

Autism Research Review

I N T E R N A T I O N A L

A quarterly publication of the Autism Research Institute—www.Autism.com

Reviewing biomedical and educational research in the field of autism and related disorders

Pilot study: microbiota transplant improves behavior, GI symptoms of children with ASD

Fecal transplants may improve the gastrointestinal (GI) symptoms and behavior of children with autism spectrum disorders (ASD), a pilot study suggests.

Fecal transplants have already gained attention as a treatment for *C. difficile* infection and inflammatory bowel disease. Dae-Wook Kang and colleagues are interested in the potential of this approach for treating children with ASD, who have high rates of diarrhea, constipation, and other bowel problems that may be connected to their behavioral issues.

In the study, 18 participants with ASD and GI problems underwent Microbiota Transfer Therapy, or MTT. They first received two weeks of antibiotic treatment and a bowel cleanse to prepare the GI tract. Next, they received one high dose of microbiota administered either orally or rectally, followed by a lower oral daily maintenance dose for 7 to 8 weeks. The researchers used a standardized product containing more than 99% bacteria obtained from healthy individuals and carefully tested to ensure safety. The children also took an acid pump inhibitor in order to reduce stomach acidity and increase the survival rate of the microbes. The researchers followed up on the children for eight weeks after treatment ended.

Participants in the study were between the ages of 7 and 16. The researchers also enlisted 20 neurotypical children (who did not receive treatment) as controls.

Using multiple measures, the researchers detected marked changes in GI symptoms and behavior in the children with ASD. Among their findings:

- The average score on the Gastrointestinal Symptom Rating Scale (GSRS) dropped 82% from the beginning to the end of treatment. At the eight-week follow-up, it remained 77% lower than at baseline.
- Only two of the 18 children with ASD showed less than a 50% reduction in the average GSRS score.
- There was a significant decrease in the number of days with abnormal or no stools, and this improvement also was maintained at the eight-week followup.
- The Parent Global Impressions-III (PGI-III) scale revealed significant improvements in behavior, and there was a significant correlation between GSRS scores and PGI-III scores.
- Scores on the Childhood Autism Rating Scale, which measures core autism symptoms, decreased by 22% from the beginning to the end of the study, and were 24% lower than baseline at the eight-week follow-up.

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- Participants with ASD also showed improvements on the Social Responsiveness Scale and the Autism Behavior Checklist.
- On the Vineland Adaptive Behavior Scale II, the average developmental age of participants with ASD increased by 1.4 years and improved across all domain areas.

The researchers also detected significant changes in the gut bacteria of the children with ASD. While these children initially had significantly less diverse gut bacteria than controls, the researchers say that “median richness at week 18 was statistically indistinguishable between the ASD and control groups.” Importantly, they say, “the donor bacterial community was at least partially engrafted in the recipient gut,” indicating that their therapy overcame “colonization resistance.”

The researchers also studied changes in phages, which are viruses that play a role in gut health. They detected no significant changes, but did see evidence that phage communities also responded to MTT.

The researchers conclude that MTT “appears to be a promising approach to alter the

gut microbiome and virome and improve GI and behavioral symptoms of ASD.” They caution, however, that their study was small and non-blinded, and that researchers need to follow up with randomized, double-blind, placebo-controlled studies.

“Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study,” Dae-Wook Kang, James B. Adams, Ann C. Gregory, Thomas Borody, Lauren Chittick, Alessio Fasano, Alexander Khorruts, Elizabeth Geis, Juan Maldonado, Sharon McDonough-Means, Elena L. Pollard, Simon Roux, Michael J. Sadowsky, Karen Schwarzberg Lipson, Matthew B. Sullivan, J. Gregory Caporaso, and Rosa Krajmalnik-Brown, *Microbiome*, January 2017 (free online). Address: Matthew B. Sullivan, mbsulli@gmail.com.

“Leaky gut,” blood-brain barrier problems may play important role in autism

A “leaky gut” and a compromised blood-brain barrier may play key roles in autism spectrum disorders (ASD), according to new research.

Increasingly, evidence is pointing to a gut-brain connection in autism. One possible scenario is that an overly permeable (“leaky”) gut allows neuroactive molecules to escape into the bloodstream, crossing an inadequate blood-brain barrier and entering the brain where they cause neuroinflammation and affect behavior.

To explore the gut-brain axis in autism, Maria Fiorentino and colleagues analyzed postmortem cerebral cortex and cerebellum tissues from 8 individuals with ASD, 10 individuals with schizophrenia, and 15 neurotypical controls. In addition, they analyzed intestinal epithelial tissue from 12 individuals with ASD and 9 controls.

The researchers say that brain tissue samples from individuals with ASD exhibited altered expression of genes associated with blood-brain barrier integrity and function, as well as genes associated with inflammation. In addition, 75% of intestinal epithelial

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“Leaky gut,” blood-brain barrier problems may play important role in autism

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samples from individuals with ASD exhibited reduced expression of barrier-forming cellular components, and 66% showed a higher expression of molecules that increase intestinal permeability. The researchers say that “these findings seem to be specific for ASD,” although some anomalies were also seen in tissues from individuals with schizophrenia.

Fiorentino comments, “This is the first time anyone has shown that an altered blood-brain barrier and impaired intestinal barrier might both play a role in neuroinflammation in people with ASD.”

Fiorentino’s next project will involve analyzing the possible connection between gut microorganisms, intestinal permeability, and behavior. She says, “There is definitely something going on between the gut and the brain with ASD and other neurodevelopmental disorders, and of course the microbiome has a big role to play. It has already been shown that ASD kids have an altered composition of gut microbial communities. If we can figure out what is required or missing, then maybe we can come up with a treatment that might be able to improve some of the behavioral issues and/or the gastrointestinal symptoms.”

“Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders,” Maria Fiorentino, Anna Sapone, Stefania Senger, Stephanie S. Camhi, Sarah M. Kadzielski, Timothy M. Buie, Deanna L. Kelly, Nicola Cascella, and Alessio Fasano, *Molecular Autism*, Vol. 7, No. 49, 2016. Address: Maria Fiorentino, Mucosal Immunology and Biology Research Center, Massachusetts General Hospital for Children, Boston, MA 02114, mrfiorentino@mgh.harvard.edu.

—and—
“Study finds alterations in both blood-brain barrier and intestinal permeability in individuals with autism,” news release, Mass General News, January 18, 2017.

ARI Survey: Seniors with Autism Spectrum Disorder

If you or a person you care for is on the autism spectrum and is 50 years of age or older, we would appreciate it if you could complete an online survey on quality of life issues associated with senior adults on the autism spectrum. We hope the results from this survey will provide much insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers. Once the data from this survey are collected and analyzed, we will send responders a summary report of the findings.

Website: ASDSeniorSurvey.com

Defects in single gene lead to autism or infantile seizures

Researchers say that defects in a single gene can lead to either autism or infantile epilepsy, depending on whether the defects increase or decrease the effects of the gene.

The gene, SCN2A, encodes a sodium channel protein called NaV1.2, which plays a critical role in allowing neurons to communicate electrically. Previous research showed that the SCN2A variants seen in infantile seizures lead to increased neuronal excitability, and the new study sought to discover the effects of the variants associated with autism.

Roy Ben-Shalom and colleagues investigated 12 SCN2A mutations associated with autism to see how they affected the electrical properties of NaV1.2 channels in cultured human cells. They found that all 12 reduced the function of the sodium channel, but in different ways. The effects ranged from preventing the channel from forming at all to blocking the pore through which sodium needs to flow for the channel to function. Using computer modeling, the researchers determined that unlike the mutations seen in individuals with infantile seizures, the mutations associated with autism made it more difficult for the modeled neurons to send electrical signals.

Ben-Shalom says, “It was remarkable to see how consistently neuronal function was

disrupted by these different mutations seen in patients with autism. The mutations all affected the channel in slightly different ways, but they ended up affecting neurons in almost exactly the same way.”

The researchers’ computer simulations also indicated that the mutations associated with autism would only have a major impact on the brain during development, because the neurons transition away from relying on NaV1.2 channels as they mature. They say this is consistent with the idea that autism begins prenatally or before one year of age.

Study coauthor Kevin Bender says, “These findings solidify SCN2A’s status as one of the most important genes in autism.” He and his colleagues next plan to investigate whether the severity of autism can be predicted by a child’s specific SCN2A mutation.

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“Opposing effects on NaV1.2 function underlie differences between SCN2A variants observed in individuals with autism spectrum disorder or infantile seizures,” Roy Ben-Shalom, Caroline M. Keeshen, Kiara N. Berrios, Joon Y. An, Stephan J. Sanders, and Kevin J. Bender, *Biological Psychiatry*, January 2017 (open access). Address: Kevin Bender, kevin.bender@ucsf.edu.

—and—
“Autism researchers discover genetic ‘Rosetta Stone,’” Nicholas Weiler, UCSF News, January 26, 2017.

Brain scans may be able to detect signs of ASD in infancy

Early brain changes may help predict autism spectrum disorders (ASD) in high-risk children, a new study reports.

Heather Cody Hazlett and colleagues performed MRI scans on 106 high-risk infants whose older siblings had an ASD diagnosis. (Children with an older sibling with ASD have a 1-in-5 chance of developing ASD themselves.) In addition, they performed scans on 42 low-risk infants. The researchers scanned the children’s brains at 6, 12, and 24 months of age.

Fifteen of the children in the high-risk group received an ASD diagnosis by the age of 24 months. MRI scans showed that the volume of these children’s brains grew faster between 12 and 24 months than the brains of children who did not develop ASD, and that behavioral symptoms began to appear during this period of accelerated growth. In addition, the cortical surface area grew faster between 6 and 12 months in children later diagnosed with autism.

The researchers then used a computer-generated algorithm to predict autism based primarily on brain surface area information from the MRIs of 6- to 12-month-old children. They say this algorithm “predicted the diagnosis of autism in individual high-

risk children at 24 months (with a positive predictive value of 81% and a sensitivity of 88%).”

Study coauthor Joseph Piven says, “This finding suggests that in the future, early brain imaging may be able to predict later autism risk and identify those infants who might benefit the most from intensive interventions before the symptoms emerge, and during a time when the brain is most malleable.” The researchers note, however, that their findings need to be replicated in a larger set of children.

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“Early brain development in infants at high risk for autism spectrum disorder,” Heather Cody Hazlett, Hongbin Gu, Brent C. Munsell, Sun Hyung Kim, Martin Styner, Jason J. Wolff, Jed T. Elison, Meghan R. Swanson, Hongtu Zhu, Kelly N. Botteron, D. Louis Collins, John N. Constantino, Stephen R. Dager, Annette M. Estes, Alan C. Evans, Vladimir S. Fonov, Guido Gerig, Penelope Kostopoulos, Robert C. McKinstry, Juhui Pandey, Sarah Paterson, John R. Pruett, Robert T. Schultz, Dennis W. Shaw, Lonnie Zwaigenbaum, Joseph Piven, and the IBIS Network; *Nature*, February 15, 2017 (online). Address: Heather Cody Hazlett, heather_cody@med.unc.edu.

—and—
“Experimental test can spot autism in infancy,” HealthDay, February 15, 2017.

EDITORIAL: Stephen M. Edelson, Ph.D.

Highlights of ARI's First Fifty Years

This year marks the Autism Research Institute's 50th anniversary. As part of our year-long celebration, we have created a timeline of many of our major accomplishments. I would like to thank Denise Fulton, ARI's administrative director, for creating this celebratory commemorative booklet about ARI. You can download a copy at www.ARI50th.com or write to ARI for a hardcopy version.

1950s

Dr. Bernard Rimland's son, Mark, is born in 1956. While an infant, Mark displays unusual behaviors. Rimland and his wife, Gloria, bring him to several pediatricians, but none of them provide any help. Rimland then reads an old college textbook that describes autism and soon realizes that parents, especially mothers, are blamed for causing autism in their children.

1960s

1964—Rimland publishes *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*. In the book, he argues convincingly that autism is biologically based and not a result of emotional trauma due to poor parenting. *A 50th anniversary edition of the book, along with updates written by researchers, was published in 2004.*

1965—Rimland establishes the Autism Society of America (formerly known as the National Society for Autistic Children) to network parents of children on the autism spectrum as well as to promote the use of behavioral techniques commonly known today as Applied Behavioral Analysis (ABA).

1967—The Institute for Child Behavior Research (renamed in the mid-1980s as the Autism Research Institute) is established with the aim to conduct, encourage, and fund research as well as to network scientists with one another and with parents.

1969—Dr. Leo Kanner speaks at the first NSAC conference and states that parents do not cause autism in their children. Kanner once blamed parents, but he changed his thinking, primarily after reading Rimland's *Infantile Autism* and corresponding with him.

1970s

1971—Rimland co-authors a study with Dr. Mary Coleman. This is one of the first

biochemical studies on autism. They find a correlation between serotonin levels in blood platelets and his diagnostic checklist.

1973—Rimland publishes the first large-scale study on autism, involving 190 children on the autism spectrum. He concludes that vitamin B6 may be beneficial to many individuals on the spectrum. *More than a dozen placebo-controlled, double-blind studies have supported the use of vitamin B6.*

1978—Rimland publishes an article titled "The Autistic Savant" in *Psychology Today*. He argues that the original term used to describe someone with an unlearned skill, "idiot savant," should be replaced with the term "autistic savant."

1980s

1984—Rimland retires from his job at the Navy and devotes himself full-time to autism. Edelson finishes his graduate training on the same day. Soon after, they begin a 20-year collaboration.

1986—Temple Grandin publishes her first book, *Emergence: Labeled Autistic*. Rimland edits the book and writes the foreword.

1987—Rimland publishes the first hard-copy science newsletter on autism, the *Autism Research Review International*. The quarterly newsletter is still published today.

1988—Because of Rimland's publications on savant abilities, the producer of the movie *Rain Man* asks him to be the head consultant. Rimland reads the script and suggests that Raymond have autism rather than be mentally challenged.

1989—Edelson moves to Oregon and opens the Center for the Study of Autism (CSA) in Newberg, Oregon. Families throughout the world travel to Newberg to participate in research as well as learn how to help their children.

1990s

1992—ARI is the first national autism organization to publicly criticize the use of the now-debunked therapy Facilitated Communication (FC).

1993—Rimland is instrumental in guiding Catherine Maurice, author of *Let Me Hear Your Voice: A Family's Triumph Over Autism*, and helping her promote the book. The book

is credited by many as creating widespread awareness about ABA throughout the U.S.

1994—Rimland and Edelson publish the first research paper examining the efficacy of auditory integration training (AIT). *Recently, Dr. Manuel Casanova replicated their findings, detecting significant improvements in individuals on the spectrum following auditory processing.*

1995—ARI convenes the first international think tank on autism, consisting of more than 30 researchers and experienced physicians. This is the first time that a group of professionals discuss GI issues associated with autism. Later, Rimland uses the title Defeat Autism Now! or DAN! to describe the biomedical approach to autism research.

1996—ARI publishes a 41-page booklet, *Clinical Assessment Options for Children with Autism and Related Disorders: A Biomedical Approach*, written by Drs. Sidney Baker and Jon Pangborn. (A total of five editions are published over a 10-year period.)

1997—ARI begins to sponsor national conferences, called DAN! conferences.

1999—Edelson and Rimland release the Autism Treatment Evaluation Checklist (ATEC) to help researchers, parents, and therapists assess treatment efficacy. Parents also rely on the ATEC to monitor the progress of their children over time. *As of 2016, over half a million ATECs have been completed.*

2000s

2003—Edelson and Rimland co-edit a book titled *Treating Autism: Parent Stories of Hope and Success*. A second, revised edition titled *Recovering Autistic Children* is published in 2006. This is one of the first books to discuss the possibility of recovery.

2004—ARI funds gastrointestinal (GI) research (\$100k) at Harvard/MassGeneral. These funds are used as "seed money" to start the Autism Treatment Network.

2006—Rimland passes away in November, 2006. The board selects Edelson to become executive director of ARI. Jane Johnson and Denise Fulton join Edelson to help move ARI's grassroots efforts to a contemporary platform, allowing ARI to reach even more families and professionals worldwide.

2007—ARI publishes the book *We Band*
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Research Updates

“Male” brain may up ASD risk for females

Having a brain anatomy typical of males may increase the odds of a female having an autism spectrum disorder (ASD), according to a new study.

Christine Ecker and colleagues analyzed MRI scans from 98 individuals with high-functioning ASD and 98 neurotypical controls. All participants were right-handed, and all were between 18 and 42 years of age.

Measuring cortical thickness, which differs for men and women, the researchers found that the probability of autism increased significantly among participants whose brain phenotype was more typical of males. For instance, they found that women with a characteristically “male” brain anatomy were approximately three times more likely to have ASD than women with a characteristically female brain anatomy. However, men with a characteristically female brain anatomy did not have a lower likelihood of having autism.

The researchers next plan to study younger individuals with ASD, to see if they detect the same pattern. If so, they say, MRI scans measuring cortical thickness may aid in the early diagnosis of autism.

“Association between the probability of autism spectrum disorder and normative sex-related phenotypic diversity in brain structure,” Christine Ecker, Derek S. Andrews, Christina M. Gudbrandsen, Andre F. Marquand, Cedric E. Ginestet, Eileen M. Daly, Clodagh M. Murphy, Meng-Chuan Lai, Michael V. Lombardo, Amber N. V. Ruigrok, Edward T. Bullmore, John Suckling, Steven C. R. Williams, Simon Baron-Cohen, Michael C. Craig, and Declan G. M. Murphy, *JAMA Psychiatry*, February 8, 2017 (free online). Address: Christine Ecker, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Goethe University, Deutschordenstrasse 50, 60528 Frankfurt am Main, Germany, christine.ecker@kgu.de.

—and—
“Typical male brain anatomy associated with higher probability of autism spectrum disorder,” news release, JAMA Journal Networks, February 8, 2017.

Stress, GI distress may be linked in ASD

An elevated response to stress may play a role in the gastrointestinal (GI) symptoms often seen in autism spectrum disorders (ASD), a new study suggests.

The study, by B. J. Ferguson and colleagues, involved 120 individuals with ASD. The participants’ parents completed a questionnaire assessing their children’s GI symptoms. Fifty-one of the individuals had GI symptoms, while 69 did not.

Each participant underwent a 30-second stress test, and the researchers measured their saliva levels of cortisol—a hormone released during times of stress—before and after the test. They report that participants with GI symptoms had higher levels of cortisol following the stress test than those without GI problems. The relationship between cortisol response to stress and GI function was strongest for children with a history of regressive autism.

Study coauthor David Beversdorf comments, “When treating a patient with autism who has constipation and other lower gastrointestinal issues, physicians may give them a laxative to address these issues. Our findings suggest there may be a subset of patients for which there may be other contributing factors. More research is needed, but anxiety and stress reactivity may be an important factor when treating these patients.”

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“Associations between cytokines, endocrine stress response, and gastrointestinal symptoms in autism spectrum disorder,” Bradley J. Ferguson, Sarah Marler, Lily L. Altstein, Evon Batey Lee, Micah O. Mazurek, Aaron McLaughlin, Eric A. Macklin, Erin McDonnell, Daniel J. Davis, Anthony M. Belenchia, Catherine H. Gillespie, Catherine A. Peterson, Margaret L. Bauman, Kara Gross Margolis, Jeremy Veenstra-VanderWeele, and David Q. Beversdorf, *Brain, Behavior, and Immunity*, Vol. 58, November 2016, pp. 57-62. Address: David Beversdorf, DC 069.10, One Hospital Drive, University of Missouri, Department of Radiology, Columbia, MO 65212, beversdorfd@health.mssouri.edu.

—and—
“Increased reaction to stress linked to gastrointestinal issues in children with autism,” news release, University of Missouri-Columbia, January 4, 2017.

— AUTISM.JOBS —

The Autism Employment Resource Center

A Free Resource for Job Seekers, Families and Caregivers, Job Coaches, and Employers

At this site, you can discover the advantages of hiring individuals with autism, access practical information designed to help candidates with autism become “job ready,” and learn how to create autism-friendly workplaces.

This database is a searchable collection of autism employment resources with a wealth of practical advice. It includes links to a variety of resources including articles, videos, books and more. Guides highlight key steps in the employment process.

Visit www.Autism.Jobs

Mother’s allergies during pregnancy could alter fetal brain

Maternal allergies during pregnancy may play a role in neurological conditions such as autism and ADHD, a new study suggests.

Kathryn Lenz and her colleagues sensitized female rats to ovalbumin, a protein found in egg whites, before the rats became pregnant. Fifteen days into pregnancy, the rats were exposed to the allergen, triggering an immune response.

The researchers found that both male and female offspring of these rats had increased numbers of immune cells in the brain called mast cells and reduced numbers of a different type of immune cells called microglia. The offspring of allergic mothers were also hyperactive, demonstrated less anxiety-like behavior, and engaged in less “rough and tumble” play.

Lenz says, “The males born to the allergen-exposed mothers looked more like females. They were more socially reserved. They were really hyperactive but socially disengaged. That looks a bit like ADHD.”

In addition, rats born to allergic mothers exhibited less mental flexibility than control rats. (To test mental flexibility, the researchers hid Cheerios in terra-cotta pots, concealing them in different ways.) Both male and female offspring of allergic mothers had difficulty with mental flexibility, with males showing the most marked impairment.

Lenz and her team also examined the density of dendritic spines in the rats’ frontal cortexes. These synaptic connections are crucial for communication between brain cells. The researchers found that male offspring of allergen-exposed mothers had a reduced number of dendrites, while females had an increased number.

Lenz concludes, “This is evidence that prenatal exposure to allergens alters brain development and function and that could be an under-appreciated factor in the development of neurodevelopmental disorders.”

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“Allergies during pregnancy contribute to changes in the brains of rat offspring,” Misti Crane, news release, Ohio State University, November 16, 2016. Lenz and her team presented their findings at Neuroscience 2016 on November 16, 2016.

Moving?
Please let us know well in advance, so your next issue will reach you on time!

Research Updates

Prenatal exposure to meconium may up autism risk slightly

Babies who have a bowel movement before birth have an increased risk of autism, researchers report, but the risk is very small.

K. M. Miller and colleagues analyzed the hospital records of nearly 10 million children born in California between 1991 and 2008, comparing children exposed

before birth to meconium (the first bowel movement) to those who had their first bowel movement after birth. In addition, they identified children who experienced meconium aspiration syndrome (MAS), in which meconium enters the lungs and can cause breathing problems.

The researchers found that children with meconium-stained amniotic fluid caused by a prenatal bowel movement had an 18 percent increase in autism risk. Surprisingly, children with MAS had a smaller risk that failed to achieve significance. Study coauthor Cheryl Walker speculates that the interventions that children with MAS typically receive, such as oxygen and intravenous fluids, may reduce their risk for brain damage.

“Meconium exposure and autism risk,” K. M. Miller, G. Xing, and C. K. Walker, *Journal of Perinatology*, Vol. 37, February 2017, 203-7. Address: CK Walker, Mind Institute, Department of Obstetrics & Gynecology, 4869 Y Street, Suite 2500, Sacramento, CA 95817, ckwalker@ucdavis.edu.

Animal study hints that resveratrol may reduce symptoms in ASD

A new study suggests that resveratrol, an antioxidant found in grapes and berries, may be a beneficial treatment for autism spectrum disorders (ASD).

Ranjana Bhandari and colleagues infused propanoic acid (PPA) into the brains of male rats to create a mouse model of ASD. The PPA-exposed rats exhibited autistic-like symptoms including abnormal social interactions, stereotyped behaviors, anxiety, depression, sensorimotor problems, hyperactivity, and learning and memory issues. In addition, they showed evidence of oxidative stress, mitochondrial dysfunction, and neuroinflammation.

The researchers administered resveratrol to three groups of the rats in different daily doses (5, 10, and 15 mg/kg), with a fourth group serving as controls. They report, “Treatment with resveratrol for four weeks restored, significantly and dose dependently, all the neurological, sensory, behavioral, biochemical, and molecular deficits in PPA induced autistic phenotype in rats.” They conclude that resveratrol “has strong potential to be explored clinically as an adjunct therapeutic agent for mitigating the neurobehavioral, biochemical and molecular alterations in ASD.”

“Resveratrol suppresses neuroinflammation in the experimental paradigm of autism spectrum disorders,” Ranjana Bhandari and Anurag Kuhad, *Neurochemistry International*, December 23, 2016 (epub ahead of print publication). Address: Ranjana Bhandari, akb10in@yahoo.co.uk.

Extended aerobic workouts can reduce behavior problems in kids with ASD, ADHD

Extended sessions of aerobic exercise can dramatically reduce behavior problems in children with autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and other behavioral issues, a new study indicates.

In a 14-week study, April Bowling and colleagues randomly assigned 103 students at a therapeutic day school to participate in regular physical education (PE) classes or a seven-week program of aerobic cybercycling. At the end of the first seven weeks, participants switched groups. All participants were between 7 and 16 years of age.

During the intervention, the children cycled twice weekly during PE classes. The cycles included video screens allowing the children to ride different courses, play games, and engage in other activities while cycling. Control students participated in the standard PE curriculum, which focused primarily on socialization, team skills, and motor skills and did not provide extended bouts of aerobic exercise.

“Across the intervention period,” the researchers report, “odds that children would display clinically disruptive behaviors, including impulsivity and emotional lability, were 32% to 51% lower than during the control condition. These effects strengthened on days when children participated in an intervention cybercycling class; here, odds of disruptive levels of behavioral dysregulation declined between 71% and 76% relative to the control condition.” In addition, children in the cybercycling group spent significantly less time out of the classroom due to behavioral issues.

The researchers say, “Aerobic cybercycling PE shows promise for improving self-regulation and classroom functioning among children with complex behavioral health disorders. This school-based exercise intervention may significantly improve child behavioral health without increasing parental burden or health care costs, or disrupting academic schedules.”

“Cybercycling effects on classroom behavior in children with behavioral health disorders: an RCT,” April Bowling, James Slavet, Daniel P. Miller, Sebastien Haneuse, William Beardlee, and Kirsten Davison, *Pediatrics*, January 2017 (free online). Address: April Bowling, Department of Nutrition, Harvard T.H. Chan School of Public Health, 665 Huntington Ave., Building 2, Room 320, Boston, MA 02115, april.bowling@mail.harvard.edu.

Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

May 2:
Organizational Strategies in
Middle School and Up*

May 8:
Supporting Sensory Needs in
Children & Teens

May 16:
Nutrition Interventions to Improve Sleep*

May 24:
Serotonin and the Gut in ASD

June 1:
Behavioral Strategies to Improve Sleep*

June 13:
Diagnosis of Autism in Adults

June 27:
ASD and Technology*

July 11:
Social Media & People with ASD*

These webinars are offered at 1 p.m. Eastern time (U.S.). Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links.

You can view previous webinars in our archives at <https://www.autism.com/webinars>.

* We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.

Highlights of ARI's First Fifty Years (continued from page 3)

of Mothers: Autism, My Son & the Specific Carbohydrate Diet, written by Judith Chinitz and Sidney M. Baker

ARI premieres a monthly e-newsletter. Currently, there are more than 80,000 subscribers.

ARI collaborates with Unlocking Autism to sponsor a toll-free resource calling center.

ARI enters an agreement with the National Institute for Child Health and Human Development and the University of Maryland to establish a tissue bank.

ARI begins a collaboration with the Autism Network for Hearing and Visually Impaired Persons.

ARI begins a Rural Outreach Pilot Project to provide needed information about autism to various regions in the U.S.

2008—ARI is instrumental in the publication of *Families of Adults with Autism: Stories and Advice for the Next Generation*. This is one of the first books focusing on adults on the spectrum.

2009—ARI enters an agreement with the Digestive Function Laboratory Repository at Massachusetts General Hospital.

ARI launches a two-day training program for nutritionists and dietitians at its national DAN! conferences.

2010—ARI is instrumental in the publication of *Siblings: The Autism Spectrum Through Our Eyes*. This is one of the first books focusing on siblings of individuals on the spectrum.

ARI is instrumental in the publication of two papers published in *Pediatrics* that review the research on GI problems in autism and provide treatment recommendations.

ARI premieres a quarterly e-newsletter focused on topics related to adults on the autism spectrum. The editor is an adult on the spectrum, and the majority of articles are written by adults on the spectrum.

2011—ARI sponsors adult tracks at its national conferences, giving adults on the spectrum a platform to describe their needs and provide suggestions for helping other adults on the spectrum.

ARI establishes the Autistic Global Initiative (AGI), an ARI program run by adults on the spectrum.

ARI begins publishing a quarterly e-newsletter focused on individuals on the autism spectrum who have hearing and/or visual impairments.

Dr. Margaret Creedon, one of the top clinical psychologists in the autism field, joins the staff of ARI.

ARI transitions from brick-and-mortar conferences to online webinars in order to offer support to families worldwide.

ARI premieres a bimonthly e-newsletter for obstetricians, pediatricians, and nurses titled *Clinical Research in Autism*.

ARI receives NGO (non-government organization) status from the United Nations.

ARI establishes the Global Autism Alliance with representatives from Australia, Barbados, Brazil, Canada, Chile, Dubai, France, Ghana, Italy, Japan, Mexico, Nigeria, and Puerto Rico.

AGI publishes a two-volume, 750-page curriculum and training for direct support providers for adults on the autism spectrum.

2013—ARI publishes the book *Nutritional Supplement Use for Autistic Spectrum Disorder*, written by Dr. Jon Pangborn.

ARI begins co-sponsoring an annual think tank in Boston in collaboration with Massachusetts General Hospital.

ARI sponsors two discussion panels on Autism Awareness Day at the United Nations.

AGI premieres an online 12-week comprehensive daily living/residential course for providers for adults on the spectrum.

2014—ARI produces webcasts, in collaboration with the Cleveland Clinic, on medical and biomedical issues for physicians.

ARI premieres an Internet portal, autismjobs, on employment for those on the spectrum, parents, and potential employers.

2015—ARI premieres an online job interview course for adults on the spectrum.

2016—ARI is instrumental in the publication of *Understanding and Treating Self-Injurious Behavior in Autism*. This is the first multi-disciplinary book focusing on a challenging behavior.

Animal study: ketogenic diet reduces ASD symptoms in mice

A new study adds to evidence that a ketogenic diet—which is high in fat, has adequate protein, and is very low in carbohydrates—may ameliorate symptoms of autism spectrum disorder (ASD).

The ketogenic diet has been used for decades to treat childhood epilepsy. By drastically lowering carbohydrate intake, the diet—which requires medical supervision—reduces the blood glucose available to the body and forces it to burn ketone bodies for energy. There is evidence that the diet lowers inflammation, which plays a key role in both epilepsy and autism.

David Ruskin and colleagues focused their study on autism linked to maternal immune activation, or MIA. Research indicates that children of mothers who experience MIA due to viral or bacterial infections during the first two trimesters of pregnancy have an elevated risk for ASD. The researchers replicated the effects of MIA by injecting a viral mimic into pregnant mice.

Between weaning and five weeks of age, all offspring of the exposed mice ate a typical control diet. After five weeks of age, one group of mice remained on the control diet while a second group was switched to a ketogenic diet. When the mice were 8 to 9 weeks of age, the researchers tested their behavior and analyzed their blood.

The researchers say that male mice eat-

ing the standard diet exhibited autistic-like behaviors including reduced sociability and increased repetitive behavior. “However,” they say, “ketogenic diet feeding partially or completely reversed all MIA-induced behavioral abnormalities in males.” Female offspring were unaffected by maternal exposure to the viral mimic, which the researchers say is not surprising given the high male prevalence in autism.

However, while the female mice were unaffected in this study, Ruskin and colleagues note that other research using a different mouse model found that the ketogenic diet reduced autistic-like symptoms in females. In addition, they say, several clinical studies have shown that the diet can improve core symptoms in girls as well as boys with ASD.

“Together,” they say, “these studies suggest a broad utility for metabolic therapy in improving core ASD symptoms, and support further research to develop and apply ketogenic and/or metabolic strategies in patients with ASD.”

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“Ketogenic diet improves behaviors in a maternal immune activation model of autism spectrum disorder,” David N. Ruskin, Michelle I. Murphy, Sierra L. Slade, and Susan A. Masino, *PLOS One*, February 6, 2017 (free online). Address: David Ruskin, Department of Psychology, Neuroscience Program, Trinity College, Hartford, CT 06106, david.ruskin@trincoll.edu.

Lack of single protein may cause a third of cases of ASD

As many as one third of cases of autism spectrum disorder (ASD) may involve a shortage of a single protein in the brain, according to researchers at the University of Toronto.

Earlier research by Mathieu Quesnel-Vallières and colleagues demonstrated that the protein, called nSR100, is reduced in the brains of individuals with ASD. In the new study, the researchers genetically engineered mice with reduced levels of this protein. The mice developed autistic-like behaviors, including avoidance of social interaction and heightened sensitivity to noise.

“We previously reported an association between nSR100 protein levels and autism,” study coauthor Sabine Cordes says. “But this time we show that reduced levels of this protein could really be causative—that’s a big deal. Just by reducing the nSR100 levels by 50%, we observe hallmarks of autistic behavior.”

In the brain, nSR100 is a key regulator of alternative splicing, which involves removing non-coding DNA and bringing protein-coding segments together to make a finished protein template. The researchers speculate that autism stems in part from an accumulation of incor-

rectly spliced proteins in brain cells, resulting in errors in brain wiring. They detected changes in alternative splicing and brain wiring in their nSR100-deficient mice.

Cordes says, “Instead of focusing on individual mutations linked to autism, it’s much more powerful to identify regulatory hubs like nSR100. In the future, if you turned this protein up a little bit in autistic patients, you might be able to improve some of the behavioral deficits.”

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“Misregulation of an activity-dependent splicing network as a common mechanism underlying autism spectrum disorders,” Mathieu Quesnel-Vallières, Zahra Dargaei, Manuel Irimia, Thomas Gonatopoulos-Pournatzis, Joanna Y. Ip, Mingkun Wu, Timothy Sterne-Weiler, Shinichi Nakagawa, Melanie A. Woodin, Benjamin J. Blencowe, and Sabine P. Cordes, *Molecular Cell*, Vol. 64, No. 6, pp. 1023-34, December 15, 2016. Address: Benjamin Blencowe, Department of Molecular Genetics, University of Toronto, Toronto, ON M5S 1A8, Canada, b.blencowe@utoronto.ca.

—and—
“U of T researchers make autism breakthrough,” Jovana Drinjakovic, University of Toronto, December 15, 2016.

Maternal herpes infection may raise odds of ASD in males

Women who are actively infected with genital herpes during early pregnancy have double the typical odds of having a child with autism spectrum disorder (ASD) if the child is male, according to a new study.

Milada Mahic and colleagues examined blood samples from 412 mothers of children with ASD and 463 mothers of neurotypical children. The samples were taken when the women were approximately 18 weeks pregnant and again at birth. The researchers analyzed the samples for levels of antibodies to *Toxoplasma gondii*, rubella, cytomegalovirus, and herpes simplex viruses type 1 and 2.

The researchers found that high levels of antibodies to herpes simplex virus 2 (HSV-2), but none of the other viruses, correlated with ASD risk. The association was detected only in the samples taken during early pregnancy.

Mahic says, “We believe the mother’s immune response to HSV-2 could be disrupting fetal central nervous system development, raising risk for autism.” She and her colleagues believe that the risk stems not from direct infection of the fetus but from inflammation in the mother.

The researchers say, “Our findings are consistent with experimental data from mouse models of gestational infection wherein vulnerability of offspring to neurodevelopmental damage depends on timing

of the infection of the maternal host and associated activation of the prenatal innate immune system. Epidemiological data suggest that activation of the maternal immune system during early to midpregnancy is associated with long-term developmental brain and behavioral abnormality in the offspring.”

The association between maternal HSV-2 infection and ASD was seen only for male children. However, the researchers note that the number of females with ASD in their study was small.

The researchers say that 13% of the mothers in the study tested positive for anti-HSV-2 antibodies at mid-pregnancy. Of this subgroup, only 12% had herpes lesions before pregnancy or during the first trimester, indicating that the majority were asymptomatic.

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“Maternal immunoreactivity to herpes simplex virus 2 and risk of autism spectrum disorder in male offspring,” Milada Mahic, Siri Mjaaland, Hege Marie Bøvelstad, Nina Gunnes, Ezra Susser, Michaeline Bresnahan, Anne-Siri Øyen, Bruce Levin, Xiaoyu Che, Deborah Hirtz, Ted Reichborn-Kjennerud, Synnve Schjølberg, Christine Roth, Per Magnus, Camilla Stoltenberg, Pål Surén, Mady Hornig, and W. Ian Lipkin, *mSphere*, Volume 2, No. 1, January/February 2017 (free online). Address: W. Ian Lipkin, wil2001@cumc.columbia.edu.

—and—
“Autism risk linked to herpes infection during pregnancy,” news release, Mailman School of Public Health, February 22, 2017.

Effects of mitochondrial supplements in children with ASD investigated

A new study offers insights into how nutritional supplements may benefit children with ASD and mitochondrial disease. Approximately 5% of children with ASD have classic mitochondrial disease, while up to 50% of children with ASD may have biomarkers of mitochondrial dysfunction.

The study, by Leanna Delhey and colleagues, evaluated the mitochondrial function of individuals with ASD who were taking or abstaining from supplements that affect the mitochondria. The researchers analyzed data collected on 127 children with ASD, all between three and fourteen years of age. Of these participants, 15% were clinically diagnosed with mitochondrial disease. In addition, the study used data from 68 neurotypical individuals matched for age and gender.

The researchers measured the effects of specific mitochondrial supplements on the activity of three mitochondrial components—ETC Complexes I and IV and citrate synthase—using swabs from inside participants’ cheeks. They note, “We not only examined the absolute level of activity of mitochondrial components, but also the relationship between the components, to better understand whether treatments not only modulated the activity level but how the mitochondrial components work together.”

They report, “Complex I activity was increased by fatty acid and folate supplementation, but folate only affected those with mitochondrial disease. Citrate synthase activity was increased by antioxidant supplementation but only for the mitochondrial disease subgroup. The relationship between Complex I and IV was modulated by folate while the relationship between Complex I and citrate synthase was modulated by both folate and B12.”

The researchers conclude, “This study provides empirical support for common mitochondrial treatments and demonstrates that the relationship between activities of mitochondrial components might be a marker to follow in addition to absolute activities.” In addition, they say it indicates that noninvasive techniques such as buccal swabs may be very useful in monitoring the biochemical effects of mitochondrial targeted treatments.

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“The effect of mitochondrial supplements on mitochondrial activity in children with autism spectrum disorder,” Leanna M. Delhey, Ekim Nur Kilinc, Li Yin, John C. Slattery, Marie L. Tippet, Shannon Rose, Sirish C. Bennuri, Stephen G. Kahler, Shirish Damle, Agustin Legido, Michael J. Goldenthal, and Richard E. Frye, *Journal of Clinical Medicine*, February 13, 2017 (free online). Address: Richard Frye, refrye@uams.edu.

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