Editor's Notebook: Bernard Rimland, Ph.D.

Secretin: The controversy continues

On January 5, 2004, the Repligen Corporation released the long-awaited preliminary results of its Phase III study of secretin efficacy in autism. To the surprise and dismay of many, the results, though incomplete, were reported by Repligen's Walter Herlihy as negative. The negative report contrasted sharply with a great deal of very positive earlier data, and with Herlihy's previously expressed enthusiasm for secretin.

Following is an open letter to Dr. Herlihy regarding this matter.

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Walt Herlihy, Ph.D., CEO
Repligen Corporation

Subject: Proposal for definitive Phase III research on secretin for autism

Dear Walt,

I am amazed that you wrote, "We have not had much interest in secretin from the parent/physician community since the announcement in January."

Very much the opposite is true here. We have gotten, and continue to get, communications from upset parents and physicians, many of whom are Repligen stockholders.

Phase III: These people feel, as I certainly do, that the early Phase III findings, while not spectacularly positive, were far from discouraging, and not at all consistent with the excellent Phase II data. There were some very encouraging bright spots in the Phase III data, including:

- The significant improvement in "Social and Interaction" in the higher functioning half of the population (68 patients).
- Your statement in the conference call on January 5th ".... there were several children who went from autism... all the way to normal . . . Those are very dramatic changes... and they were in the drug group, not the placebo group." A remarkable finding!
- The parents reported great improvement, but in both the placebo group and the secretin group. This is supposedly the most important negative finding, but it is an infinitely better finding than parents reporting *no* improvement in either group.
- The positive findings above, and in Phase II, came about in the face of two very difficult obstacles: (a) The absence of a useful means of identifying the appropriate subgroup for study, and (b) the widely acknowledged lack of sensitive instruments for measuring improvement.

Phase II: In your October 2001 talk at our Defeat Autism Now! Conference in San Diego you cited many very positive and encouraging results from the Phase II studies, including:

- No serious adverse results ever reported with secretin, including in "the quarter of a million doses given to adults . . ."
- You said, "...of the 126 patients...you now know there is a 98% chance that that's a drug (secretin) effect, and only a 2% chance that it is due to spurious variation."
- You also said, "...twice as many kids responded on secretin than placebo. And that is 98% probably due to the drug. So it's pretty clear-cut evidence of a drug effect."
- You also said, in commenting on four previous studies by others, "If you add all this up, these four studies, we have 37 versus 21, 98% confidence level. It's called a meta-analysis, where you aggregate small under-powered studies together to look at what happens. So there actually is, through this analysis, evidence of a very significant treatment effect."
- You commented, "I think we've developed some biomarkers for patient selection. They are not selectors for who might respond, but for who really shouldn't be studied until they have some other things done to clean up the gut." (Was there an attempt to clean up the gut in the phase III study?)

All of the Phase II kids, but only 30 percent of the Phase III kids, had GI problems. That could easily explain the worse Phase III results. Many parents and physicians have commented on this.

You stated in your Phase II report that none of the subgrouping criteria, such as age, chymotrypsin or calprotectin levels, etc., had proven effective in identifying the autistic kids who were most likely to respond to secretin. That is why you had to use essentially useless criteria for selecting subjects for the Phase III research. You said, "...I'd be absolutely thrilled to be participating in the development of a drug that would help in one symptom or another, make clinically meaningful differences, in 10% of the population." You said you knew there were responders, because you'd seen them yourself, but the problem is of course, how do you identify in advance the children who are going to respond positively to secretin?

That question has a simple and straightforward answer: I strongly urge that in your discussions with the FDA you propose to do a double-blind, placebo-controlled cross-over study of autistic individuals (including adults) who are known to be responders to secretin. I would have no trouble referring secretin responders—parents and physicians are eager to see secretin tested on the autistic kids they have identified as responders.

You used 126 patients in your Phase II studies, and 132 children in the Phase III research—five or six times as many as would be needed for a properly designed study.

In a placebo-controlled, cross-over study, where each subject is a known responder, and where each subject serves as his or her own control, you can expect statistically significant results with as few as 16 subjects. Sixteen is the number I used in my study, published in the *American Journal of Psychiatry* in 1978, on the use of vitamin B6 in autism, which proved B6 to be effective.

My coauthors, psychiatrist Enoch Callaway of the UCSF Medical School and neurologist Pierre Dreyfus of UC Davis Medical School, were skeptical of the positive results in my earlier study of B6 in autism (Rimland 1973). With the collaboration of the research design team at NIMH, we designed and executed what was intended to be, and in my opinion was, and still is, the most air-tight study ever conducted in psychiatry. It was accomplished with a $19,000 (as I recall) grant from NIMH.

A similar design was used, again with significant results, in a study by Rowe and Rowe published in the *Journal of Pediatrics* in 1994. They used children who were reportedly reactive to synthetic food colorings. Clear reactions to the food dye were found in 19 of 23 "suspected reactors," 3 of 11 "uncertain reactors," and in only 2 of 20 "control subjects." Striking results!

Small numbers, efficient design, inexpensive and easy-to-do, and significant results. What more can you ask for?

In the obvious absence of any other reliable way of identifying the subgroups who need secretin, studying a small number of already known responders will do the job. This must be done!

Cordially,
Bernard Rimland, Ph.D.*

**The patent for secretin use in autism was granted to Victoria A. Beck and Bernard Rimland, and purchased by Repligen. Bernard Rimland donated his share of the proceeds to the Autism Research Institute.*

Rimland, B. (1973). High-dosage levels of certain vitamins in the treatment of children with severe mental disorders. *Orthomolecular Psychiatry*. Edited by Hawkins D. & Pauling L. San Francisco, WH Freeman & Co., 1973, 513-539.

Rimland, B., Callaway, E., & Dreyfus, P. (1978). The effects of high doses of vitamin B6 on autistic children: a double-blind crossover study. *American Journal of Psychiatry*, 1978, April,135, 472-475.

Rowe, K.S. & Rowe, K.J.. (1994). Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study. *Journal of Pediatrics*, 1994, Nov; 125 (5 Pt 1) 691-8.