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Historical Vignette

Unintended Consequences: The Story of PERF

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In the days before widespread internet use, iPhones, and iPads, the American Board of Psychiatry and Neurology part II oral board examination provided a unique opportunity for examiners to meet, mingle, and network. Sometimes interesting collaborations developed. Such was the case in 1994 when we had the same hour off on Dr. Alan Percy's child neurology team.

We were discussing infantile spasms and the reports out of Europe that vigabatrin was showing efficacy in treating infantile spasms.[1,2] We thought, "Wouldn't it be neat if we could get access to vigabatrin for our patients?" We knew Hoechst Marion Roussel had submitted a new drug application for vigabatrin for adult patients with complex partial seizures. We expected approval in the United States within 3-4 years and thought it would be great for our infantile spasms patients if we could get access to it while awaiting Food and Drug Administration (FDA) approval. Thus was born the journey that eventually would lead to the Pediatric Epilepsy Research Foundation (PERF).

Over the summer of 1994, we developed a compassionate use protocol for treating infantile spasms with vigabatrin. This was presented to a preliminary group of investigators at the 1994 San Francisco Child Neurology Society meeting, most of whom would eventually form the Vigabatrin Infantile Spasms Study Group. Over the next 6 months or so, the details were hammered out and the Vigabatrin Infantile Spasms Study Group was formalized (see Table).

Hoechst Marion Roussel agreed to provide an unrestricted grant and three large barrels (55-gallon drums with 165,000 pills) of 500-mg vigabatrin tablets to support the effort.

The protocol was submitted to the FDA and Hoechst Marion Roussel sent a check that was promptly deposited into our bank account. Twenty-nine days after submitting the protocol, the FDA put a hold on the study, indicating that they did not want to allow a compassionate use protocol. We contacted the FDA, and Dr. Russell Katz advised us he wanted us to do an efficacy study because someday someone might want our data to get vigabatrin approved for infantile spasms.

Because Hoechst Marion Roussel had submitted a new drug application for vigabatrin for adult patients with complex partial seizures, they wanted no part of our study. They did not want it to affect their new drug application, so they would not allow us to work under their investigational new drug application. However, they thought our project was a way to deal with the FDA's desire for them to have a compassionate release study for vigabatrin, but were not interested in supporting an efficacy trial. The saving grace was that we had their money in our bank account and had no intention of returning it. We did not have the funds to allow us to do a placebo controlled trial as Dr. Katz had wanted, but over about 6-9 months, we met with the FDA and it was decided that a randomized high-dose–low-dose study was acceptable to all. In the spring of 1996, our study began.

By 2001, we had enrolled more than 250 patients, of which 221 were evaluable. Unfortunately, about this time, the owner of vigabatrin (now Aventis Pharma) decided to withdraw their new drug application. With no promise that vigabatrin would be marketed in the United States, the FDA asked us to close our study. We had published one report on our study,[3] but without adequate funding to complete the full data analysis, we had to pack up the data (which we owned), thinking it would never see the light of day again. (A final report was published after vigabatrin was purchased by Ovation.)[4]

In the 1990s, individually, we had interacted with Mike Burke, then with Abbott Laboratories. In 2000, Burke, along with several colleagues, formed a small orphan-focused pharma company, Ovation Pharmaceuticals. Burke

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TABLE.
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contacted us and asked what drugs were needed in pediatric neurology that were not being developed by "big pharma." From those discussions, it was suggested vigabatrin for infantile spasms and clobazam for Lennox-Gastaut syndrome. Burke again contacted us in 2002 and indicated that Ovation had an interest in purchasing vigabatrin from Aventis. They wanted to market it for infantile spasms and refractory complex partial seizures in adults in the United States. Ovation did not want to make the purchase unless they had access to our data. An offer was made by Burke (Ovation) that in return for our data, Ovation would provide a royalty to support a not-for-profit foundation that would fund research in pediatric neurology if vigabatrin was approved by the FDA. Ovation also provided seed money to start this foundation.

The Pediatric Epilepsy Research Foundation was formed as a Texas Corporation in 2004. Our original mission statement was:

> "to enhance the quality of life of children with epilepsy and/or other neurologic disorders. To accomplish this mission, the Foundation, in particular seeks to support: efforts to improve treatment options for infants, children and adolescents with epilepsy and meritorious clinical and basic science research related to epileptic conditions in children."

This was recently expanded by adding:

> "the encouragement of the recruitment and education of young physicians in the field of child neurology."

In August 2009, the FDA approved vigabatrin for use in infantile spasms and in refractory complex partial seizures in adults. PERF received its first royalty payment in April 2010. Later that year, PERF made its first research grant to Dr. Gabrielle deVeber at Toronto Sick Kids Hospital for her project "Impact of Seizures in Infants and Children with Ischemic Stroke."

As of December 31, 2014, PERF has funded 21 projects for more than $6 million. PERF continues to thrive and hopes to provide funding for pediatric neurology for years to come. You can find more information about PERF (how to apply for grants) at our web site: www.pediatricepilepsyresearchfoundation.org.

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