royal College of Physicians and Surgeons and Medical Research Council of Canada, the Osler Award, the J. Wendell MacLeod Award, the Distinguished Service Award of Ben Gurion University and the Symons Award of the Association of Commonwealth Universities.

Definitions

Apotex	means Apotex Inc., a manufacturer of pharmaceuticals.
Board	means the Board of Trustees of The Hospital for Sick Children in Toronto
CAUT	means the Canadian Association of University Teachers.
CAUT Inquiry	means the inquiry into the case involving Dr. Nancy Olivieri, The Hospital for Sick Children, the University of Toronto and Apotex Inc. established by the Canadian Association of University Teachers (CAUT).
CAUT Report	means the Report of the CAUT Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, The Hospital for Sick Children, the University of Toronto and Apotex Inc. published in October, 2001.
HSC	means The Hospital for Sick Children in Toronto.
HSC Report	means the report titled "Clinical Trials of L1 (Deferiprone) at The Hospital for Sick Children in Toronto - A Review of Facts and Circumstances". The report was published December, 1998 and the archival version in January, 1999.
HSC Review	means the review of the clinical trials of L1 (Deferiprone) at The Hospital for Sick Children in Toronto established by the Board of the HSC in 1998.
Inquiry Committee	means the Committee of Inquiry established by the CAUT consisting of Prof. Jon Thompson, Dr. Patricia Baird and Prof. Jocelyn Downie.
L1	means the orally active iron chelator 1,2-dimethyl-3-hydroxipyridin -4-one (also known as "deferiprone")
REB	means the Research Ethics Board of the Hospital for Sick Children
Review Panel	means the Panel of Reviewers established by the Board of the HSC consisting of Dr. Arnold Naimark, Prof. Bartha Maria Knoppers and Dr. Frederick H. Lowy.
University	means the University of Toronto

Summary

In its 1998 HSC Report on the controversy surrounding clinical trials of the drug L1 and involving Dr. Nancy Olivieri, the Hospitals for Sick Children and Apotex Inc., the HSC Review Panel stated:

> *"If at any time we come into possession of evidence which contradicts any material aspect of our Report we feel honor-bound to report that to the Board of Trustees and to make that report public."*

The commentary summarized here (the "Commentary"), and the agreement of the Board of Trustees to make it public by having it posted on the HSC web-site, fulfills that undertaking. The Commentary deals only with those aspects of the CAUT Report bearing on the conclusions and recommendations of the HSC Report issued in December 1998. It does not deal with matters outside the scope of the 1998 HSC Review, nor does it deal with events occurring after the release of HSC Report except where, as in the case of Dr. Koren, they have a bearing on the evaluation of facts and circumstances antedating the completion of our Report. The Commentary also does not cover matters in the CAUT Report that were considered to be contextual from the perspective of the HSC Review (e.g. personnel actions and grievances arising from them, disputes between the University and Dr. Olivieri, disputes between Apotex and Dr. Olvieri about the details of trial management and data provision, etc.). We express no opinion on the CAUT Report's representations of fact or conclusions related to these issues at this time.

In the following summary the numbers in boldface and parentheses refer to the numbered sections of the Commentary.

The CAUT Inquiry and the HSC Review - General Observations (Sections 1-7)

In this part of the Commentary we note:

i the differences in the mandate of the CAUT Inquiry and the HSC Review. Unlike the CAUT Inquiry, the HSC Review was not intended to be a forum for the adjudication of scientific disagreements, of personnel issues and grievances or disputes between Dr. Olivieri and Apotex. The HSC Review was conducted for prospective and constructive purposes whereas the CAUT Inquiry appears to have been, in large measure, a grievance investigation designed to find fault, lay blame and call for redress.

ii the differences in timing of the CAUT Inquiry and the HSC Review. The CAUT Inquiry considered events that occurred after the publication of the HSC Report. Although the HSC Review Panel had no involvement with any of these *post facto* matters, it is clear that the CAUT Inquiry Committee viewed the HSC Report through the prism of these later

events.

iii the relative "independence" of the CAUT Inquiry Committee and the HSC Review Panel. The Inquiry Committee was no more independent than the Review Committee. Both were constituted unilaterally and both were limited because of non-participation of key individuals. The HSC Review was open to all interested parties, the CAUT Inquiry was not. We take particular note of the fact that the CAUT Inquiry Committee did not invite any of the Review Panel members to meet with it to provide clarification or other assistance about matters concerning the HSC Review that seem to have perplexed the Inquiry Committee.

The Role of Dr. Koren (Sections 8.1 and 8.2)

Dr. Gideon Koren, a key figure in the L1 trials and related events was found, after the release of the HSC Report in December of 1998, to have been the author of anonymous abusive correspondence directed to colleagues who were supportive of Dr. Olivieri. In this section of the Commentary consideration is given to the following questions: To what extent did the HSC Review Panel rely on Dr. Koren's input? To what extent did the evaluation of this input depend on Dr. Koren's trustworthiness? To what extent did Dr. Koren's input influence the main conclusions of the HSC Review? After considering each of these questions, the Commentary notes that:

iv when the references to information provided by Dr. Koren for which he was the sole source are removed from the HSC Report, the main conclusions and recommendations of the Report remain unimpaired.

v there is one document identified in the CAUT Report of which the HSC Review Panel was unaware. It was not provided to the Panel by either Dr. Olivieri or Dr. Koren. It showed that Dr. Koren was informed about the issue of liver toxicity of L1 earlier than he had represented to the Review Panel. The significance of this fact is addressed below.

Reporting of Liver Toxicity of L1 to the Research Ethics Board (Section 9)

The question of the obligation to report the finding of serious adverse reactions to the REB observed in the course of administering an experimental drug to patients, is one of the central issues of the Olivieri case. The Commentary addresses the argument put forward by the CAUT Inquiry Committee to the effect that there was no obligation on the part of Dr. Olivieri to report her findings of liver toxicity of L1 to the REB. The Commentary demonstrates that:

vi the HSC Review Panel's finding that there was a sufficient basis for reporting the finding of L1 liver toxicity to the REB remains valid.

vii the CAUT Inquiry Committee was incorrect in its conclusions, because of incomplete consideration of all of the available evidence.

viii the CAUT Inquiry Committee has taken far too narrow a view of the obligations of clinical investigators - a view that is an inadequate guide to ethical clinical behavior.

ix contrary to the allegation in the CAUT Report that the HSC Review found Dr. Olivieri to be "negligent". The HSC Review Report did not state that Dr. Olivieri was negligent nor did the Panel have any reason to believe that she was negligent.

With respect to Dr. Koren's obligations, the Commentary discusses the import of the document (referred to in para *v* above) that shows he had received information about liver toxicity earlier than he had acknowledged. The Commentary concludes that:

x notwithstanding the fact that Dr. Olivieri was the practitioner in clinical charge of the patients receiving L1, Dr. Koren, upon learning of her conclusion about the toxicity of L1, should have promptly inquired of Dr. Olivieri if she had reported the matter to the REB and, if she had not, Dr. Koren should have done so promptly even if he disagreed with her analysis.

The Matter of Liver Biopsies (Section 10)

The question of whether Dr. Olivieri was justified in continuing to have liver biopsies performed on patients receiving L1 after she had concluded that the drug should not be used in the treatment of thalassemia has been a matter of debate and disagreement both before and after the HSC Review was conducted and its Report released. The CAUT Inquiry Committee argues that liver biopsies are used as a standard practice in the care of patients with thalassemia. The Commentary notes that:

xi the issue is not whether liver biopsies are part of clinical practice but rather whether the patients who "remained on the study" were exposed to an increased frequency of liver biopsies compared to those who did not participate in the trials and whether that was acceptable even though a conclusion had been reached that the drug should not be administered on grounds of toxicity.

xii the essential point was and is that questions such as the one about the use of liver biopsies are clearly of a kind that should be considered by an REB upon having been informed of an unexpected risk by a clinical investigator acting in a timely fashion.

When Is a Trial Not a Trial? When is a Protocol Not a Protocol? (Sections 11.1-11.8, 12, 13)

The CAUT Report takes the position that Dr. Olivieri had no obligation legally or "by policy and practice" to report the finding of liver toxicity of L1 to the REB on the grounds that after May 24,

1996, the date upon which when Apotex terminated their sponsorship of the L1 trials, there were no trials and no subjects - only patients receiving L1 under Health Canada's Emergency Drug Release Program. The Inquiry Committee also alleges that the HSC Review relied on faulty testimony by Dr. Hugh O'Brodovich (Chief of Pediatrics) and Dr. Aideen Moore (Chair of the REB) in reaching its conclusions. Our Commentary demonstrates that:

xiii the contention of the CAUT Inquiry Committee that the HSC Review Panel formed its views on this issue through reliance on statements made to it by Dr. O'Brodovich and Dr. Moore is incorrect. We took all documents provided to us into account, including those from several persons other than Dr. O'Brodovich and Dr. Moore, and including Dr. Olivieri, who were directly involved with the circumstances surrounding the administration of L1 to patients after May 24, 1996.

xiv there is clear evidence, much of it originating with Dr. Olivieri herself, indicating that studies (investigations, research, trials) continued after May 24, 1996;

xv the CAUT Inquiry Committee erred in relying on declarations that the trials were terminated. What matters is not who declares what, but what was actually given and done to patients and under what circumstances. From the patients/subjects perspective, trials of L1 were in effect until the interventions and procedures, for which REB approval was required in the first instance, were no longer being carried out.

xvi the CAUT Inquiry Committee's categorization as either subjects or patients is a false dichotomy. Clearly a person can be both a subject and a patient. Moreover, to argue as the Committee does that the source of an experimental drug, or the circumstances under which it is obtained, determines whether a trial is being conducted is obviously wrong. The subjects in the LA-03 trial - a trial approved by the REB pursuant to an application by Drs. Olivieri and Koren - were, from its inception, patients receiving L1 on compassionate grounds through an emergency release mechanism.

xvii unlike the CAUT Inquiry Committee, we take the view that clinical investigators have ethical obligations to act in the best interests of their patients/subjects even in the absence of legal or contractual obligations to do so and that one of these ethical obligations is to subject one's own judgment to peer review where that would be in the interests of patients/subjects.

The CAUT Inquiry Committee contends that because Apotex declared the L1 trials to be terminated the protocols associated with them were "inactivated" *ipso facto*. We note that:

xviii the CAUT Inquiry Committee's contention is wrong. A protocol is a plan for a course of treatment and/or a clinical investigation. The protocol for a clinical trial is not only described in a specific document signed by the investigators and the sponsor, it is also described in layperson's terms in patient information and consent forms, such as those

submitted for approval to the REB by Dr. Olivieri after May 24, 1996.

Missing Documents (Section 14)

The CAUT Report identifies 16 documents characterized as "missing" from the HSC Review's list of some 506 documents and said to be material. The Commentary distinguishes between documents that are material to the nature and purpose of the HSC Review (in the sense that they warrant an alteration of any of the findings, conclusions and recommendations in the HSC Report) and those that are material to other aspects of the Olivieri case covered by the CAUT Inquiry. The Commentary notes that:

xix the most significant of the missing documents, in terms of materiality, are relevant to issues that the HSC Review was not designed to adjudicate (e.g. disputes between Dr. Olivieri and Apotex as to the issues of confidentiality and interpretation of data) and therefore have no bearing on the conclusions and recommendations in the HSC Report;

xx others are purported to contradict the HSC Report but, as noted above, do not.

xxi some of the documents provide information that was available to the HSC Review from other sources or reinforce conclusions drawn by the HSC Reviewers.

Two documents, had they been made available to the HSC Review, would have changed the representation of fact in the HSC Report. One of these is not material in that it has to do with the provenance of a meeting between Dr. Olivieri and officials in the Health Protection Branch of Health Canada. The other, as noted earlier, is more significant. It establishes that Dr. Koren received information about the liver toxicity of L1 sooner than he stated in other correspondence.

Findings and Recommendations of the CAUT Report (Sections 15-21)

The following points are made in the section of the Commentary dealing with the findings in the summary section of the CAUT Report pertaining to the HSC Review.

xxii The findings in the CAUT Report bearing on the nature, scope and intent of the HSC Review are incorrect in that the HSC Review is criticized for not investigating or examining matters that it was never intended to investigate and examine.

xxiii The CAUT Report's insistence in interpreting declarations by Apotex, Dr. Olivieri and others that the "L1 trials were terminated" on May 24, 1996 to mean that no studies, investigations or research on L1 involving patients were carried out after that date is based on incorrect or incomplete consideration of all of the evidence available.

xxiv The findings in the CAUT Report, concerning the evidence upon which the HSC Review

based its findings, are incorrect.

xxv The CAUT Report makes a point of the fact that some of the persons interviewed during the HSC Review did not provide some important and relevant information but, astonishingly, the CAUT Report says nothing about one of the most important issues related to the HSC Review; namely, that Dr. Olivieri et al. withheld information from the Review and did so in a deliberate attempt to diminish the credibility of the Review.

xxvi The CAUT Report states that: "The adverse findings against Dr. Olivieri in the reports of the Naimark Review and HSC's Medical Advisory Committee are incorrect and based on incomplete, incorrect and false testimony." As the foregoing observations and discussion indicate, this statement is itself incorrect, at least as far as the HSC Report is concerned. The HSC Review Panel had completed its work before the reference of matters to the MAC. The HSC Report drew no conclusions and made no recommendations about the pursuit of any matters by any individual or body within the HSC or elsewhere other than those pertaining to the future development of policies and procedures.

The following observations deal with the recommendations of the CAUT Inquiry Committee insofar as they relate to teaching hospitals in general and the HSC in particular, since the HSC Review was not intended to, and did not, make recommendations on specific personnel issues.

xxvii The recommendations in the CAUT Report concerning teaching hospitals generally (pertaining to the review and administration of research contracts, the role of research ethics boards and their procedures, and other policy matters) are in accord with the recommendations made in the HSC Report with respect to the HSC specifically.

xxviii the CAUT Committee's recommendations did not address adequately the roles and responsibilities of clinical investigators. We call for a significantly increased emphasis in national and institutional regulations and guidelines on the responsibilities of investigators to act ethically even in the absence of contractual or regulatory obligations and to be fully accountable to appropriate peer-review bodies as part of a general commitment to quality assurance and to the safety and welfare of subjects of research. We also state that institutional mechanisms must be in place to support investigators who act in good faith in meeting these responsibilities.

Supplementary Recommendations of the HSC Review Panel (Sections 22-25)

The HSC has devoted a good deal of time and effort to reforming its policies pertaining to research and related matters, taking into account the recommendations of the HSC Report. Some matters remain to be addressed. As a result of our analysis of the CAUT Report we have been prompted to reinforce and supplement the recommendations we made in the December 1998 HSC Report. We recommend that:

xxix our earlier recommendation that the HSC develop comprehensive policies and procedures pertaining to the role, appointment, evaluation and termination of heads of programs be expedited;

xxx the recently established policies on research, be accompanied by carefully worked out regulations and guidelines dealing with standard operating procedures and methods to deal with exceptional circumstance. This is essential so that there be no doubt in the minds of clinical investigators and other researchers about their obligations.

xxxi the HSC establish definitions and a lexicon of standard usage pertaining to terms used to describe various aspects of clinical research including clinical trials and that the definitions and lexicon be kept under continuing review and refinement.

xxxii policies, procedures, rules and regulations related to human subjects, including patients, be drafted with a subject/patient-centered focus rather than a researcher-centered focus

xxxiii the HSC establish such a patient-centered regulation that clearly sets out the obligations of investigators involved in clinical trials to report adverse findings to the REB that are discovered after an external sponsor or an investigator declares a trial or trials to have been terminated. We provide an example of such a regulation.

Commentary

Preamble

In October 2001, the CAUT published the report of its Committee of Inquiry into the Olivieri case. The CAUT Report claims that the 1998 HSC Review erred in some of its findings either because it was not in possession of material facts or was misinformed by certain individuals. In its 1998 HSC Report, the Review Panel stated:

> *If at any time we come into possession of evidence which contradicts any material aspect of our Report we feel honor-bound to report that to the Board of Trustees and to make that report public.*

This commentary, and the agreement of the Board to make the commentary public by posting it on the HSC web-site, is intended to fulfill that undertaking. For present purposes we define the phrase "evidence which contradicts any material aspect of our Report" as meaning findings of fact represented in the HSC Report that are contradicted by corroborated evidence brought to light by the CAUT Inquiry and are material to the nature and purpose of the HSC Review and Report . We judged such new evidence to be material if it would warrant an alteration of any of the conclusions or recommendations contained in the HSC Report.

The commentary identifies items of documentation cited in the CAUT Report that are purported to contain new information but do not, items of documentation said to be missing from the HSC Review database that are not and items purported to be material that are not, because they are not relevant to the nature and purpose of the HSC Review or to the conclusions and recommendations in the HSC Report.

It should be noted that the commentary does not cover matters in the CAUT Report that were considered to be contextual from the perspective of the HSC Review (e.g. personnel actions and grievances arising from them, disputes between the University and Dr. Olivieri, disputes between Apotex and Dr. Olvieri about the details of trial management and data provision, etc.). This should not be taken to mean that we accept all of the representations of fact or conclusions derived from them as being in accord with our own findings. Additional comments may be provided to the Board on these contextual issues after further reflection on the CAUT Report. It should also be noted that the commentary does not address those aspects of the CAUT Report dealing with issues arising from events that took place after the HSC Review was completed; including the reference of certain matters to the Medical Advisory Committee, the events leading up to and following the negotiation of an agreement as to her continuing role, involving Dr. Olivieri, the HSC and the University, matters involving Dr. Koren except where they have a bearing on the evaluation of facts and circumstances antedating the completion of the HSC Report.

The CAUT Inquiry and the HSC Review - General Observations

1. In response to the controversy involving Dr. Olivieri, the HSC and Apotex, the HSC administration had proposed a review of the HSC's policies and procedures related to externally sponsored clinical research. However, having considered and accepted the argument that such a review required an understanding of the issues raised by the controversy, the Board decided on a two-stage process; the first stage being a review of the facts and circumstances giving rise to the controversy and a second stage being the process of revision of policies and procedures in accordance with the outcome of the first stage. The first stage, referred to here as the HSC Review (and referred to in the CAUT Report as the "Naimark" Review) as stated clearly in the HSC Report, ***the Review ".. was not intended to be a forum for either the resolution of scientific disagreements or for the arbitration of personnel issues and grievances."***

   The primary focus of the HSC Review was on the disputes between Dr. Olivieri and HSC. Other disputes (between Dr. Olivieri and Apotex, between Dr. Olivieri and members of the staff and administration of HSC concerning matters unrelated to the L1 trials, between Dr. Olivieri and the University), although clearly important, were regarded as contextual

2. A key difference between the HSC Report and the CAUT Inquiry is that the former only deals with events that took place prior to its publication in early December 1998 while the latter also deals with events after that date including, notably: the initiation of an inquiry by the Medical Advisory Committee pursuant to a reference from the Board, personnel actions involving Dr. Olivieri and her colleagues, the negotiation of an agreement, involving Dr. Olivieri, the Hospital and the University and events arising from its implementation, the coming to light of actions by Dr. Koren resulting in his removal from certain positions and a flurry of grievances and lawsuits. ***Although the HSC Review Panel had no involvement with any of these* post facto *matters, it is clear that the CAUT Inquiry Committee viewed the HSC Report through the prism of these later events.***

3. As we understand it, the CAUT Inquiry was initiated in response to complaints or grievances brought forward by Dr. Olivieri or on her behalf by the University of Toronto Faculty Association. Unlike the HSC Review, which was conducted for prospective and constructive purposes, the CAUT Inquiry appears to have been, in large measure, a grievance investigation designed, in part at least, to find fault, lay blame and call for redress. We understand that Dr. Olivieri and some of her colleagues joined the University's Faculty Association specifically to engage the Association's support in her ongoing grievances with the Hospital, University and Apotex.

4. Since the purpose of the HSC Review was to point the way to improvements in policies and procedures the Review Panel examined documentary evidence primarily from the

perspective of its relevance to policies and procedures. Thus, as the HSC Report states, in discussing the matter of documentation, "***..the most important point we had to consider was not whether we had every last bit of documentary evidence available, but rather whether we had enough information to allow us to identify the key issues which, in our opinion, should be pursued in the next phase of the Review process."***

By contrast, the CAUT Report tends to portray and evaluate documentation and evidence primarily on the basis of its contribution to the adjudication of disputes: between Dr. Olivieri and Apotex, between Dr. Olivieri and the HSC, between Dr. Olivieri and the University and between Dr. Olivieri and one or more colleagues. This is not to suggest in any way that grievances and disputes should not be adjudicated by appropriate means. However, ***for the CAUT Inquiry Committee to criticize the HSC Review Panel for not doing what the HSC Review was explicitly not intended to do (a fact which the CAUT Committee knew or should have known) is unfair and unwarranted.***

5. The CAUT Report makes much of the provenance of the Inquiry Committee - as if it were free of the limitations of the HSC Review. Although, Dr. Olivieri et al., in a letter to the HSC Review Panel dated 20 November 1998, stated:

> *"Because the "Naimark review" has been constituted unilaterally by the Board of Trustees to 'examine' this matter, we cannot in good conscience impart credibility to it by our participation. We nonetheless continue to seek a full, independent, open, consultatively appointed true inquiry into the serious issues that surround this affair."*

and, although Dr. Olivieri has expressed satisfaction with the CAUT Report, in fact ***the CAUT Inquiry Committee was also constituted unilaterally, was no more independent than the HSC Review Panel and was not open.*** [1] The CAUT Report, in its appendices, reproduces selected items of correspondence to and from Dr. Arnie Aberman (former Dean of Medicine of the University). A communication from Dr. Aberman to Prof. Jon Thompson on December 3, 1999, bearing on the independence of the CAUT Inquiry, was not reproduced. In that communication, Dr. Aberman notes:

[1] The CAUT Report states on page 281 that "Dr. Naimark had raised money from Apotex while President of the University of Manitoba". This is misleading.. The term "raised money" means "to solicit or collect money". Dr. Naimark did not solicit or collect money from Apotex while President of the University. Any donations from Apotex to the University were made without his involvement. To imply that Dr. Naimark was somehow less independent than say Professor Jon Thompson (who headed an important standing committee of the CAUT, the body that appointed him as Chair of Inquiry Committee) is at the very least unwarranted.

> "*...CAUT, and its alter ego UTFA* [University of Toronto Faculty Association]*, have, as is their right, vigorously expressed their position on the Olivieri case and cannot credibly claim to be impartial. To "ensure independence" (your words) of the Committee of Inquiry, you sought to change the way your report will be handled, to muzzle CAUT with respect to advocacy on the Olivieri case and to bar UTFA officers from participating in CAUT deliberations on the Olivieri case. However the Jim Turk* [Executive Director of CAUT] *memo specified that although CAUT will not play an advocacy role UTFA will..."*

Dr. Aberman's communication then goes on to outline several connections between CAUT and UTFA (individuals holding positions in both organizations, the CAUT policy on Inquiry Committees that provides that the CAUT and the local Faculty Association work together on complaints, an understanding that the Committee of Inquiry would prepare a final report only after submitting a draft copy to the CAUT Academic Freedom and Tenure Committee [AF&T] for its comments). Dr. Aberman also expressed the view that: "...It is simply impossible to separate CAUT, UTFA, the AF&T Committee, and the Committee of Inquiry with respect to the Olivieri case." The communication also notes that a member of the Inquiry Committee (identified by Professor Jon Thompson in later correspondence as Professor Jocelyn Downie) had "injected herself into the Olivieri case" prior to being appointed to the Inquiry Committee. Dr. Aberman also observed that: "Bill Graham's [President of both CAUT and UTFA] characterization of the Naimark Investigation – 'we [CAUT] believe that the process set up is a flawed one and creates a reasonable apprehension of bias, which will certainly affect the credibility of the Naimark report' - better describes the CAUT Committee of Inquiry".

The CAUT Report (page 53) states that Dr. Patricia Baird declined Dr. Naimark's invitation to assist him in the review of the L1 controversy because she did not feel that the arrangement proposed gave her sufficient independence. Since the arrangement proposed was the same one that applied to Prof. Knoppers and Dr. Lowy, who accepted appointment as Associate Reviewers, it is important to record what the "arrangement" in fact was. The Reviewers were advised that, while the mandate of the HSC Review did not provide for separate, independent reports or sections of the Review Report, it did not prevent the inclusion of annotations prepared by any of the reviewers (with attribution) identifying material points of disagreement about any matter pertaining to the Review.

The Review Panel invited any and all interested parties to participate in the review process in addition to extending special invitations to key individuals - but the CAUT Inquiry Committee selected whom it wished to hear from. ***It is surprising that - in view of the many instances in the CAUT Report in which the authors speculate or wonder about why the HSC Review Panel said or didn't say something, why it did or did not refer to***

particular items of information, why it pursued or did not pursue particular lines of investigation, or why it arrived at or did not arrive at particular conclusions - the Inquiry Committee did not invite any of the Review Panel members to meet with Inquiry Committee to provide clarification.

6. Dr. Olivieri et al. refused to participate in the HSC Review and deliberately withheld what they regarded to be critically important information. HSC and University officials refused to participate in the CAUT Inquiry.

7. The CAUT report contains information that was unknown to the HSC Review Panel prior to the release of its Report in December 1998. Some of that information became generally known through the media after the HSC Review Panel submitted its Report. (e.g., Dr. Koren as the author of anonymous letters). Other items of important information cited in the CAUT Report were either inadvertently or deliberately withheld from the HSC Review. Some of these other items are relevant to the HSC Review because they have a bearing on issues of policy and procedure. Others are important because they bear on matters of principle and ethics or provide additional insights into issues involved in disputes between and among the parties involved in the Olivieri case. In this commentary we are concentrating mainly on those relevant to the HSC Review.

The Role of Dr. Koren

8. The CAUT Report goes into considerable detail about Dr. Gideon Koren's role in the L1 trials, his relationship with Apotex and his relationship with Dr. Olivieri and her close supporters. With a few notable exceptions, most of the information pertaining to events prior to December 1998, cited in the CAUT Report, was known to the HSC Review Panel.

8.1 ***The Trustworthiness of Dr. Koren***

The revelation that Dr. Koren, despite initial denials, was proven to have written anonymous and abusive letters to colleagues came to our attention through reports in the media in late 1999. We considered the implications of those revelations concerning Dr. Gideon Koren for the findings and conclusions of the HSC Review.

The following comments speak to this matter with the following questions in mind: To what extent did the HSC Review rely upon Dr. Koren's input?; To what extent did the evaluation of this input depend on Dr. Koren's trustworthiness? To what extent did Dr. Koren's input influence the main conclusions of the Review? In commenting on these questions reference will be made to the archival version of the HSC Report dated January, 1999.

To what extent did we rely on Dr. Koren's input?

As a general context, we draw attention to the following quotation from page 4 of the Review Report.

> *As will be seen from the text of the Report and the reference list of documentation (supplemented substantially since the October 20, 1998 version), there is voluminous correspondence and other documentary material which antedates the period when the issue of an external review arose but covers the period of the L1 Clinical Trials and related matters. Much of this is correspondence to and from Dr. Olivieri. We also had the benefit of the identification of issues of concern in correspondence from Dr. Gallie and others. As readers of the Report will note, our findings are based almost entirely on the written record. We have not taken as established fact any matter represented to us that is not corroborated by documentary evidence.*
>
> *However, the most important point we had to consider was not whether we had every last bit of documentary evidence available, but rather whether we had enough information to allow us to identify the key issues which, in our opinion, should be pursued in the next phase of the Review process. We believe that to be the case.*

Dr. Koren was interviewed in person on one occasion and there were three telephone calls seeking clarification of the sequence of certain events or requesting documentation. Except as noted below, all of the documents provided to us by Dr. Koren were also provided to us from other sources.

The points in the Report at which observations are made based on information provided by Dr. Koren, and for which he was the sole source, are listed below.

- Page 20: Dr. Koren provided an account of the events leading up to the approach to Apotex as a potential sponsor of the studies on L1.

- Page 43: Dr. Koren provided a copy of a note to Dr. Olivieri dated December 18, 1996, inquiring about information he had received indicating that she had presented evidence of liver toxicity due to L1. He also provided a copy of a letter to Dr. Olivieri, dated February 8, 1997 expressing shock and dismay at Dr. Olivieri not informing him of her conclusions about the safety of L1. The CAUT Inquiry Committee reports that, based on testimony from Dr. Olivieri, "It is open to question whether these two letters were actually written."

- Page 77: Dr. Koren provided copies of letters he had written to Dr. Gallie concerning comments she had made to the press that he considered to be defamatory. We have seen no evidence indicating that these letters were either not written- or written and not sent or received.

- Page 102: The role of Dr. Koren in arranging for continuation of support by Apotex for research fellows following non-renewal of support for the L1 trials, and the concurrence of Dr. Olivieri in this, was described by Dr. Koren. The role of Dr. Koren in this regard has not been challenged or questioned.

- Page 102: The statement that Dr. Koren did not conduct studies pertaining to the safety of L1 independently of Dr. Olivieri. [2]

- Page 103: The statement that "Dr. Koren has not had any consulting contracts with Apotex" came from Dr. Koren.

- Page 138: The statement "No information was provided by Dr. Olivieri...to Dr. Koren...about this serious adverse reaction until inquiries were made of her in the latter part of February 1997" was based on information provided by Dr. Koren.

To what extent did the HSC Review Panel's evaluation of Dr. Koren's input depend on his trustworthiness?

The items of correspondence cited on pages 43 and 77 between Dr. Koren and Drs. Olivieri and Gallie respectively were cited as evidence of strained and deteriorating relationships (see page 43, 77 and 78 of the HSC Report) - a feature abundantly corroborated by other evidence the reliability of which is undisputed. Trustworthiness is of relevance with respect to the items cited from pages 102, 103 and 138 of the Report in that they are based on declarations by Dr. Koren himself. We have seen no evidence to indicate the statements on pages 102 and 103 are incorrect. However, let us suppose that, contrary to his declaration, Dr. Koren did receive consulting contracts from Apotex during the conduct of the L1 trials. This would have put him in the same position, with respect to the propriety of such contracts, as Dr. Olivieri who had a personal consulting contract with Apotex. If he had other personal contracts with Apotex following the L1 trials then he could be, or have been, in a potential conflict of interest in respect of any dispute between Apotex and Dr. Olivieri. See section 8.2 below with respect to the statement on page 138**.**

To what extent did Dr. Koren's input influence the main conclusions of the Review?

[2] The Inquiry Committee, on pages 154 and 155 of its Report, cites a computation and reference to a listing of grant funds that indicates to them that Dr. Koren continued to receive contract and/or grant funds from Apotex after May 1996. But the Committee acknowledges that the purpose for which the funds were ostensibly provided is not cited in the documentation available to them. The funds may have been used for ongoing toxicity studies in animals or for support of research fellows - both uses having been identified in the HSC Report. Further investigation is necessary before one can conclude that the Committee's imputations are justified.

The HSC Review dealt with four main topics: patient safety at the Hospital, conflicts of interest, release and publication of research information and support for investigators (the latter having been added by the Review Panel with the agreement of the Board).

In this connection it is important to reiterate the nature of the HSC Review. As stated in the HSC Report:

> *...(The Review) was not intended to be a forum for either the resolution of scientific disagreements or for the arbitration of personnel issues and grievances. However, an understanding of the role of these factors in the current controversy was seen as important in identifying their implications for the further development of the Hospital's policies and practices.*

To examine the extent to which Dr. Koren's input influenced the main conclusions of the HSC Review one need only strike out the foregoing references to Dr. Koren, and the information he provided, contained in the HSC Report. When this is done the main conclusions and recommendations of the Review remain unimpaired.

8.2 ***Information Provided to Dr. Koren About Liver Toxicity of L1***

The CAUT Report makes a special point of noting purported discrepancies between statements made by Dr. Koren, and cited in the HSC Report, as to when Dr. Olivieri provided information to Dr. Koren about liver toxicity of L1. The CAUT Report states that: "..he [Dr. Koren] had received Olivieri's report by February 8. Yet the [HSC] Report simultaneously [sic] accepted his information that he had received no information ***from*** Dr. Olivieri on this important matter until February 19." (our emphasis). There is in fact no discrepancy in these particular statements insofar as they refer to different proximate sources of the information, namely Apotex in the case of material received on February 8 and Dr. Olivieri on February 19.

But the CAUT Report goes further to indicate that Dr. Koren had (according to the "Humphrey Report") in fact received information about liver toxicity from Dr. Olivieri's counsel in early February 1997". The Humphrey investigation and report came many months after the HSC Report was published. The HSC Review Panel has not been provided with a copy of the transcript of Humphrey Report and therefore cannot comment on its findings or the representation thereof in the CAUT Report. More specifically, the CAUT Report states that information on liver toxicity was sent by Dr. Olivieri through their "joint legal counsel" to Dr. Koren on February 5, 1997. **No information was provided to the HSC Review by either Dr. Koren or Dr. Olivieri about a communication to Dr. Koren from Dr. Olivieri's legal counsel on February 5, 1997 concerning liver toxicity.**

The section of the CAUT Report in which the foregoing matters are discussed concludes with the question of why the HSC Review Report did not remark upon the fact that Dr. Koren did not convey concerns about liver toxicity of L1 to the REB when they came to his attention. This matter will be addressed in the following section of the commentary dealing with the matter of reporting liver toxicity of L1 to the REB.

Reporting of Liver Toxicity of L1 to the Research Ethics Board (REB)

9. The CAUT Report cites the question of the obligation to report to the REB serious adverse events observed in the course of administering an experimental drug to patients, as one of the central issues of the Olivieri case insofar as the HSC is concerned. We agree.

9.1 ***The CAUT Inquiry Committee Position***

The issue is addressed at many points in the CAUT Report and from a variety of perspectives all of which appear to be oriented toward making the case that:

- the period between the time when Dr. Olivieri et al. were ostensibly really convinced that L1 was associated with a high likelihood of causing liver toxicity and the time this was made known to the REB was significantly shorter than appears to be the case from the record and is therefore insignificant; and,

- in any case, Dr. Olivieri had no obligation legally or "by policy and practice" to report the finding of liver toxicity of L1 to the REB on the grounds that after May 24, 1996 (the date upon which when Apotex terminated their sponsorship of the L1 trials) there were no trials and no subjects - only patients receiving L1 under Health Canada's Emergency Drug Release Program.

On the basis of the latter contention, the CAUT Inquiry Committee criticizes Dr. Hugh O'Brodovich (Head of Pediatrics at HSC) and Dr. Aideen Moore (Chair of the REB during the period in question) for incorrectly informing the HSC Review that Dr. Olivieri had an obligation to communicate her finding of liver toxicity to the REB. The Committee concluded that the Review had relied on the input from Drs. O'Brodovich and Moore in arriving at its findings related to Dr. Olivieri. The Inquiry Committee also criticized the Review for using "language in a way that obscured important issues." ***As we will show, the CAUT Inquiry Committee was incorrect in its conclusions, and has taken far too narrow a view of the obligations of clinical investigators - a view that is an inadequate guide to ethical clinical behavior. Moreover, the CAUT Inquiry Committee has itself used language and advanced arguments that have obscured important issues and principles.***

9.2 ***The General Perspective of the HSC Review***

The HSC Review identified the REB as a key element of the "security system" in the HSC for the protection of children who are subjects of research. The REB is a critically important locus of responsibility and accountability for investigators. It provides for peer review of proposed research primarily focused on its ethical aspects and has as its primary focus the interests and welfare of the subjects. It also has an important role in monitoring and surveillance of ongoing research with special consideration being given to any material changes in the procedures affecting subjects and to unexpected findings including adverse reactions to any interventions.

The reason studies involving human subjects, and indeed animals generally, require approval of an independent body of peers is that all investigators face a fundamental potential conflict of interest. On the one hand they are interested, in varying degrees, in advancing knowledge and enhancing their reputations and scientific careers. On the other hand they have a duty of care with respect to the subjects of their studies. This duty of care is especially salient when the investigator is also acting as the subject's physician given the power and influence such investigators have over patients who are dependent on them. While it is true that the vast majority of clinical investigators act ethically and in good faith, the strength of the REB arrangement is that all investigators, no matter how expert and experienced, come under the same system of evaluation and oversight. It is not only important that the right things be done to protect the subjects' interests and welfare but that they are also seen to be done by others and especially by those who share both a concern and a duty to protect the subjects' interests and welfare (e.g., clinical supervisors and others with institutional responsibility).

When determining what constitutes proper conduct in a clinical setting, be it clinical care or clinical investigation, the essential criterion must be whether the conduct meets the test of being in the highest and best interests of the subjects.

9.3 ***The Particular Circumstances of the HSC Review***

9.3.1 ***With what aspects of patient safety did the HSC Review concern itself?*** In creating the mandate of the Review the Board included, among the topics it wished to be considered, facts and circumstances bearing on patient safety. As noted earlier the objective was to obtain guidance as to the development of improved policies and procedures pertaining to clinical investigation. Thus the Review Panel concentrated on what we referred to earlier as the "security system" and to note how the elements of the system came into play in the L1 case. In other words, our review dealt with patient safety as a generic issue and not with the safety or other aspects of the management of individual patients. We did not examine, nor did we make any finding or draw any conclusions about the safety or other aspects of the management of individual patients. Moreover, we did not examine nor did we make any findings or draw any conclusions about the clinical management of the HSC patients receiving L1 as a cohort. This point

was reinforced publicly by Dr. Lowy in response to a question about patient safety raised during the media conference held at the time of the release of the HSC Report.

9.3.2 ***What information did the HSC Review Panel rely on in considering the issue of the reporting of liver toxicity to the REB?*** The Panel found the following items of information to be most salient:

- In early December of 1996, Dr. Olivieri et al. became concerned about the potential liver toxicity of L1.

- Olivieri et al. prepared and submitted an abstract of a presentation on L1 in time to meet a January 10, 1997 deadline. The abstract entitled "*Exacerbation of Hepatic Fibrosis in Patients With Thalassemia Major Receiving the Orally Active Iron Chelator Deferiprone (L1)"* contained the following conclusion:

  > ***"These results suggest that, despite preventing an increase in liver iron, deferiprone exacerbates hepatic fibrosis and cirrhosis in patients with thalassemia major."*** (our emphasis)

- In the period between early December, 1996 and January 22, 1997, Olivieri et al. had investigated the evidence for liver toxicity sufficiently to prompt them to prepare a detailed report bearing the latter date to be submitted to the US Food and Drug Administration. The covering letter dated January 22, 1997 was captioned: *Exacerbation of hepatic fibrosis during chronic treatment of iron overload with the orally active iron cheater 1,2-dimethyl-3-hydroxipyridin-4-one (deferiprone, L1, CP20, DMHP)*. The letter was signed by Drs. Olivieri, Brittenham and Cameron (University of Toronto pathologist) and indicated that studies, in animals, of a compound closely related to L1, which revealed worsening of hepatic fibrosis with chronic administration, had prompted them to review the liver histology data in patients in the LA-03 trial. Olivieri et al. assessed the results of that review as follows (matter in boldface reflects our emphasis).:

  > *...despite preventing an increase in mean liver iron from continued transfusion, deferiprone exacerbates hepatic fibrosis and cirrhosis in patients with thalassemia major....This adverse effect of deferiprone therapy...was unanticipated and has not been recognized previously, in part because earlier studies did not include serial evaluations of hepatic histology....**The development of cirrhosis in a substantial proportion (37.5%) of our patients is likely to be a grave prognostic sign ... and is therefore a severe adverse effect**.... Because our long-term prospective study of deferiprone has been observational rather*

> *than a randomized, blinded clinical trial, and because the adverse effect on hepatic fibrosis has not been confirmed by challenge and dechallenge,* ***the relationship cannot be classified as definite. Nonetheless, in the absence of other established causes for the progression of hepatic fibrosis and in view of the lack of an increase in the mean hepatic iron, the relationship must be considered probable, and on clinical grounds, highly likely****.*
>
> *In our best clinical judgment, based on (i) the high proportion (87.5%) of patients in whom hepatic fibrosis worsened and (ii) the clinical and laboratory evidence now available* ***we conclude that deferiprone should not be used in the treatment of iron overload, even in patients unable or unwilling to use standard deferoxamine therapy****.*

- The finding of liver toxicity was not reported to the REB until after it was brought to the attention of Dr. Aideen Moore, Chair of the REB, by Dr. O'Brodovich.

- In considering the question of why Dr. Olivieri had not reported the finding of liver toxicity to the REB prior to that time, the HSC Review Report noted that on February 20, 1997, Dr. Olivieri wrote to Dr. O'Brodovich enclosing the full summary of data obtained to date which she and her colleagues planned to send to Dr. Fredd (of the USFDA) later that week. Dr. Olivieri stated that she and Dr. Brittenham had been cautioned by their respective legal counsel to forward the information to Apotex prior to notifying the Research Ethics Boards of either the Toronto Hospital or the Hospital for Sick Children. She outlined her plans for dealing with patients and then elaborated on the matter of legal advice as follows:

> *I have proceeded throughout this with the advice of my legal counsel. In June 1996, the decision was made by the administration of The Hospital for Sick Children not to provide me with the services of the Hospital's legal counsel with respect to the issue of lack of adequate control of body iron during deferiprone therapy [note: there is no documentation of a June, 1996 decision. This may be referring to the meeting of July, 18,1996]. I am informed that this decision was made because there was reported to be "scientific disagreement" with my interpretation of these findings. As above,* ***the only reason that the chairs of the research ethics boards were not informed prior to this time is that my legal counsel, provided through the Canadian Medical Protective Association, had recommended that Apotex***

Pharmaceuticals be informed prior to any other body… (our emphasis)

- The Review Panel noted that the REB had approved a "Renewal of Ongoing Clinical Research Studies" on July 1, 1996 (i.e., after the May 24th notice of "termination" issued by Apotex.) The Panel also noted that, when on February 20, 1997 she was called upon to do so by Dr. Moore of the REB, Dr. Olivieri provided information on how she proposed to deal with patients receiving L1 given her finding related to liver toxicity. On May 1, 1997, Dr. Olivieri replied to inquiries from Dr. Moore by providing information about the status of liver biopsy analysis.

9.3.3 ***What did the HSC Review Panel conclude about the issue of reporting the finding of liver toxicity to the REB and has that conclusion changed as a result of the CAUT Report?*** The HSC Review Panel found and reaffirms its finding that there was clearly a sufficient basis for reporting the finding of probable liver toxicity of L1 to the REB at the time the investigators had reached the conclusions which prompted them to develop a submission to the FDA. Indeed, it can be argued that the evidence presented in the abstract prepared to meet a January 10, 1997 deadline was a sufficient basis for reporting to the REB.

The HSC Review Panel concluded, on the basis of her own declarations, that Dr. Olivieri was placed in a conflict of interest situation when she came under legal threats from Apotex. The Panel observed: "Her [Dr. Olivieri's] understandable interest in protecting herself legally came into conflict with her obligation to report this serious adverse reaction to the Research Ethics Board. This caused her, on the advice of legal counsel, to delay reporting to the REB."[3] We reaffirm that conclusion. However, in the light of the arguments advanced in the CAUT Report, we must elaborate on the question of the nature of the obligation to report to the REB.

9.3.4 ***Why does the Review Panel state that Dr. Olivieri was obliged to report to the REB when the CAUT Report says she was not?*** The answer to this question lies in understanding the nature of the obligation to report serious adverse reactions to the REB in the particular circumstances of the administration of L1 to patients at the HSC. As Black's Law Dictionary points out the word obligation has "many, wide and varied meanings, according to the context in which it is used." Since this is not the occasion on which to embark on a legal or philosophical treatise on this subject, let us for argument's sake accept that there are two general kinds of obligation: legal (statutory or contractual) obligations and ethical obligations (i.e. "those which rest on ethical obligations alone and are not imposed or enforced by positive law"- [Black's Law

[3] The HSC Review Report, Archive Version, January 1999 p 103

Dictionary]). We argue both from the standpoint of ethics and the undertakings of the investigators involved. The ethical requirement is obvious. We noted earlier that the interests, safety and welfare of patients in general are best served when clinical investigators submit their judgments about the procedures to be applied to the subjects of clinical studies to a body of disinterested peers for assessment and guidance.

The CAUT Inquiry Committee argues only from the standpoint of legal or contractual obligations. The Committee claims that, since there were no provisions in policy or practice in place at the time of the emergence of the liver toxicity issue, that "required treatment with a drug [obtained] through EDR [Emergency Drug Release] be subject to ethics review."

We draw attention to the following obligation, accepted by Dr. Olivieri, when on April 29, 1990 she submitted an "Application for Studies Involving Human Subjects" (later approved) to the Human Subjects Review Committee of the HSC concerning the long-term efficacy trial of L1 (the "compassionate use trial"):

> ***"The principal investigator/unit director (where applicable) will assume full responsibility of the study as detailed in the protocol and will notify the human subjects review committee should any unexpected results or any detected or proposed departures from the study arise."***

It is of particular note that Dr. Olivieri herself did not advance the argument that she was not required to report to the REB. She quite forthrightly declared: "***The only reason that the Chairs of the Research Ethics Boards were not informed prior to this time is that my legal counsel, provided through the Canadian Medical Protective Association, had recommended that Apotex Pharmaceuticals be informed prior to any other body."*** *(our emphasis)* We took this to mean that Dr. Olivieri as an expert, thorough and careful clinical investigator recognized an obligation to report to the REB but that she found herself in an ethical dilemma, sought advice and followed that advice. Our purpose in commenting on this issue in the HSC Review Report was to highlight one of the most pernicious effects of confidentiality clauses in contracts between clinical investigators and private companies; namely, that such clauses can create serious conflicts between meeting contractual obligations to third parties and institutional obligations designed to protect the interests of patients.

We took special note of the Inquiry Committee's reference to there being no "provisions in policy or ***practice***..." (our emphasis). It is not clear what "a provision in practice" means. It could mean that serious adverse reactions were noted in other studies that were not reported to the REB and this was unknown to, or known and tolerated by, the HSC. If that is so, it would be helpful if the CAUT Inquiry Committee made the

documentation available to the HSC so that better measures to ensure compliance with the requirement to report adverse reactions can be instituted.

9.3.5 ***Did the HSC Review Panel conclude that Dr. Olivieri was negligent?***

As indicated earlier the Panel did not examine, nor did we draw any conclusions about Dr. Olivieri's care of individual patients or her interactions with groups of patients. We saw the matter of reporting to the REB as a procedural issue, albeit an important one.

The CAUT Report states that HSC Review found Dr. Olivieri to be "negligent" in respect of her not reporting the finding of liver toxicity to the REB. That is not correct. The Panel did not state she was negligent nor did the Panel have any reason to believe she was negligent. Dr. Olivieri did not, as far as we can tell, act or fail to act through inadvertence, inattention, carelessness, ignorance or indifference. As our quotations from her own declarations indicate, she pursued a carefully considered course of action deemed to be legally prudent.

9.3.6 ***Why did the Review Panel focus on Dr. Olivieri in relation to obligations to report liver toxicity to the REB and make no mention of Dr. Koren?*** As the HSC Review Report indicates, by the end of 1996 the relationship between Dr. Olivieri and Dr. Koren had broken down. He was by then, no longer privy to data on L1 being gathered by Dr. Olivieri. Thus, through December 1996 and January 1997 Dr. Koren was not in a position to know if there was a basis for reporting to the REB. The CAUT Report indicates that Dr. Koren received the detailed information upon which Dr. Olivieri had based her conclusion about L1 liver toxicity in early February, 1997. The Review Panel made no mention of Dr. Koren in relation to reporting to the REB because we were not given, during the course of our Review, evidence indicating that he received information about L1 liver toxicity in early February, 1997. It was, presumably, among the documents deliberately withheld from us by Dr. Olivieri and was not provided to us, and may have been deliberately withheld, by Dr. Koren.

As the CAUT Report points out, the positions of Drs. Koren and Olivieri, in respect of the administration of L1 to patients, were different. The CAUT Report states on page 317: "...Dr. Koren was not the practitioner, Dr. Olivieri was. No one could reasonably have supposed otherwise: he did not have the expertise required of a physician treating patients with thalassemia." Nonetheless, if Dr. Koren was informed of Dr. Olivieri's findings with respect to the liver toxicity of L1 in early February, he should have inquired if Dr. Olivieri had reported the matter to the appropriate authorities, including the REB, and if she had not, Dr. Koren should have done so promptly even if he disagreed with Dr. Olivieri's analysis.

The Matter of Liver Biopsies

10. The question of whether Dr. Olivieri was justified in continuing to have liver biopsies performed on patients receiving L1 after she had concluded that the drug should not be used in the treatment of thalassemia has been a matter of debate and disagreement both before and after the HSC Review was conducted and its Report released. The CAUT Report correctly points out that the Review did not take a position on the matter. The reason the Review Panel did not do so is that the Review was not intended to adjudicate disputes about specific clinical practices. Rather we were concerned with whether appropriate steps were taken and the appropriate bodies engaged to evaluate the issues involved.

    The Review Panel was aware of the following:

    - A background document submitted by Dr. Olivieri as part of an "Application for Studies Involving Human Subjects", and received by the REB on April 29, 1990, indicates the rationale for performing liver biopsies in order to measure the level of tissue iron stores directly, as follows:

      "...It should be noted that serum ferritin is used as a guide to the degree of body iron overload in thalassemia major patients on standard therapy with DFO [deferoxamine]...Serum ferritin while an acceptable guide to the efficacy of iron chelation in patients on DFO therapy now that this is standard therapy, is not an informative serial measurement ***in the evaluation of a new chelator."*** *(our emphasis).*

    - A letter written on July 24, 1996 by Dr. Olivieri to Dr. Moore of the REB enclosing revised consent forms which included the following statement:

      "...Both MRI and liver biopsy are part of clinical care for thalassemia patients in Toronto, but these tests ***will be obtained more often in patients who remain on the study as compared to those who do not****."* (our emphasis)

    - A letter from Dr. Moore of the REB dated November 9, 1998 in response to a query from Dr. Naimark as to whether the REB had formed any views about the justification for liver biopsies in the case of L1. Dr. Moore reported that she had been advised by Dr. Olivieri that liver biopsy was established practice in patients with thalassemia major.

    Although this latter contention is contrary to what Dr. Olivieri said in 1990 (see above), one must acknowledge that clinical practices evolve over time. Whatever the case may be, the issue is not whether liver biopsies are part of clinical practice but rather whether the patients who "remained on the study" were exposed to increased frequency of liver biopsies

compared to those who did not and whether that exposure continued to be acceptable even though a conclusion had been reached that the drug should not be administered on grounds of toxicity. Answering such a question in retrospect would require looking at data such as the actual frequency of liver biopsies in patients who "remained on the study" compared to those who did not and the particular circumstances in each case. We do not know what such a retrospective examination would reveal and, in any event, our focus was on prospective precautionary processes. Our point was and is that questions like the one about the use of liver biopsies are clearly the kind that should be considered by an REB having been informed in a timely fashion of an unexpected risk by a clinical investigator.

When Is a Trial Not a Trial?

As indicated above, the CAUT Report takes the position that Dr. Olivieri had no obligation legally or "by policy and practice" to report the finding of liver toxicity of L1 to the REB on the grounds that after May 24, 1996, the date upon which when Apotex terminated their sponsorship of the L1 trials, there were no trials and no subjects - only patients receiving L1 under Health Canada's Emergency Drug Release Program.

11.1 As noted earlier, Dr. Olivieri as far back as 1990 had undertaken to:

> ***"..assume full responsibility of the study as detailed in the protocol and ..[to].. notify the human subjects review committee should any unexpected results or any detected or proposed departures from the study arise."*** (our emphasis)

Moreover, we also indicated that clinical investigators must be concerned with ethical obligations even when such obligations are not imposed or enforced by "positive law". Obviously such obligations must be seen in the context of particular and possibly extenuating circumstances such as those faced by Dr. Olivieri. It is of some concern that the CAUT Inquiry Committee would criticize the Hospital and University for not taking actions in support of important principles that they were not legally obliged to take, but say nothing about the need for clinical investigators to be held to the same standard.

11.2 We now turn to why we believe the CAUT Inquiry Committee has taken far too narrow a view of the obligations of clinical investigators - a view that is an inadequate guide to ethical clinical behavior. First one must understand that the term "clinical trial" in a general sense refers to a test or investigation of a new diagnostic or therapeutic intervention in human subjects or to a systematic evaluation of an established intervention. In certain kinds of trials the human subjects may be normal individuals and in others the subjects may be patients with diseases or disabilities. To contend that one is either a subject or a patient is clearly to posit a

false dichotomy. Some kinds of trials are governed by legislated requirements, some are subject to guidelines of sponsoring agencies such as research granting councils, some are governed by institutional requirements and some by a combination of two or more sets of requirements. All trials, under whatever *aegis,* must be carried out with due regard to ethical obligations and not just to legal or contractual obligations.

11.3 From the standpoint of the HSC and its duty of care, a clinical trial is being pursued when an experimental intervention is being used under its aegis (i.e., within its premises, involving its employees or patients etc.). The fact that the sponsorship of a trial is terminated by an external sponsor (whether a drug company, or a government agency or a charitable organization) does not mean that the testing or investigation of a new diagnostic or therapeutic intervention has been discontinued. ***If after termination of sponsorship the experimental intervention continues and the subjects continue to be studied, the correct and prudent interpretation is that a trial is continuing.***

11.4 Since approval by the REB to administer L1 to patients of the Hospital was based not on who the sponsor was but on what was actually going to be given and done to patients and under what circumstances, a trial of L1 was in effect until the interventions and procedures, for which approval was required in the first instance, are no longer being carried out. In fact, under Health Protection Branch Guidelines when there is no external sponsor, the institution in which the trial is being conducted becomes the *de facto* sponsor.

11.5 To argue that in some way the source of an experimental drug or the circumstances under which it is obtained determines whether a trial is being conducted makes no sense. In 1988 Drs. Olivieri and Dr. Koren undertook to investigate the efficacy of L1 (which they arranged to have produced in the Chemistry Department of the University) in patients of the Hospital with the permission of the Health Protection Branch and the approval of the Hospital's REB. As the HSC Report states, the investigators argued for regulatory approval on compassionate grounds; i.e., "that unless patients who were unwilling or unable to take deferoxamine had access to L1 many of them would be dead in a few years". In fact the investigation was often referred to as the "compassionate use trial". The fact that after termination of Apotex sponsorship the basis upon which L1 was obtained reverted to compassionate use under the Emergency Drug Release (EDR) program of Health Canada has no bearing on whether an investigation (trial) was or was not continuing.

11.6 The CAUT Inquiry Committee, refers to a book authored by Dr. Koren in which he states that approval of the REB is not required to administer a drug obtained by Emergency Drug Release, as if this were relevant to the circumstances of the L1 trials. Dr. Koren, may have been referring to situations in which a physician caring

for an individual patient arranges for emergency release of a drug on compassionate grounds before it has received a Notice of Compliance.

If Dr. Koren intended his statement to carry the implication that patients who were part of a sponsored clinical trial, and therefore under the purview of an REB, are removed from the purview of the REB after the sponsorship is terminated merely by virtue of continuing to receive the drug under EDR he would be wrong. If one accepted that line of argument, as the CAUT Inquiry Committee seems to have done, one would be led to the absurd conclusion (from a patient safety and welfare perspective) that the LA-03 trial should never have come before the REB in the first place because the drug was being administered on compassionate grounds. It is ironic that the CAUT Inquiry Committee, which seems to have seized every opportunity to denigrate Dr. Koren, would rely on him as an authoritative source when it is convenient for them to do so.

11.7 It is important to emphasize that we do not believe it was inappropriate for Dr. Olivieri et al. to continue to study L1 systematically after Apotex terminated its sponsorship. There were, after all, several important scientific questions about the safety and efficacy of L1 that needed to be addressed and Dr. Olivieri by way of her mastery of the field and her clinical and scientific expertise was eminently qualified to pursue those questions.

11.8. The issue of whether or not Dr. Olivieri et al. were or were not conducting continuing scientific and clinical investigations on L1 after May 24, 1996 is, as the CAUT Report indicates, an important one. The contention of the CAUT Inquiry Committee that the HSC Review Panel formed its views on this issue through reliance on statements made to it by Dr. O'Brodovich and Dr. Moore is incorrect. We took all documents provided to us into account, including those containing the following statements made by persons, other than Dr. O'Brodovich and Dr. Moore, who were directly involved with the circumstances surrounding the administration of L1 to patients after May 24, 1996. (All of the matter in boldface in this section represents our emphasis.)

- On June 19, 1996 Dr. Zlotkin (then Chair of the REB)faxed a handwritten note from Chicago to Dr. Olivieri suggesting changes to consent forms in addition to those proposed by Dr. Olivieri. On June 27, 1996 he wrote again to Dr. Olivieri "..to obtain written confirmation from you regarding the ***above noted studies*** [referring to the randomized trial and the long term efficacy trial] ..If you are planning on ***proceeding with either study*** I will require your revised consent/assent forms (as per my fax from Chicago) ***before conditional approval is given***. ***Study amendments*** will be submitted to the full REB [for] approval following receipt of the revised forms."

- On July 4, 1996, Ms. Margo Farren of the REB wrote to Dr. Aideen Moore (who had succeeded Dr. Zlotkin as Chair of the REB) that "..Nancy's data manager, Naomi Klein, dropped by yesterday with the revised consent forms for ***Nancy's 2 studies***...Naomi's understanding is that ***the studies will be proceeding..."***

- On July 15, 1996, Drs. Olivieri and Koren wrote to Dr. Zlotkin describing their proposed course of action with respect to patients who had been enrolled in the LA-01 and LA-03 trials following the discontinuation of sponsorship by Apotex. They noted that in both trials, conditionally-approved information and consent forms stated that, "**to continue in this study,** the patients must agree to continue to undergo certain assessments, including a liver biopsy."

- The following note appears on a chronology prepared by the REB pertaining to the LA-03 trial dated August 21, 1996. "..REB Chair confirms with Investigator July 17 in telephone conversation that ***study ongoing; enrolled patients will continue in study if showing efficacy. No new patients..."***

- As noted earlier, on July 24, 1996 in a letter Dr. Olivieri wrote to Dr. Moore of the REB, enclosing revised patient information forms, Dr. Olivieri stated:

  "...Both MRI and liver biopsy are part of clinical care for thalassemia patients in Toronto, but these tests ***will be obtained more often in patients who remain on the study as compared to those who do not****."* (our emphasis)

  The consent forms include the following statements in the Clinical Information Form for patients [matter in boldface is our emphasis]:

  - *INTRODUCTION:*
    "We will carefully monitor you using the procedures described below should you choose to remain ***in the study"***

  - PURPOSE OF **THIS STUDY**
    "...**we are evaluating** an alternative orally active...drug, deferiprone to see if it is both safe and effective.."

  - *DESCRIPTION OF* ***THE RESEARCH***
    "If you agree to participate ***in the study*** *you will be asked to."*

- *PARTICIPATION IN **STUDY***
  ***"Participation in research** is voluntary."*

and in the Consent Form:

- *"I acknowledge that **the research procedures described above** have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right to not to participate and the right to withdraw..."*

- On February 20, 1997, in a letter to Dr. O'Brodovich, Dr. Olivieri stated *"...**The only reason that the chairs of the research ethics boards were not informed prior to this time** is that my legal counsel, provided through the Canadian Medical Protective Association, had recommended that Apotex Pharmaceuticals be informed prior to any other body..." (our emphasis)*

- On May 28, 1997 Ms. Farren of the REB wrote to Dr. Olivieri stating: "Your [LA-03] project was approved for the period of one year by the Research Ethics Board in June, 1996. Attached you will find a renewal form for this study..If we have not received the signed and completed form by this date...***approval of the study*** will therefore lapse as of July 11, 1997. After this date activities involving the use of human subjects must be suspended...The form should be returned even if you have completed or terminated your research. If your research has been completed please briefly indicate your findings."

The CAUT Report rationalizes the several occasions when those involved in the continued administration of L1 to patients after May 24, 1996 referred to them as being in "studies" or in "trials" on the basis that they were merely using those terms in a casual sense and as "shorthand"; and, that the patients were not really in such trials, or in studies, or involved in research- a rationalization that is blatantly inconsistent with the representations in the patient information and consent forms. Surely the Inquiry Committee is not suggesting that an experienced, thorough and careful investigator such as Dr. Olivieri would use language casually in patient information and consent forms.

Moreover, the CAUT Report insists on interpreting the phrase "Apotex terminated the trials" when used by Dr. Olivieri and others in a literal sense when in fact it could very well be that the phrase was also used in a casual sense and as shorthand to mean simply that Apotex discontinued sponsorship. A sponsor has no automatic

right to prevent continued investigation of a drug following termination of sponsorship as long as that drug can be obtained and administered lawfully by the investigators. It is, of course, clear why Apotex would have wished to maintain that the trials were terminated. They were not interested in having Dr. Olivieri continue to investigate a drug about which she had serious reservations.

When Is a Protocol Not a Protocol?

11. Not only does the CAUT Inquiry Committee err with respect to what determines whether a trial is or is not underway, it also errs by declaring that when a sponsor terminates sponsorship of a trial the protocol associated with that trial is automatically "inactivated". Presumably the Committee took this position to bolster its claim that Dr. Olivieri ceased to be under the purview of the REB merely because Apotex declared it had terminated the L1 trials. First of all, let us be clear about what a "protocol" is. In the clinical setting it is simply a plan for a course of treatment or clinical investigation. In the case of clinical investigation the protocol is active as long as the plan is being followed, irrespective of the nature of the sponsorship supporting the implementation of the protocol or even if there is no external sponsor. To argue otherwise is to imply that it would be acceptable for a clinical investigator to continue to carry out all of the procedures and expose subjects to all of the risks involved in a trial with no accountability to the REB or to clinical supervisors, simply as a result of a unilateral decision by a sponsor to terminate sponsorship.

12. From the standpoint of protecting the interest, safety and welfare of patients involved in clinical investigation, what matters is not declarations by any party (investigators, supervisors, reviewers, inquiry committee members, administrators) about whether a trial is or is not underway, whether a protocol is or is not in effect. What matters is the procedures that are actually carried out on the individuals receiving an experimental drug and whether or not those procedures both in kind and degree are of such a nature that it is in the patients' interest for those procedures to continue to be subject to the oversight of the Research Ethics Board.

"Missing" Documents

13. The foregoing observations are mainly based on the different perspectives of the CAUT Inquiry Committee and the HSC Review Panel on the documentary record both groups had access to. Let us now turn to the documents the CAUT Report identified as missing from our database.

    Before doing so, we wish to take exception with what could be regarded as inappropriate language used in the CAUT Report to describe the provenance of these documents. It refers to the "*omission* of all these relevant documents from the Review's record" (our emphasis) knowing full well that the word omission can be read to mean deliberate exclusion. When

coupled with the statement "We do not know *with certainty* whether or not Dr. Naimark received any of these sixteen documents" (our emphasis) there is an implication that the Inquiry Committee has some reason to believe that documents were received and deliberately excluded. We hope that is not what was intended since such use of innuendo is unworthy of anyone or any group claiming objectivity and fair-mindedness.

We comment on these items of correspondence in the order in which they are listed on pages 288 and 289 of the CAUT Report.

"(i)a contract governing the LA-03 trial issued by Dr. Spino on October 2, 1995 and co-signed by each of Drs. Olivieri and Koren later that month;"

As the CAUT Report states, this "is a pivotal document". The fact that it contains no confidentiality clause is material to the dispute between Dr. Olivieri and Apotex. It is relevant to the HSC Review in that it represents yet another occasion in which Drs. Olivieri and Koren entered into a contract with an industrial sponsor without the knowledge of the HSC. It does not however change the conclusions and recommendations in the HSC Report and is immaterial in that sense. The question of the significance of the right of Apotex to "terminate the LA-03 trial" in relation to the HSC Review is dealt with in section 11 of this commentary. Suffice it say at this point, the right to terminate does not mean that one necessarily has the power to terminate when the right is invoked.

This is a convenient point at which to take up a matter that seems to have perplexed the CAUT Inquiry Committee; namely, the use, in the HSC Report, of the term "the Trials [plural] contract". We used the singular of the word contract because we were unaware of the 1995 contract pertaining to LA-03. The HSC Report cites Dr. Spino's letter of May 24, 1996 in which he said: "...Apotex has decided not to extend or renew the LA01 Agreement. Effective immediately, the deferiprone clinical trials are being discontinued..." and later in the same letter: "As you know, paragraph 7 of the LA01 Agreement and the LA01 and LA03 Protocols provide...". The wording implies that there was only one "Agreement" but two protocols. This phraseology was not to our knowledge challenged by the investigators or by their legal counsel at the time. In fact in a May 25, 1996 letter to Dr. Haslam informing of Apotex's action, Drs. Olivieri and Koren stated "...Now that *this* contract has been prematurely terminated." (our emphasis; quote appears on page 32 of the HSC Report [Archive Version]).

The CAUT Report refers many times to items of correspondence in which it is declared that the L1 trials were "terminated" or "discontinued" as if multiple instances of the use of the same term increases its relevance and significance or, indeed, even establishes it as a fact. Clearly this is incorrect.

"(ii)an REB information form confirming termination by Apotex of the long-term (LA-03) trial, signed by Dr. Olivieri on July 20, 1996 and by Dr. Freedman, her division head in Hematology, on July 25, and stamped as received by the REB on August 1, 1996;"

See section 11 of this commentary.

"(iii) a letter dated October 3, 1995 from Dr. Spino to Dr. Brittenham, copied to Dr. Olvieri and Koren;"

This document is relevant to the dispute between Dr. Olivieri and Apotex. The HSC Review was not intended to adjudicate that dispute.

"(iv) a letter dated May 8, 1996 from Dr. Spino to Dr. Olivieri, copied to Dr. Koren;"

This document is relevant to the dispute between Dr. Olivieri and Apotex and as noted above, the HSC Review was not intended to adjudicate that dispute. Much related correspondence was available to the Review and the interaction with REB on this issue was given considerable attention in the HSC Report.

"(v) the full report of Apotex's Advisory Panel, dated July 12-13, 1996;"

Contrary to the Inquiry Committee's contention, this is not a "missing" document. It is listed as item 154 in the Reference List of Documentation in the HSC Report. It was not referred to *in extenso* because it dealt with the difference between Dr. Olivieri and Apotex in interpretation of data and the HSC Review was not intended to adjudicate such differences. As to the reference in the report to the 'discontinuation' of the trials, see section 11 of this commentary.

"(vi) a letter dated July 21, 1998 from Dr. Corey to Dr. Buchwald;"

This document is relevant to the disagreement between Apotex and Dr. Olivieri. the HSC Review was not intended to adjudicate such differences.

"(vii) a chapter written by written by Dr. Koren in a 1993 book on research ethics which he edited;"

This is an important reference. We disagree with the CAUT Report's interpretation of its applicability to the specific circumstances of the administration of L1 to patients after May 24, 1996 (see section 11.5 and 11.6 of this commentary). As of this writing we are unable to confirm the statement in the CAUT Report that "..under HSC policy, Dr. Olivieri was not required to obtain REB approval to treat patients under EDR [Emergency Drug Release]". It is not clear whether it is intended to mean that there is no stated requirement or that there is an explicit HSC policy

statement saying that REB approval is not required. We are continuing to look into the matter.

"(viii) a letter dated August 12, 1996 from Dr. Spino to Dr. Olivieri, copied to Dean Aberman, Dr. Koren and Mr. Kay, the President of Apotex, Inc.;"

The letter contains a warning to Dr. Olivieri and an attempt to deter her from presenting her findings at a scientific meeting. We agree with the CAUT Report that this constitutes an infringement on Dr. Olivieri's academic freedom and is against the public interest. Similar interventions of Apotex along these lines are clearly described in the HSC Report.

"(ix) a letter dated August 13, 1996 from Dr. Spino to Dr. Agnes Klein of Health Canada's Bureau of Pharmaceutical Assessment;"

The CAUT Report indicates that this letter and a letter dated August 14, 1996 contradicts a statement in the HSC Report that a planned meeting between Dr. Olivieri with the regulatory agency was "in accordance with the agreement in the June [1996] mediation meeting convened by Dean Aberman." We have not seen the August 13 letter but accept that the phrase "in accordance with" was not sufficiently precise. We used it to mean that Dr. Olivieri's planned meeting with the regulators was in accordance with the agreement that the finding of loss (variability) of response to L1 would be reported to the regulators. However, Dr. Olivieri's planned meeting was not in accord with the agreement as described by Dean Aberman in that the latter agreement envisioned that "Nancy and Apotex would go jointly to HPB. [Health Protection Branch of Health Canada]." The August 13 and 14 letters are relevant to the issue of Apotex's opposition to Dr. Olivieri's commitment to reporting her findings to appropriate authorities. It is also relevant to the evaluation of the consistency of Dr. Koren's views about the efficacy of L1. The correspondence is supplementary to other information we had along the same lines, but is not material from the standpoint of the HSC Report in that it does not change our conclusions and recommendations.

"(x) a letter dated February 5, 1997 from Mr. Colangelo to his clients, Drs. Koren and Olivieri;"

This correspondence is important and material in respect of the HSC Review. It is addressed in section 9.3.6 of this commentary.

"(xi) a letter dated May 8, 1997 from Apotex counsel Mr. Brown. to Mr. Colangelo;"

This letter refers to a meeting of Dr. Spino with Dr. Olivieri's patients on the day corresponding to the date on the letter, in which it is claimed he attested to the

efficacy and safety of L1. What Dr. Spino is reported to have said apparently comes from a letter from Dr. Olivieri (97/05/05) to her counsel, summarizing notes taken by a social worker who attended the meeting. Assuming the representation of what he said is correct, his comments are relevant to the dispute between Apotex and Olivieri but are not material to the conclusions and recommendations in the HSC Report and do not contradict any of its findings.

"(xii) a letter dated July 3, 1998 from Apotex counsel Dr. Saunders to Dr. Buchwald;"

This letter is said to indicate that the HSC had reviewed and approved a contract (apparently in 1998) that was "at least as restrictive on communication as the one Dr. Olivieri had signed in 1993." The CAUT Report speculates that: "The Naimark Review might have made stronger recommendations about policy on research contracts and its implementation by HSC had it been aware of this. [the approval of the contract referred to by Dr. Saunders]" If the circumstances are as reported, we agree.

"(xiii) a memo dated September 5, 1998 from Dr. Olivieri et al. to Provost Sedra and to HSC Board members"

The HSC Review did see an e-mail message dated September 2, 1998 giving notice that Dr. Olivieri et al. would, in later correspondence, be disputing a characterization of events distributed by the HSC Executive, correspondence, but we did not receive a copy of a memo dated September 5, 1998. We have been informed that it is not in the files of the Board of the HSC or in the personal files of Board members contacted so far. According to the CAUT Report it includes information to the effect that Dr. Olivieri "met with patients on February 4, 1997 to advise them of the risk of liver fibrosis." The CAUT Report then alleges that "..The Naimark Report implied that she not [sic] fulfilled this obligation." This is incorrect and reinforces the concern that the CAUT Inquiry Committee uses language in such a way as to obscure issues. To contend that, because the HSC Report did not refer to information that it did not know about, the Report was implying anything in respect of that information makes no sense. As noted in section 9.3.5 of this commentary, the Review Panel did not examine, nor did we draw any conclusions about Dr. Olivieri's care of individual patients or her interactions with groups of patients. We saw the matter of reporting to the REB as a procedural issue, albeit an important one.

"(xiv) Apotex correspondence with regulatory agencies on and after May 24, 1996, including letters to Health Canada by Dr. Spino on January 28,1997 and by Mr. Woolcock on February 25, 1997, and documents pertaining to L1 licencing submissions to regulatory agencies, January 1998;"

The issue of Apotex stating that it had "stopped" both trials of L1 is dealt with elsewhere in this commentary (sections 11 and 12). We disagree with the CAUT Report about the import of such a declaration by Apotex. The matter in the documents cited relating to the status of the short-term international trial and the question of protocol violations as the basis for Apotex wishing to discontinue the trials are related to the dispute between Apotex and Dr. Olivieri. As noted earlier, the HSC Review was not intended to adjudicate such disputes.

"(xv) a letter dated October 28, 1996 from Dr. Olivieri to Dr. Koren (copied to Dean Aberman);"

This letter is material to the issue of the import of declarations that the trials were terminated" on May 24 ,1996. The matter is dealt with in sections 11 and 12 of this commentary. Assuming the letter says what the Inquiry Committee says it does, it is unfortunate that Dr. Olivieri refused to provide the Review with relevant documentation which presumably would have included her October 28 letter to Dr. Koren and that Dr. Koren also did not include the letter in the material he provided to the Review). Had they done so the HSC Report would have dealt with the issue of when a trial is no longer a trial and the specious distinction between "patients" and "subjects". The HSC Report would also have pointed out the inconsistencies between what may have been said in the October 28 letter and other declarations made by Dr. Olivieri.

"(xvi) relevant documents from the MRC [Medical Research Council] application files of Dr. Olivieri and Dr. Koren;"

Whether or not Dr. Moore erred in stating that some patients were transferred from the LA-01 to the LA-03 trial is not material to the conclusions and recommendations of the HSC report. The CAUT Report notes that some of these documents refer to the professorial status of Drs. Olivieri and Koren presumably because such reference confirms the linkage of the University to the L1 trials and their aftermath.

While on this point, we wish to repudiate the contention of the CAUT Inquiry Committee that the HSC Review did not investigate or address the question of why the HSC did not defend the principle of academic freedom and free communication. The HSC Review investigated, and addressed in its Report, the role of institutional

conflicts of interest, administrative disputes and interpersonal relationships as possible significant factors.

The CAUT Report criticizes the HSC Review for not investigating or addressing why the University did not take effective action to defend academic freedom and investigator independence. This is just one of many occasions in the CAUT Report where the Inquiry Committee criticizes the HSC Review for not doing something it was never intended to do. We were not mandated to investigate the University. We did however wish to understand the position of the University because it is an important part of the context in which the HSC operates. The statement in the CAUT Report that the HSC Review "appears to have taken these claims by the University [of a lack of involvement in the L1 affair] at face value" is just one example of the kind of gratuitous speculation that is rife in the CAUT Report. In fact, the importance of the linkage with the University is reflected in one of the major recommendations of the HSC Report dealing with the need to harmonize the policies of the HSC and the University, given their mutual interests and responsibilities.

Findings and Recommendations of the CAUT Inquiry Committee

The following observations pertain only to the findings relating to the HSC Review that appear in the summary section of the CAUT Report. We express no opinion at this time regarding the summary of other findings set out in this section of the CAUT Report.

15. The findings in the CAUT Report bearing on the nature, scope and intent of the HSC Review are incorrect in that the HSC Review is criticized for not investigating or examining matters that it was never intended to investigate and examine.

16. The CAUT Report's insistence in interpreting declarations by Apotex, Dr. Olivieri and others that the "L1 trials were terminated" on May 24, 1996 to mean that no studies, investigations or research on L1 involving patients were carried out after that date is based on incorrect or incomplete consideration of all of the evidence available.

17. The findings in the CAUT Report, concerning the evidence upon which the HSC Review based its findings, are incorrect.

18. The CAUT Report notes that: "The Naimark Review and the MAC inquiry were not provided with some important, relevant information by persons they interviewed" The failure of such persons to provide some relevant in formation is certainly correct but the criticality of the specific items of documentation, in the examples cited, is overblown since the information they contain was available from other sources. The real issue is a difference between the CAUT Inquiry Committee and the HSC Review Panel with respect to the import of that information.

It is astonishing that the CAUT Report, in its summary of findings, would take note of the lack of provision of information by persons we interviewed and say nothing about one of the most important issues related to the HSC Review; namely, that Dr. Olivieri et al. deliberately withheld information from the Review and did so in an attempt to diminish the credibility of the Review.

19. The CAUT Report states that: "The adverse findings against Dr. Olivieri in the reports of the Naimark Review and HSC's Medical Advisory Committee are incorrect and based on incomplete, incorrect and false testimony." As the foregoing observations and discussion indicate, this statement is itself incorrect, at least as far as the HSC Report is concerned. The HSC Review Panel had completed its work before the reference of matters to the MAC. The HSC Report drew no conclusions and made no recommendations about the pursuit of any matters by any individual or body within the HSC or elsewhere other than those pertaining to the future development of policies and procedures.

The following observations deal with the recommendations of the CAUT Inquiry Committee. We make observations only on matters of policy and procedure insofar as they relate to teaching hospitals in general and the HSC in particular, since the HSC Review was not intended to, and did not, make recommendations on specific personnel issues.

20. The recommendations in the CAUT Report concerning teaching hospitals generally (pertaining to the review and administration of research contracts, the role of research ethics boards and their procedures, and other policy matters) are in accord with the recommendations made in the HSC Report with respect to the HSC specifically.

21. There is however one aspect of sound academic governance the CAUT Report's recommendations did not address; namely, the roles and responsibilities of investigators. In academia, it is generally accepted that academic freedom and responsibilities go hand in hand. The body of the CAUT Report rightly points out that among the limitations of the current Tri-Council Policy on use of human subjects in research is the fact that it deals mainly with institutional responsibilities and provides insufficient guidance to investigators. Such guidance should address the responsibilities of investigators to act ethically even in the absence of contractual or regulatory obligations and to be fully accountable to appropriate peer-review bodies and supervisors as part of a general commitment to quality assurance and fidelity to the safety and welfare of subjects of research. Institutional mechanisms must be in place to support investigators who act in good faith in meeting these responsibilities.

    Moreover, to be operationally comprehensive, such guidelines pertaining to investigators and perhaps the guidelines pertaining to institutions should have a wider provenance than the research granting councils. This is a matter we would encourage the Association of

Universities and Colleges of Canada, the CAUT, the granting councils and the teaching hospitals to take up collectively.

Supplementary Recommendations of the HSC Review Panel

22. We note that the HSC has devoted a good deal of time and effort to reforming its policies pertaining to research and related matters, taking into account the recommendations of the HSC Review. There are some matters that, as far as we are aware, have not yet been addressed and continue to be worthy of attention by appropriate bodies within the HSC; for example, the policies and procedures pertaining to the role, appointment, evaluation and termination of program heads.

23. The new policies on research are understandably written in general terms but their implementation requires that they be accompanied by carefully worked out regulations and guidelines dealing with standard operating procedures and methods to deal with exceptional circumstances. This is essential so that there is no doubt in the minds of clinical investigators and other researchers about their obligations.

24. While we disagree with the CAUT Inquiry Committee about the import of certain phrases, we certainly acknowledge the confusion that arises when words or phrases are used by different people to mean different things. Had we imagined that anyone would interpret the word "trial" in the narrow sense employed in the CAUT Report, we certainly would have been more precise in our use of that term. Accordingly, we recommend that the HSC establish definitions and a lexicon of standard usage pertaining to terms used to describe various aspects of clinical research including clinical trials and that the definitions and lexicon be kept under continuing review and refinement. We also recommend that policies, procedures, rules and regulations related to human subjects, including patients, be drafted from a subject/patient-centered focus rather than a researcher-centered focus. An example is given in section 25 below.

25. One of the critical issues discussed in the CAUT Report and in this commentary is the question of the obligations of investigators involved in clinical trials to report adverse findings to the REB that are discovered after an external sponsor declares a trial or trials to have been terminated. Let us, in the case of industrially sponsored drug trials involving patients, suppose three situations:

    - The drug ceases to be administered at the time the sponsor declares the trial to be terminated but the adverse reaction emerges some time later; or, an adverse reaction is found by retrospective analysis to have occurred before administration of the drug was stopped.

- The drug (however it is obtained) continues to be administered after the trial has been declared to be terminated by the sponsor but the procedures involving the patients continue to be applied, in substantial kind and degree, as they had been prior to the declaration of termination.

- The drug (however it is obtained) continues to be administered after the trial has been terminated (say on compassionate grounds) but the procedures being applied to the patients are standard clinical procedures normally applied to patients with the same or similar disorders who were not participants in the trial.

Clearly, the considerations arising from these scenarios are different and require different courses of action. There are two general approaches to formulating regulations to deal with these differences. One is to have a specific regulation for each situation. The other is to have a rigorous general regulation that allows for exceptions. We are inclined to favor the latter. An example is given below:

> *Whenever an experimental drug (a drug not yet approved by Health Canada for general clinical use but approved for experimental use or use on compassionate grounds) is to be administered to a patient or patients at the HSC, or by a member of the clinical or scientific staff of the HSC to persons who are not patients of the HSC, approval to do so must be obtained from [indicate appropriate authority - e.g. one or more of REB, clinical research secretariat, division head etc.]*
>
> *The administration of the drug and the clinicians and scientists responsible for its administration, and the care of patients involved, shall continue to be under the purview and regulation of the [indicate appropriate authority - e.g. one or more of REB, clinical research secretariat, division head etc.] for as long as the drug is administered and for a period of [n] years thereafter or until there are no longer patients who are receiving or have received the drug under the care of a member of the clinical or scientific staff of the HSC. The foregoing shall include continuation of all obligations, including all reporting requirements [e.g. to report adverse reactions] established when approval for administration of the drug was first given or as formally amended by [indicate appropriate authority].*
>
> *Exceptions to the foregoing may be made to deal with special circumstances upon formal written application to, and specific written authorization by, [indicate appropriate authority - e.g. one or more of REB, clinical research secretariat, division head etc.]*