

"The Drug Trial: Nancy Olivieri and the Science Scandal that Rocked the Hospital for Sick Children"

Miriam Shuchman, 2005, 451 pages, Random House Canada, \$24.95

Review by Norman M. Goldfarb

"The Drug Trial: Nancy Olivieri and the Science Scandal that Rocked the Hospital for Sick Children" explains how a Nancy Olivieri, a physician-researcher; Toronto's Hospital for Sick Kids; Apotex, a Canada's largest pharmaceutical company; and dozens of supporting characters created and eventually resolved a hugely complicated and damaging controversy involving public health, academic freedom, scientific misconduct, conflict of interest, and academic politics. The book reflects how all parties lost sight of what should have been the central issue: the academic right to publish.

The author has sorted through voluminous conflicting information to tell a unique and fascinating story. Although Dr. Olivieri emerged from the controversy as a sort of patron saint of academic freedom, the truth is much more complicated. She would no doubt hotly contest much of the story that follows and may be correct on some points. This review presents the reviewer's perspective on the controversy, based on a reading of the book.

Dr. Olivieri, a physician at the Hospital for Sick Kids in Toronto, Canada, fiercely advocated use of deferiprone, an experimental drug for treating thalassemia, a genetic blood disorder. Thalassemia requires frequent blood transfusions. Over time, these transfusions cause iron to build up in the blood, damaging the liver, heart and other organs. The accepted treatment at the time required daily injections of an expensive drug with side effects that caused many patients to risk death rather than take the drug. Deferiprone was inexpensive to manufacture and could be taken as a pill, with better patient compliance. Dr. Olivieri was able to obtain numerous research grants and contracts despite serious misgivings by leading authorities about the safety of deferiprone.

Prior to the deferiprone controversy, Dr. Olivieri had a long record of being "difficult." For example, she routinely humiliated subordinates in meetings. Her behavior was tolerated because of her reputation as a brilliant scientist in an important area of research. She also had intelligence, dedication, diligence, passion, charm and other positive attributes. During the controversy, her supporters and enemies focused on very different sides of her behavior and personality.

Apotex became Dr. Olivieri's primary source of funding. She eventually determined that the drug lost its effectiveness in a high percentage of study subjects. When, after months of delay, she informed Apotex, it terminated her study and refused to fund new studies that she proposed. Infuriated, she became deferiprone's fiercest opponent, arguing that the drug became ineffective because it caused liver scarring, a potentially fatal complication. She based her argument on observations of her study subjects and the findings of a pathologist who evaluated liver biopsies and found scarring. However, the samples were unblinded and the biopsies were examined chronologically.

Apotex, having invested many millions of dollars in deferiprone research and with promising interim results in other studies, asked Dr. Olivieri to delay publicizing her findings until they could be confirmed. She refused, so Apotex threatened to sue her for breach of contract; the clinical trial agreement she had signed gave Apotex the right to block publication of study results and data. (During the ensuing controversy, Apotex largely kept its head down and never did sue Dr. Olivieri.)

Dr. Olivieri eventually published a paper expressing her concerns about liver scarring and the ineffectiveness of deferiprone. The paper ignored the findings of two independent pathologists, who examined the same biopsies properly and contradicted her pathologist's findings. These pathologists noted that the number of subjects was small, many of the samples were deficient, and many of the subjects had liver-scarring viral hepatitis. High levels of iron also cause liver scarring. In addition, her findings of drug ineffectiveness were contradicted in much larger studies by other researchers and probably resulted from incorrect statistical analysis or her small subject population.

Few people involved in the controversy emerged with their reputations intact. The last of many official investigations vindicated Nancy Olivieri, but it appears that she was far from an innocent victim. In addition to the problems mentioned above:

- She did not complete case report forms for months after study visits.
- After Apotex terminated her deferiprone study and declined to fund a new study, she informed the FDA about her deferiprone concerns and presented her findings at a scientific meeting. However, she did not inform the research ethics committee, her toxicology collaborator, or the study subjects. She also continued prescribing the drug to patients.
- She accused her employer, the Hospital for Sick Kids, of not providing legal support in her conflict with Apotex, but she had never asked for it.
- She accused the Hospital for Sick Kids of firing her after it accepted the resignation she threatened if it did not meet a deadline she set. (Her employment continued.)
- She accused others of conflicts of interest but did not mention her own consulting agreement with Apotex.
- To obtain leverage over the Hospital for Sick Kids, she asked the University of Toronto to end its relationship with the Hospital, a move that would have damaged the careers of numerous physicians in training.

As a result of the controversy, academic freedom has been strongly reinforced in Canada and throughout the world. The Hospital for Sick Kids and other leading research institutions no longer sign clinical trial agreements that allow study sponsors to arbitrarily block publication of study results. Many scientific publications have instituted policies supporting the freedom to publish. On the other hand, although deferiprone is widely used to treat thalassemia patients in Europe and Asia, it is not marketed in Canada or the U.S., where patients have probably died as a result.

The book is available in bookstores.

Reviewer

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