HSC clinical trials controversy continues

To the editor—We write to correct inaccuracies in your October issue editorial and news article concerning the controversial clinical trial involving Nancy Olivieri, The Hospital for Sick Children (HSC) and Apotex Inc. Whereas there is no question that this case is complicated and that there are as many interpretations of the facts as there are involved parties, the allegation that the HSC administration “completely failed to support the efforts of Olivieri” is false and the implication that we did not support Olivieri’s right to publish is unwarranted.

In a letter dated 24 May 1996, Apotex notified Olivieri (and her collaborator Gideon Koren) that they would not renew the contract supporting the trial of L-1 (Deferiprone). Apotex also warned Olivieri and Koren that they would pursue legal remedies if they breached the obligations in their previous three-year contract. In a letter dated 25 May, Olivieri and Koren informed the hospital that they had already sought legal counsel, who had advised them to contact the Canadian Medical Protective Association (CMPA). When Olivieri subsequently met with university officials on 6 June, and with hospital representatives on 18 July, she was represented by a lawyer from McCarthy Tetrault, the firm retained by the CMPA. It was not until the hospital board of directors initiated an independent external review that Olivieri requested legal assistance from the hospital in this matter. Olivieri has been continuously represented by lawyers from McCarthy Tetrault.

At the 18 July 1996 meeting, Olivieri and her lawyer requested that the hospital take a position against Apotex, backing her scientific findings. The hospital’s opinion was that the conflict was a scientific dispute among Olivieri, Koren, Apotex and several other scientists regarding the effectiveness of L-1 and, as such, should be resolved through the scientific literature. The hospital supported and encouraged Olivieri’s initiative to submit her findings for presentation at the December 1996 meeting of the American Society of Hematology, which she did. She also reported her findings in an article in the *Medical Post* (January 1997), in April 1997 at the Sixth International Conference on Thalassemia and Hemoglobinopathies, and at the December 1997 meeting of the

American Society of Hematology and in the *New England Journal of Medicine* (339, 417; 1998).

After Apotex did not renew the L-1 clinical trial contract, Olivieri wished to continue to use L-1 to treat thalassemia patients at HSC and Apotex agreed to provide the drug under the Canadian government’s Emergency Drug Release (EDR) program. Later, Apotex on several occasions contacted hospital officials requesting that the hospital help them gain access to the data generated while Olivieri treated patients under the EDR program, and HSC supported Olivieri in refusing these requests. Olivieri’s complaint that her data was used without her permission was brought to The University of Toronto for adjudication (in keeping with the university’s *Procedures to Address and Manage Scientific Misconduct*). An investigating committee was established and reported in September 1997, dismissing the allegation and exonerating the faculty member against whom the charge was made.

The connection between HSC and Michael Spino, now a vice president of Apotex, should be clarified. Spino was a member of The Hospital for Sick Children

Research Institute for several years. When Spino began working for Apotex, he left the staff of the hospital but became an unpaid consultant to HSC. Since joining Apotex, Spino has not maintained a laboratory at HSC, but has done collaborative research in Koren’s laboratory. Koren and Spino co-supervised a graduate student and a research technician. Spino was, and continues to be, a professor at The University of Toronto.

Arnold Naimark, former dean of Medicine and President of the University of Manitoba, has conducted a review to determine the facts and circumstances of this complex case. We anticipate that his report will further clarify facts in the case and make useful recommendations for future practice at the Hospital for Sick Children. [As *Nature Medicine* went to press this report was released and is available at <http://www.sickkids.on.ca/HSCWeb/zReview/TheReview>]. Furthermore, a second-phase review is also planned to examine current hospital policies and procedures relating to the broader issues of clinical trials and third-party funding. The outcome of these reviews may also be of value to other institutions.

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DNAVEC gene therapy on course

In your November issue, you carried a news story (“Japan renews gene therapy efforts”) regarding progress on gene therapy in Japan. We think that your discussion of DNAVEC Research was misleading, and we would like to clarify a few points.

We disagree with your suggestion that DNAVEC has failed in its aims or is behind schedule. Our aim is to develop new gene therapy-related technologies, to sell these to our investors and third parties and to proceed to clinical trials with companies experienced in clinical trials. At our inception (March 1995) and thereafter, we stated our intention to invest three to five years in new vector development, followed by animal studies, development of the methodologies required for the initial phase of the commercial production of vectors, and preliminary safety studies. Our development of a Sendai virus-based vector is on schedule and has received favorable reviews from the scientific review committee of the Organization for Pharmaceutical Safety and Research, an extra-governmental organization of the Ministry of Health and Welfare, Japan.

Your news story failed to recognize our precise research policy—we are neither a contract vector production facility nor a safety assessment facility. Incidentally, the preparation to launch DNAVEC started in 1993, well in advance of the approval of the first gene therapy clinical trial in Japan.

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Olivieri replies—The facts of this case are quite straightforward. The allegation that the Hospital for Sick Children (HSC) and the University of Toronto “completely failed to support the efforts of Olivieri” is absolutely true, as is the implication that it did not support my right to publish findings about L-1 (Deferiprone).

Ultimately, the only support to me for legal protection came from the Canadian Medical Protective Association (CMPA), an organization that serves to protect physicians in Canada from legal threats arising in the practice of medicine. The CMPA first limited its support to the issue of full disclosure of the perceived risk of Deferiprone to my Toronto patients only. The CMPA declined to support disclosure of perceived risks to patients in international trials (of which I was the chair of the steering committee), to regulatory agencies (to which applications were being made by Apotex for licensing, based in large part on earlier work by us) or to the scientific community. Two months after the abrupt termination of these trials by Apotex, I was unable to fulfill these last three obligations without the risk of legal action by Apotex. The Hospital nevertheless stated, unequivocally, that it would not provide legal counsel for me in this matter. Written records of this refusal are available.

The HSC excused their action by saying it “...was a scientific dispute....” This is alarming for an institution with a mandate to protect patients. In the face of uncertainty over possible harm to patients, to do nothing is a dereliction of a physician’s duty by every international standard of ethics in medical research. It is also illegal under Canadian criminal law. (Incidentally, although we raised our concerns at a time when others were still enthusiastic about the drug, we never requested that anyone at the HSC take a position against Apotex, backing our scientific findings.)

The HSC Institutional Review Board had, in parallel with disclosure to patients, recommended disclosure to regu-

latory agencies. This recommendation was dismissed by the senior HSC administration, who stated that “the matter could be settled without the help of regulatory agencies.” Fortunately, the CMPA, recognizing that I was “subject to the ethical obligations of a physician as well as the obligations imposed by the Institutional Review Board, the Declaration of Helsinki, and Medical Research Council of Canada’s Code of Conduct for Research Involving Humans,” subsequently agreed to support disclosure to the Canadian Health Protection Branch. Noting that I was “rightly concerned about the safety and well-being of persons throughout the world,” the CMPA observed that such disclosure would be “in compliance with statutory requirements.” That I was able to submit and present data at scientific meetings was solely the result of support ultimately provided by CMPA.

In January 1997, two abstracts endorsing the long-term effectiveness of Deferiprone presented to a scientific meeting were co-authored by Apotex-paid research fellows, a full-time employee of Apotex and two University of Toronto investigators^{1,2}. These abstracts and other subsequent communications³ continue to provide a favorable interpretation of data arising from the Toronto clinical trials of Deferiprone directed by me. The abstracts were submitted without my knowledge or consent, or that of Gary Brittenham, whose NIH-funded laboratory generated these data. An investigating committee at the University convened to investigate this conduct ruled, incomprehensibly, that it is acceptable practice under the current leadership of the Faculty of Medicine at the University of Toronto for a scientist to publish NIH- and MRC-funded data without the knowledge, consent or participation of the scientists who generated the data.

With regard to attempts by Apotex to gain access to data generated by me and my colleagues—data that I repeatedly refused to provide them—Gideon Koren, an Apotex-paid research fellow, gained unauthorized access to my confidential patient files. This is well documented. The senior HSC administration did not reprimand Koren or Apotex, but did advise me in writing that I should refrain from informing patients whose charts had been accessed without authorization.

The name of Michael Spino, the vice

president of Apotex, appeared on the letterhead of the Division of Clinical Pharmacology at HSC as recently as March 1998. Spino has confirmed that he maintained laboratory space at HSC, a fact allegedly unknown by the director of the hospital’s research institute. Spino’s technician confirmed in August 1998 that work on Deferiprone was still ongoing in his laboratory.

Finally, as is now a matter of public record, the pursuit of a \$20 million donation by Apotex to the University of Toronto is the ‘top’ priority of the University of Toronto.

Throughout 1997 and 1998, I and several other concerned scientists have requested an independent inquiry into this matter. We have refused to participate in Naimark’s ‘review’ because of grave concerns about the fairness of a panel appointed by one of the parties implicated in this controversy. Therefore, presentation of the legal records, transcripts of tape-recorded messages, other communications and unassailable facts that will not be presented to Naimark will be included in a future full, independent and unbiased inquiry.

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1. Tricta, F. *et al.* Long-term chelation therapy with the orally active iron chelator deferiprone in patients with thalassemia major. Proceedings of the 6th International Conference on Thalassemia and the Haemoglobinopathies, April, 1997.
2. Tricta, F. *et al.* Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major. Proceedings of the 6th International Conference on Thalassemia and the Haemoglobinopathies, April 1997.
3. Diav-Citrin, O., Atanackovic, G. & Koren, G. Correlation between initial hepatic iron concentration and response to deferiprone (L1) in patients with beta-thalassemia major. *Clin. Pharm. Ther.* 192, PII-77 (1998).

LETTERS TO THE EDITOR

Nature Medicine encourages brief letters to the editor (no more than 500 words) on topics that have been reported in previous issues or on subjects of interest to the biomedical research community. Letters should be addressed to *Nature Medicine*, 345 Park Avenue South, New York, NY 10010, USA, or sent by fax (212.683.5751) or by e-mail (medicine@natureny.com).