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Autism Research Review

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

Sleeping sickness drug improves symptoms of ASD in children, offers insight into causes

A hundred-year-old drug used to treat sleeping sickness may transiently improve symptoms of autism spectrum disorder (ASD) and offers intriguing clues about the roots of the condition.

In the small trial, Robert Naviaux and colleagues administered a single IV infusion of the drug suramin to five boys with ASD. Five boys in a matched placebo group received a single IV infusion of saline. The study followed earlier experiments showing that suramin could reduce autistic symptoms in a mouse model of ASD.

The researchers report that all five boys who received the suramin infusion showed improvements in language, social behavior, restricted or repetitive behaviors, and coping skills. Scores also improved on standardized tests including the Autism Diagnostic Observation Schedule-2 (ADOS-2), the Autism Treatment Evaluation Checklist (ATEC), the Aberrant Behavior Checklist (ABC), and the Clinical Global Impression (CGI) questionnaire.

Of the four nonverbal children in the treatment group, two said their first sentences approximately one week after receiving the suramin infusion. For all of the children, Naviaux says, "the benefit from speech therapy, occupational therapy, applied behavioral analysis and even from playing games with other children during recess at school skyrocketed."

Naviaux and his colleagues believe that suramin may work by correcting a metabolic dysfunction stemming from abnormal persistence of the cell danger response (CDR), which is a natural cell response to injury or other stresses. CDR causes cells to harden their membranes and stop communicating with other cells until a danger has ended.

Naviaux says, "Sometimes CDR gets stuck. This prevents completion of the natural healing cycle and can permanently alter the way the cell responds to the world." He and his team theorize that this abnormal persistence of CDR underlies autism and many other chronic childhood disorders. They believe that CDR, rather than being the sole cause of these disorders, combines with other factors such as genetics or environmental toxins.

Naviaux says suramin works by inhibiting the signaling function of adenosine triphosphate, which is produced by the cellular mitochondria and released from cells to signal danger. He explains that suramin signals that "the cellular war is over, the danger has passed and cells can return to 'peacetime' jobs like normal neurodevelopment, growth and healing."

The researchers caution that their study was a very small trial, and their findings need to be confirmed by larger studies. They also stress, "Suramin is not approved for the treatment of autism. Like many intravenous drugs, when administered improperly by untrained personnel, at the wrong dose and schedule, without careful measurement of drug levels and monitoring for toxicity, suramin can cause harm. Careful clinical trials will be needed over several years at several sites to learn how to use low-dose suramin safely in autism, and to identify drug–drug interactions and rare side effects that cannot currently be predicted. We strongly caution against the unauthorized use of suramin."

Note: This study was partially funded by the Autism Research Institute.

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Study offers more support for protective effects of vitamin D

Additional evidence that adequate maternal vitamin D may protect offspring from autism comes from a study by Australian researchers.

Stephanie Vuillermot and colleagues exposed pregnant mice to a viral mimic in order to replicate a viral infection and trigger maternal immune activation (a risk factor for ASD). In addition, they gave some of the pregnant mice injections of vitamin D.

The researchers found that the offspring of the mice injected with the viral mimic but not vitamin D during the first trimester exhibited autistic-like deficits. However, they say that co-administration of vitamin D "blocked the emergence of the ASD-relevant deficits in social interaction, stereotyped behavior, and emotional learning and memory."

Interestingly, vitamin D did not affect maternal or fetal levels of pro-inflammatory cytokines. The researchers say this suggests that "the ASD-preventive potential of this hormone at least in this maternal immune activation model is not primarily related to its anti-inflammatory effects."

Study coauthor Wei Luan notes that the active hormonal form of vitamin D used in this study cannot be given to pregnant women because it may affect the skeleton of the developing fetus. Luan says the team will now try to determine "how much cholecalciferol—the supplement form that is safe for pregnant women—is needed to achieve the same levels of active hormonal vitamin D in the bloodstream."

The new research is consistent with a previous study (see *ARRI* Vol. 30, No. 4) by researchers at the same institute. In that study, A. A. E. Vinkhuyzen and colleagues analyzed data on the vitamin D status of 4,229 children (measured by cord blood levels at delivery) and their mothers (measured at mid-gestation). They also evaluated the children's scores on an abridged version of the parent-administered Social Responsiveness Scale (SRS) when the children were approximately six years of age. The researchers reported, "In all analyses, 25OHD deficiency or lower 25OHD concentrations were associated with higher (more impaired) SRS scores."

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"Vitamin D treatment during pregnancy prevents autism-related phenotypes in a mouse model of maternal immune activation," Stephanie Vuillermot, Wei Luan, Urs Meyer, and Darryl Eyles, *Molecular Autism*, March 2017 (open access). Address: Darryl Eyles, Queensland Brain Institute, University of Queensland, Brisbane 4072, Queensland, Australia, d.eyles@uq.edu.au.

—and—

"Link between vitamin D treatment and autism prevention," news release, University of Queensland, March 16, 2017.

—and—

"Gestational vitamin D deficiency and autism-related traits: the Generation R Study," A. A. E. Vinkhuyzen, D. W. Eyles, T. H. J. Burne, L. M. E. Blanken, C. J. Kruithof, F. Verhulst, V. W. Jaddoe, H. Tiemeier, and J. J. McGrath, *Molecular Psychiatry*, November 29, 2016 (epub prior to print publication). Address: J. J. McGrath, Queensland Brain Institute, University of Queensland, St. Lucia, Brisbane, QLD 4072, Australia, j.mcgrath@uq.edu.au.

Metabolites in blood can predict autism diagnosis

An algorithm based on levels of metabolites in the blood can predict whether a child has autism spectrum disorder (ASD) with a remarkable degree of accuracy, a new study reports.

"Instead of looking at individual metabolites," senior author Juergen Hahn says, "we investigated patterns of several metabolites and found significant differences between metabolites of children with ASD and those that are neurotypical. These differences allow us to categorize whether an individual is on the autism spectrum. By measuring 24 metabolites from a blood sample, this algorithm can tell whether or not an individual is on the autism spectrum, and even to some degree where on the spectrum they land."

Hahn and colleagues analyzed data from 149 children, focusing on metabolites relevant to two cellular pathways linked to ASD: the methionine cycle and the transulfuration pathway. About half of the children had ASD, while the other half were neurotypical.

The researchers deliberately omitted data for one individual at a time, subjected the remaining data to advanced analysis techniques, and used the results to generate an algorithm to predict the data from the omitted individual. Repeating this process for all 149 children, the researchers correctly identified 96.1% of neurotypical children and 97.6 percent of children with ASD.

The researchers say, "This level of accuracy for classification as well as severity prediction far exceeds any other approach in this field and is a strong indicator that the metabolites under consideration are strongly correlated with an ASD diagnosis." Hahn concludes, "This is the first physiological diagnostic and it's highly accurate and specific."

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"Classification and adaptive behavior prediction of children with autism spectrum disorder based upon multivariate data analysis of markers of oxidative stress and DNA methylation," Daniel P. Howsmon, Uwe Kruger, Stepan Melnyk, S. Jill James, and Juergen Hahn, *PLOS Computational Biology*, March 16, 2017 (free online). Address not listed.

—and—

"A blood test for autism," news release, Rensselaer Polytechnic Institute, March 16, 2017.

TOLL-FREE CALLING CENTER:

The Autism Research Institute maintains a toll-free calling center:

866-366-3361

If you are a parent struggling to find help, our volunteers can help you locate the information and resources you need.

Cord blood infusions pass first test as treatment for autism

Researchers conducting a phase one trial to investigate the safety of autologous cord blood infusions as a treatment for autism spectrum disorders (ASD) report that the procedure appears safe and may result in significant improvements in behavior.

Autologous infusions involve the use of a child's own umbilical cord blood, stored at birth. Many parents store cord blood in case their child needs a transfusion later in life due to an illness or injury.

A large body of evidence indicates that ASD involves inflammatory processes and alterations in brain connectivity. Geraldine Dawson and colleagues note, "Preclinical models have shown that umbilical cord blood contains effector cells that… alter brain connectivity and also suppress inflammation." Thus, they speculate that autologous blood transfusions—already used experimentally to treat cerebral palsy and other conditions—might be beneficial for individuals with ASD.

To help determine the safety of this procedure, Dawson and colleagues enrolled 25 children between two and five years of age in an open-label trial. The children underwent extensive behavioral testing before and 6 and 12 months after receiving a single infusion. In addition, the researchers identified any adverse events associated with the procedure.

Dawson and her team report that the treatment was safe and well-tolerated, with only 12 mild or moderate adverse effects—primarily allergic reactions leading to temporary skin rashes or coughs—attributable to the infusion. In addition, they say, "Significant improvements in children's behavior were observed on parent-report measures of social communication skills and autism symptoms, clinician ratings of overall autism severity and degree of improvement, standardized measures of expressive vocabulary, and objective eye-tracking measures of children's attention to social stimuli." They add, "Behavioral improvements were observed during the first six months after infusion and were greater in children with higher baseline nonverbal intelligence quotients."

While their findings are encouraging, the researchers note that their trial involved a small sample and was open-label rather than including a control group. They plan to follow this trial with a double-blind, placebo-controlled study.

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"Autologous cord blood infusions are safe and feasible in young children with autism spectrum disorder: results of a single-center phase 1 open-label trial," Geraldine Dawson, Jessica M. Sun, Katherine S. Davlantis, Michael Murias, Lauren Franz, Jesse Troy, Ryan Simmons, Maura Sabatos-DeVito, Rebecca Durham, and Joanne Kurtzberg, *Stem Cells Translational Medicine*, April 5, 2017, open access. Address: Jessica Sun, Robertson Clinical and Translational Cell Therapy Program, Duke University School of Medicine, DUMC 3850, 2400 Pratt Street, Durham, North Carolina 27705, jessica.sun@duke.edu.

Treating sleep apnea can improve symptoms in kids with ASD

A new study from Japan indicates that correcting obstructive sleep apnea (OSA) in children with autism spectrum disorders (ASD) can significantly improve their behavior.

OSA, which affects up to ten percent of children, causes symptoms including snoring and gasping during sleep, bedwetting, daytime sleepiness, and behavior problems. Treatments for pediatric OSA include weight loss, nasal steroids, and adenotonsillectomy (removal of the tonsils and adenoids).

The new study, by E. Murata and colleagues, evaluated the effects of adenotonsillectomy on 30 children with ASD and OSA. The children ranged in age from five to fourteen years. Before and after performing the surgeries, the researchers used the Child Behavior Checklist (CBCL) to evaluate the children's behavior, comparing them to 24 children with ASD who did not have OSA.

The researchers found that overall, CBCL scores improved significantly in the children who underwent surgery, while the controls exhibited no changes. Children who improved after surgery had significantly worse baseline scores on the CBCL than children whose behavior did not improve or deteriorated after surgery.

The researchers conclude, "Early detection and treatment of children with OSA is essential to prevent behavioral problems and to support mental development."

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"Evaluation of behavioral change after adenotonsillectomy for obstructive sleep apnea in children with autism spectrum disorder," E. Murata, I. Mohri, K. Kato-Nishimura, J. Iimura, M. Ogawa, M. Tachibana, Y. Ohno, and M. Taniike, *Research in Developmental Disabilities*, May 14, 2017, Vol. 65, 127-39. Address: I. Mohri, Department of Child Development, United Graduate School of Child Development, Osaka University, 2-2 Yamadaoka, Suita, Osaka, 5650871, Japan, ikuko@kokoro.med.osaka-u.ac.jp.

ARI's Deaf/HOH & Blind/Visually Impaired Network

This is a group of parents, affected individuals, and professionals with special interest in people with autism and deafness, or autism and blindness. There is no charge to join. You may join our network by filling out the email form at https://www.autism.com/autism_network_for_hearing_and_visually_impaired or printing it out and mailing it to ARI .

EDITORIAL: Stephen M. Edelson, Ph.D.

Moving forward in our understanding of autism

Fifty years ago, when Dr. Bernard Rimland founded the Autism Research Institute (ARI), he challenged virtually every accepted belief about autism. At a time when most authorities believed that autism stemmed from bad parenting, he stated unequivocally that parents were their children's strongest allies. In addition, he made the following assertions—all considered radical at the time:

- The majority of individuals with ASD have one or more co-morbid medical conditions.
- Many "autistic" behaviors are a result of an underlying medical and/or sensory issue.
- Many forms of autism result from an interaction between genes and environmental insults.

These three premises, which we now know to be true, revolutionized research in the field of autism. ARI has been at the forefront of this research, focusing our efforts on uncovering the underlying causes of autism and establishing an evidence-based standard of treatment.

While we are excited by the progress made in the past 50 years, we often pose this question at ARI: "What is the next step?" In my opinion, there are several important areas of research that currently deserve our attention. They include:

Subtyping

Many pioneers in the autism field, including Drs. Leo Kanner and Bernard Rimland, initially focused their efforts on a small group of children referred to as having Kanner's syndrome or "classical autism." However, the definition of autism has expanded considerably over the years, and the umbrella phrase "autism spectrum disorder" (or ASD) is now used to refer to many types of individuals who share similarities but who are also quite different in many ways.

There is debate within the autism community as to whether the autism spectrum is a continuum or includes many unique subgroups of individuals. Some argue that if it is a continuum, ADHD marks one end of the distribution and Asperger syndrome marks the other end. With respect to subgrouping, the individuals in each subgroup share many similarities and have few differences.

One possibility is that there is a continuum of individuals with ASD who share a similar genetic vulnerability, and that subgroups reflect different environmental insults. This would lead to unique differences among those with ASD. Furthermore, some variability within each subgroup would be expected based on the timing, amount, and duration of exposure.

This view is consistent with Dr. Mary Coleman's argument that the autism spectrum reflects separate disease entities, but they all share a common dysfunctional signaling pathway within the central nervous system that leads to similar symptoms and behaviors. It also is consistent with Dr. Manuel's Casanova's "triple-hit" hypothesis, which proposes that autism stems from the interaction of a genetic predisposition, an environmental insult, and the time window during brain development when the environmental exigency acts. According to this hypothesis, variability in each or all of these factors could account for the clinical heterogeneity of ASD.

If there truly are subgroups of autism, identifying them will allow researchers to begin studying the underlying cause, prognosis, and most effective treatments for each type of autism. ARI has been working on this for several years, and our preliminary results are encouraging.

Multidisciplinary research

There is now enough scientific evidence for us to state with confidence that autism affects multiple organs and cellular processes, including the brain, the gastrointestinal system, and the immune system, via its effects on metabolism. A recent report published by Autism Speaks concludes: "We now know, beyond doubt, that for many people, autism is a whole-body disorder."

Although most researchers agree that these biological systems are interdependent, little attention has been focused on their interaction. If one of the primary aims of autism research is to uncover the biological underpinnings of autism, multiple organ systems as well as processes need to be investigated *simultaneously* in the *same individuals*. Such multifaceted research can be accomplished through better networking among researchers and the establishment of multidisciplinary funding opportunities. ARI has focused much of our attention recently on networking, encouraging, and funding such studies.

Medical and sensory issues associated with challenging behaviors

At ARI we often receive letters and emails from parents who are struggling to find ways to help children who engage in challenging, sometimes devastating behaviors. These include self-injury, aggression, and severe tantrums. Although behavioral and medical interventions can often manage these behaviors, they do not necessarily treat the underlying causes. In addition, medications are often associated with side effects.

For many years Dr. Rimland and I—as well as many others—have argued that challenging behaviors may result from underlying medical and/or sensory issues that lead to discomfort or pain. During their lectures, Drs. Tim Buie and Margaret Bauman often show videos of patients exhibiting severe behaviors. These behaviors are often reduced or eliminated when these patients' GI symptoms are properly treated.

Interestingly, a group of neurotypical students who were enrolled in a high school criminal science class recently agreed to be pepper-sprayed. Soon after, many of them reacted to the severe pain by exhibiting "autistic-like" behaviors such as hand-flapping, rocking, and posturing. To view a video of their reactions, simply log on to YouTube and search "pepper-sprayed students."

With respect to sensory issues, many individuals with ASD have difficulty recognizing discomfort or pain resulting from medical problems such as ear infections, stomachaches, and migraine headaches. Sensory processing of internal sensations is referred to as *interoception*. (See my editorial in *ARRI, Vol. 30(4)*, 2016.) There are at least three different ways in which those on the autism spectrum may process internal sensations in a non-optimal way. With respect to discomfort or pain, these include:

- Experiencing little or no feeling (for instance, exhibiting no response to a ruptured appendix).
- Over-reacting to "normal" levels of discomfort such as a stomachache.
- Feeling that something is wrong, but being unable to pinpoint its location.

ARI is currently collaborating with sensory experts, behavior specialists, and physicians to develop ways to help individuals with ASD recognize and communicate their internal discomfort or pain. I encourage other researchers and organizations to consider studying this important issue.

Sleep

Sleep problems are a major challenge for many individuals with ASD, and quite often disrupt the lives of their family members as well. Based on a recent survey by ARI, common sleep problems include difficulty

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Research Updates

Excess CSF may be early clue in autism

Excess cerebrospinal fluid (CSF) in one region of the brain may be a very early marker for autism risk, a new study suggests.

In a small 2013 pilot study, Mark Shen and colleagues at UC Davis detected substantially greater volumes of CSF in babies who later developed autism. In the new study, Shen collaborated with colleagues at the University of North Carolina at Chapel Hill to study 343 infants, 221 of whom were at high risk of developing ASD because they had a sibling with an ASD diagnosis. Forty-seven of these children later developed ASD.

Analyzing MRI scans of the infants' brains, the researchers found that many of those later diagnosed with autism had a significantly greater amount of CSF between the brain and skull—called extra-axial CSF—at 6 and 12 months of age than infants who did not become autistic. In addition, the more CSF detected at 6 months, the more severe autistic symptoms were at 2 years of age.

The CSF between the brain and the skull acts as a filtration system for the byproducts of brain metabolism. Study coauthor Joseph Piven says, "We can't yet say for certain that improper CSF flow *causes* autism. But extra-axial CSF is an early marker, a sign that CSF is not filtering and draining as it should. This is important because improper CSF flow may have downstream effects on the developing brain; it could play a role in the emergence of autism symptoms."

Piven adds, "The CSF is easy to see on standard MRIs and points to a potential biomarker of autism before symptoms appear years later. We also think this finding provides a potential therapeutic target for a subset of people with autism."

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"Increased extra-axial cerebrospinal fluid in high-risk infants who later develop autism," Mark D. Shen, Sun Hyung Kim, Robert C. McKinstry, Hongbin Gu, Heather C. Hazlett, Christine W. Nordahl, Robert E. Emerson, Dennis Shaw, Jed T. Elison, Meghan R. Swanson, Vladimir S. Fonov, Guido Gerig, Stephen R. Dager, Kelly N. Botteron, Sarah Paterson, Robert T. Schultz, Alan C. Evans, Annette M. Estes, Lonnie Zwaigenbaum, Martin A. Styner, David G. Amaral, Joseph Piven, and the IBIS Network, *Biological Psychiatry*, March 6, 2017. Address: Mark Shen, University of North Carolina at Chapel Hill School of Medicine, Carolina Institute for Developmental Disabilities, Campus Box #3366, Chapel Hill, NC 27599. mark_shen@med.unc.edu.

—and—

"Researchers link increased infant brain fluid to autism," news release, University of North Carolina, March 7, 2017.

Accidental deaths a major risk in ASD

Individuals with autism are at significantly elevated risk for accidental death, according to a new study.

Joseph Guan and Guohua Li screened more than 32 million U.S. death certificates, identifying 1,367 individuals with autism who died between 1999 and 2014. The researchers found that deaths in individuals with autism have increased 700 percent in the past 16 years and are three times more likely to be caused by injuries than deaths in the general population.

The average age at death for individuals with autism was 36 years younger than for the general population (36 years of age, compared to 72). Twenty-eight percent of the deaths of individuals with autism were attributed to accidents. Suffocation, asphyxiation, and drowning were the most common causes, accounting for nearly 80% of injury-related deaths.

Li notes that children with autism are 160 times as likely to die from drowning as children overall, in part because they are prone to wandering. "Given the exceptionally heightened risk of drowning for children with autism," he says, "swimming classes should be the intervention of top priority. Once a child is diagnosed with autism, usually between 2 years and 3 years of age, pediatricians and parents should immediately help enroll the child in swimming classes, before any behavioral therapy, speech therapy or occupational therapy. Swimming ability for kids with autism is an imperative survival skill."

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"Injury mortality in individuals with autism," Joseph Guan and Guohua Li, *American Journal of Public Health*, March 2017 (online). Address: Guohua Li, Center for Injury Epidemiology and Prevention, Columbia University Medical Center, 622 W. 168th St., PH5-505, New York, NY 10032, gl2240@cumc.columbia.edu.

—and—

"Individuals with autism at substantially heightened risk for injury death," news release, Columbia University Mailman School of Public Health, March 21, 2017.

Maternal hirsutism linked to higher odds of ASD in children

New evidence suggesting a link between autism spectrum disorders (ASD) and elevated prenatal exposure to male hormones comes from a study involving women with hirsutism.

Hirsutism is a condition in which individuals grow heavy hair in regions where it normally does not appear. Women with hirsutism may grow hair on their upper lips, chin, chest, and back. The condition is associated with an excess of androgens (male hormones).

In an earlier, large-scale study, Brian Lee and colleagues found that children of women with polycystic ovarian syndrome (PCOS)—a condition that results in elevated levels of androgens—had increased odds of receiving an ASD diagnosis. In the new study, they determined that maternal hirsutism also increases the odds of ASD in children. They report, "The most adjusted odds ratios for associations with ASD for hirsutism diagnosis before birth and lifetime diagnosis of hirsutism were 1.64 and 1.26."

They conclude, "The presence of an association of maternal hirsutism with child ASD is consistent with the hypothesis that androgens may be involved in the etiology of ASD."

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"Maternal hirsutism and autism spectrum disorders in offspring," B. K. Lee, S. Arver, L. Widman, R. M. Gardner, C. Magnusson, C. Dalman, and K. Kosidou, *Autism Research*, April 6, 2017 (epub prior to print publication). Address: Brian K. Lee, bklee@drexel.edu.

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Research Updates

Therapy balls may improve behavior of ASD students in class

A small study suggests that changing classroom seating may improve the behavior of some students with autism spectrum disorder (ASD).

Fifteen students with autism participated in the eight-week study. The researchers analyzed the students' behavior under three different conditions: with the students seated in regular classroom chairs, on therapy balls, or on chairs with air cushions.

The researchers say 13 of the 15 children spent significantly more time in their seats and 8 of the 15 increased their on-task behavior while seated on the therapy balls. In addition, students exhibited significantly fewer stereotyped movements and better communication and social skills when sitting on the therapy balls. No significant effect of the air cushions was seen.

The results are similar to those of a 2004 study that reported "substantial improvements in engagement and in-seat behavior" when participants with ASD were seated on therapy balls. A 2010 study, however, found that while sitting on a therapy ball benefited some children with ASD, children with poor postural stability actually performed more poorly in this condition.

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"The impact of dynamic seating on classroom behavior of students with autism spectrum disorder," N. Matin Sadr, H. A. Haghgoo, S. A. Samadi, M. Rassafiani, E. Bakhshi, and H. Hassanabadi, *Iranian Journal of Child Neurology*, Vol. 11, No. 1, 29-36,Winter 2017. Address: N. Matin Sadr, Department of Occupational Therapy, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

—and—

"Alternative seating for young children with autism spectrum disorder: Effects on classroom behavior," Denise Lynn Schilling and Ilene S. Schwartz, *Journal of Autism and Developmental Disorders*, Vol. 34, No. 4, August 2004, 423-32.

—and—

"Effectiveness of therapy ball chairs on classroom participation in children with autism spectrum disorders," Nancy Bagatell, Gina Mirigliani, Chrissa Patterson, Yadira Reyes, and Lisa Test, *American Journal of Occupational Therapy*, Vol. 64, November/December 2010, 895-903. Address: Nancy Bagatell, Quinnipiac University, 275 Mount Carmel Avenue, EC-OCC, Hamden, CT 06518, nancy.bagatell@quinnipiac.edu.

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*Research: Making a Difference

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Nutritional Strategies for PANS & POTS

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Prevalence of infection with cytomegalovirus before birth is higher in children with ASD

Prenatal cytomegalovirus (CMV) infection may play a role in a surprising number of cases of autism spectrum disorder (ASD), a new study from Italy suggests.

CMV is a common virus, with more than half of adults over the age of 40 and more than a third of children over the age of five having been infected at some point. The virus causes few or no symptoms in most people, but prenatal infection leads to illness or long-term problems in about one of five exposed children. Consequences can include premature birth, seizures, hearing loss, vision loss, and intellectual disability.

Because several case studies have reported an association between CMV infection and the onset of ASD, Ivan Gentile and colleagues decided to evaluate the prevalence of congenital CMV infection in children with ASD as compared to neurotypical controls. Using polymerase chain reaction (PCR) tests on dried blood spots collected at birth from 38 children with ASD and 44 controls, they found that "the prevalence of congenital CMV infection was 5.3% in [ASD] cases and 0% in controls." In addition, they note, "The infection rate was about 10-fold higher in patients with ASD than in the general Italian population at birth."

Based on their findings, Gentile and colleagues suggest that doctors consider including screening for CMV in workups for children with autism. They also say their finding is important "given the potential prevention and treatment of CMV infection."

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"Prevalence of congenital cytomegalovirus infection assessed through viral genome detection in dried blood spots in children with autism spectrum disorders," I. Gentile, E. Zappulo, M. P. Riccio, S. Binda, L. Bubba, L. Pellegrinelli, D. Scognamiglio, F. Operto, L. Margari, G. Borgia, and C. Bravaccio, *In Vivo*, Vol. 31, No. 3, May-June 2017, 467-473. Address: Ivan Gentile, Department of Clinical Medicine and Surgery, Section of Infectious Diseases, University of Naples "Federico II," Naples, Italy, ivan.gentile@unina.it.

CORRECTION:

In our list of highlights of the Autism Research Institute's first fifty years, we stated that Dr. Bernard Rimland established the Autism Society of America (initially called the National Society for Autistic Children) in 1965.

Credit for the establishment of ASA actually belongs jointly to Dr. Rimland and Dr. Ruth Sullivan. It was Dr. Sullivan who initiated a meeting of parents in New Jersey and first suggested creating a national parent organization, a goal that she and Dr. Rimland worked together to achieve.

We apologize for this oversight, and wish to acknowledge the prominent role that Dr. Sullivan played in the creation of ASA.

Three studies cast doubt on association between autism spectrum disorders, antidepressants

Three new studies suggest that there is little or no association between maternal antidepressant use during pregnancy and autism spectrum disorders (ASD) in children.

In the first study, Ayesha Sujan and colleagues reviewed data from more than 1.5 million children born in Sweden between 1996 and 2012. In their initial analysis, the researchers found that first-trimester exposure to antidepressants was significantly associated with ASD, attention-deficit/hyperactivity disorder, preterm birth, and small size for gestational age.

However, the researchers used three additional approaches to test their findings. "First," senior author Brian D'Onofrio says, "we compared siblings where mothers had used antidepressants in some pregnancies but not others. Second, we compared children of women who used antidepressants before pregnancy but not during or after pregnancy to children of women who used antidepressants during the first trimester of pregnancy. And third, we assessed the risk of the outcomes among children of fathers who took antidepressants during the first trimester of pregnancy." When the researchers added these factors to their analyses, they found that the use of antidepressants during the first trimester of pregnancy was associated only with a slightly higher risk for preterm birth.

D'Onofrio says, "These findings provide further support that family factors, rather than the specific exposure during pregnancy, explain associations between maternal antidepressant use during pregnancy and autism spectrum disorder and ADHD."

In the second study, Hilary Brown and colleagues analyzed data from nearly 36,000 births in Ontario, Canada between 2002 and 2010. While the researchers found a strong association between maternal antidepressant use during pregnancy and ASD in offspring, this association disappeared when the researchers controlled for a large number of potential confounders and when they compared exposed and unexposed siblings.

In the third study, Antonia Mezzacappa and colleagues performed a meta-analysis of ten studies investigating a possible association between maternal antidepressant use during pregnancy and ASD in children. The researchers report, "There is a significant association between increased ASD risk and maternal use of antidepressants during pregnancy; however, it appears to be more consistent during the preconception period than during each trimester. Maternal psychiatric disorders in treatment before pregnancy rather than antenatal exposure to antidepressants could have a major role in the risk for ASDs."

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"Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring," Ayesha C. Sujan, Martin E. Rickert, A. Sara Öberg, Patrick D. Quinn, Sonia Hernández-Díaz, Catarina Almqvist, Paul Lichtenstein, Henrik Larsson, and Brian M. D'Onofrio, *Journal of the American Medical Association*, Vol. 317, No. 15, April 18, 2017, 1553-1562. Address: Brian D'Onofrio, Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana 47405.

—and—

"Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children," Hilary K. Brown, Joel G. Ray, Andrew S. Wilton, Yona Lunsky, Tara Gomes, and Simone N. Vigod, *Journal of the American Medical Association*, Vol. 317, No. 15, April 18, 2017, 1544-1552. Address: Simone Vigod, Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada.

—and—

"Risk for autism spectrum disorders according to period of prenatal antidepressant exposure: a systematic review and meta-analysis," Antonia Mezzacappa, Pierre-Alexandre Lasica, Francesco Gianfagna, Odile Cazas, Patrick Hardy, Bruno Falissard, Anne-Laure Sutter-Dallay, and Florence Gressier, *Journal of the American Medical Association*, April 17, 2017 (online). Address: Antonia Mezzacappa, Department of Psychiatry, Assistance Publique-Hôpitaux de Paris, Bicêtre University Hospital, Le Kremlin Bicêtre, France.

—and—

Additional comments from Dr. D'Onofrio are available at https://news.iu.edu/doc/donofrio-antidepressant-faq.pdf.

Greater ability to detect sounds seen in individuals with ASD

Individuals with autism have an increased capacity for processing sounds, according to a new British study whose authors say this ability confers both advantages and disadvantages.

Anna Remington and Jake Fairnie asked 17 adults with autism and 19 neurotypical controls to perform two computer-based tasks. In the first task, the participants listened to an array of animal sounds played simultaneously and seemingly coming from different locations. In addition, they heard a non-animal sound (a car) during 50% of the trials. The participants were asked to identify two target sounds (a dog's bark and a lion's roar) and also to indicate whether the car sound was present or absent. In this task, the individuals with autism performed much better than controls at spotting the car sound while also identifying the animal sound.

In the second task, the researchers asked participants to listen to a recording of two men and two women preparing for a party, and to focus on what the two women in the group said so they could answer questions about the conversation later. Again, the scene was recorded in a way that conveyed three-dimensionality. During the scene, an additional male character entered, continually repeating the phrase, "I'm a gorilla." While both groups did equally well on the primary task, individuals with autism were much more likely to notice this distraction, with 47% of them noticing the "gorilla" man as opposed to only 12% of controls.

In short, the researchers found that individuals with autism are better at detecting a target sound within a group of sounds, and also notice irrelevant background information more often when listening to a conversation. In light of these results, the researchers say, "While it is clear that further research is warranted, our findings reframe the altered behaviors [seen in autism] in terms of increased capacity, rather than a filtering deficit or inability to maintain focus." They add, "This reinterpretation fits well with anecdotal reports from autistic people who describe their ears being 'like microphones,' picking up all the surrounding sounds indiscriminately."

Remington says, "This increased capacity may offer an explanation for the auditory superiorities seen in autism such as heightened pitch detection: if you can take in more information, then you can perform many tasks more efficiently. However, somewhat counterintuitively, this same 'skill' could result in the sensory overload that is often reported in autism—an issue which can be very distressing, and subsequently interfere with social communication."

Reminton concludes, "While we must not downplay the challenges associated with autism, our study raises awareness of a more positive side to the condition. By promoting the idea that we can harness strengths to improve outcomes, we embrace neurodiversity and undermine the traditional view that autism is only associated with deficits. This is an important message that is currently being championed by many in the autistic community,"

—

"A sound advantage: Increased auditory capacity in autism," Anna Remington and Jake Fairnie, *Cognition*, May 3, 2017 (online). Address: Anna Remington, Centre for Research in Autism and Education, UCL Institute of Education, 55-59 Gordon Square, London WC1H 0NU, United Kingdom, a.remington@ucl.ac.uk.

—and—

"Greater capacity to detect sound gives autistic people an advantage," UCL News, May 3, 2017.

—and—

"People with autism can hear more than most—which can be a strength and a challenge," Anna Remington, *The Conversation*, Medical Xpress, May 3, 2017.

Colorful classroom displays may impair learning for both neurotypical kids and those with ASD

Colorful classroom displays appear to distract students and impair their learning, a new study reports, and the effect is stronger for children with autism spectrum disorders (ASD) than for neurotypical children.

In the study, Mary Hanley and colleagues matched 17 children with ASD to 17 neurotypical children based on verbal ability. The children were between five and 13 years of age.

Hanley and her team created videos of a teacher offering two lessons. The first lesson involved a storybook read-aloud session during which the children merely needed to listen, while the second involved a mini-lesson that required the children to listen and answer questions afterward.

The researchers filmed the videos in front of a green screen so they could later create a colorful background display (the *high visual display* or HVD condition) for one pair of lessons and a plain background (the *no video display* or NVD condition) for another pair. They then used eye-tracking technology to determine the effects of each background on attention and learning.

The researchers report, "Overall we found a clear effect of the presence of visual displays on attention for all children. Whether viewing stories or lessons, children spent more time looking at the background in HVD compared to NVD." In addition, all children had lower learning scores in the HVD compared to the NVD condition when the researchers controlled for age.

The researchers also found that while neurotypical children still prioritized their attention toward the teacher in the HVD condition, children with ASD responded differently. "Not only did they look at the visually distracting background more than typically developing children in both story and lesson videos," the researchers say, "but they looked more at the background than the teacher in HVD."

The researchers note, "Considering the tendency for children with autism spectrum disorders to prioritize non-social over social information for attention, in the context of a classroom scenario it may mean that non-social information such as classroom displays captures attention more readily than a teacher."

The researchers note that the children with ASD responded differently from the neurotypical children in all conditions except for the NVD mini-lessons. "When viewing stories without specific instruction (spontaneous viewing) children with ASD had atypically reduced attention to a teacher in NVD and HVD, and visual displays had a greater impact on their attention compared to typically developing children," they report. "When instructed to pay attention to the lessons, children with ASD showed a more typical pattern of attention to the teacher and background, although this was not maintained in the presence of visual displays."

The researchers conclude that their study "has implications for the use of classroom visual displays for all children, but particularly for children with ASD.'

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"Classroom displays—attraction or distraction? Evidence of impact on attention and learning from children with and without autism," Mary Hanley, Mariam Khairat, Korey Taylor, Rachel Wilson, Rachel Cole-Fletcher, and Debbie Riby, *Developmental Psychology*, May 4, 2017 (epub prior to print publication). Address: Mary Hanley, Department of Psychology, Durham University, Science Site, South Road, Durham DH1 4JJ, UK, mary.hanley@durham.ac.uk.

Moving forward in our understanding of autism

(cont. from page 3)

falling asleep, night waking, waking early, and poor sleep quality. Unfortunately, only a handful of researchers are studying this quality-of-life issue.

Research shows that sleep issues are often related to gastrointestinal problems. Insufficient sleep may also affect brain development, especially in the childhood years. Given the importance of sleep, more resources should be focused on understanding and treating sleep problems in autism.

Adults/Seniors

Much attention has focused—and deservedly so—on employment, residential settings, and recreational needs for adults and seniors on the spectrum. However, other issues affecting this rapidly growing population need urgent attention, including medical problems, anxiety, depression, behavioral and sensory challenges, and sexuality.

Dr. Margaret Bauman has often stressed that we need to understand how individuals with autism progress throughout their lifetime. Although this sounds obvious, there are no ongoing longitudinal studies designed to document changes in these individuals' physiology and behavior beginning in childhood and continuing into the senior years. Such monumental research would provide much insight into many issues, such as prognosis as well as the development of medical co-morbidities and symptoms over time.

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Large funding agencies, such as the National Institutes of Health (NIH), the Simons Foundation, and Autism Speaks, play a central role in determining what topics will be funded and thus studied. I hope the areas described above are currently on their radar. Teamwork among researchers and funding agencies will empower us to find the real answers and effective solutions that individuals with ASD and their families desperately need.

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.

Website: ASDSeniorSurvey.com

Suramin (cont. from page 1)

"Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial," Robert K. Naviaux, Brooke Curtis, Kefeng Li, Jane C. Naviaux, A. Taylor Bright, Gail E. Reiner, Marissa Westerfield, Suzanne Goh, William A. Alaynick, Lin Wang, Edmund V. Capparelli, Cynthia Adams, Ji Sun, Sonia Jain, Feng He, Deyna A. Arellano, Lisa E. Mash, Leanne Chukoskie, Alan Lincoln, and Jeanne Townsend, *Annals of Clinical and Translational Neurology*, May 2017 (open access online). Address: Robert K. Naviaux, The Mitochondrial and Metabolic Disease Center, University of California, San Diego School of Medicine, 214 Dickinson St., Bldg. CTF, Rm. C102, San Diego, CA 92103, Naviaux@ucsd.edu.

—and—

"Researchers studying century-old drug in potential new approach to autism," Scott LaFee and Heather Buschman, news release, UC San Diego Health, May 26, 2017.

Autism Treatment Effectiveness Survey Gauges Improvements, Side Effects

Researchers at Arizona State University are conducting a survey to evaluate the effectiveness of treatments for autism, including medications, nutritional supplements, diets, therapies, and education. The investigators hope to learn which treatments are most effective for different symptoms (language, anxiety, sleep, GI, etc.). Survey results will be posted online for families and clinicians, and published in a scientific journal.

Share your experiences—take the survey here: https://autism.asu.edu/

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The Autism Research Institute (ARI) is the oldest autism research organization in the world, founded by Dr. Bernard Rimland in 1967.

ARI'S WORK INCLUDES:

Conducting and sponsoring research on the causes of and best treatments for autism (more than $400,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

•

Networking researchers, physicians, and parents to speed the development and dissemination of safe and effective treatment methods.

•

Hosting webinars and one of the largest informational websites on autism in the world.

•

Sponsoring one or two major think tanks a year, involving researchers and experienced clinicians.

ARI's work relies on charitable contributions from individuals and organizations. All donations are tax deductible. We are proud to have earned Charity Navigator's highly respected "Four Star Award" for fiscal management, accountability, and transparency.

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