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

Secretin update: a negative placebo effect?

The placebo effect is a consistent tendency for patients to over-report benefits from a treatment that they believe in. To control for placebo effects, researchers conduct blind or double-blind experiments, in which the subjects do not know whether they are being given an active treatment, e.g., a drug, or a placebo. The double-blind study is considered to be the "gold standard." But the gold is tarnished.

Blind studies are employed because patients are human beings, and as such have expectations of either help or harm from the treatments they are subjected to. But the experimenters are also human beings, and they too have expectations, which it would be unwise to overlook. The researchers' expectations may have strong and perhaps overriding effects on the results of the experiments they conduct. That is our concern here.

Recently there have been accounts in the popular media, as well as in the professional literature, of trials of the use of the hormone secretin. On the one hand we have many reports of dramatically good results attested to by the parents of autistic children and by their physicians. Children who have never slept the night through begin to sleep soundly, immediately after the secretin infusions. Children who have had chronic diarrhea for months or years suddenly begin having normal bowel movements. Children who have never spoken, or made eye contact with their parents, suddenly begin to show remarkable improvement in these symptoms. Very convincing!

However, the half dozen or so research studies which have been formally reported have (supposedly) not produced positive results. Why these conflicting conclusions?

Skeptics have repeatedly tried to explain away the conflicting results by saying that the positive responses were merely placebo effects—the products of wishful thinking by parents or physicians whose objectivity has been overcome by the desire for good results.

I recognize the plausibility of that argument, but an equally plausible argument can be made that the negative results may be the consequence of the researchers' expectation that the secretin will *not* have beneficial effects, and therefore their conclusions are driven by what may be called the "negative placebo effect." It is easy to shoot down a new treatment in a double-blind trial—just refuse to see change in either group.

Example: a *Wall Street Journal* article (March 10, 1999), cited a number of very positive reports from parents and physicians who had tried secretin on autistic children, and stated that a study by neurologist Michael Chez of Chicago had shown no benefit.

Shortly after the *Wall Street Journal* article appeared, I was approached by a mother whose child had been treated with secretin by Dr. Chez. She told me that her son had "just soared" after the treatment, and that his improvement was noted by everyone who came in contact with the child. A speech therapist who had recently tested the boy retested him and the difference was so great that the speech therapist, unaware of the secretin, was baffled and kept insisting that she must have made a mistake in the earlier assessment. When the mother brought the child back to Dr. Chez's office, the office staff remarked that the boy had better eye contact and had obviously improved. Nevertheless, this mother was told by Dr. Chez that he could see no improvement, and it was just her wishful thinking that led her to believe the child had improved. Victoria Beck also was contacted by several mothers with similar stories.

> Experimenters are also human beings, and their negative results may be the consequence of their expectation that secretin will *not* have beneficial effects.

Recently Chez and his co-workers published their study in the *Journal of Autism and Developmental Disorders*. They reported that the results were negative, that that they had seen no benefit from secretin.

In my commentary on the article, I pointed out that even though the research had many deficiencies, including the use of a very insensitive means of measuring improvement in the autistic children, the findings, contrary to the authors' declaration, were really quite *positive*. A number of significant differences were found, all favoring those given the secretin.

In a study recently published in the *New England Journal of Medicine*, Adrian Sandler et al. reported that they found no benefit from the administration of secretin to a sample of autistic children. Yet these authors also reported that 69% of the parents wanted their children to be continued on the secretin, even after they had been told that the study supposedly showed no benefit from the secretin. I have spoken to several mothers whose children were in that study, and was told that they have continued the secretin in their autistic children, with outstanding results.

In another study, Jennifer R. Lightdale et al. evaluated 20 autistic children for language skills and behavior before and after receiving secretin. No control group was used. The researchers reported no differences in the children's ability either to understand speech or to express themselves. However, 15 of 18 parents said they saw moderate to significant improvement in the language skills of their autistic children following the secretin infusion.

Bruce Roseman and his colleagues conducted a secretin study on 10 children, to determine the effect on the children's behavior and language. A speech and language therapist, unaware of which children received secretin, tested the children. While the test results were supposedly negative, the speech therapist was able to correctly identify the children on the secretin 90% of the time.

In some of the studies cited above, the researchers acknowledged that their supposedly objective, scientific results conflicted with the observations of others, and agreed that further research is needed to help resolve these differences. Some also admitted that their single-dose studies were not conclusive; multi-dose studies have been started.

The negative placebo effect—bias in favor of seeing negative results—often hinges on the subjectivity of the measure employed, on the tendency to see the glass as half empty, versus half full; or to regard a 6-point difference on a rating scale as indicating trivial rather than worthwhile improvement.

In other cases, the negative placebo effect is built into the design or conduct of the study. For example, a recent study by Findling et al., evaluating vitamin B6 and magnesium as a treatment in autism, neglected to include a "washout" period between the vitamin and placebo phases of the double-blind study. Apparently it was the authors' belief that since the B6 could not possibly have any beneficial effect, there was no need to include the usual several-week "washout" period in their study design. These authors also used unflavored vitamin B6, despite the fact that B6 is very bitter and most parents report that it is impossible to get their children to take unflavored B6. They did not use urine analysis to see if the vitamin had actually been consumed.

Similarly, in a study of vitamin B3 in autism (vitamin B3 tastes even worse than vitamin B6), Greenbaum reported the children had taken unflavored vitamin B3 tablets. Many of the parents told me that their children had totally refused to take the tablets. The parents had complained to the study nurses, but the nurses just shrugged, and the study results were reported as though the children had taken the B3 and had shown no benefit. In fact, very few of them had consumed the vitamin.

The medical community looks with a jaundiced eye at reports that do not involve the use of placebo-controlled blind studies, dismissing them as merely anecdotal. I believe that the medical community should be looking with an equally jaundiced eye at controlled studies. The negative placebo effect—the expectation of and therefore the frequent finding of negative results by possibly biased researchers—is a problem that must be recognized if potentially useful treatments are to be properly evaluated and not prematurely rejected.