Thalidomide Retrospective: What Did We Learn?

F.C. FRASER
McGill Centre for Human Genetics, Montreal, Canada H3A 1B1

The year 1986 was the 25th anniversary of the recognition that thalidomide is a potent human teratogen, and our president, Lewis Holmes, asked me to organize a symposium at our 26th annual meeting to commemorate that event which, disastrous though it was, provided an immense stimulus to the development of teratology. I was able to gather a panel of speakers all of whom were deeply involved in the story, and whom I would like to thank, most gratefuly, for their participation. The following papers summarize their presentations and, in some cases, extend the discussion to areas there was no time to include in the symposium.

One of the most central figures in the drama was Widukind Lenz, then a pediatric geneticist at the University of Hamburg, who reviews the history of thalidomide embryopathy. With characteristic modesty, he does not mention his own central role in establishing the causal connection. He does tell us that the first case of thalidomide embryopathy was a girl born Christmas day of 1956. Other cases started to appear as the drug was released in various countries. By September 1961 there were enough examples that Wiedemann was able to describe the syndrome, though he did not make the association. On November 8 Lenz realized that Contergan (thalidomide) had been reported by a number of the mothers of cases he had seen. He informed the manufacturer, resulting in withdrawal of the drug from his hospital, thus shortening the period of exposure to the drug in Australia to less than a year. In December 1961, after three more affected babies had been born, McBride wrote a letter to the *Lancet* and this, along with Lenz's corroborative report in January 1962, led to general recognition of the problem.

My first awareness of thalidomide came from a headline in *La Stampa*, which I happened to see on a newsstand in Geneva, in November 1961, telling of the German gynecologist [sic!] W. Lenz and his suspicions. I remember my first reaction of incredulity. This was also the reaction of Josef Warkany, who tells us about why he was at first skeptical. Dr. Warkany knew more about teratogenically induced malformations than anyone I can think of, having been the founder of experimental mammalian teratology, and no one has given more unstintingly of his time for the innumerable consultations, committee work, symposia, and other demands that must have radically changed his life. He, also, underplays his role, and comments, instead, on how thalidomide changed the lives of many people, for better or worse.

Recognition of the teratogenic association was occurring almost simultaneously in Australia, where thalidomide was undergoing clinical trials. I am indebted to David Walsh, School of Veterinary Medicine, Sydney, Australia, for providing the Australian information. William McBride delivered the first affected Australian baby in May 1961. Since he had never seen such a case in his 7 years at the hospital (which delivered 4,000 babies a year) he had no suspicion that it was caused by a drug. After two more affected babies had been born he reviewed the records and realized that all three women had taken thalidomide, and no other drugs, during their pregnancies. The drug company was informed but did not respond. McBride immediately withdrew the drug from his hospital, thus shortening the period of exposure to the drug in Australia to less than a year. In December 1961, after three more affected babies had been born, McBride wrote a letter to the *Lancet* and this, along with Lenz's corroborative report in January 1962, led to general recognition of the problem.
A third person who was deeply involved with the thalidomide problem was Frances Kelsey, who became a heroine for not allowing thalidomide on the U.S. market. She traces how recognition of the thalidomide embryopathy has changed the drug-regulatory process for the better, yet leaving some unsolved problems.

Fourthly we hear from someone who was more personally involved than any of us. Tim Heshka was born with serious limb defects in the midst of the thalidomide epidemic, and his account of what it’s like to be affected is both instructional and inspirational.

There was no time, at the symposium, for a discussion of the mechanism by which the drug has its teratogenic effects. Trent Stephens has bravely volunteered to fill this gap with a scholarly review of the many proposed mechanisms, none of which is generally accepted. But, he says, we have learned a lot along the way.

Finally, our editor and former president, Robert Brent, reflects on the important clinical information that has resulted from the thalidomide tragedy and on the immense increase in birth defect litigation which began in the thalidomide era. Our grateful thanks go to all of these for their fine contributions.