INTERVIEW

Nancy Olivieri: Sometimes, truth has only one face

SANDHYA SRINIVASAN

Introduction

Nancy Olivieri is a senior haematologist and professor at the University of Toronto, Canada. In the early 1990s, she was conducting investigator-initiated research of an experimental drug, deferiprone, in children with thalassaemia, for which a pharmaceutical company, Apotex, started giving some supplemental support. In the course of her work, Dr Olivieri found that deferiprone might not be very effective and was also possibly toxic. When she signalled her intent to disclose the risks to participants, the trials were immediately shut down and she was threatened with "all legal remedies" should she disclose her concerns. This led to 18 years of attacks from the CEO of Apotex as well as fabricated charges and harassment from the University and the Hospital for Sick Children where she worked.

Though independent investigations by the Canadian Association of University Teachers and the provincial licensing body cleared Dr Olivieri of all charges, she continues to face harassment.

In November 2023, Dr Olivieri was awarded *The John Maddox Prize* for "courageously advancing public discourse with sound science". The prize is given by the journal *Nature*, where John Maddox was editor, along with the organisation *Sense about Science,* where he was a founding trustee. Dr Olivieri spoke to Sandhya Srinivasan, Consulting Edtior of *IJME*, on how she withstood the attacks, on the responses of the academic establishment and the bioethics community, on those who stood by her, and those who did not, and what drives her work today.

Excerpts from the interview:

Sandhya Srinivasan (SS): *The John Maddox prize "…recognises individuals who stand up for science and evidence, advancing public discussion around difficult topics despite challenges or hostility." And that's the key part of it, right?*

Dr Nancy Olivieri (NO): That's absolutely the key, because many of us hear, "Oh, many people work to advance science." And yes, many people do stand up for honest science, but many don't encounter such prolonged hostility as my colleagues and I did: the firings, the dismissals, the harassment, and the overt and covert aggressions. In my long story, there was anonymous hate mail aimed at destroying my reputation, severe financial sanctions imposed by the hospital administration then in power, attempts by the Apotex CEO Barry Sherman to portray me as incompetent and dishonest, systematic efforts by the then hospital administration to erode support to my research and clinical programmes, and active harassment and bullying of the few colleagues who stood up in the face of all this. I don't know if a lot of people recognise how powerful that hostility is, especially when it's not just industry. Pressure against inconvenient findings about a drug is often blamed on industry (that is, Pharma), but university and academic hospital administrations — the enclaves on which we should be able to rely for honest, non-conflicted science — are often important forces imposing that hostility.

So that is a very long answer to say: yes, the key phrase in the Sir John Maddox prize is that the individual has stood up for science and evidence "in the face of hostility". The Maddox Prize was a great honour. The congratulations were very welcome, of course, and I am very grateful to *Sense About Science* for this honour, which was very meaningful to me. And I thought — this is great, a high-profile award that may, to some people, in some way, legitimise a position I took 25 years ago. But it is itself remarkable that I am suggesting that standing up for patient safety should have to be "legitimised". I don't mean to imply that the award was merely symbolic. But the sad fact is that many in academia do not seem to appreciate the significance of a struggle until it is honoured with public recognition — which of course almost never happens — and until or unless it does happen, many view it as simply a fight with two "opinions", not between right and wrong.

SS: *How has the ethics community responded to your situation?*

NO: Well, my situation is nearly 30 years old, the struggle continues, and there has been essentially very little "response".

About 20 years ago, I attended an ethics meeting at Toronto where a student of ethics commented about this story: "Well, there are two sides to everything." And I asked: "Really?" I asked her: "If I have a family whose child was taking a drug

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from which they may have sustained unknown damage, I'm not supposed to speak up against the legal threats and a signed contract? Is that the other side to the story?" Possibly the ethics community in Toronto needs a lesson in informed consent.

As for the Canadian community of ethicists, Professor Arthur Schafer was the only one from there who stood up. He and I often ask in frustration: "What's so complicated about this story?"

SS: *Tell us about yourself and your work.*

NO: I grew up wanting to be a physician. My father was a paediatrician, and he was perfectly placed to practise during what I now realise was, in some ways, a golden age of medicine and conveyed his love of medicine to me and others. I attended McMaster University Medical School in Hamilton, Canada. I later obtained fellowships in internal medicine and haematology. While still in my clinical haematology fellowship, in early 1982, I expressed an interest in clinical research to my then-mentor who suggested, "Well, there's this thalassemia clinic at the Hospital for Sick Children in Toronto..."

The reason that the thalassemia patients were cared for at a hospital for children was because at that time the mean survival in children affected with thalassemia, an inherited disorder of haemoglobin that is one of the two most common single-gene disorders in the world, was only around 20 years. Such poor survival is still true in many countries. When I arrived at the Hospital for Sick Children in the fall of 1982, a drug to remove iron from the bodies of these children had recently been introduced — the first widely used "iron chelating" drug deferoxamine.

To explain: removal or "chelation" of iron is necessary because of the toxic levels of the iron accumulated from the monthly transfusions that are required to support the health and lives of thalassemic patients. In other words, patients with thalassemia have severe anaemia; they need transfusion to survive; but transfusions create a second disease while managing the first, and the inexorable accumulation of iron within the vital organs of the body leads eventually, without iron chelation therapy, to complications and death.

I spent an initial four months at the Hospital for Sick Children, Toronto, working in the thalassemia clinic. The first problem that I (and everyone else) recognised was that deferoxamine was often very difficult for children to use; it required regular, usually nightly, prolonged infusions — a needle taped on the arm or leg, to allow (liquid) deferoxamine to be infused under the skin overnight. The issue of administration usually rose in adolescence, when patients would protest the inconvenience of administering a needle 12 hours every night and this is the time at which adherence to this regimen — which is life-saving — often becomes irregular. Some patients would quit altogether for periods of time and in some, it became quite challenging to maintain such a demanding regimen.

But that said, again, deferoxamine is life-saving! Over a few short years, as a result of its regular treatment, the prognosis for children with thalassemia became very different — we observed survival into age 25 and beyond then past the age of 30 years (and now in 2024 thalassemia patients living into their 50s is common). We observed the virtual disappearance of complications. It was a remarkably rapid and dramatic transformation of a deadly disease. Deferoxamine was one of the safest, most effective drugs ever developed. Its problem was the method through which it needed to be administered, because it could not be absorbed by mouth.

Then in 1987, I read a paper in the *British Medical Journal* about a new drug, *deferiprone*, an iron chelating drug that was available by mouth; that is, in pill form. I phoned one of the authors of the paper, but he was not interested in working with me. So, I sought help from a colleague at the University of Toronto Chemical laboratories. I showed him the chemical structure of the drug and he agreed that the drug would be simple to synthesise, and he agreed to do that — except for the raw materials — for free in his lab. Another company, Novopharm, agreed to encapsulate, also without charge, the fluffy powder of the drug which my colleague synthesised, into capsules to be swallowed by patients.

I obtained permission from the Hospital for Sick Children's Research Ethics Board (IRB) to administer the new drug, deferiprone, in a comparison with the old drug, deferoxamine, in a three-week balance study[a]. I also obtained approval for this study from Health Canada, the Canadian drug regulator. After this balance study was completed (fast forwarding a couple of years or so), I applied for and obtained a research grant from the Medical Research Council (then the Canadian federal funder of research) to test the drug in an open label trial[b].

I conducted that open label trial enrolling patients who were resistant to adherence to the old drug, deferoxamine, all of whom agreed after signing a consent form to enter this trial for the short term. I also enrolled a few patients who had developed intolerance to deferoxamine infusions including those with skin inflammation around the infusion site, and others who had sustained complications from the deferoxamine. This trial was not randomised and did not compare deferiprone to deferoxamine.

I also want to emphasise that it was an *investigator-driven trial*. By 1991, we (my colleagues and I) had spent time and money in (as above) arranging to have the drug synthesised, obtaining approvals to administer it, and enrolling patients. No money was paid to us (the costs of the trial were paid from the grant from the Medical Research Council [MRC], but MRC grants don't provide a salary). My US colleague Gary Brittenham, an authority on iron metabolism and on evaluation and measurement of iron, and I had worked out an arrangement to evaluate the patients. Gary had developed a machine, which provides quantitative

measurements of *liver iron concentration,* the only measurement correlated with survival in thalassemia. Obtaining liver iron concentration was important because uncontrolled iron overload is fatal and there is already a safe drug to effectively treat this, and we could not take chances with a new experimental drug.

Anyway, our open label trial eventually showed very promising results. In 1995, we published the favourable short-term findings of deferiprone in these patients [1]. In the meantime, Gary had suggested that he and I seek advice from the US Food and Drugs Administration (FDA) to determine the pathway for potential FDA approval for this drug. Officials at the FDA advised us to compare the new drug deferiprone with the old drug, deferoxamine, in a randomised, controlled trial (RCT). The FDA had also advised that we would need to obtain the collaboration of a pharmaceutical company to ensure what is called Good Manufacturing Practice.

We didn't know any interested drug company. But a doctor at the Hospital for Sick Children in Toronto had connections to a CEO of one company, Barry Sherman of the Canadian-based generic drug company, Apotex. We signed a contract under which Sherman would synthesise the drug for the open label trial. Sherman also agreed to provide partial funding to the RCT which, after the advice we'd received from the FDA, we were launching. Sherman had not — as is clear from the above — contributed any of the heavy lifting to the early development of the drug. In return, he would obtain worldwide patent rights on the drug.

Some months after our first paper, we found that liver iron concentration in some of the patients in whom liver iron concentration had initially shown a good response during early deferiprone exposure, appeared to increase. In some, they were close to or exceeding the defined threshold for heart disease and premature death (These were not debatable levels; they had been established long ago in the medical literature). Gary and I presented our findings to Sherman very clearly: how several patients' responses had initially been promising, but then began to increase above acceptable levels, suggesting inadequate long-term effectiveness in many. We offered several hypotheses for this and proposed a modification of the trial to allow us to continue to explore the potential usefulness of deferiprone. We also indicated our plan to draft a revised consent form to inform the patients of these concerns. We certainly did not suggest the trials — either the open label or the RCT — be stopped. In parallel we conferred with the Head of the Research Ethics board (REB) — who we would later remember as the last man in authority who did the right thing — who confirmed that if we as investigators believed we must revise the consent forms to make the risks known to the patients, then we must do so, and quickly.

Accordingly, we revised the consent forms to inform the patients and their parents about our concerns, and we submitted these to the REB on May 20, 1996. Sherman was copied on the correspondence, and he was sent the revised consent forms on that day as well. Three days later, on May 24, 1996, I returned to my office at the Hospital for Sick Children (HSC) to find a letter had been slipped under my door from Sherman which informed me he would exercise legal action ("all legal remedies") if I told patients, parents, regulatory agencies, or the scientific community about my concerns. Sherman also informed me he was prematurely and unilaterally as of that day, terminating both trials. Three days after that Sherman's employees came to the Hospital pharmacy and swept all the deferiprone from the pharmacy shelves so that patients who had been receiving deferiprone for years were suddenly without the drug.

The trials were never reinstated making it impossible to generate more long-term data (which may have proven even more harmful to Sherman's financial interests).

SS: *What was the university's response to Sherman's actions?*

NO: The then Dean of Medicine at the university of Toronto opened with this comment: "But Sherman is funding the trials. He can stop them if he wants. Don't you think this will all blow over?" Nothing as it turned out, could have been more wrong. I tried to explain that not only had Sherman no intellectual input into the trials nor was he the only funder (MRC was still funding the RCT), but that aside, no private company has the right to prematurely and abruptly shut down a trial to attempt to stop the possibly emergence of more unfavourable data, or to threaten independent researchers with legal action against disclosure.

I notified Canada's Medical Research Council which was still funding 50% of the RCT. That agency said and did nothing. It never objected to these actions by Sherman, or his later actions.

After Sherman threatened me with legal action, I sought help from the Canadian Medical Protective Association (CMPA), the Canadian medical defense union, which usually defends doctors against challenges in clinical practice. Over the next year, through the CMPA, I had the benefit of free legal counsel. It was because of this potential defense (Sherman was still issuing weekly threats of legal action) that I was able to inform the patients, to notify regulatory agencies and other investigators working in the field, and finally to publish the results of our long-term findings with respect to deferiprone in the *NEJM* which we did in 1998 [2]. Whenever I undertook any of these actions, I would receive a letter from Sherman, threatening to sue me. But he didn't sue at that time, knowing I had full access to free legal advice. He would sue me only later.

It is only in the last few years I have recognised how significant the support of the CMPA was in that first critical year I would have been bankrupted by Sherman and I would have been fired as most whistleblowers are. Sherman's threats and bullying continued of course. And as for what happened at the University of Toronto and the

Hospital for Sick Children, I refer to the Canadian Association of University Teachers' (CAUT) later, authoritative report: [3]

> *The Hospital for Sick Children took actions that were harmful to Dr Olivieri's interests and professional reputation, and disrupted her work*.

As for why this happened: To quote Professor Schafer:

> *It was discovered during this period of conflict and controversy that the University of Toronto was negotiating for a twenty million dollar donation from Apotex (with additional millions promised for its affiliated hospitals). Some were led to speculate that the university's failure to recognize and support Olivieri's academic freedom might not have been unconnected to its eagerness to secure financial support from Apotex for its [the university's] proposed molecular medicine building project. Indeed, it was subsequently revealed that the University's then president had gone so far as to lobby the Government of Canada on behalf of Apotex.* [4]

SS: *Could you explain what it meant to keep the trial going?*

NO: Gary and I had proposed some hypotheses including that the new formulation of the drug (after Sherman had undertaken its synthesis) might be related to the new evidence of inadequate effectiveness. As above, we wanted to continue the trial but to inform patients, formally, and ensure that they understood, and to sign the revised consent form. Most parents told me: "If you think there are safety issues at all, I want my child back on the infusions no matter what." But many older patients told me, "I don't want to go back to the infusions. I am informed, but I still want to make the choice and I would like give my full informed consent." It is important to remember that we had proceeded on the advice and instruction of the Hospital REB which would not allow the trial to continue without a new consent form. But I never got a chance. As above, Sherman shut down the trial 72 hours after he was sent those revised forms.

SS: *Some people have suggested that you broke a confidentiality clause*

NO: There was indeed a contract that I signed with Sherman, with the oversight of the Hospital's Research Institute (although the Director of this would later attempt to claim it did not adhere to hospital policy at the time, this was not true), and it contained a confidentiality clause which stated that I could release the findings of the RCT only after one year after its termination. But this clause didn't cover the trial (the open label trial) in which we became concerned about the inadequate effectiveness of deferiprone; there was no confidentiality agreement attached to the data in this first trial.

But this in fact is not relevant: a confidentiality clause which would prevent patients from full consent violates public policy and must always be overridden when patient safety is concerned.

Many years later on the *60 Minutes* programme highlighting my struggle, journalist Lesley Stahl asked Dr David Nathan, head of the Dana Farber Cancer Institute and one of my mentors and supporters: "What about that contract Dr. Olivieri signed?"

And David replied, "I don't care if she signed the Gettysburg address."

Stahl asked David, "Why do you say this?"

David told her "Because these are children. These are patients. And you don't take chances with human lives."

That pretty much sums up how important a contract is when human lives and health are at stake.

SS: *What are the biggest lessons these years have taught you?*

NO: That if it had not been for the support and solidarity of my colleagues, which many whistleblowers do not find, I would have been fired, ostracised, probably living without resources or employment. All this may sound highly dramatic. But it is what happens to many who speak against power and money. I was up against daunting forces of power — not only Sherman but most individuals within the University and Hospital Administrations — and we had little power. I had my few colleagues at the hospital, my colleague Gary Brittenham, and the strong ongoing support of my colleagues in the thalassemia field, Professor David Weatherall of Oxford and Dr David Nathan of Harvard.

SS: *Why is this important?*

NO: My colleagues at the HSC included four highly respected scientist-researchers who provided support almost immediately. The five of us would meet several times a day, over years, discussing how to battle the hospital administration and threats from all other sides. Gary was a highly respected expert in the field as were David Nathan and David Weatherall who had made the most significant contributions to thalassemia over the previous 25 years. They were all clear on the issues — the threat to academic freedom and scientific integrity, but also to the safety of patients in research.

I have interacted with many whistleblowers over the years, and they, especially in the medical field, would say they didn't have support and that understanding of the issues. This wasn't about personal loyalty. It was about the violation of patient safety, and that galvanised my intrepid supporters. On the flipside, we underestimated the power that pharma has with academia. The patina of respectability that is afforded academics is an illusion. You don't need this story to understand that academics are aligned with Pharma. Most of the aggression came not from Sherman but from academics.

SS: *Should academics have to rely on industry?*

NO: Do we want evidence to be generated by those who are

critical? Pharma data generally present only one way: the drug as favourable when it may not be so favourable, or safe. Of course, many see the situation as a reliance on Pharma for publications and career advancement. But research misconduct is certainly, indisputably, on the rise, and one influence on that, I believe, is the influence of pharma money. This of course isn't easy to summarise but the issues have been discussed in many excellent books. There is a larger context and that is the direct conflict of interests when institutions for the public depend on private money. And it is not just academia. Nearly 65% of the US FDA's budget comes from user fees from industry. That's the fox guarding the henhouse.

SS: *A subject expert is quoted as saying: "One can't work in this field without working with drug manufacturers." Could you comment?*

NO: I find that comment naïve. He's essentially saying: "Sure you had a bad experience, but we have to work with Pharma and other companies aren't like that." Really? But, why should we "work with Pharma"? To generate me-too drugs using misleading data so Pharma can charge exorbitant prices for so-called innovative research? I suggest that this expert may not recognise that Pharma-funded trials are much more likely to produce data favourable to the company — to claim the drug is safer and more effective than it really is. "Working with pharma" implies we're getting essential drugs to people and saving lives. In most cases, the data show that isn't the case. It's more often about the 17th lung cancer "me too" drug with sadly limited effectiveness. Sure, you want a big CV, to go to pharma meetings with all the perks… then yes, you'll likely choose to work with Pharma.

The presumption in that comment is also that whistleblowers don't know how to play the game. But they know all the rules; they just don't have the same goals any more. Many, like me after this kind of experience, do not quest to appear on a panel or education session of the next meeting — those meetings are now swarmed by the pharma shills and the "key opinion leaders" working for Pharma, all the time claiming they are independent and aren't influenced by Pharma money. It's really not what I want to do. I have been working in Sri Lanka for 27 years with a group of doctors which my mentor David Weatherall helped to train. When we discuss patients on our monthly zoom, no one suggests: "Let's try out that $94,000 drug."' The fact is that most (over 80%) of the world's patients with thalassemia are not getting expensive fancy drugs; they don't have access to safe transfusions. As far as I am concerned in this disease, more efforts should be expended to provide safe transfusions and access to truly essential medicine.

You find yourself, after an experience like this, isolated from your old life. But that's just the way it is. And I wouldn't change that. Just yesterday, a drug company called me and said we'd like to work with you and I responded: *No, you wouldn't.*

Notes:

[a] *A three-way balance study is a short term, comparative "iron balance" study in which patients were admitted to hospital and while receiving a low iron diet, underwent measurement of iron excretion without exposure to any drug (baseline), and then during exposures to deferoxamine, and to deferiprone. Any iron excreted over baseline would reflect the short-term effectiveness of the relevant drug.*

[b] *In an open label trial, all the patients and all investigators are aware of the treatment, all the patients receive the same treatment and there is no comparison or control group. A randomised controlled trial would follow.*

Useful links:

https://www.researchgate.net/publication/8778512_The_Olivieri_Debacle_Where_Were_the_Heroes_of_Bioethics

https://www.researchgate.net/publication/338463626_Institutional_conflict_of_interest_attempting_to_crack_the_deferiprone_mystery

https://inthepatientsinterest.org/

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