Editor's Notebook: ARI's ambitious agenda for 2007

(continued from page 3)

manner, and our six-month pilot test program may begin as early as April.

Other Projects

Each year, ARI publishes the results of its treatment ratings survey. The latest data were compiled early this year (and are provided as an insert with this newsletter). In addition, almost 1,200 parents of children and adults with Asperger syndrome completed the survey. We also analyzed the data for this population—see back side of insert.

Related to these results, I am writing a computer program to assist parents in selecting appropriate treatments for their children. The program will ask parents to indicate which treatments were given to their children and how well they responded to each one. Next, the computer program will search through the database of more than 25,500 cases and find those individuals who responded in the same way to those treatments. It will then provide a printout showing how well these "matches" responded to other treatments. I hope to have this program up and running on ARI's Web site in 2007.

ARI is very proud of its record of funding "research that makes a difference." Unlike other autism organizations that fund research, ARI funds only research that has direct implications to help children and adults alive today. Last year we funded $500,000 in research. This year our aim is to double this—funding more than $1 million. Of course, this goal will depend on the generosity of our donors.

In addition, I plan to travel the United States this year to meet with parents and professionals to keep them abreast of ARI's endeavors, and visit autism clinics and research facilities. In mid-February I'll drive north from San Diego to Seattle. I hope to visit various cities in the Midwest in May and June, and then the east coast in September. My "road trip" travel schedule will be posted on ARI's Web site.

Lastly, I want to thank everyone who sent cards and letters to me and to ARI's staff over the past two months. Your encouraging thoughts and best wishes have meant a great deal to us.

—SCHOOLS AND SERVICES—

The Autism Research Institute maintains a list of schools and services for autistic individuals. If your facility should be included on our list, and you believe it may not be, please send a self-addressed, stamped envelope to receive our referral list questionnaire.

Biomedical Update:

More support for role of oxidative stress

In a pioneering 2004 paper, Jill James and colleagues implicated oxidative stress as a culprit in autism (see ARRI 18/4). A new study by the researchers supports and extends their earlier findings.

Oxidative stress occurs when rogue molecules called "free radicals" attack the body's cells. James and her associates are focusing on two processes, critical to protecting against oxidative stress, that appear to be abnormal in autism:

• Methylation, a chemical process in which genes are "turned on" or "turned off." Methylation affects the function of the entire body, including the immune and nervous systems.

• Glutathione metabolism. Glutathione is an important antioxidant (a substance that helps protect the body against the effects of heavy metals and other toxins). Low levels of glutathione can lead to oxidative stress, potentially damaging brain, gut muscosal, and immune cells—all of which are often impaired in autistic children.

The best measure of methylation capacity is the ratio of two substances, S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH). (This is called the SAM/SAH ratio.) When James and colleagues tested 80 autistic children and 73 age-matched control children, they found that the autistic children's SAM/SAH ratio was significantly lower than that of unaffected control children. Many autistic children also exhibited a dramatic reduction in the ratio of "active" glutathione (GSH) to "inactive" glutathione (GSSG). Cysteine, another substance needed for GSH synthesis, was also significantly reduced. This indicates, the researchers say, that the building blocks for GSH synthesis are insufficient.

The researchers evaluated genes known to directly or indirectly modulate these metabolic pathways, and found significant increases in the frequency of certain genetic variants (polymorphisms) as well as significant gene-gene interactions.

They conclude, "We propose that an increased vulnerability to oxidative stress (endogenous or environmental) may contribute to the development and clinical manifestations of autism."

—

"Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism," S. J. James, S. Melnyk, S. Jernigan, M. A. Cleves, C. H. Halsted, D. H. Wong, P. Cutler, K. Bock, M. Boris, J. J. Bradstreet, S. M. Baker, and D. W. Gaylor, *American Journal of Medical Genetics*, August 17, 2006 (epub ahead of print publication). Address: S. Jill James, Arkansas Children's Hospital Research Institute, 1120 Marshall St., Slot 512-40B, Little Rock, AR 72202, jamesjill@uams.edu.

Gene affecting brain, GI, immune systems may play role in autism

A common variant of a gene called MET may double the risk of autism, according to a new study.

Daniel Campbell and colleagues note that while most autism researchers are focusing on genes that predominantly affect brain development, individuals with autism often have gastrointestinal, immunological, or nonspecific neurological symptoms as well. Campbell et al. decided to investigate the MET gene because this gene contributes to immune function and gastrointestinal repair, as well as playing a crucial role in the development of the cerebral cortex and cerebellum (brain areas that are often abnormal in autism). In addition, the gene is located on a region of chromosome 7 that is already linked to autism.

Campbell and colleagues analyzed the MET gene in a family-based study of 1,231 autistic individuals. Many of the families involved in the study were "multiplex," meaning that they had more than one autistic child.

The researchers discovered that children with two copies of the "C" allele of the gene were 2.27 times more likely to have autism than children with two copies of the "G" variant. The association of the "C" variant with autism was strongest in multiplex families. The researchers note, however, that the "C" variant is very common, occurring in 47 percent of the population, and does not in and of itself cause autism.

Campbell and colleagues note that environmental factors most likely contribute to autism, and theorize that the "C" allele of the MET gene—in conjunction with other genes and/or "epigenetic" changes (which alter gene function but not structure)—can make some individuals more vulnerable to these environmental stressors.

The researchers say that because of the MET gene's effects on different body systems, the gene variant could lead to "parallel although independent" disruption of the brain and the neurological, gastrointestinal, and immune systems.

—

"A genetic variant that disrupts MET transcription is associated with autism," Daniel B. Campbell, James S. Sutcliffe, Philip J. Ebert, Roberto Militerni, Carmela Bravaccio, Simona Trillo, Maurizio Elia, Cindy Schneider, Raun Melmed, Roberto Sacco, Antonio M. Persico, and Pat Levitt, *Proceedings of the National Academy of Sciences,* October 2006 (epub ahead of print publication). Address: pat.levitt@vanderbilt.edu.