

Editor's Notebook: Stephen M. Edelson, Ph.D.**Autism and GI problems: A major milestone**

In January, *Pediatrics* (a journal of the American Association of Pediatrics) published two articles on gastrointestinal (GI) problems associated with autism. One, titled "Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals with ASDs: A Consensus Report," is a scientific review of the most current research on GI problems. The second article, titled "Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children with ASDs," is a detailed description of diagnosis and treatment recommendations for GI disorders in these children. These landmark papers are a result of many years of perseverance; much of this effort was spearheaded by the Autism Research Institute (ARI).

Here is some historical perspective: in his seminal 1943 paper—in which he coined the term *autism*—Dr. Leo Kanner described eleven cases in detail. In 2007, Dr. Bryan Jepson, author of the book *Changing the Course of Autism*, pointed out that seven of the children in Kanner's case studies suffered from some form of GI disorder, including feeding problems, diarrhea, and vomiting. Although Kanner's paper has been widely cited and is considered a concise description of autism, physicians and researchers have failed to pay attention either to Kanner's inclusion of GI symptoms or to such GI problems in patients with autism spectrum disorders.

Prior to the year 2000, GI problems were rarely mentioned at parent support groups, at conferences, or in published papers and books. This of course did not mean that GI problems did not exist for people with autism. Many adults on the spectrum have shared with me that they suffered from GI problems throughout childhood and adulthood. In the 1980s, Drs. Bernard Rimland and Edward Ritvo debated whether some children on the autism spectrum had a yeast overgrowth that in turn could affect their behavior. Their discussion was published as a series of letters in the Autism Society of America's magazine, *The Advocate*. Dr. Rimland argued that some children on the spectrum do suffer from yeast overgrowth, and he offered several case studies in which the children were properly diagnosed and treated effectively. By contrast, Dr. Ritvo argued that he never saw this problem in his clients. However, it was Dr. Rimland's belief, as he shared with me in conversation, "You won't find it unless you look for it."

As more and more parents stepped forward with concerns about GI problems in their children, and as more doctors encountered such complications in their autistic patients, ARI sponsored the first think tank on biomedical issues in autism, in 1995 in Dallas, Texas. Approximately 30 research-

ers and physicians convened to discuss the various health issues they commonly encountered in their research or practices. By the end of the meeting, there was general consensus that two areas—the immune and the GI systems—were of great importance in understanding and treating individuals on the autism spectrum. According to Dr. Rimland, this was the first time in history that a group of autism experts had agreed that GI problems could contribute to many of the symptoms and behaviors associated with autism.

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issues they had identified. As years passed and they grew more knowledgeable as a community of practitioners and researchers, their efforts took on the name Defeat Autism Now! (DAN!), which is best described as a philosophy or general approach to treating the medical conditions that many people with autism seem to have.

After the founding of Defeat Autism Now!, the autism community began to hear about a talented English researcher who had documented specific GI problems in autism. His name was Andrew Wakefield, M.D., and in 2000 he termed the disorder "autistic enterocolitis." Dr. Wakefield hypothesized that these problems might be linked to the measles/mumps/rubella (MMR) vaccine. Prior to the 1998 publication of his groundbreaking paper in the *The Lancet*, Dr. Wakefield spoke at the very first Defeat Autism Now! conference, in San Diego in 1997.

Another important step forward was in 2002, when ARI awarded the newly-formed Autism Treatment Network (ATN) a grant for \$100,000. This went to support the research of three Harvard scientists, Drs. Timothy Buie, Harland Winter, and Dr. Rafail Kushak, to investigate GI disorders. Dr. Rimland had high expectations for this area of research because he felt that high-level academic work would lead to further insight into GI problems and eventually appropriate treatment. He was so excited about their research that he gave away what amounted to three months of ARI's pay-

roll at the time. The staff and I didn't mind. We trusted Dr. Rimland's judgment, and we knew that only good would come of it.

Throughout the first decade of the new millennium, ARI continued to award grants for research on GI problems, probably funding more research studies than any other autism organization or government agency. In addition, Board members of the Northwest Autism Foundation (NWAf), led by Richard Fade, Gleason Eakin, Wayne Hamersly and Dave Humphrey, granted several million dollars to fund gastrointestinal projects led by Drs. Buie, Winter, and Kushak.

ARI continued to foster interest and awareness in the autism community by setting discussion agendas on biomedical approaches for GI problems at our biannual think tanks, scheduling presentations at our two- and three-day Defeat Autism Now!/ARI conferences, and presenting information in our quarterly newsletter, the *Autism Research Review International*, and on our website, www.autism.com.

Then, in 2007, an important turning point arrived when ARI and NWAf board member Dave Humphrey and I had a conversation in which we commented on the number of research studies that focused on GI problems associated with autism. At the time, we were aware of a total of 44 published studies. Given the rich material available in the research community on this issue, Mr. Humphrey, the Northwest Autism Foundation (NWAf), and the Autism Forum set out to recruit outstanding doctors and scientists to write an objective article that reviewed the current research literature on GI issues and autism. Mr. Humphrey asked Drs. Harland Winter and Timothy Buie, two respected GI experts at Harvard University, to co-chair such an expansive report; they both wholeheartedly agreed. This resulted in a consensus meeting in Cambridge, Massachusetts, hosted by NWAf. NWAf was instrumental in coordinating this unprecedented event, at which top researchers from around the world met to review and summarize the state of the art in GI research and treatment in autism.

Twenty-six scientists contributed to the consensus report, including Drs. Rafail Kushak, Margaret Bauman, the late Ted Carr, Harumi Jyonouchi, Judy Van de Water, Susan Hyman, and many more. Finally, in 2009, two important advocacy organizations, the Autism Society of America and Easter Seals Oregon, joined NWAf's and ARI's efforts in sponsoring the report, building a powerful coalition of research- and advocacy-based organizations to address families' urgent wish to have their children's challenges with GI issues acknowledged and tested by research, and to move the medical treatment agenda forward.

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Abnormal pupil response may be biomarker for autism

The response of children's pupils to light may offer doctors a clue about which youngsters are at high risk for autism, a new study suggests.

Xiaofei Fan and colleagues tested 24 children with autism spectrum disorders (ASD) and 44 nondisabled controls. Children in the control group were an average of 12 years old, while controls were around 10 years of age. All of the children had normal vision correctable to 20/20 or better and no history of eye disorders.

Fan and colleagues measured the children's response to a 100-millisecond flash of light. The researchers report that the pupils of children with ASD responded significantly more slowly than the pupils of controls. The children with ASD also exhibited differences in other parameters of PLR, including reduced pupil constriction amplitude and velocity.

The researchers say that based on their

initial results, measurements of PLR may allow clinicians to identify individuals with ASD with about 92 percent accuracy. Study coauthor Gang Yao comments, "If these results are successfully validated in a larger population, PLR response might be developed into a biomarker that could have clinical implications in early screening for risks of autism."

"Abnormal transient pupillary light reflex in individuals with autism spectrum disorders," Xiaofei Fan, Judith H. Miles, Nicole Takahashi, and Gang Yao, *Journal of Autism and Developmental Disorders*, Vol. 39, November 2009, 1499-1508. Address: Gang Yao, Department of Biological Engineering, University of Missouri-Columbia, 1406 E. Rollins St. #249, Columbia, MO 65211, YaoG@missouri.edu.

—and—

"Children with autism show slower pupil responses, MU study finds," news release (via EurekAlert), University of Missouri-Columbia, November 10, 2009.

Low prenatal levels of folate linked to ADHD

A new British study tentatively links low prenatal levels of folate (the natural form of folic acid) to attention deficit hyperactivity disorder (ADHD).

Wolff Schlotz and colleagues measured maternal red blood cell folate (RCF) in 100 women at 14 weeks of pregnancy and calculated the women's total folate intake from food and supplements in early and late pregnancy. In addition, the researchers measured the head circumference and body weight of the women's children at birth and in infancy. The mothers assessed their children's behavior problems when the children were seven to nine years of age.

Schlotz and colleagues report, "Lower maternal RCF and total folate intake in early pregnancy were associated with higher childhood hyperactivity and peer problems scores in the offspring." In addition, RCF was positively associated with head circumference at birth. This may suggest, the researchers say, that low folate leads to a reduced rate of prenatal brain growth.

They conclude, "our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood."

"Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring," Wolff Schlotz, Alexander Jones, David I. W. Phillips, Catharine R. Gale, Sian M. Robinson, and Keith M. Godfrey, *Journal of Child Psychology and Psychiatry*, October 2009 (epub prior to print publication). Address: Wolff Schlotz, School of Psychology, University of Southampton, Southampton SO17 1BJ, UK, ws@southampton.ac.uk.

Editorial: GI Problems in Autism (continued from page 3)

In addition to the consensus review, a second helpful report published in *Pediatrics* contains recommendations on how to diagnose, evaluate, and treat such problems. You can read the consensus report online at www.GIConsensusReport.com. A hardcopy reprint of both articles is available by writing to us at ARI (4182 Adams Ave., San Diego, CA 92116). Please send \$5 to cover the cost of mailing.

Throughout the consensus report, the authors make it clear that GI problems are strongly associated with autism. They also indicate that much more research is needed to properly understand these problems and how best to treat them. I hope that larger autism research organizations as well as the federal government will begin to acknowledge the importance of the work done thus far. More funding is required now to continue on this crucial path of research. ARI will remain committed, just as it has been since the first insights and efforts of Bernard Rimland and key biomedical researchers in the 1980s, to funding and advocating for more pressing inquiry into GI issues and autism.

Some highlights of the report:

- Key statement: "Individuals with ASDs who present with gastrointestinal symptoms warrant a thorough evaluation, as would be undertaken for individuals without ASDs who have the same symptoms. Evidence-based algorithms for the assessment of abdominal pain, constipation, chronic diarrhea, and gastroesophageal reflux disease (GERD) should be developed." (Page 53)

- Table 2 provides a list of "behaviors that may be markers of abdominal pain or discomfort in individuals with ASDs." (Page 54)

- Table 3 provides a list of symptoms (e.g.,

sleep disturbance), their possible relationship with a GI problem (e.g., GERD), and diagnostic evaluations to be considered (e.g., a trial of a proton-pump inhibitor and a pH probe, EGD). (Page 55)

- "For a person with an ASD who presents for treatment of a problem behavior, the care provider should consider the possibility that a gastrointestinal symptom, particularly pain, is a setting event, that is, a factor that increases the likelihood that serious problem behavior (e.g., self-injury, aggression) may be exhibited." (Page 58)

- "Education of caregivers and health care providers is necessary to impart knowledge of how to recognize typical and atypical signs and symptoms of gastrointestinal disorders in individuals with ASDs." (Page 59)

- "Pediatricians and other primary care providers should be alert to potential nutritional problems in patients with ASDs." (Page 59)

Final note: The authors also stated, "Available research data do not support the use of a casein-free diet, a gluten-free diet, or combined gluten-free, casein-free (GFCF) diet as a primary treatment for individuals with ASDs" (page S10). They commented that there are few studies that have examined such diets, and they were aware of only one published study utilizing a double-blind, placebo-controlled experimental design. Although some critics have taken this issue out of context and cited the above statement to argue that the gluten-free and casein-free diets are ineffective, the truth is, as the authors wrote, that "additional studies are needed to assess risk factors and possible markers that identify individuals who might benefit from these diets."

QUOTABLE....

"Substantial research documents the effectiveness of ABA treatments for autism. The most robust gains have been demonstrated when ABA is provided according to the EIBI (Early Intensive Behavioral Intervention) model: 30 to 40 hours per week of one-to-one ABA intervention, for two or more years, beginning before age five. Although it is highly recommended that individuals with autism access EIBI, ABA has also been demonstrated to be effective in addressing particular challenging behaviors and skill deficits in older children and adolescents."

—Doreen Granpeesah,
Annals of Clinical Psychiatry,
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