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Secretin as a Treatment for Autism: A Review of the Evidence

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Secretin is used in the United States for diagnosis of pancreatic gastrointestinal (GI) dysfunction and disease. Repeated therapeutic use has not been approved. Widespread interest in secretin as a treatment for autism followed media reports of behavioral improvements in an autistic child who received the hormone during a GI diagnostic procedure. International demand for secretin soared in the absence of experimental evidence of its efficacy for autism. This review presents a brief history of secretin's rise to popularity and summarizes research on secretin as a treatment for autism. Seventeen studies are reviewed comparing the effects of secretin forms, dosage levels, and dosing intervals on outcome measures with approximately 600 children. Twelve of 13 placebo-controlled studies failed to demonstrate the differential efficacy of secretin. Implications for advocating treatment in the absence of empirical evidence are discussed.

KEY WORDS: Secretin; autism; efficacy.

INTRODUCTION

Autism is a severe, lifelong, neurodevelopmental disorder characterized by impairments in multiple domains. It is usually identified before the age of three by behavioral assessment of qualitative impairment in social interaction, qualitative impairment in communication, and markedly restricted, repetitive patterns of behavior and interests (American Psychiatric Association, 1994; APA). Prevalence has been estimated at 2–5 per 10,000 (APA, 1994) although some estimates are as high as 1 in 250 (Bertrand *et al*., 2001). Approximately 75% of children with autism also meet the diagnostic criteria for mental retardation and about half never acquire functional speech (Hardman, Drew, & Egan, 1999). The etiology of autism remains unknown; however, recent studies suggest a likely genetic basis for the disorder (see Veenstra-Vanderweele & Cook, 2003).

Although there is no known cure for autism, a number of intervention strategies have been evaluated over the years (Herbert, Sharp, & Gaudiano, 2002), with extremely promising results in some areas (e.g., applied behavior analysis; Smith, 1999). A few examples of the varied and numerous treatments recommended for autism include vitamin supplements, dietary manipulations, auditory integration training, facilitated communication, hyperbaric oxygen treatment, live- and stem-cell therapy, anti-fungal treatment, detoxification for heavy metals, biofeedback, and craniosacral therapy.[1] Unfortunately, many of these treatments have not been adequately tested using proper scientific methods.

One treatment for autism that has been recently popularized is secretin. Secretin is a hormone secreted by the duodenum in response to increased acidity in the stomach. It stimulates the release of bicarbonate and enzymes from the pan-

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[1]For commentary on these treatments, see www.acsh.org/publications/priorities/1301/autism.html and www.healing-arts.org/children.

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creas, thus acting as "a sort of built-in Alka-Seltzer dispenser" (Shutt, 1998, p. 21). Porcine secretin was approved by the United States Food and Drug Administration in 1981 for use in the diagnosis of gastrointestinal (GI) disorders. In the United States, secretin is commonly given in a single dose to patients experiencing pancreatic insufficiency during a diagnostic procedure for this GI complaint or to aid in the diagnosis of pancreatic tumor. A synthetic form of human secretin is available which has been found to be equipotent in its pharmacological effects to the porcine form (Christ *et al*., 1988).[2]

In 1998, Horvath *et al*. reported a case series in which three children with autistic spectrum disorder received a single infusion of intravenous porcine secretin during diagnostic GI endoscopy for chronic diarrhea. Within 5 weeks, all children evidenced not only amelioration of their GI symptoms but parents also reported dramatic improvement in their children's communication and social behavior.[3] The authors speculated that these clinical observations might suggest an association[4] between GI and brain function in individuals with autism although the mechanism for this link was not (and has not been) clearly defined. Horvath (2000) noted that empirical studies, not case reports, would be necessary to fully articulate the role of secretin in central nervous system function and emphasized the importance of placebo control in such future studies. By contrast, improvements that were seen in the 1998 case series were incidental to the endoscopic medical procedure for GI complaints; thus, no control group was included nor were behaviors that were specifically related to autism assessed.[5] Thus, although improvements may have occurred, the methods inherent in this type of study preclude attributing any such improvements to the action of secretin.

On October 7, 1998, NBC's *Dateline* reported the dramatic improvement observed in one of the Horvath *et al*. (1998) participants. Widespread Internet and lay media attention ensued (Coniglio *et al*., 2001; Sandler *et al*., 1999) and parents immediately began to request secretin infusions for their children with autism (Aman & Armstrong, 2000), often paying highly inflated prices for the injections which at times reportedly contained no secretin in the preparation (National Institutes of Health News Alert, 1999). The overwhelming demand for secretin jeopardized the nation's available supply (Rimland, 1999). Websites for The Autism Research Institute in San Diego (www.autism.com/ari) and the University of Sunderland's Autism Research Unit in the United Kingdom (osiris.sunderland.ac.uk/autism) began to post regular research updates and anecdotal reports of the possible benefits of secretin as well as provide commentary on secretin-related issues. Sandler *et al*. (1999) and Owley *et al*. (1999) speculated that thousands of children might have received secretin injections following the initial highly publicized case, all in the absence of empirical support.

Accompanying the early media and Internet coverage of secretin were many voices urging caution to limit or suspend its therapeutic use until efficacy studies[6] could be completed. Commenting on the downside of the sudden media attention to secretin, Volkmar (1999) stated, "what makes an interesting television program may not, of course, be the same as what makes good science" (p. 1844). He admonished physicians to help patients and their families make informed decisions, presumably based on empirical data instead of unfounded claims. Reacting to the interest of some parents in continuing to seek unproven secretin treatment for their children, Volkmar (2000) stated that, unfortunately, treatment efficacy could not be judged by treatment popularity.

Although McMillin, Richards, Mein, and Nelson (1999) suggested that it was entirely plausi-

[2]The chemical structure of these two forms of secretin differs by two amino acids (cf. Carey *et al*., 2002), a subtle but potentially important difference although the direction or relevance of any difference (e.g., clinical, biologic) has not been determined.

[3]Horvath (2000) noted that in the majority of patients in a similar study (Horvath, Papadimitriou, Rabsztyn, Drachenberg, & Tildon, 1999), gastrointestinal changes were noted after a single dose of secretin whereas behavioral improvements were seen gradually and after repeated injections.

[4]GI dysfunction in many children with autism has led to common speculation of a possible causal connection between abnormal brain function and intestinal tract problems. This connection is often referred to as the "brain-gut" hypothesis. However, causality in either direction has not been substantiated and thus the "hypothesis" remains as such.

[5]The authors reported that developmental and psychological evaluations were administered prior to the procedure.

[6]Some of the important variables to include in these studies were identified by Aman and Armstrong (2000). In a survey of parents whose children had previously received secretin, they queried dosage level, patient demographics, presence of GI disturbances prior to treatment, latency and duration of treatment effect, and any observed side effects. All of these components were ultimately addressed in the (collective) subsequent studies reviewed here.

ble that neurologic syndromes (e.g., autism) that are frequently accompanied by GI symptoms could be linked to an "abdominal nervous system," Shutt (1998) warned of the "... dangers in tinkering with the 'bottle of hydrochloric acid' we all carry in our stomachs" (p. 24). He suggested some children might form immunities to the porcine form of secretin, resulting in rejection of their own secretin with potentially devastating effects.

DiCicco-Bloom (1998) advised parents not to allow secretin infusion without evidence of its efficacy in controlled studies that replicated and extended the incidental findings of the Horvath *et al.* (1998) case series. In remarks addressed to parents, he contrasted the available evidence, characterized as "merely a report" (p. 24), with specific research procedures that would provide databased information. He reminded parents that the uncontrolled case series report (Horvath *et al.*) had not yet proven the efficacy of secretin as a treatment for autism. Other concerns were the off-label (i.e., non-FDA-approved) use of secretin in the absence of controlled scientific studies (American Academy of Child and Adolescent Psychiatry Policy Statement, 1999) and the possibility of allergic reaction if multiple doses of the animal-derived form of secretin were infused (Hirsch, 1999).

Given the remarkable claims regarding secretin's effects, the overt significance of treating autism via intravenous hormone therapy, and the flurry of recent scientific attention secretin has received, the purpose of the current paper is to critically review the peer-reviewed quantitative research on secretin as a treatment for the symptoms of autism. Articles were identified through the PsycINFO™ and MEDLINE® databases from 1986 to 2002 using the keywords "autism" and "secretin." An earlier review by McQueen and Heck (2002) reported the results of eight[7] efficacy studies published through 2001. The purpose of the present paper is to expand the earlier review to include additional studies that were either omitted or have been subsequently published.

Seventeen studies were identified and included in our review (see Table I). Sixteen studies included children as participants and one study evaluated secretin with adults. All participants had diagnoses within the autism spectrum disorder (autistic disorder, pervasive developmental disorder [PDD], or pervasive developmental disorder not otherwise specified [PDDNOS]). Because the initial case series report (Horvath *et al.*, 1998) leading to this line of research suggested a possible relation between autism and GI disorder, some of the subsequent studies reviewed here either specifically included or excluded that demographic characteristic. The studies ranged in duration from 3 to 16 weeks. Thirteen of the studies were double-blind and placebo-controlled and four were uncontrolled open-label case studies. Porcine secretin was used in 11 of the investigations, synthetic human secretin was administered in 4, one used a homeopathic secretin preparation, and another compared both the biologic and synthetic forms of porcine secretin to placebo. A single dose of secretin was used in 14 studies; the remaining three studies investigated the effects of multiple doses.

RESEARCH COMPARING SYNTHETIC SECRETIN TO PLACEBO

In the first controlled study[8] of the effects of secretin to ameliorate the symptoms of autism, Sandler *et al.* (1999) studied 56 children with a diagnosis of autism or PDD. This double-blind, placebo-controlled study used a single dose of human synthetic secretin. Randomly assigned participants received either a single infusion (slow injection) of secretin or a single infusion of a volume-comparable saline placebo.

Autism-related behaviors were rated by parents using the Autism Behavior Checklist (AuBC) and the Clinical Global Impression Scale (CGIS). Study clinicians and teachers rated communication behaviors using the Vineland Adaptive Behavior Scales (VABS) and clinicians assessed adverse treatment effects with the Treatment Emergent Symptoms Scale. Measurements were taken 2 weeks and 1 week before treatment, at 1 and 2 days post-infusion, and at the end of weeks 1, 2, and 4 post-treatment. Although both groups demonstrated improvement (i.e., decrease in severity of symptoms) on 6 out of 16 outcome measures, results failed to show a significant difference between the secretin and placebo groups on any of the outcome measures. No particular subgroup of responders was identified with respect to age, severity of autism symptoms, GI symptoms, or the

[7]The review also included two studies on the safety of secretin and its intestinal permeability.

[8]Sponsored by the National Institute of Child Health and Human Development (NICHD).

Table I. Summary of Controlled Studies and Case Reports

Article	Type of study	N	Participant ages	Diagnoses	Type and Dose[a]	Outcomes: Clinician rating	Outcomes: Caregiver rating	Outcomes: Other	Positive results
Carey *et al.* (2002)	Randomized, double-blind, placebo controlled, crossover	8	2–8 yr	AD or PDD Some with GI	Single dose 2 CU/kg compounded Synthetic secretin	×	×		No
Chez *et al.* (2000)—study 1	Uncontrolled, open-label	56	Mean 6.4 yr	AD or PDDNOS Some with GI	Single dose 2 IU/kg porcine secretin		×	×	Yes Transient ⩽1 wk
Chez *et al.* (2000)—study 2	Randomized, double-blind, placebo controlled, crossover	25	Mean 6.0 yr	AD or PDDNOS Some with GI	Single dose 2 IU/kg porcine secretin		×		No
Coniglio *et al.* (2001)	Randomized, double–blind, placebo controlled	60	3–10 yr	AD	Single dose 2 CU/kg porcine secretin	×	×		3 wks – yes 6 wks – no
Corbett *et al.* (2001)	Randomized, double-blind, placebo controlled, crossover	12	4–12 yr	AD Excluded GI	Single dose 2 IU/kg porcine secretin	×		×	No
Dunn-Geier *et al.* (2000)	Randomized, double-blind, placebo controlled	95	2–7 yr	AD	Single dose 2 CU/kg porcine secretin	×	×	×	No
Horvath *et al.* (1998)	Case-series report	3	3–5 yr	AD or PDDNOS All with GI	Single dose 2 IU/kg porcine[b] secretin	×	×	×	Yes
Kern *et al.* (2002)	Randomized double–blind placebo controlled crossover	19	3–10 yr	AD or PDD/ PDDNOS Some with GI	Single dose 2 CU/kg porcine secretin	×	×	×	Yes (GI subgroup only)
Lightdale *et al.* (2001)	Uncontrolled, open-label, blind rating	20	3–8 yr	AD All with GI	Single dose 3 CU/kg porcine secretin	×	×		No
Molloy *et al.* (2002)	Randomized, double-blind, placebo controlled, crossover	42	2–15 yr	AD Some GI excluded	Single dose 2 IU/kg Synthetic human secretin	×	×	×	No
Owley *et al.* (1999)	Randomized, double-blind, placebo controlled, crossover	20	3–12 yr	AD	Single dose 2 CU/kg porcine secretin	×	×		No
Owley *et al.* (2001)	Randomized, double-blind, placebo controlled, crossover	56	3–12 yr	AD	Single dose 2 CU/kg porcine secretin	×	×		No
Roberts *et al.* (2001)	Randomized, double-blind, placebo controlled	64	2–7 yr	AD	Multiple doses (2) 2 ml/kg porcine secretin	×	×	×	No
Robinson (2001)	Uncontrolled, open-label	12	24–43 yr	AD	Multiple doses homeopathic secretin[c] Orally twice daily for 12 wks	×			No

Sandler *et al.* (1999)	Randomized, double-blind, placebo controlled	56	3–14 yr	AD or PDDNOS Some GI excluded	Single dose 0.4 mcg/kg synthetic human secretin	×	×		No
Sponheim *et al.* (2002)	Randomized, double-blind, placebo controlled, crossover	6	3–12 yr	AD No pronounced GI	Multiple doses (3) 4 CU/kg synthetic human Secretin	×	×	×	Small differences (no clinical significance)
Unis *et al.* (2002)	Randomized, double-blind, placebo controlled	85	3–12 yr	AD or PDDNOS	Single dose 2 CU/kg porcine secretin or 0.4 mcg/kg Synthetic porcine secretin	×		×	No

[a] Secretin potency is designated in clinical units (CU) or international units (IU); conversion comparison is 0.2 mcg = 1 CU.
[b] Personal communication with first author, January 8, 2003.
[c] Secretin 6C (centesimal dilution).
Note: AD = autistic disorder, GI = gastrointestinal complaint, PDD = pervasive developmental disorder, PDDNOS = pervasive developmental disorder not otherwise specified. The descriptor "uncontrolled" refers to no placebo control and nonrandomized samples.

use of adjunctive medication. No treatment-limiting side effects were observed in any of the children.

In discussing the suspected placebo effects from their 1999 study (i.e., 30% of both groups showed improvement on outcome measures), Sandler and Bodfish (2000) recalled that a majority of parents in the 1999 study continued to express interest in secretin even after being informed of their child's group assignment and in the absence of clinical effect attributable to secretin. The authors offered several factors that could account for this. Most parents have a strong desire to improve their child's quality of life. This, coupled with possible dissatisfaction with other treatment options, may contribute to continued interest in a treatment that has not been conclusively disproved. Moreover, the disruptions inherent in living with a child who has autism might give rise to seeking out any reasonable treatment that might promise relief, despite the lack of scientific support.

There were some limitations of the Sandler *et al.* (1999) study. It was short-term; a few weeks may not have been enough time to observe significant behavior change. In addition, multiple doses of secretin may have demonstrated greater effects than a single dose. However, the Horvath *et al.* (1998) case series also used a single dose and improvements were anecdotally reported within a similar time frame (i.e., 4–5 weeks). Another limitation concerns the inclusion criteria used in the study. Specific subgroups of participants with differing potentials for response to treatment might be identified using certain diagnostic instruments (e.g., children with particular GI problems might be more responsive to secretin treatment than children without these symptoms). Finally, whereas most anecdotal reports of positive secretin effects followed infusion of the porcine derivative of secretin, this study used synthetic human secretin. These limitations notwithstanding, Alexander (1999) recommended that, based on the Sandler *et al.* results, the use of secretin as a treatment for autism be suspended until further empirical studies could be completed.

Carey *et al.* (2002) also evaluated the effects of synthetic human secretin. In a randomized, double-blind, placebo-controlled study, eight children received first either secretin or placebo, and then "crossed over" (via a crossover design) to the alternative treatment 4 weeks later. Thus, participants served as their own controls. Changes in autism-related abnormal behaviors were evaluated

using the Aberrant Behavior Checklist (ABC). Consistent with the Sandler *et al.* (1999) investigation, Carey *et al.* found no reliable improvements attributable to secretin. The study was treated as a clinical replication series due to small sample size and data were analyzed accordingly. The study was further limited by the use of only one outcome measure. It is possible that clinically significant change might have been detected with the use of additional measures. Similarly, a single dose of secretin may have been insufficient to effect measurable behavior change. Finally, the study may have been limited by carry-over effects due to the crossover design. Data are not definitive on the duration of possible secretin effects so the possibility of treatment-order effects within participants could not be eliminated.

In a study that addressed some of the limitations of the Carey *et al.* (2002) investigation, Molloy *et al.* (2002) reported the results of another randomized, double-blind, placebo-controlled crossover study of 42 children using a single dose of synthetic human secretin in which a comprehensive battery of tests was used to assess behavioral outcomes. Measurements were taken five times (prior to the first infusion, at week 3, at week 6 prior to the crossover infusion, and at weeks 9 and 12). Receptive and expressive language was evaluated by two speech and language pathologists using the Peabody Picture Vocabulary Test-3 (PPVT-3) and the Receptive Language Scale of the Mullen Scales of Early Learning (MSEL-RLS). Cognitive skills and autism-related behaviors were assessed by a clinical psychologist using selected tests of the Merrill–Palmer Scale, the Developmental Test of Visual Perception (DTVP), the Childhood Autism Rating Scale (CARS), and the Gilliam Autism Rating Scale (GARS). In addition, parents were asked to periodically provide information about their child's medical condition and stool patterns. Blood-chemistry profiles were also obtained for all participants.

No significant differences were found between those who received secretin compared to placebo, nor were there treatment-order effects between groups who received either secretin or placebo as the first treatment. Negative results were also obtained for differential effects of secretin on a subgroup of participants with GI symptoms. The study may have been limited because of the self-referred population with males being heavily over-represented; however, the use of random assignment should mitigate these concerns.

In a two-part crossover study, and the second (cf. Sandler *et al.*, 1999) secretin investigation sponsored by NICHD, Owley *et al.* (1999) studied 20 children with a diagnosis of autism using a randomized, double-blind, placebo-controlled crossover trial of porcine secretin. Participants received either secretin or a saline placebo at baseline followed by the other substance at the second infusion (week 4). The primary outcome measure was the Autism Diagnostic Observation Scale-Generic (ADOS-G), which provided scores in social communication behavior. Additional behavioral outcome data were obtained at the same intervals (baseline, after weeks 4 and 8) using the DTVP or the fine motor subscale of the Mullen Scales of Early Learning, the PPVT or the MSEL-RLS for receptive language assessment, and the CGIS. At the same intervals, parents were interviewed using the VABS. They also completed the GARS and the ABC, Community version (ABC-C) at baseline and at weeks 2, 4, 6, and 8.

Although randomly assigned, the two groups (secretin-first and placebo-first) differed at baseline on the ADOS-G social impairment score with the secretin-first group functioning at a significantly lower level. Conversely, baseline scores on the ADOS-G stereotypy measure were higher for the secretin-first group. Owley *et al.* (1999) speculated that the secretin-first participants might represent a group that is less likely to benefit from secretin infusion, although no ceiling effect was exhibited by this group in which improvement would be difficult to detect.

The placebo–secretin group did not improve after the second infusion (secretin). This is a relevant finding because the group acts as its own control and no carry-over effects are expected following the placebo infusion. Although minimal improvement was noted in both groups during the first 4 weeks, there were no statistically significant differences between the two groups at the end of 8 weeks. The initial improvement in both groups could be attributed to expectancy effects since the trend for both groups was the same. None of the participants demonstrated adverse effects that appeared related to secretin infusion.

The Owley *et al.* (1999) study was part of a larger multi-site investigation (Owley, McMahon, & Cook, 2001) and these preliminary data were reported in an effort to inform parents about the

potential efficacy of secretin as a treatment for autism. As such, the small sample size is recognized as a temporary limitation. Of more concern is the possibility that positive effects might have been obtained with a stronger dose or with repeated infusions. However, the dosage strength was the same as that of Horvath *et al.* (1998) in which improvement was reported following only one infusion.

Owley *et al.* (2001) subsequently reported the results of the multi-site investigation using a randomized, double-blind, placebo-controlled, crossover design to study the effects of secretin in 56 children with autism. The outcome measures and testing intervals were identical to those in the preliminary study (i.e., Owley *et al.*, 1999) and results again failed to demonstrate any significant effects attributable to secretin.

Dunn-Geier *et al.* (2000) used a randomized, double-blind, placebo-controlled trial to examine the effects of a single dose of porcine secretin in 95 children with autism. Clinicians and parents rated social interaction, communication, and behavioral characteristics before secretin infusion and at a 3-week follow-up using the Preschool Language Scale-3 (PLS-3), the CARS, the AuBC, as well as GI and side-effect questionnaires. No serious adverse effects were reported nor were any significant problems noted in terms of safety. Results were consistent with previous findings. The study failed to demonstrate any differential treatment effect from a single infusion of secretin and thus could not corroborate the earlier report (Horvath *et al.*, 1998) of improvement in language and behavior of children with autism following secretin administration.

The anecdotal success of secretin prompted a two-part clinical investigation by Chez *et al.* (2000). The first study employed an uncontrolled open-label trial of porcine secretin with 56 children diagnosed with either autism or PDDNOS. Behavioral effects were measured with the CARS, which was completed by parents at baseline and again at follow-up approximately 4 weeks later. Treatment effect was analyzed both statistically and clinically. Clinically significant change was defined by researchers as a 6-point or greater improvement on the CARS.

In terms of clinical improvement, 13 participants (23%) classified with severe autism demonstrated the requisite gain for significance, although no dramatic improvements in speech or typical autistic characteristics were observed. The majority had either clinically insignificant change, no change, or were rated as "worse." Some of the adverse effects noted by parents included increased hyperactivity, increased agitation, and decreased focusing and responsiveness to others. Some parents reported improvements in GI function, eye-contact, and expressive and receptive speech. However, these improvements dissipated within a week. There was a statistically significant difference from baseline to follow-up for the entire group in several categories of the CARS including relating to people, emotional response, and verbal communication. While statistically significant, this difference did not qualify as clinically significant according to the criterion of a $\geqslant$6-point improvement on the CARS.

To determine whether the statistically significant improvements were due to rater bias or true effects of the hormone, a second study was conducted. In order to maximize the probability of detecting a difference in this follow-up study, a randomized, double-blind, placebo-controlled, crossover design was used. Participants were alternately assigned to one of two groups upon entry and received either porcine secretin or placebo at baseline, followed by the alternate injection at the 4-week follow-up. Some of the participants who were reported by their parents as "improved" in the first study were selected for Study 2. Chez *et al.* (2000) reasoned that if improvements were due to the secretin infusions, then a repeat injection should make previously subtle changes more detectable.

A total of 25 children completed Study 2. Assessments (neurologic interviews, clinical assessments, and CARS) were completed at baseline and at the end of 4 and 8 weeks. In addition, parents kept diaries of any behavior changes they observed in their children. The results from Study 2 failed to demonstrate any significant difference in CARS scores between the two groups. Even though all raters were blinded to eliminate bias, the results showed that parents reported (the unknown) saline placebo as beneficial as secretin. This finding, coupled with the use of a crossover design, argues for an expectancy effect and against any clinical improvement provided by secretin. The interpretation of reporting bias is further supported by the transient gains observed in Study 1 because the blind Study 2 failed to demonstrate even mild improvements in behavior change.

Several criticisms of the Chez *et al.* (2000) studies were made by Rimland (2000); two issues in

particular should be mentioned. The lack of a washout period to eliminate residual effects of secretin was cited by Rimland as the "most severe problem" (p. 95) limiting the findings of the second study. If such carry-over effects of a drug are present, subsequent treatment effects (or lack of effects) may be masked. Thus, conclusions drawn from such data are necessarily circumscribed. However, Chez and Buchanan (2000) dismissed the Rimland charge, stating that all participants were drug-free for a period of 6–8 weeks prior to receiving injections, a period that was more than adequate for effects to dissipate considering secretin has a drug half-life of 2 minutes when administered intravenously.

The second criticism concerned sample selection. At the time of the first study, approximately 80% of the participants were receiving medications, a statistic that Rimland (2000) asserted rendered the sample atypical. However, Chez and Buchanan (2000) defended their sample as representative of those reported in the literature with respect to varied drug regimens. Moreover, in other studies reviewed in this article that also reported on-going pharmacotherapy with their participants (Dunn-Geier *et al.*, 2000; Owley *et al.*, 1999, 2001; Sandler *et al.*, 1999), no evidence was found for the differential efficacy of secretin.

Corbett *et al.* (2001) also used a randomized, double-blind, placebo-controlled crossover design to examine the effects of porcine secretin in 12 children with autism. Outcome measures taken at baseline and 1 week post-treatment included the ADOS-G to assess social and communication improvement, the Minnesota Preschool Affect Rating Scales (MNPARS) to assess change in affect, and the Communication and Symbolic Behavior Scales (CSBS) to determine improvement in expressive language skills. Neurologic evaluations were also completed at each visit, and parents kept a daily log of GI-related episodes.

In general, the results did not demonstrate the efficacy of secretin over placebo. Although two variables on the MNPARS (i.e., affect and activity) achieved statistical significance, the authors did not interpret these results since they occurred in isolation (i.e., the CSBS showed no difference in affect between groups). None of the other dependent measures showed significant differences on behavioral, social, or communication measures. The study may have been limited by the testing schedule, which was restricted to a single administration 1 week after treatment; however, other studies (e.g., Molloy *et al.*, 2002; Sandler *et al.*, 1999) in which repeated testing was done after treatment also failed to demonstrate the efficacy of secretin.

Coniglio *et al.* (2001) conducted a randomized, double-blind, placebo-controlled trial of secretin with 60 children with autism who received a single dose of either porcine secretin or a saline placebo. Behaviors were assessed at baseline and at 3 and 6 weeks following injection using the CARS, GARS, and the PLS-3. None of these measures showed significant differences at 6 weeks between children receiving secretin and those administered a placebo. There was marginally statistically significant improvement in autistic behaviors in the treatment group after 3 weeks; however, the authors were unable to identify the characteristics of a subgroup (e.g., GI responders) responsible for this difference.

Unis *et al.* (2002) recently reported the results of a randomized, double-blind, placebo-controlled investigation that compared two forms of secretin (synthetic porcine and biologic porcine) to placebo in addition to evaluating the benefit of secretin for children with GI problems. Eighty-five children with autism were evaluated for changes in language skills (Expressive One-Word Picture Vocabulary Test-Revised and MacArthur Communicative Development Inventory [MCDI]), social and communication skills (ADOS-G and the Secretin Outcome Survey), and problem behaviors (ABC-C).

A comprehensive analysis of the results failed to show evidence for the superiority of either biologic porcine secretin or the synthetic porcine form over placebo in reducing the symptoms of autism. Similarly, no evidence of secretin efficacy was found for the subgroup of responders with GI problems. In emphasizing the importance of including multiple, and qualitatively different, outcome measures (i.e., direct observation and rating scales) in such investigations, Unis *et al.* (2002) noted the comparatively high expectancy effects in this and other studies (Coniglio *et al.*, 2001; Dunn-Geier *et al.*, 2000) that incorporated rating-scale measures. It is important to note that, by contrast, direct observation tends to yield smaller expectancy effects[9] and thus would mitigate (to some extent) overestimations.

[9]While multiple outcome measures (i.e., objective and subjective) may be potentially problematic, this is less a concern when results of these measures are concordant as they are in the majority of studies reviewed here.

RESEARCH EVALUATING MULTIPLE DOSES OF SECRETIN

The first study to investigate the effects of repeated doses of secretin was reported by Roberts *et al.* (2001) in which 64 children with autism were randomly assigned to receive two doses of either secretin or a placebo, 6 weeks apart. This double-blind study used a variety of outcome measures (ADOS-G, Leiter International Performance Scale-Revised or existing VABS data, PLS-3, visual performance tasks, AuBC, a GI questionnaire, and a side-effect rating scale) to rate improvements in typical autistic behaviors and language and/or cognitive functioning. With the exception of the cognitive tests (completed only at baseline and follow-up), all assessments were repeated 3 weeks after each injection.

No significant treatment differences were found between the secretin and placebo groups. A further analysis of participants by subgroups (i.e., GI symptomatology, cognitive level, and history of regression) also failed to reveal any differential effect of the drug. Although parents reported marked improvement in some cases, these gains were not clinically sustained. Moreover, the fact that such improvements were noted in both the treatment and placebo groups strongly argues for explanatory variables such as maturation and practice and expectancy effects and against the differential action of secretin.

In the only study with adult participants, Robinson (2001) reported an uncontrolled, open-label, clinical pilot investigation of the effects of multiple doses of homeopathic secretin. Twelve adults with a diagnosis of autism were evaluated by caregivers at a residential care facility over 14 weeks (2 weeks in baseline, 12 weeks in treatment). The secretin preparation was administered orally twice daily in a glass of water. Behaviors were measured once each week using the CARS.[10]

Comparisons of mean scores pre-treatment and weekly during treatment showed a surprising increasing trend, suggesting a worsening of symptoms while on secretin, but these differences failed to reach statistical significance. Thus, although secretin was not shown to significantly increase autistic symptoms, neither was it found to decrease those symptoms.

[10]See Mesibov, Schopler, Schaffer, and Michal (1989) for a discussion of the use of the CARS with adolescents and adults.

As an uncontrolled, open-label study, this research is limited in its utility toward extending our understanding of any relation between secretin and autism. Reliability is impacted due to inconsistency in raters across the duration of the study and the absence of inter-rater reliability assessment. In addition, rater bias is possible because of the unblind design. Further, this is not a placebo-controlled study, which limits any conclusions about drug effects. Finally, the homeopathic preparation is not described with respect to its equipotence to either the porcine or synthetic form of secretin and, therefore, comparisons with other studies are restricted.

Thus, while this study is unique in its participant sample (adult), form of secretin (homeopathic), and frequency of dose (twice daily for 12 weeks), the results must be interpreted with considerable caution due to its methodological limitations. Nevertheless, it should be noted that the study's outcome is similar (i.e., no identifiable secretin effect) to most of the other studies reviewed in this article.

Sponheim, Oftedal, and Helverschou (2002) also investigated the effects of repeated doses of secretin. In this randomized, double-blind, placebo-controlled crossover design, six children received three injections of secretin and three of placebo, randomized, every 4 weeks for a total of six injections. It should be noted that dosages were higher per kilogram of body weight (see Table 1) than those used in the other studies reviewed here. Each week, teachers and parents assessed behavior change in 16 categories (e.g., activity, communication, imitation, eye-contact, initiation, stereotypy) using the visual analogue scale (VAS), a rating scale similar to a Likert scale. In addition, the ABC was completed monthly to further assess treatment effects.

Whereas significant effects for secretin were found for one of the six participants using parent VAS ratings, the opposite rating by teachers resulted in positive placebo effects. Significant placebo effects were also found for four other participants. These findings and clinical impressions through visual inspection of the graphs led researchers to conclude that the observed effects of secretin were not different from placebo.

A comment should be made about a potential confound in the three aforementioned studies using repeated doses of secretin. As previously noted, in order to eliminate carry-over effects of the drug, a washout period is recommended to allow effects to

dissipate. However, this period varied from 6 weeks between injections and 3 weeks between testing periods (Roberts *et al.*, 2001) to 4 weeks between injections and weekly testing (Sponheim *et al.*, 2002) to hours between drug administration and weekly testing (Robinson, 2001). If carry-over effects are present, and depending upon treatment order (secretin vs. placebo), results may be positively or negatively skewed. Although carry-over effects may not alter overall findings in any of these studies, to the extent that there are carry-over effects and raters are influenced by repeated assessments (e.g., practice, results), this variable should be taken into account when interpreting the results of these studies.

RESEARCH TO IDENTIFY A SUBGROUP OF RESPONDERS

In contrast to previous negative outcomes, a recent investigation identified a subgroup of children with autism who may benefit from secretin infusion. Kern, Miller, Evans, and Trivedi (2002) evaluated the effects of a single dose of porcine secretin in a randomized, double-blind, placebo-controlled, crossover study of 19 children with autism, nine who had GI problems. Of those in the GI group, five had chronic diarrhea, two had a history of chronic diarrhea in remission at the time of the study, and two had chronic constipation.

After the initial assessments were completed, either secretin or placebo was infused. At week 3, the alternative substance was infused, and all participants returned for follow-up at week 6. Using the ABC, raters scored participants' inappropriate and maladaptive behaviors at baseline, week 3, and again at week 6. Spoken language was measured using the MCDI. Parents provided information on GI status and global response to treatment.

Although the group with chronic diarrhea was not initially a target of special interest, during the study these children appeared to selectively respond to the secretin infusion. Therefore, their data were compared with the data from children with no history of GI problems. Although no effort had been made to balance the assignment of participants across the GI dimension initially, they were represented in near-equal numbers in the secretin–placebo group and the placebo–secretin group.

Results revealed significant decreases in some ABC scores (Subscale I: irritability, agitation, crying; II: social withdrawal; III: stereotypy; IV: hyperactivity, non-compliance; V: inappropriate speech) in participants with chronic diarrhea when they received secretin but not when they received a placebo. Similarly, this group showed greater gains on the MCDI when given secretin than when treated with placebo. Children without GI problems were either less likely than the group with chronic diarrhea to show changes or showed no changes on the same measures when treated with secretin.

Many studies (e.g., Carey *et al.*, 2002; Chez *et al.*, 2000; Coniglio *et al.*, 2001; Lightdale *et al.*, 2001; Molloy *et al.*, 2002; Roberts *et al.*, 2001; Unis *et al.*, 2002) have cited GI problems in their participants and several (Lightdale *et al.*; Roberts *et al.*; Unis *et al.*) attempted to identify a possible subtype for whom secretin might prove effective. However, none found significant differences that could provide clinical indicators. The Kern *et al.* (2002) findings are noteworthy because they suggest there may be a subgroup of children with autism whose symptoms could be diminished by secretin. Nevertheless, they are in contrast to the study by Carey *et al.* who used the same outcome measure (the ABC) and reported worse scores on two of the same subtests (hyperactivity and inappropriate speech) that were reported by Kern *et al.* to have improved.

A pilot study by Lightdale *et al.* (2001) attempted to replicate the Horvath *et al.* (1998) findings and address the issue of a possible subgroup of responders with specific GI complaints. Porcine secretion was infused in an uncontrolled, open-label trial with participants who were followed for 5 weeks. Twenty children with autism who had GI symptoms were videotaped at play before porcine secretin infusion and afterward at weeks 1, 2, 3, and 5. Research assistants conducted blind reviews of the videotapes using the Autism Observation Scale. Language data were obtained with the PLS-3 at baseline and at the follow-up intervals. A parent questionnaire was given at week 3 to provide information about perceived changes following secretin infusion.

Lightdale *et al.* (2001) found no significant increases in language, social behaviors, or developmentally appropriate play skills and there were no significant decreases in behaviors associated with autism. In contrast to these findings, 70% of parents reported moderate to high change and 85% of parents reported that they felt their children would benefit from a second infusion of secretin. This

apparent expectancy effect again strongly underscores the importance of conducting controlled studies to separate the true effects of secretin from its perceived benefits.

DISCUSSION

This article reviewed the results of 17 quantitative studies that investigated the efficacy of secretin as a treatment for the symptoms of autism spectrum disorder. These symptoms include impairment in social interaction, communication, and repetitive or stereotypic behavior.

Across these studies, approximately 600 children, ages 2–15, and 12 adults, all with diagnoses within the autism spectrum disorder, received some form of secretin (porcine, synthetic human, synthetic porcine, or homeopathic) and have been assessed for its effects. The studies were conducted at various sites throughout the United States and in Canada, Great Britain, and Norway.

All but one of the studies (excluding the initial case series report) failed to find a causal relation between secretin and the amelioration of autistic symptoms across a variety of treatment variables (e.g., type of secretin, dosage potency, frequency), observation times (e.g., immediately after infusion, every week, or after several weeks), and participant characteristics (e.g., GI status, severity of autism/PDD, age, and history of adjunctive medication use). The effect of these variables was assessed on a variety of outcome measures including 17 different rating scales and two standardized assessments (language, visual perception). Trained and untrained observers alike assessed outcomes.

In an effort to identify how secretin might have produced anecdotally reported improvements in children with autism, Connors and Crowell (1999) drew attention to the multi-ingredient composition of the secretin preparation itself. The typical preparation of secretin contains cysteine hydrochloride, added by the manufacturer to stabilize the secretin. This substance is not included in the placebo saline preparation.

According to Connors and Crowell (1999), cysteine hydrochloride has known neurotransmitter properties and is active in the central and peripheral nervous systems. The authors assert that cysteine could be responsible for the behavioral effects attributed to secretin, a prospect of particular interest since the neurotransmitter properties of secretin are unproven (Yung *et al.*, 2001). While this possibility provides interesting speculation in light of anecdotal reports of secretin's positive and often dramatic effects, it is less provocative given the negative results obtained in 12 of the 13 placebo-controlled studies in this review. If the cysteine in secretin preparations were responsible for improvements, we would expect to see a significant difference in performance between those receiving secretin and those given a placebo (in which cysteine is absent from the preparation).

The brain–gut connection to explain the reported effects of secretin has been addressed in several of the studies reviewed here. The Kern *et al.* (2002) findings certainly hint at GI status as a promising lead in examining the neurophysiology related to behaviors associated with autism, but the findings generate many questions.

One issue is whether children with autism experience GI problems in greater numbers than their non-autistic peers and, relatedly, whether autism develops subsequent to, or concurrent with, any GI dysfunction. In a recent review by Horvath and Perman (2002), a striking difference was reported in the prevalence of GI symptoms between children with autism and their healthy siblings. A comparison survey of 43 sibling pairs reported that 84% of those with autism had GI symptoms, whereas these symptoms were present in only 31% of their non-autistic siblings. In contrast, a recent population-based study in the United Kingdom (Black, Kaye, & Jick, 2002) reported equal prevalence (9%) of GI disorders among 96 children diagnosed with autism and their peers without autism (449 matched controls).

If secretin does contribute to improvement in the symptoms of autism, its mechanism of action is unclear. It is not known whether the peptide crosses the blood–brain barrier[11] to impact the central nervous system directly, if at all, or contributes in some way more peripherally (e.g., improving digestion). Thus, it would be important to determine whether GI dysfunction involves processes that include multiple organs (i.e., brain and GI-related structures) or manifests independent of, or secondarily to, the central nervous system.

At present, there is no consensus on the association between the development of autism and GI illness (Black *et al.*, 2002). In fact, several studies

[11]Banks, Goulet, Rusche, Niehoff, and Boismenu (2002) suggest that it does in mice; however, in humans the properties of possible neurotransmission of secretin are still undefined.

provide evidence against a substantial association (Black *et al.*; Fombonne & Chakrabarti, 2001; Taylor *et al.*, 2002). In contrast, Horvath and Perman (2002) cite numerous studies in the areas of endoscopy, histology, and immunology that are all suggestive of a GI connection to autism. Nevertheless, they caution that as tempting as it might be to embrace this biologic link to autism, further rigorous investigation is crucial in providing empirical support for this claim. Ultimately, it is possible that secretin would prove ineffective even with a verifiable GI connection to autism.

How do we explain the continued interest of parents in seeking secretin treatment for their children despite the inability of researchers to establish its efficacy? First, we must recognize that parents as a group are no less able to objectively evaluate the available scientific information than other laypersons. However, unusual circumstances preceded these investigations. The atmosphere in which many parents sought to participate in secretin studies was highly charged with promotion and expectations for its success. This was a unique situation since the impetus to begin this line of research was largely stimulated by intense media attention. None of the previous studies of other pharmacological treatments for autism operated in this atmosphere of media attention and rapid dissemination of anecdotal reports of success (Sandler & Bodfish, 2000).

Thus, several factors may have facilitated the initial enthusiasm for secretin. Foremost is the motivational impetus by parents to find any promising treatment for this disorder whose symptoms are often extremely stressful for parents. That these symptoms are pervasive, in contrast to the more limited impact of other physical or mental disabilities (Herbert *et al.*, 2002), may only intensify parents' desperation to find relief. Dunn-Geier *et al.* (2000) suggest that early positive reports of the benefits of secretin by a parent may have increased its initial attractiveness and perceived utility. Hope for the drug's efficacy may also have been high since it is a natural substance found in the human body and its adverse effects appear minimal; thus, it may be seen as relatively safe, and by extension, possibly helpful. In addition, there is intuitive face validity to secretin when presented in the context of the brain–gut hypothesis.

These possibilities might result in sometimes subtle expectations that can camouflage effects in drug studies and the scientific community needs to be mindful of their influence, particularly since outcome measures are frequently reported by parents. It is incumbent upon researchers and practitioners to help parents and caregivers understand placebo and expectancy effects in an effort to help them prevent expending resources on unproven treatments, particularly given the potential for health risks when applications are off-label (i.e., not FDA-approved) treatments.

Expectancy effects, however, may not wholly explain the numerous anecdotal reports from parents of diminished GI symptoms, improved sleep patterns, and better functional use of language. It is difficult to identify the factors in the Horvath *et al.* (1998) case series that resulted in reports of improved functioning following the secretin challenge for GI symptoms. Variables such as age, unique patient characteristics, anesthesia or sedatives, duration of infusion, or onset of symptoms may have operated singly or in some idiosyncratic combination to have an effect when combined with secretin administration. However, given the experimental evidence it seems likely that there was no specific effect of secretin in Horvath *et al.* but that other variables (possibly including informant and observer expectancies) were responsible for the changes reported.

Autism is a complex condition with a variety of symptoms that casually appear to wax and wane. It is not unreasonable that such variability might coincide with a treatment regimen, resulting in the perception of improvement. Furthermore, children with autism are not a homogeneous group. Not only do their behaviors vary, but their responses to a variety of treatments are often diverse.

Given this, it seems likely that many different etiologies may contribute to the behaviors seen in autism. Roberts *et al.* (2001) note there may be underlying GI pathology or other factors such as diet or anxiety responsible for symptoms of autism. Carey *et al.* (2002) identify GI permeability as a possible contributor to the pathogenesis of autism. Horvath and Perman (2002) review a variety of likely suspects including abnormal metabolism in the liver, digestive enzyme deficiency, and inflammation of the upper and lower intestinal tract. Further scientific evidence may help solve the mystery of how, or if, autism relates to a brain–gut connection. At this time, however, the role that secretin plays in solving this mystery seems negligible.

The explosion of interest in secretin resulted in hundreds, and possibly thousands, of children being exposed to this hormone. It prompted a line of

research whose costs could easily be measured in millions of dollars, and whose empirical evidence overwhelmingly suggests there is no symptomatic relief of autism from the hormone secretin beyond that which could be expected from placebo.

Despite these definitive results, parents continue to be exposed to influences that offer hope for secretin (see Herbert *et al.*, 2002). This makes the potential cost to parents very dear indeed. Time and emotion have been, and may continue to be, expended to pursue this treatment that never enjoyed empirically proven benefits for autism, nor does it yet.

Three years ago, Lightdale *et al.* (2001) observed that the interest in secretin was likely to fade if empirical studies continued to contradict its efficacy. Since that time, five more controlled studies have failed to validate secretin as an effective treatment for autism. We submit that the findings summarized here should be considered conclusive and propose that we turn our attention to guiding parents and caregivers toward proven treatments (e.g., applied behavior analysis; Smith, 1999) that have a history of success founded on rigorous science (see Tanguay, 2002).

In the meantime, other treatments will be advanced and claims will be made for their efficacy. Some of them may merit our attention; all of them may require our response. In a world where technology can instantly catapult any communication to prominence, and pseudoscience is often difficult to recognize, we must act responsibly to help parents, caregivers, and others evaluate the strengths and impact of yet unproven treatments. Above all, we must strive to advocate for rigorous scientific investigations that will define the therapeutic benefit of such treatments before anecdotal surrogates for those investigations wreak emotional and financial havoc on the lives of those we endeavor to help.

REFERENCES

Alexander, D. (1999, December). Study shows secretin fails to benefit children with autism [Comments]. *NIH News Alert,* National Institutes of Health.

Aman, M. G., & Armstrong, S. A. (2000). Regarding secretin for treating autistic disorder [Letter to the editor]. *Journal of Autism and Developmental Disorders, 30,* 71–72.

American Academy of Child & Adolescent Psychiatry. (1999, March 3). *Secretin in the treatment of autism.* [Policy statement]. Retrieved June 26, 2002, from http://www.aacap.org/publications/policy/ps30.htm#TOP.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Banks, W. A., Goulet, M., Rusche, J. R., Niehoff, M. L., & Boismenu, R. (2002). Differential transport of a secretin analog across the blood–brain and blood–cerebrospinal fluid barriers of the mouse. *The Journal of Pharmacology and Experimental Therapeutics, 302,* 1062–1069.

Bertrand, J., Mars, A., Boyle, C., Bove, F., Yeargin-Allsopp, M., & Decoufle, P. (2001). Prevalence of autism in a United States population: The Brick Township, New Jersey, investigation. *Pediatrics, 108,* 1155–1161.

Black, C., Kaye, J. A., & Jick, H. (2002). Relation of childhood gastrointestinal disorders to autism: Nested case-control study using data from the UK General Practice Research Database. *British Medical Journal, 325,* 419–421.

Carey, T., Ratliff-Schaub, K., Funk, J., Weinle, C., Myers, M., & Jenks, J. (2002). Double-blind placebo-controlled trial of secretin: Effects on aberrant behavior in children with autism. *Journal of Autism and Developmental Disorders, 32,* 161–167.

Chez, M. G., & Buchanan, C. P. (2000). Reply to B. Rimland's "comments on 'secretin and autism: A two-part clinical investigation.' " *Journal of Autism and Developmental Disorders, 30,* 97.

Chez, M. G., Buchanan, C. P., Bagan, B. T., Hammer, M. S., McCarthy, K. S., Ovrutskaya, I., *et al.* (2000). Secretin and autism: A two-part clinical investigation. *Journal of Autism and Developmental Disorders, 30,* 87–94.

Christ, A., Werth, B., Hildebrand, P., Gyr, K., Stalder, G. A., & Beglinger, C. (1988). Human secretin: Biologic effects and plasma kinetics in humans. *Gastroenterology, 94,* 311–316.

Coniglio, S., Lewis, J. D., Lang, C., Burns, T. G., Subhani-Siddique, R., Weintraub, A., *et al.* (2001). A randomized, double-blind, placebo-controlled trial of single-dose intravenous secretin as treatment for children with autism. *The Journal of Pediatrics, 138,* 649–655.

Connors, S. L., & Crowell, D. E. (1999). Secretin and autism: The role of cysteine [Letter to the editor]. *Journal of the American Academy of Child and Adolescent Psychiatry, 38,* 795–796.

Corbett, B., Khan, K., Czapansky-Beilman, D., Brady, N., Dropik, P., Zelinsky Goldman, D., *et al.* (2001). A double-blind, placebo-controlled crossover study investigating the effect of porcine secretin in children with autism. *Clinical Pediatrics, 40,* 327–331.

DiCicco-Bloom, E. (1998). Invited commentary. *Newsletter of the National Alliance for Autism Research, 4,* 24.

Dunn-Geier, J., Ho, H. H., Auersperg, E., Doyle, D., Eaves, L., Matsuba, C., *et al.* (2000). Effect of secretin on children with autism: A randomized controlled trial. *Developmental Medicine and Child Neurology, 42,* 796–802.

Fombonne, E., & Chakrabarti, S. (2001). No evidence for a new variant of measles-mumps-rubella-induced autism. *Pediatrics, 108,* Article e58. Retrieved August 18, 2003, from http://www.pediatrics.org/cgi/content/full/108/4/e58.

Hardman, M. L., Drew, C. J., & Egan, M. W. (1999). *Human exceptionality: Society, school, and family* (6th ed.). Boston: Allyn and Bacon.

Herbert, J. D., Sharp, I. R., & Gaudiano, B. A. (2002). Separating fact from fiction in the etiology and treatment of autism: A scientific review of the evidence. *The Scientific Review of Mental Health Practice, 1,* 23–43. Retrieved December 9, 2002, from http://www.scientificmentalhealth.org/SRMHP/current.html.

Hirsch, D. (1999). Secretin in the treatment of autism. *The Exceptional Parent, 29*, 94.

Horvath, K. (2000). Secretin treatment for autism [Letter to the editor]. *The New England Journal of Medicine, 342,* 1216.

Horvath, K., Papadimitriou, J. C., Rabsztyn, A.,Drachenberg, C., & Tildon, J. T. (1999). Gastrointestinal abnormalities in children with autistic disorder. *Journal of Pediatrics, 135,* 559–563.

Horvath, K., & Perman, J. A. (2002). Autism and gastrointestinal symptoms. *Current Gastroenterology Reports, 4,* 251–258.

Horvath, K., Stefanatos, G., Sokolski, K. N., Watchel, R., Nabors, L., & Tildon, J. T. (1998). Improved social and language skills after secretin administration in patients with autistic spectrum disorders. *Journal of the Association for Academic Minority Physicians, 9,* 9–15.

Kern, J. K., Miller, V. S., Evans, P. A., & Trivedi, M. H. (2002). Efficacy of porcine secretin in children with autism and pervasive developmental disorder. *Journal of Autism and Developmental Disorders, 32,* 153–160.

Lightdale, J. R., Hayer, C., Duer, A., Lind-White, C., Jenkins, S., Siegel, B., *et al.* (2001, November). Effects of intravenous secretin on language and behavior of children with autism and gastrointestinal symptoms: A single-blinded, open-label pilot study. *Pediatrics, 108,* Article e90. Retrieved June 11, 2002, from http://www.pediatrics.org/cgi/content/full/108/5/e90.

McMillin, D. L., Richards, D. G., Mein, E. A., & Nelson, C. D. (1999). The abdominal brain and enteric nervous system. *The Journal of Alternative and Complementary Medicine, 5,* 575–586.

McQueen, J. M., & Heck, A. M. (2002). Secretin for the treatment of autism. *The Annals of Pharmacotherapy, 36,* 305–311.

Mesibov, G., Schopler, E., Schaffer, B., & Michal, N. (1989). Use of the Childhood Autism Rating Scale with autistic adolescents and adults. *Journal of the American Academy of Child and Adolescent Psychiatry, 28,* 538–541.

Molloy, C. A., Manning-Courtney, P., Swayne, S., Bean, J., Brown, J. M., Murray, D. S., *et al.* (2002). Lack of benefit of intravenous synthetic human secretin in the treatment of autism. *Journal of Autism and Developmental Disorders, 32,* 545–551.

National Institute of Child Health and Human Development. (1999, December 8). [National Institutes of Health News Alert]. *Study shows secretin fails to benefit children with autism.* Retrieved June 10, 2002, from http://www.nichd.nih.gov/new/releases/secretin1299.htm.

Owley, T., McMahon, W., & Cook, E. H. (2001). Multisite, double-blind, placebo-controlled trial of porcine secretin in autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 40,* 1293–1299.

Owley, T., Steele, E., Corsello, C., Risi, S., McKaig, K., Lord, C., *et al.* (1999, October 6). A double-blind, placebo-controlled trial of secretin for the treatment of autistic disorder. *Medscape General Medicine, 1,* 1–8. Retrieved June 12, 2002, from http://medscape.com/viewarticle/408013.

Rimland, B. (1999, January). The use of secretin in autism: some preliminary answers. *Autism Research Review International.* Retrieved June 1, 2002, from http://www.autism.com/ari/newslet.html.

Rimland, B. (2000). Comments on "Secretin and autism: A two-part clinical investigation" by M. G. Chez *et al. Journal of Autism and Developmental Disorders, 30,* 95.

Roberts, W., Weaver, L., Brian, J., Bryson, S., Emelianova, S., Griffiths, A.-M., *et al.* (2001, May). Repeated doses of porcine secretin in the treatment of autism: A randomized, placebo-controlled trial. *Pediatrics, 107,* Article e71. Retrieved June 11, 2002, from http://www.pediatrics.org/cgi/content/full/107/5/e71.

Robinson, T. W. (2001). Homeopathic secretin in autism: A clinical pilot study. *British Homeopathic Journal, 90,* 86–91.

Sandler, A. D., & Bodfish, J. W. (2000). Placebo effects in autism: Lessons from secretin. *Developmental and Behavioral Pediatrics, 21,* 347–350.

Sandler, A. D., Sutton, K. A., DeWeese, J., Girardi, M. A., Sheppard, V., & Bodfish, J. W. (1999). Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. *New England Journal of Medicine, 341,* 1801–1806.

Shutt, C. E. (1998). Secretin and autism: A clue but not a cure. *Newsletter of the National Alliance for Autism Research, 4,* 21–24.

Smith, T. (1999). Outcome of early intervention for children with autism. *Clinical Psychology: Science and Practice, 6,* 33–49.

Sponheim, E., Oftedal, G., & Helverschou, S. B. (2002). Multiple doses of secretin in the treatment of autism: A controlled study. *Acta Pædiatrica, 91,* 540–545.

Tanguay, P. E. (2002). Commentary: The primacy of the scientific method. *Journal of the American Academy of Child and Adolescent Psychiatry, 41,* 1322–1323.

Taylor, B., Miller, E., Lingam, R., Andrews, N., Simmons, A., & Stowe, J. (2002). Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population-based study. *British Medical Journal, 324,* 393–396.

Unis, A. S., Munson, J. A., Rogers, S. J., Goldson, E., Osterling, J., Gabriels, R., *et al.* (2002). A randomized, double-blind, placebo-controlled trial of porcine versus synthetic secretin for reducing symptoms of autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 41,* 1315–1321.

Veenstra-Vanderweele, J., & Cook, E. H., Jr. (2003). Genetics of childhood disorders: XLVI. Autism, part 5: Genetics of autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 42,* 116–118.

Volkmar, F. (1999). Lessons from secretin [Commentary]. *The New England Journal of Medicine, 341,* 1842–1844.

Volkmar, F. (2000). [Letter to the editor]. *The New England Journal of Medicine, 342,* 1218.

Yung, W.-H., Leung, P.-S., Ng, S. S. M., Zhang, J., Chan, S. C. Y., & Chow, B. K. C. (2001). Secretin facilitates GABA transmission in the cerebellum. *The Journal of Neuroscience, 21,* 7063–7068.