

NARRATIVE

NEWSLETTER OF THE NATIONAL ALLIANCE FOR AUTISM RESEARCH

SCIENCE FEATURE

Autism in the Blood:

Can Proteins in a Newborn's Blood Predict Autism, or Lead Us to New Therapeutic Opportunities?

by Emanuel DiCicco-Bloom, M.D.

Edited by Catherine Johnson, Ph.D.

It's not often an abstract presented at the American Academy of Neurology creates front-page headlines. But last May 4 parents of children with autism and/or mental retardation woke up to confront the news that "4 Brain Chemicals in Babies May Foretell Autism and Retardation" over their morning coffee.

Dr. Karin B. Nelson, a neurologist at the National Institute of Neurological Disorders and Stroke, had discovered four "marker proteins"¹ in the blood of newborn infants who were later diagnosed with autism or mental retardation (MR), but not in the blood of typical children or of 90% of the children she sampled who had cerebral palsy (CP). If Nelson's findings prove correct her work marks a turning point in the history of the developmental disabilities. For the first time ever, physicians will be able to diagnose many cases of autism—perhaps even cases of regressive autism—at birth. The implications are staggering.

Unfortunately, staggering implications or no, it is virtually impossible for parents, or anyone outside the research community for that matter, to reach an informed judgment as to whether or not a researcher's findings *are* likely to prove correct. As a research neurologist myself, and a colleague of Dr. Nelson's, I can't tell you either, but I can give you an idea of how researchers in the field have received her work—and what her work, if confirmed, might mean.

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NEWS FEATURE

NAAR Receives \$1 Million Challenge Grant From NLM Family Foundation

Gift Kicks Off \$7.5 Million Major Gifts Campaign

The Nancy Lurie Marks Family Foundation has made an incredible \$1 million Challenge Grant to the National Alliance for Autism Research kicking off NAAR's \$7.5 Million Major Gifts Campaign for Autism Research. "The NLM Family Foundation, which previously donated \$500,000 to NAAR, has now made yet another pacesetting gift to this organization," said Karen Margulis London, NAAR's President. "This grant underscores the Foundation's belief in the urgency of significantly increasing the investment in autism research and its commitment to NAAR as the effective vehicle to do so."

The NLM Family Foundation, located in Chestnut Hill, Massachusetts, is one of the largest supporters of research and education for autism, and has been a substantial supporter of Dr. Margaret Bauman of Harvard University and other noted autism investigators. For two years, the Foundation funded all of the operating expenses of NAAR, enabling it to strengthen its organizational infrastructure and accelerate its growth. "Mrs. Nancy Lurie Marks has been an inspiration and leader in her passionate support of research aimed at understanding and finding effective treatments for the autism spectrum disorders," noted Ms. London. "She has truly been NAAR's 'guardian angel' by facilitating the growth

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NAAR NEWS

NAAR Awards Record \$1.5 Million For Research Awards & Fellowships

by Eric London, M.D.

It is with great pride and excitement that the National Alliance for Autism Research presents this year's new research awards and fellowships to our donors and supporters. This is NAAR's fourth year of funding autism research. In our first funding year, 1997, NAAR was able to fund a total of five one-year grants, each for approximately \$30,000. Now, just four years later, NAAR is committing nearly \$1.5 million to fund 21 research projects. Last fall, NAAR announced that its 2000 Autism Research Awards would be for a maximum of \$100,000 for two-year awards—up from \$60,000 in 1999. Perhaps due to this greater level of funding, combined with increased attention and funding for autism research by the National Institutes of Health, the number of promising, high caliber research proposals submitted to NAAR was especially high. In fact, NAAR received more than 80 research proposals this year from scientists all over the world.

We would like to share with you some details of the award-winning proposals and hope that you share in the excitement and high expectations of NAAR's

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Autism Tissue Program Receives \$542,744 NIH Grant

The Autism Tissue Program, a joint program of NAAR and the Autism Society of America Foundation (ASAF), has received a four-year, \$542,744 grant from the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS). This grant, which was part of a competitive supplemental grant to the Harvard Brain Bank, will underwrite most of the costs associated with this important initiative.



Jane Pickett, Ph.D.
Coordinator of the Autism
Tissue Program

“We are absolutely thrilled by this significant support of the Autism Tissue Program by the NIMH and the NINDS,” commented Dr. Eric London, NAAR’s Vice President-Medical Affairs. “Ever since NAAR hosted its first scientific ‘think tank’ on brain tissue issues in May 1997, NAAR has considered it part of its mission to help increase this crucially needed scientific resource. This NIH grant not only provides the substantial funding for us to do so but is a confirmation by the NIH itself that this collaborative effort by NAAR and ASAF to increase brain tissue donation is crucial to advancing autism research efforts.”

“These funds give us the opportunity to continue and expand the nationwide campaign to increase awareness about the Autism Tissue Program,” said the program coordinator, Dr. Jane Pickett. Plans to coordinate outreach through ASA chapters and other autism groups are already underway as well as information distribution through research and medical organizations. The grant also supports the Autism Tissue Program’s Tissue Advisory Board (TAB) which is comprised of distinguished, impartial scientists who are expert in brain banking and tissue research. This wide range of expertise is critical when the TAB screens requests for autism tissue by scientists from all over the world. The TAB determines the most appropriate tissue acquisition protocols, reviews applications for tissue, and advises on tissue distribution based on both the proposal’s scientific merit and its potential to contribute to autism

research. (See the profile of TAB member Dr. Thomas Babb on page 4)

Post-mortem brain tissue is a rare and vitally needed resource for autism neuroscience research and to follow up leads from investigations using other methods of exploration such as neuroimaging. A variety of techniques can be applied to look at brain tissue cell by cell, study cell to cell connections, stain for neurochemicals, and probe inside the cell for gene products. Often cell shape, size and number can provide clues as to the developmental period when abnormalities occurred. Brain tissue also holds the promise of providing thousands of geneticists with DNA “libraries” from the uniquely specialized cells of the brain.

Only 39 donated autism brains have been available for study in the U.S. and these were collected over a twenty-year period and are not always well-characterized with regard to diagnosis. (In comparison, several thousand Alzheimer cases helped to identify the abnormal brain areas and proteins of those patients.) Nonetheless, in just over a year’s time, the Autism Tissue Program has registered over 1600 individuals and has facilitated the collection of seven autism brain specimens. Autism advocacy groups across the U.S. are invited to become involved in educational outreach so that a family willing to donate tissue upon the death of a loved one has the information and support to do so. The *procedure* to register or donate brain tissue is simple—it takes but one call to 1-877-333-0999; the *decision* to donate takes careful thought and often many discussions with family members. “It is so crucial that these discussions take place in advance,” Dr. Pickett emphasizes. “The decision is important and personal and will always be respected by those of us involved in the Autism Tissue Program.”

For more information, call 1-877-333-0999 or visit ATP’s website: www.brainbank.org with its secure online registration. ♦

NAAR President Wins 1999 Spirit of Women Award



At the Awards Ceremony (L-R):
Talk Show Host Joy Behar (“The View”); New York Times
health writer Jane Brody; NAAR President Karen London

NAAR President and Co-founder, Karen London, was awarded the 1999 Spirit of Women Award in the category of community recipient by the University of Medicine and Dentistry of New Jersey. She was one of 48 women in the country recognized for making a difference in their communities and the lives of others. Karen was introduced with the following words:

“In just under five years, the National Alliance for Autism Research has grown to become the preeminent, nongovernmental organization pushing for a better understanding of the devastating neurobiological affliction of autism... Karen did more than just help her own son; she found a way of bringing her immense drive and skill to bear on a problem that affects as many as 500,000 families in the U.S. To the community and the nation, Karen’s life and work have brought us the creation of a vibrant national organization that will make the future brighter for many families.” ♦

Tissue Advisory Board Member Thomas L. Babb: A Profile

By Jane A. Pickett, Ph.D

Thomas L. Babb, Ph.D., a distinguished neuroscientist at the Cleveland Clinic Foundation in Ohio, has continued on a path of epilepsy research that began with his first experiences studying brain disorders as an Assistant Professor at UCLA in 1971. There he applied his training in neurophysiology and neuroanatomy to study tissue removed from patients undergoing neurosurgery to remedy persistent, debilitating, drug-resistant seizures. Dr. Babb and his colleagues studied the brain tissue (removed by en bloc temporal lobectomies) and pioneered many observations within the epileptic hippocampus which was found to have “a reliably unique pattern of neuron loss, space-occupying gliosis (overgrowth of non-neuronal brain cells), and a dense plexus of excitatory axons coming into the region. This aberrant synaptic reorganization is unique to the epileptic hippocampus and is now well-recognized as a major mechanism for generating seizures with onsets limited to this relatively small brain region.”



Dr. Thomas L. Babb

Currently, the productive Babb lab in Cleveland studies the molecular mechanisms of focal seizure activity in cortical dysplastic neurons. Dr. Babb explains that “cortical dysplasia refers to many different degrees of neuronal migration disorders characterized by neurons hyperexcitable to glutamate. In normal brain function, neurons excited by glutamate have two main receptor subtypes, AMPA and NMDA. Further, the NMDA receptor can have its own subunit variants. Our work on surgically resected adult cortical tissue specimens have demonstrated that NMDA NR2 A/B subunits are expressed almost exclusively in epileptogenic cortical dysplastic neurons.”

Pointing out that cortical dysplasia or neuronal migration disorders contribute to just one type of epilepsy (focal cortical), Dr. Babb discussed his interest in autism-associated epilepsy. “I ini-

tially became interested in similar cell dysplasias in neurological problems other than epilepsy, especially autism, while researching a chapter on multiple pathologies in epilepsy, with emphasis on neocortical dysplasias. That’s when I read several papers by Drs. Margaret Bauman and Thomas Kemper who showed various dysplasias in the brains in autism. An “association” between seizures and ‘dystopic’ neurons was reported by Alzheimer as early as 1907. In 1914, Dr. A. Jakob emphasized that abnormal differentiation of cortical neurons or microdysgenesis was consistently found at autopsy in epileptics and caused an epileptic tendency if not actual seizures. Children, as well as adults, with cortical dysplasia have varieties of cognitive dysfunctions, probably including autism.”

“That’s the major reason why I’m enthusiastic about the autism brain research program, modeled after what we now know about epilepsy. It’s simply a matter of tissue availability, good diagnoses of the extent or type of autism, and the tools to study donated brain tissue. From several sources of evidence, we now know that these cortical dysplasia or neuronal migration disorders with NR1 - NR2 subunit anomalies occur prenatally, indicating a problem with neurodevelopment.”

Dr. Babb and his associates are currently studying the molecular and genetic mechanisms of cortical dysplasia using an animal model. They have found neuronal migration disorders induced in rats also have significantly upregulated NR2 A/B receptors. These rats subsequently mated producing a second generation with dysplastic neurons with increased NR2 A/B receptors - although these were less dense than the first generation.

The Autism Tissue Program is privileged to have Dr. Babb as a member of its Tissue Advisory Board. ♦

(continued from page 1 ~\$1 million Challenge Grant~)

and development of this organization so that it can continue to make a significant impact on the autism research agenda.”

The \$1 Million Challenge Grant also kicked off NAAR’s \$7.5 Million Major Gifts Campaign—the first such campaign ever to be launched on behalf of autism research. The five-year Major Gifts Campaign is aimed at securing significant gifts and multi-year pledges (i.e. gifts payable over three to five years). The Major Gifts Campaign will enable NAAR to significantly increase the amount of funding it contributes to autism research now and in the immediate years to follow. “We never want to be in the position,” commented NAAR Chairman Clarence Schutt, “where NAAR is unable to fund promising research due to a lack of funding. The success of the Major Gifts Campaign will go a long way to ensuring that every meritorious research project submitted to NAAR gets funding and will help us to further encourage the neuroscience world to commit itself to autism research.”

When the NLM Family Foundation made its \$1 million gift to NAAR, Director Eric Cushing said, “We hope our Challenge Grant will assist in launching NAAR’s exciting new Major Gifts Campaign and encourage other substantial donations so that autism truly gets the intensified research attention it merits.” The

NLM Challenge Grant has already had that impact—attracting **an additional \$1.3 million in major gift donations**, including one extraordinary commitment of \$500,000 from another family foundation. NAAR is also thrilled to announce that it received a \$50,000 grant from the Doug Flutie, Jr. Foundation for Autism in December when that Foundation announced its first grants. We are particularly pleased to receive that gift from the foundation of our Honorary Board members, Doug and Laurie Flutie.

“We hope as many people as possible will make contributions—both large and small—to help NAAR meet the NLM Family Foundation’s Challenge Grant. In addition, we hope that we will continue to attract major gifts to reach—and exceed—our goal of \$7.5 million in significant gifts. \$7.5 million is not a lot of money to raise for many other disease-specific nonprofit organizations,” said Karen London. “But for the autism community, it would be a landmark achievement and one that would, without a doubt, stimulate millions and millions of dollars of autism research around the world. It is a goal that NAAR—with the help of our many friends and supporters—must and will achieve for the sake of our children, grandchildren and future generations.” ♦

To learn more about the Major Gifts Campaign, please contact Karen London, President, or Ken Farber, Director of Development, at 1-888-777-NAAR.

NAAR and NLM Foundation Sponsor Scientific Retreat to Promote Collaboration Among Autism Genetics Researchers

About 40 scientists affiliated with seven of the major autism genetics research groups from around the world convened for a three-day retreat co-sponsored by NAAR and the NLM Family Foundation. The retreat, which was held on March 9-12, 2000 near Atlanta, Georgia, provided the opportunity for these research groups to discuss and share each other's research findings and to explore ways to "pool" the groups' data in order to obtain greater statistical power. Together, the researchers attending the Atlanta conference have **over 600 sibling pair families and over 70 other multiplex families**, all of whom have been carefully diagnosed using research criteria (using the revised Autism Diagnostic Interview) and for whom blood samples have been obtained.

The scientists included senior investigators and team members from the Collaborative Linkage Study of Autism (Tufts, Vanderbilt, University of Iowa and University of North Carolina); Stanford University; Mt. Sinai's Seaver Center; Duke University/University of South Carolina; University of Missouri; McMaster University, McGill University and the University of

Toronto (the "Canadians"); and the Paris Autism Research International Sib Pair Study ("PARIS"). All of these groups have or are about to complete their first genome screens on 50-100 sib-pair families. The conference provided the opportunity for the groups to extensively consider phenotyping issues, plan the common genotyping of chromosomal areas of interest, and consider common approaches to linkage analysis, among other topics.

"In evaluating NAAR's conference funding this year," commented Eric London, NAAR's Vice-President-Medical Affairs, "we believed that sponsoring this conference was of the highest priority. Although collaboration among so many independent groups is undoubtedly an ambitious effort, the goal of combining the genetics data from over 600 multiplex families with autism spectrum disorders—all of which is available and already funded by the NIH—could be extremely significant. The stated common goal of these research groups is nothing less than to find a treatment for autism. As a research advocacy organization, NAAR will continue to do everything possible to promote such collaborations and to support and enhance NIH-funded efforts." ♦

NAAR Welcomes New Board Members

NAAR is pleased to introduce several newly appointed members of its Board of Trustees. The Board has grown from its original five members to seventeen members as the organization has matured and expanded in geographic scope. Several of these new trustees are also NAAR Research Partners and all have a commitment to the fulfillment of NAAR's mission. We welcome them and thank them all for their dedication to our cause.

Norma M. Baker is a founding board member of the Achievable Foundation, a California based organization which provides services for individuals with developmental disabilities. Prior to her work as an advocate for individuals with developmental disabilities, Mrs. Baker was an educator in the New York City school district. She earned her BA from Tufts University, graduating with honors. She is the mother of two adult sons, one of whom has autism, and lives in Beverly Hills, California.

Keith Daniel is a Vice President and General Manager of SilverStream Software, Inc., a provider of internet software and services. He is a 1984 graduate of the University of Dayton with a Bachelor of Science degree in Electrical Engineering and received his MBA from Duke University in 1990. Keith, his wife Joyce, and their three children live near Dayton, Ohio.

Vicki Hennelly, Esq. is an attorney and office manager with the firm of Hennelly & Grossfeld in Pacific Palisades, California. She received her BA degree magna cum laude from the University of Southern California in 1980 and her J.D. degree from the same institution in 1983. She is a board member of the Juniors of Social Service and is also active in various civic organizations. She is the mother of a twelve year old with autism.

Prisca Chen Marvin, Esq. is a 1985 graduate of the Massachusetts Institute of Technology with a bachelor of science degree in Chemical Engineering. She received her J.D.

degree in 1988 from Georgetown University Law Center. She is a registered patent attorney, specializing in chemical patents, and was an associate with the firms of Finnegan, Henderson, Farabow, Garrett and Dunner in Washington, DC and Connolly, Bove, Lodge and Hutz in Wilmington, Delaware. She has two daughters, one of whom has autism, and lives in Denton, Maryland.

David C. Phifer is founder of Phifer Systems Inc., a software development company providing network management and consulting services to the telecommunications industry. Additionally, he operates PCG Inc., a management consulting firm supporting high-technology growth companies. He is a 1984 graduate of Washington State University with a bachelor of science degree in Electrical Engineering. Dave is the father of four children, including a daughter with autism, and lives outside of Seattle, Washington. ♦

NYFAC Presents Award to NAAR

New York Families for Autistic Children (NYFAC) presented NAAR with the "Excellence in Advancement of Research Opportunities Award" at its February 2000 annual fundraiser. The award read in part:

"For a genuine commitment and dedication in helping and supporting the families of children with autism...For looking to the future with research, and brightening the present with teamwork."

Dr. Eric London, representing NAAR, was also presented with a Proclamation from The Council of the City of New York recognizing NAAR's contributions to autism research advancement. Our thanks to Andrew Bauman and the Board of NYFAC for their thoughtful recognition. ♦

NAAR Autism Research Awards and Fellowships 2000 Awards

- **David G. Amaral, Ph.D.**, University of California, Davis, for “**Postmortem Neuroanatomical Evaluation of the Amygdaloid Complex in Autism**”. 2-Year Award: \$68,000.
Research Partner: *Autism Society of Cincinnati*
- **Gene J. Blatt, Ph.D.**, Boston University Medical School, for “**Cerebellar Circuitry in Autism**”. 2-Year Award: \$94,878.
Research Partner: *The Nancy Lurie Marks Family Foundation*
- **Ira L. Cohen, Ph.D.**, New York State Institute for Basic Research in Developmental Disabilities, for “**Epidemiology of Autism on Staten Island**”. 2-Year Award: \$79,504.
- **John N. Constantino, M.D.**, Washington University School of Medicine, for “**A Quantitative Genetic Measure of Autistic Traits**”. 2-Year Award: \$58,762.
Research Partner: *The Autism Coalition for Research and Education*
- **Deborah A. Fein, Ph.D.**, University of Connecticut, for “**Early Detection of Pervasive Developmental Disorders**”. 2-Year Award: \$70,658.
Research Partner: *Autism Society of America Foundation*
- **Morton Ann Gernsbacher, Ph.D. & H. Hill Goldsmith, Ph.D.**, University of Wisconsin, for “**Toward a Dyspraxic Subtype of Autistic Spectrum Disorder**”. 2-Year Award: \$96,571.
Research Partner: *The Nancy Lurie Marks Family Foundation*
- **Scott E. Hemby, Ph.D.**, Emory University, for “**Gene Expression Profiling of Autism: Alterations in Temporal Lobe Profiles**”. 2-Year Award: \$70,658.
Research Partner: *Madeline and Arthur Millman on behalf of the Autism Society of America Foundation*
- **Cynthia R. Johnson, Ph.D.**, University of Pittsburgh, for “**Assessment and Treatment of the Cognitive Basis of Behavioral Impairments in Autism**”. 2-Year Award: \$40,218.
Research Partner: *Pittsburgh Friends of NAAR*
- **William G. Johnson, M.D.**, UMDNJ–Robert Wood Johnson Medical School, for “**MHC Extended Haplotypes as Risk Factors for Autism**”. 2-Year Award: \$80,000.
Research Partner: *The Doug Flutie, Jr. Foundation for Autism*
- **Ami Klin, Ph.D.**, Yale University Child Study Center, for “**Visual Scanning Patterns and Mental Representations of Social Interaction in Infants and Toddlers Suspected of Having Autism**”. 2-Year Award: \$97,080.
Research Partner: *Toys ‘R’ Us, Inc.*
- **Jeffrey D. Macklis, M.D., D. HST**, Children’s Hospital/Harvard Medical School, for “**Neocortical Callosal Projection Neuron Survival and Differentiation Control**”. 1-Year Award: \$50,000.
Research Partner: *Audrey Flack and H. Robert Marcus on behalf of the Autism Society of America Foundation*
- **Ron C. Michaelis, Ph.D.**, J.C. Self Research Institute, Greenwood Genetic Center, for “**Mapping the Breakpoints of a Balanced Translocation, t(9;15)q32;q22), in a Patient with Autism**”. 2-Year Award: \$57,475.
Research Partner: *Pittsburgh Friends of NAAR*
- **Yan Ni, Ph.D.**, Yale University, for the **NAAR/Bristol-Myers Squibb Research Fellowship in Autism and Neuropharmacology**. 1-Year Award: \$60,000.
- **Jorge J. Prieto, M.D., Ph.D.**, Universidad Miguel Hernandez (Spain), for “**A Microscopical Study on the Neuroanatomical Abnormalities of Language-Related Cortical Areas in Autistic Patients**”. 2-Year Award: \$66,000.
Research Partner: *The Nancy Lurie Marks Family Foundation*
- **Raju K. Pullarkat, Ph.D.**, New York State Institute for Basic Research in Developmental Disabilities, for “**Neurochemical Studies on Infantile Autism**”. 1-Year Award: \$49,973.
- **Moyra Smith, M.D., Ph.D.**, University of California at Irvine, for “**Analysis of Chromosome 15q22 Deletion Associated with Autism and Immune Deficiency**”. 1-Year Continuation Award: \$30,000.
- **James S. Sutcliffe, Ph.D.**, Vanderbilt University Medical Center, for “**Modeling Autism-Related Chromosome 15 Duplications in the Mouse**”. 2-Year Award: \$100,000.
- **Fred R. Volkmar, M.D. & Katarzyna Chawarska, Ph.D.**, Yale University Child Study Center, for “**Precursors of Joint Attention Skills in Autism and Related Conditions**”. 2-Year Award: \$62,337.
Research Partner: *The Nancy Lurie Marks Family Foundation*
- **Ching H. Wang, M.D., Ph.D.**, University of Missouri, for the **Roland D. Ciaranello, M.D. Memorial Career Development Award in Basic Research**. 2-Year Award: \$100,000.
- **Larry J. Young, Ph.D.**, Emory University, for “**An Oxytocin Knockout Mouse Model for Social Deficits**”. 2-Year Award: \$71,250.
- **Deborah A. Yurgelun-Todd, Ph.D.**, McLean Hospital/Harvard Medical School, for “**Visual Spatial Attention in Autism: An fMRI Study**”. 2-Year Award: \$82,259.
Research Partner: *Richard and Susan Smith Family Foundation*

Donors who contribute \$30,000 or more a year to NAAR are given the opportunity, if they so choose, to be designated a “NAAR Research Partner” for a year of funding for a selected research award. Those donors listed more than once herein have donated \$30,000 or more for each of the specified projects. We are profoundly indebted to all of our major donors—those who choose to be designated a “Research Partner” and the many others who do not—for making this level of autism support possible.

NAAR Autism Research Awards and Fellowships Ongoing Funding for 1999 Awards

● **David R. Cool, Ph.D.**, Wright State University, for “**Neuro-Endocrine Peptide Hormones are Implicated in Social Behavior Development: Oxytocin Involvement in Autism**”. Second Year Award Amount: \$30,000.

Research Partner: *Solving the Mystery of Autism Foundation, Inc.*

● **Guinevere Eden, D.Phil.**, Georgetown University, for “**Functional Neuroanatomy of Reading in Hyperlexic Children Studied with Functional Magnetic Resonance Imaging**”. Second Year Award Amount: \$30,000.

Research Partner: *The Autism Coalition for Research and Education*

● **Judith Miles, M.D., Ph.D.**, University of Missouri, for “**Identification of Dysmorphology Based Autism Groups**”. Second Year Award Amount: \$30,000.

● **Timothy P.L. Roberts, Ph.D.**, University of California at San Francisco, for “**Cortical Processing of Complex Sounds: Implications for Language Impairment in the Autistic Brain**”. Second Year Award Amount: \$29,019.

Research Partner: *The Autism Coalition for Research and Education*

● **Donald C. Rojas, Ph.D.**, University of Colorado, for “**Anatomical and Functional Development of the Auditory Cortex in Children with Autism**”. Second Year Award Amount: \$26,674.

Research Partner: *New Orleans Friends of NAAR*

● **Gleb P. Shumyatsky, Ph.D.**, Columbia University, for “**A Genetic Analysis of the Role of the Amygdala in Autistic Behavior using Genetically Modified Mice**”. Second Year Award Amount: \$29,954.

Research Partner: *The Mellanby Family/Autism Society of Broward County*

● **Christopher J. Stodgell, Ph.D.**, University of Rochester, for the **Roland D. Ciaranello, M.D. Memorial Fellowship in Basic Research**. Second Year Award Amount: \$50,000.

● **Katherine D. Tsatsanis, Ph.D.**, Yale University Child Study Center, for the **Roland D. Ciaranello, M.D. Memorial Fellowship in Basic Research**. Second Year Award Amount: \$50,000.

● **Karen M. Weidenheim, M.D.**, Albert Einstein College of Medicine, for “**Role of Connectivity in Autism**”. Second Year Award Amount: \$29,920.

Research Partner: *The Mellanby Family/Autism Society of Broward County*

● **John P. Welsh, Ph.D.**, New York University School of Medicine, for “**Functional Analysis of Rodent Autism Model**”. Second Year Award Amount: \$30,000.

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Board of Trustees and Scientific Advisory Board. We also wish to express our enormous gratitude to the distinguished scientists on NAAR's Scientific Advisory Board—volunteers all—who reviewed the submitted proposals during the weeks prior to our April 2 review meeting and then engaged in an extraordinary day of discussion and deliberation in order to provide NAAR with their best recommendations. Finally, we want to take this opportunity to thank all of NAAR's donors, both large and small, who helped us to reach this level of research support and, hopefully, who will enable NAAR to do even more in subsequent years. We hope and trust that the collective efforts of the autism community and these dedicated scientists lead to hastened progress and treatments for our children and family members.

Autism and Attentional Deficits

As parents of children with autism know, one of the key symptoms of autism is a deficit in the ability to attend to appropriate stimuli. Examples are a disinterest in most toys, the play of other children and, most of all, spoken language. In fact, one of the best predictors of very young children (18 mos.) who later receive a diagnosis of autism or pervasive developmental disorders-not otherwise specified (“PDD-NOS”) is a deficit in joint attention. By “joint attention” we mean the capacity of a child for sharing visual attention with another person to an object of mutual interest. In autism, joint attention is almost uniformly impaired although scientists have not yet determined why. Many scientists believe that attentional difficulties are at the core of the language and social impairments found

in individuals with autism spectrum disorders. Therefore, to devise better treatments we need to understand a great deal more about the neurobiology of attention.

This year, NAAR is sponsoring three projects that explore the nature of attentional difficulties in autism. Two of them are at Yale Child Study Center (“**Precursors of Joint Attention Skills in Autism and Related Conditions**” and “**Visual Scanning Patterns and Mental Representations of Social Interaction in Infants and Toddlers Suspected of Having Autism**”) and the third is at McLean Hospital/Harvard Medical School (“**Visual Spatial Attention in Autism: An fMRI Study**”).

In the studies from Yale, a “state-of-the-art” device called the ISCAN will be used. This device is mounted on a baseball hat which can precisely track the eye movements of even very young children. In their preliminary work, the Yale team has found that, when observing a social interaction, the gaze of their autistic subjects focused exclusively on the mouths—rather than the eyes— of the speaker and that they seemed not to attend at all to the non-speaking participant. In the two projects to be funded by NAAR, one group (**Fred R. Volkmar, M.D. and Katarzyna Chawarska, Ph.D.**) will examine some of the very basic parameters of joint attention. They will study whether children scan the eye region, take notice of eyes moving in a direction, discriminate when being looked at directly or not looked at directly, recognize the moods states of the faces they observe, and understand the meaning of the gaze of oth-

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ers. Drs. Volkmar and Chawarska will be studying this in children as young as 18 months old and following the development of these skills over the course of a year.

Ami Klin, Ph.D., also at Yale Child Study Center and working with several of the same collaborators, will use a similar methodology but with an emphasis on the social understanding which mediates joint attention. Dr. Klin will study in depth the social interpretations that the child does or does not make. In order to understand social situations, a person must have a mental representation of what is happening. By using computer simulations of stick figures, shapes and dots, Dr. Klin will study the level of understanding which very young children with autism have with respect to social interactions.

These two basic studies aim to “fine tune” our understanding of the attentional deficits in children with autism. This, in turn, could help to devise more sophisticated teaching methods for children with autism and also lead to the development of rational pharmaceutical interventions to address attention deficits. **Deborah A. Yurgelun-Todd, Ph.D.** at McLean Hospital is moving in that direction. She will use functional MRI (fMRI) to study attention and the shifting of attention in individuals with autism. In her preliminary work, she has found that when required to rapidly shift attention, individuals with autism cannot engage the same mechanisms found in the non-autistic brain. She speculates that the autistic brain compensates for this by staying in a state of heightened generalized arousal. The application of fMRI techniques provides a method that can identify the parts of the brain which function during a specific task. The images collected from adults with autism will highlight anatomical regions that differ in their functional abilities. These findings may help lead to more rational treatments.

Treatment of Severe Behaviors

This funding cycle, NAAR made a specific request for more treatment-oriented research proposals, specifically research focused on the treatment of “severe behaviors.” In response to that call, **Cynthia R. Johnson, Ph.D.** of the University of Pittsburgh submitted a project focused on school-aged children with high functioning autism and Asperger’s Syndrome (“**The Assessment and Treatment of the Cognitive Basis of Behavior Impairments in Autism**”). Over the past decade, neuropsychologists have documented several cognitive problems in this population. Among them are initiation, planning, problem solving and flexibility skills, organization and time-management skills, and self-regulation skills. Until now, it is not known how the deficits in these brain functions lead to problematic behaviors. Dr. Johnson intends to test these children and correlate their behaviors with these cognitive skills. She then will institute a treatment phase using “cognitive-behavioral” therapy—a treatment which has been used successfully with several other disorders including schizophrenia, depression and attention deficit disorder. Dr. Johnson’s hypothesis is that by helping children with their cognitive understanding, there will be a concordant decline in their levels of aberrant behaviors.

Genetics and Immunology of Autism

Given the importance of genetics research for autism—autism is one of the most heritable (that is, genetically caused) diseases of all the brain diseases—NAAR is funding a number of genetics proposals. Three of this year’s grantees will investi-

gate areas of interest on Chromosome 15 and two of the projects focus on the association of immunologic abnormalities and autism. The fourth of our funded genetics projects is aimed at identifying and validating a subtype of autism. Finally in the realm of genetics, as technology moves into the twenty-first century, NAAR will fund two projects that apply one of the newest of techniques to the study of autism—a new methodology known as “microarray”. These projects are described below.

Various lines of evidence have led geneticists to be very interested in the same areas on Chromosome 15 with respect to autism spectrum disorders. Although the linkage studies have not found the areas to rise to significance, 3-5% of autistic individuals have been shown to have some chromosomal abnormalities in these areas. At least one candidate gene (one that mediates a type of GABA receptor) that is in this area has been found by several groups to be significantly associated with autism. In addition, two types of mental retardation (which have some commonalities to autism) are known to be caused by chromosomal abnormalities in this same area. Last year, NAAR funded **Moyra Smith, M.D., Ph.D.** of the University of California at Irvine to study a chromosomal abnormality in a child with both autism and an immune deficiency. Her initial NAAR-supported studies have led to the isolation of DNA segments on Chromosome 15 that contain candidate genes for autism. In the research submitted this year to NAAR (“**Analysis of Chromosome 15q22 Deletion Associated With Autism and Immune Deficiency**”), Dr. Smith will continue her study by looking specifically at genes on Chromosome 15 that can have an effect on brain development.

NAAR will also be funding **Ron C. Michaelis, Ph.D.** of the J.C. Self Research Institute, Greenwood Genetics Center in Greenwood, South Carolina to undertake work on the same area of chromosome 15 (“**Mapping the Breakpoints of a Balance Translocation, t(9;15) (q32;q22), in a Patient with Autism**”). Dr. Michaelis also has a single subject who has a “balanced translocation”; that is, pieces of DNA from chromosome 9 and chromosome 15 broke off and switched places. It is likely that at these breakpoints there is the loss of functioning of a specific gene. As with the research group at University of California at Irvine, Dr. Michaelis hypothesizes that this area on chromosome 15 has candidate genes that may be responsible for at least some types of autism. NAAR’s Scientific Advisory Board thought that funding two studies on the same chromosomal area with different subjects could enhance the chances of identifying a gene. NAAR also intends to urge the collaborative efforts of these two research teams.

NAAR is also funding **James S. Sutcliffe, Ph.D.** of Vanderbilt University who will be studying chromosome 15 with a completely different methodology. Dr. Sutcliffe, in his proposal “**Modeling Autism-Related Chromosome 15 Duplications in the Mouse**”, proposes to study the behavior of mice with a chromosome abnormality similar to some cases of human autism, caused by an extra copy of a portion of chromosome 15. He will characterize segments of human chromosome 15 DNA and use them to create another type of mouse model by inserting them into the mouse DNA. By studying mice with different segments inserted, he is hoping to find which gene or segment in this chromosome 15 region can

produce behavioral and/or neurological features of relevance to autism and use that knowledge to find the genes in humans. This strategy has been used successfully in Down Syndrome research.

There has been much attention to the possibility of an immunological abnormality either being associated with autism or possibly even causing it. NAAR will be funding **William G. Johnson, M.D.** of the University of Medicine and Dentistry of New Jersey to look at this issue (“**MHC Extended Haplotypes as Risk Factors for Autism**”). One of the compelling reasons to pursue this line of investigation is the 1992 study by Dr. Reed Warren that found an association of the MHC complex with autism. The MHC complex is highly associated with the immune system. Dr. Warren further found that the abnormal findings were found in mothers but not fathers and, in some cases, in the mothers but not the affected child. This has led Dr. Johnson to propose a replication of the original study. The genetic methodology used in the original study by Dr. Warren is known to be subject to false positives and so Dr. Johnson will use a more elegant design called transmission/disequilibrium testing. Further, he will study the maternal effect reported by using the “parent of origin likelihood test”. If Dr. Warren’s findings can be replicated, it would lead to studies exploring the possibility that genetic and environmental factors transmitted *in utero* from the mother based on her abnormal immune system contribute to autism. This could have important implications for therapy and prevention.

Morton Ann Gernsbacher, Ph.D. and H. Hill Goldsmith, Ph.D. of the University of Wisconsin-Madison are scientists as well as parents of a young child with autism. Both are distinguished in their fields (psycholinguistics and behavioral genetics) with an excellent track record of NIH-sponsored research. In their NAAR-funded research (“**Toward a Dyspraxic Subtype of Autistic Spectrum Disorder**”), they will combine their expertise to work on defining an autism subtype that they call the “developmental verbal dyspraxia (DVD) subtype”. Dyspraxia is a neurologic phenomenon that consists of the brain being unable to tell the body what to do even though it may “know” what to do. (For example, stroke patients may be unable to dress themselves even though they might know the sequence and procedures involved in the dressing process). In autism, the investigators hypothesize a DVD subtype that experiences difficulty in coordinating and sequencing the movements necessary to produce and combine speech sound to form syllables, words, phrases and sentences. The researchers speculate that this subtype, if defined and validated, would refine genetic, neuroimaging and neuroanatomic studies and may also have a direct impact on treatment approaches. The researchers propose to screen all children with autism in a metropolitan area, identify those who are also characterized as DVD, collect extensive behavioral, medical and developmental histories, obtain neuroanatomical (MRI) data, and collect and store DNA for future candidate gene studies.

Brain Tissue Studies: Genetics Using Microarray

This year NAAR is funding two scientists who are using an innovative, new technique known as “microarray”. Using this technique, investigators can study the actual functioning of many genes by looking at what products (RNA) the genes produce. This technique can be used to examine thousands of

genes at once and so create a type of molecular “fingerprint” of autism. What is needed is to isolate the cells in the brain that we believe are abnormal and to study those cells. This will be done with brain tissue from the Autism Tissue Program (ATP) as well as from collaborators of the ATP program. These two research projects, as well as several others to be discussed later, would not be possible without the availability of the post-mortem tissue though donations made by the families.

Scott E. Hemby, Ph.D. is the new Director of the DNA Microarray Facility at Emory University. In studies on schizophrenia and Alzheimer’s disease, Dr. Hemby has studied more than 30,000 genes from two brain regions and single cells within these regions—the entorhinal cortex and the hippocampus—areas that have also been found to be abnormal in autistic brain tissue. With this NAAR grant (“**Gene Expression Profiling of Autism: Alterations in Temporal Lobe Profiles**”), Dr. Hemby will study those same areas in autism. In addition, the investigators at the Yerkes Primate Research Center have created an animal model for symptoms associated with autism based on rearing monkeys in an impoverished social environment. Dr. Hemby proposes to study these genes first in the monkeys and then using human post-mortem brain tissue to investigate the same areas. His research, using state of the art molecular biological procedures, will provide previously unattainable information of how the complex neural circuitry of these brain regions may be altered in autism.

Ching H. Wang, M.D., Ph.D., this year’s recipient of NAAR’s **Roland D. Ciaranello, M.D. Memorial Career Development Award in Basic Research**, is a neurologist at the University of Missouri (as well as the parent of a child with autism). Dr. Wang is also engaged in research using a microarray method. He is using the hint from the recent discovery of the MECP2 gene for Rett’s Syndrome—another pervasive developmental disorder—and trying to clone the genes for autism. The MECP2 gene is a DNA binding protein that regulates the gene expression through a chemical mechanism called methylation. Abnormal DNA methylation and gene expression is also found in Fragile X syndrome. Dr. Wang will apply the microarray technology to search for abnormally methylated genes in autism. Next he will study the functional significance of these abnormally methylated genes.

Brain Tissue Studies: Neuroanatomy and Neurochemistry

In addition to the two microarray projects this year, NAAR is funding four other projects that could only be done with the availability of brain tissue. Three of these research projects are neuroanatomical and one is biochemical. **Gene J. Blatt, Ph.D.** at Boston University Medical School has been working closely with Drs. Margaret Bauman and Thomas Kempner (both leaders in the field of autism neuroanatomy). Dr. Blatt proposes to study areas of the brain including the inferior olive and the cerebellar cortex (“**Cerebellar Circuitry in Autism**”). These areas appear to be extremely important in understanding autism. The abnormally low numbers of Purkinje cells in the brains of autistic subjects is the most consistent neuroanatomical finding we have in autism. It is believed that these cells are either lost very early in fetal development or never formed. Dr. Blatt, by carefully studying the anatomy of that region, seeks to provide evidence of the developmental timing of the neuro-

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logical basis of autism. This is important since the ability to more precisely identify the commencement of abnormal developmental processes will help elucidate the causes of autism. Further, Dr. Blatt will be looking at the pathway connecting the inferior olive in the brainstem to the cerebellum. This pathway is very significant for attention and learning. Dr. Blatt's characterization of the neurochemical systems involved in these abnormalities may lead to new pharmaceutical treatments for learning problems.

The limbic system is another area of the brain that is extremely important to autism research. Drs. Bauman and Kempner have carried out qualitative neuropathological studies of this region and reported abnormalities in cell size and packing density. It would be very important to use modern quantitative neuroanatomical procedures to confirm and extend these findings. **David G. Amaral, Ph.D.**, Research Director of the M.I.N.D. Institute at the University of California-Davis is acknowledged to be one of the world's experts on the structure known as the amygdala (part of the limbic system). This relatively small structure is considered to be important for both social cognition and aspects of emotional behavior. For example, patients with disorders of the amygdala show an inability to discriminate facial expressions and show poor social judgment. In his NAAR-funded study ("**Post-mortem Neuroanatomical Evaluation of the Amygdaloid Complex in Autism**"), Dr. Amaral and his colleagues intend to study some of the structural and neurochemical abnormalities that may be present. Specifically, they will be using modern stereological and computer-aided analytic techniques to study the size and number of neurons in various subdivisions of the autistic and control amygdala. They will also study the GABA system which has been suggested to have a genetic abnormality in autism on chromosome 15. The study of the amygdala is essential to our understanding the brain mechanisms found in autism and is a needed link in the exploration of many other hypotheses regarding autism.

NAAR has an ongoing commitment to research aimed at understanding and treating language and communications impairments characteristic of individuals with autism. One of the consistent findings in many children is the abnormality in auditory language processing. Nonetheless, at this time, we do not know the precise identification of the neuropathological substrates responsible for the communication deficits. **Jorge J. Prieto, M.D., Ph.D.** of the University of Miguel Hernandez in Spain will be funded by NAAR to undertake a study of the auditory language centers of the cerebral cortex in autistic individuals and compare them to controls ("**A Microscopical Study on the Neuroanatomical Abnormalities of Language-Related Cortical Areas in Autistic Patients**"). The knowledge of where in the brain the auditory processing is abnormal is essential to search for genetic and/or environmental causes of autism and may enable the formulation of rational treatments. Dr. Prieto is one of the world's leading experts on this part of the brain and, with this NAAR grant, is applying his expertise to autism research for the first time.

Biochemist **Raju K. Pullarkat, Ph.D.** of the New York State Institute for Basic Research in Developmental Disabilities is a member of the team that recently found the genetic defect in the disease, late-infantile neuronal ceroid lipofuscinosis. Dr. Pullarkat proposes to use the same methodology with respect

to autism ("**Neurochemical Studies on Infantile Autism**"). He has already found a protein in the brain tissue of three autistic subjects that is absent in his non-autistic controls and, conversely, a protein in the controls which is absent in the autism samples. He speculates as to whether this protein in autism is intended to be transformed by enzymes into the normal protein. Dr. Pullarkat's project is to isolate and characterize these proteins and determine whether abnormalities of these proteins can be used as diagnostic markers for autism. If successful, this research could lead to a biological marker for autism (and be used for early diagnosis) and perhaps a candidate gene.

Finally, this year's recipient of the **NAAR/Bristol-Myers Squibb Research Fellowship in Autism and Neuropharmacology** is **Yan Ni, Ph.D.** of Yale University. Dr. Ni is going to study the serotonin system in autism. Part of Dr. Ni's research involves looking directly at the changes in brain serotonin receptors and transporter which, again, can only be undertaken with the availability of post-mortem brain tissue of individuals with autism. Because the medications that affect the serotonin system have proved beneficial in autism, Dr. Ni's project could lead to the development of more rational drug therapies.

Animal Models

Other than studying post-mortem brain tissue from individuals with autism, the only way that basic scientists can study autism is through the development of animal models. Until recently, there was little work going on in this area. In the past couple of years, however, several animal models for autism have been under development. This year NAAR is funding research on two mouse models.

Jeffrey D. Macklis, M.D., D. HST, of Children's Hospital/Harvard Medical School, has noted that there is evidence that there are abnormalities of the callosal projections in autism. These cells have the function of connecting the two halves of the brain and are thought to be instrumental in high level associative cognitive functioning. In other words, they assist in different parts of the brain communicating with each other in order to effectuate "higher thinking". Dr. Macklis is studying the basic science of the formation of these projections in terms of their growth and then connection to other cells ("**Neocortical Callosal Projection Neuron Survival and Differentiation Control**").

The connection with oxytocin and autism is a very interesting and developing story. It has long been noted that oxytocin mediates many social behaviors, which made it an appealing area to study in autism. In a very important study in 1998, Modahl reported oxytocin levels in autism of only one half that of the control children. In 1999, NAAR funded Dr. David Cool to study the biochemistry of oxytocin in autism and that study is ongoing. This year, NAAR is funding **Larry J. Young, Ph.D.** of Emory University who will investigate the social deficits in oxytocin knockout mice ("**An Oxytocin Knockout Mouse Model for Social Deficits**"). Dr. Young will study the ability of these mice to "recognize" familiar mates and determine whether there is an inability to process social information or, rather, to recall social information. Further he will study the neuroanatomy of the oxytocin's func-

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Couture for a Cure: Westchester Fashion Show Benefits NAAR

The second annual *Couture for a Cure* Luncheon and Fashion Show, held by The Autism Coalition for Research and Education (ACRE) at the Westchester Country Club in Rye, New York, raised \$70,000 to be shared by NAAR and several other autism organizations. The fashion show was hosted by Razooks of Greenwich, Connecticut, and featured designs by Alberta Ferretti, Moschino, James Purcell, Richard Tyler, and Christian LaCroix, to name a few.

Two hundred and seventy women attended this elegant event, among them representatives of NAAR, the Foundation for Educating Children with Autism (FECA), the Autism Society of America (ASA), and the Greenwich Autism Program (GAP). Keynote speaker Susan Varsarnes Young, Director of the



Top Row (L-R): Karen Greene, Rita Bigelow (FECA), Ann DiChiara (FECA), Carey Mougis (NAAR), Susan Varsarnes Young (WCEED)
Bottom Row (L-R): Barbara Kimmel (FECA), Catherine Johnson (NAAR), Tammy Turnage (GAP), Catolyn Scali (GAP), Sara Wolf (Director of GAP)



(L-R): Models Meredith Milianta, Suzy Armstrong; Event Chair Susan Murray; ACRE Founder Kevin J. Murray; Models Karina Verni, Deborah Walker, Cortni Wilson

Westchester Center for Educational and Emotional Development (WCEED), gave the audience a new understanding of autism, focusing on the concerns that are still ahead and how we can make a difference for the future of autism research.

Event chair Susan Barton Murray, a director of GAP, said "The focus of this event is not only to raise money for research and education but to raise awareness. The idea is to reach 'outside' the autism community for support and to further educate communities about the disorder." Mrs. Murray is the wife of ACRE founder Kevin J. Murray, who also serves on the Board of FECA.

The next ACRE event is the Celebrity Golf Outing, to be held on August 14, 2000 at the Winged Foot Country Club in Mamaroneck, New York. For more information about this function please call (203) 618-4934. ♦

Stepping Into the Future Scheduled for November 10 & 11

The Foundation for Educating Children with Autism (FECA) and NAAR will co-sponsor the seventh annual "Stepping into the Future" conference on November 10 & 11 at the Crowne Plaza Hotel in White Plains, New York. This year the Westchester Institute for Human Development will join FECA and NAAR in hosting this event. Also new to the 2000 conference will be the availability of Continuing Education Credits for New York teachers.

Friday's session, which centers on the education of children with autism, will feature leading researchers and clinicians in the field of applied behavioral analysis. Dr. Glen Dunlap from the University of South Florida will be the keynote speaker. Dr. Dunlap will present a review of current issues in behavioral support, functional assessment, school and community based interventions, and an overview of the Florida Model of Supports. A panel on supported inclusion will follow, led by Dr. Len Levin of the Alpine Learning Group. It will feature a regular educator, school principal and shadow; techniques and perspectives for providing successful support to the included child will be presented.

Participants will choose between two workshops on Friday afternoon. Peter Gerhardt, Ph.D. and Jennifer Halligan will discuss how to prepare for and obtain supported employment. Lori Overland, M.S. CCC will give an overview of using oral motor therapy to facilitate speech production.

Saturday's presentations will focus on medical and research topics. Dr. Margaret Bauman will give participants a guided tour through her classic studies of the autistic brain and the work in imaging and genetics that have come since. Dr. Robert DeLong will speak about the medical and pharmacological treatments of learning disabilities, his study of Prozac as a treatment for language, and his new work on Prozac as an early intervention in autism with the potential to improve the course of development in children with autism. Dr. Michael Chez will discuss his study of Aricept to treat language in children ages 2-8; and Drs. Theodore Shapiro, Margaret Hertzog, and Jeanne Greenblatt will comprise a panel of leading child psychiatrists who will answer questions about medications for children with autism.

Saturday's workshops will be conducted by Pamela Wolfberg, Ph.D. who will explain how to promote cooperative pretend play in children with autism through the use of integrated play groups. Cindy Alterson, Ph.D. and Allison Lavin of the Devereux Millwood Learning Center will discuss how to use activity schedules to promote independence, choice, and self-management skills for individuals with autism spectrum disorders.

Registration materials will be mailed on September 1, 2000. Call 914-941-3322 for more information. ♦

NAAR Launches *Walk F.A.R. for NAAR* Inaugural Pittsburgh Walk a Phenomenal Success

Dark clouds and a light rain did not begin to put a damper on NAAR's inaugural "Walk F.A.R. for NAAR" walkathon that was held in Pittsburgh, Pennsylvania on Saturday, May 20. Despite the weather, nearly 3,000 walkers turned out for the walk and raised more than \$230,000 for NAAR! Within the initial hour of registration, all of the 1,000 "Walk F.A.R. for NAAR" T-shirts had already been distributed. It was clear that the first walkathon for autism research in the nation was going to be a tremendous success.

The Pittsburgh walk is a testament to the dedication and hard work of Renee Georgi and her friend, Joan Pyles, who co-chaired the event and to the incredible effort of their committee chairs and volunteers who worked to make this inaugural walk such an extraordinary achievement. As a result of Pittsburgh's efforts, NAAR's Board determined on June 7 to fund more autism research projects this year than it had originally planned to fund.

"Saturday's walk sent a strong message that there are thousands of people from this area touched by autism who want to see more funding for research into the causes of this condition," said Renee, the mother of a five-year old son who has autism. "Walk F.A.R. for NAAR not only gives us hope but the feeling that we are not alone in our daily struggles." Among the throngs of walkers was Dr. Nancy Minshew, a prominent autism researcher at the University of Pittsburgh.

"This is what collaborative efforts on the part of the autism community can accomplish!" said NAAR's President Karen



Event Co-Chairs Renee Georgi (L) and Joan Pyles (R)



At the Starting Line

London who participated in the walk with her husband, Dr. Eric London, and their children. "It was an overwhelmingly emotional experience for Eric and me to stand at the starting



ribbon with Renee and Joan and, looking back, be unable to see the end of the long line of walkers behind us. It was an incredible feeling of community, joy, commitment and hope. The tremendous outpouring of support from the Pittsburgh community demonstrates that the effort to accelerate autism research is long overdue. Pittsburgh has set an example of what we can do everywhere."

With Dan and Claire Marino as National Honorary Walk Chairs, NAAR has already scheduled five additional walks in four more states. "Walk F.A.R. for NAAR" walkathons—the "F.A.R." stands for "Families and Friends for Autism Research"—are also scheduled in Los Angeles, CA (October 15, 2000), Long Island, NY (October 21, 2000), Central New Jersey (October 29, 2000), Miami, FL (November 4, 2000) and Broward County, FL (November 12, 2000).

"This was a great event in which not only the Pittsburgh autism community but also the local business community and extended family, friends and co-workers could join together for a great cause", said Renee. "It was wonderful to see all the different team t-shirts, buttons, banners and hats with the various family and corporate team names proudly displayed with their own colorful designs. It truly is a fun, family-oriented event in which our children with autism and their siblings can participate and really contribute—grandmas and grandpas, aunts and uncles, friends and neighbors can all support the goal of improving awareness and funding for autism research. We are already gearing up to make next year's "Walk F.A.R. for NAAR" even more successful!"

The aim of the “Walk F.A.R. for NAAR” walk program is simple—to raise as much money as possible so that no promising and meritorious autism research goes unfunded. “The number of scientists requesting grants from NAAR increases significantly each year,” said Eric London, NAAR’s Vice President-Medical Affairs. “The walk program offers a great way to help raise money to fund essential autism research nationally and even internationally.”



in walk revenues from \$3.8 million 1993 to \$44 million in 1999 under his leadership. “I know from my experience with JDF and other non-profits that these walks can be an excellent way to substantially increase funding for medical research”, commented Mr. Leonard. “As NAAR plans to increase the number and locations of walk sites in 2001, I look forward to hearing from NAAR’s supporters who would like more information and who might be interested in planning “Walk F.A.R. for NAAR” walks in their geographic area.” ♦

NAAR has retained Stephen Leonard to serve as its walk program consultant to provide each walk committee with necessary assistance, guidance and support to make their walk a success. Mr. Leonard previously directed the walk program of the Juvenile Diabetes Foundation, a program that saw an increase

If you are interested in helping with one of the scheduled Walk F.A.R. for NAAR walks in the fall or in organizing a “Walk F.A.R. for NAAR” walk in your geographic area, please call Steve Leonard or Tom Stanback, NAAR’s Director of Operations, at 1-888-777NAAR.

Faces from

Pittsburgh



Photographs by Greg Ellis

We Can’t Do It Without You!:
NAAR Supporter Chip Gordon

NAAR depends on donations large and small to support its mission. We are especially touched when siblings of children with autism also contribute to our work. Chip Gordon, then the President of the Student Council of Farmland Elementary School in Rockville, Maryland, spearheaded a charity campaign to benefit NAAR. Chip is pictured with principal Dr. Barbara Jasper who is presenting a check in the amount of \$500 from the Student Council to NAAR. Chip’s efforts are motivated by his love for his ten year old brother, Zak, who has autism.



An Evening at *High Point*: A Night to Remember

The New Jersey home of rock star Jon Bon Jovi and his wife Doreatha was the spectacular setting for "An Evening at High Point", a benefit on behalf of the Doug Flutie, Jr. Foundation for Autism and the National Alliance for Autism Research.

Hosted by Jon Bon Jovi and Doug Flutie, the party was attended by actress Heather Locklear and her husband Richie Sambora, actor Matthew McConaughey, hockey star Scott Mellanby, baseball's Rick Cirone, and football notables Phil Simms, Bill Parcells, Sean Landetta and O.J. Anderson.



(L-R): Richie Sambora, Heather Locklear, Jon Bon Jovi, Doug Flutie

Special Guest Bobbi Gallagher, founder of Brick POSSE (see "A Town Called Brick", NAAR-RATIVE 5), spoke movingly to the guests about life raising not one, but two, children with autism. So touched was Jon Bon Jovi by her words that he opened the night with a previously unannounced item—"a backyard concert by the second best band in New Jersey". That "extra" auction item raised an additional \$50,000!

NAAR extends its deep appreciation to Jon and Doreatha Bon Jovi for their generosity in opening up their beautiful home and hosting this very special evening. ♦

2nd Annual *An Evening with Saints and Angels*



(L-R): Event Co-Chairs Susan and Dr. Richard Doskey; NAAR President Karen London and Dir. of Operations Tom Stanback; Past Event Co-Chairs Drs. Ellen Schneider and Samuel Alexander; NAAR Honorary Board Members Lisa Clark and Will Clark

New Orleans "Friends of NAAR" hosted its second annual fund-raising benefit, "An Evening with Saints and Angels" on November 13, 1999. Held in the historic New Orleans landmark, Gallier Hall, this year's benefit was attended by several hundred guests who enjoyed wonderful jazz music and fantastic food from some of New Orleans' most famous restaurants. The evening's auction included two trips to the Indy 500 and a baseball signed by Ted Williams.

Special thanks are due to Event Chairs, Susan Doskey and Dr. Richard Doskey, and Honorary Chairs, Lisa and Will Clark for their extraordinary commitment and selfless dedication. Save the date...the third "Evening with Saints and Angels" will be held November 4, 2000 at *St. Elizabeth's*, the magnificent historic home of author Anne Rice. ♦

Bret Saberhagen Designates NAAR for *Hats Off* Charity Campaign

Boston Red Sox pitcher Bret Saberhagen designated NAAR as his charity when he was asked to participate in Merck's Hats Off Charity Campaign. Saberhagen, the uncle of a child with autism and a member of NAAR's Honorary Board, was participating with several other baseball players in a contest to determine which player would most benefit from use of the Merck medication, Propecia.

NAAR received \$25,000 from Merck for Bret Saberhagen's participation. The designated charity of the player who enjoys the most hair growth will receive an additional \$25,000. We're all keeping our fingers crossed! ♦



NAAR Trustee Eric Cushing (L) with Bret Saberhagen (R)

NAAR Honors NFL's Paul Tagliabue at Gala New York Event

More than 550 people crowded the Star-light Roof of the Waldorf=Astoria Hotel in New York City on June 6, 2000 to attend NAAR's first Award Dinner.

The benefit, honoring National Football League Commissioner Paul Tagliabue, was a phenomenal success netting more than \$500,000! NAAR is indebted to Mr. Tagliabue and to the event's dedicated Dinner Chairs, Mr. Preston Robert Tisch, co-owner of the New York Giants football team, and NAAR trustee Jeffrey Lurie, owner of the Philadelphia Eagles football team, for the extraordinary success of this benefit. NAAR Honorary Board members Doug Flutie and Dan Marino served as Honorary Chairs.

The evening was an emotional one, commencing with a touching video produced especially for NAAR by NFL Films and portraying the Marino and Flutie families as well as NAAR trustees Jeffrey Lurie and Karen London. Many wept as Jeffrey shared his love and admiration for his adult brother with autism, and as the Marinos and Fluties spoke poignantly about the challenges and dreams of parents raising a child with autism.



Co-Chair Jeffrey Lurie presenting award to Nancy Lurie Marks



Co-Chair Preston Robert Tisch presenting award to Paul Tagliabue

Following the video, NAAR presented gifts to the Marinos and Fluties in appreciation for all they have done to raise public awareness and funding for autism and Dan Marino and Laurie Flutie both spoke about the importance of NAAR and the need for increased research.

NAAR also presented a special award to Mrs. Nancy Lurie Marks for her extraordinary commitment to NAAR and autism research. When Jeffrey Lurie announced his family's gift to NAAR of \$1 million, the entire ballroom stood and applauded in gratitude.

Another glorious moment occurred when Mr. Tisch, Co-chairman of the Board of Loews Corporation, made the surprise announcement that he and his wife, Joan, would make a \$100,000 gift to NAAR!

Following dinner, Broadway star Christine Andreas—herself the mother of a special needs child—thrilled NAAR's guests by singing several hauntingly beautiful songs.

All in all, it was a glorious night for a very special cause. ♦



James Hogarth, an 11-year-old child with autism, created the original full-color artwork for this invitation to NAAR's first Awards Dinner.



Christine Andreas singing; Martin Silvestri at the piano



Master of Ceremonies Bob Cricqui, Dan Marino, Laurie Flutie, Claire Marino

CDC Findings in Brick Township: Autism Spectrum Disorders in 1 per 150 Children

By Eric London, M.D.

After more than two years of effort and study, the Centers for Disease Control and Prevention (CDC) has confirmed some of the concerns of parents in Brick Township, New Jersey.

In 1997, based on their observations of what seemed like an inordinate number of children with autism in a rather small township in central New Jersey, a group of parents of autistic children known as the "Brick POSSE" organized to try and get their observations studied and confirmed. At NAAR, we were also impressed with the POSSE's preliminary findings and, with the help of the New Jersey State Department of Health and most importantly U.S. Congressman Chris Smith and U.S. Senator Robert Torricelli, the CDC was called in to study the situation. Also participating in this investigation was a sister agency of the CDC that studies toxic exposures—the Agency for Toxic Substances and Disease Registry (ATSDR). (For a fuller account of the history of this effort see "A Place Called Brick" in *NAARRATIVE* 5, Summer 1999.)

The Prevalence in Brick

The most notable finding of the CDC report is that the prevalence of strictly defined autism in Brick Township is 4 per 1000. The prevalence of the broader spectrum of autistic disorders, including PDD-NOS and Asperger's syndrome, was found to be 6.7 per 1000. These numbers are striking. A decade ago, the accepted prevalence of autism was thought to be 0.5/1000. It was only in the past few years that the "guesstimate" was raised to 1/1000 for strictly defined "autistic disorder". The prevalence found in Brick Township reflects a rate of about 4 times the expected numbers.

Those unfamiliar with autism may question why this is striking. Many parents and advocates have long believed that the official numbers were an underestimate. The Brick Township prevalence study is only the third reported epidemiological study of autism ever done in the United States. The other two—done in the 1980s—reported numbers of about 0.5/1000. A key point to appreciate in understanding the significance of the Brick study is that the methodology was excellent. Cases were ascertained from multiple sources including local school records, with the cooperation of the schools. All suspected cases were ultimately confirmed in face-to-face evaluations using the "state of the art" in research diagnostic criteria, the Autism Diagnostic Observation Schedule-G (ADOS-G). It would be very difficult to argue that the numbers found in Brick Township are an over count. One could argue that some cases might not have been identified but *not* that the 6.7 per 1000 is an overestimate.

What is the Prevalence of Autism?

The data compiled in Brick needs to be put in perspective. Of all the studies done worldwide between 1975 and 1985, the prevalence of "autistic disorder" was found to be about 0.5/1000. In the next ten years, 1985-1995, the numbers jumped and were closer to the 1/1000 number. In a recent review by Christopher Gillberg and Lorna Wing, they noted that the prevalence numbers were rising at a rate of 3.8% annu-

ally based upon non-U.S. studies. Despite the undeniable nature of these increases, it is still not clear whether the reason is due to a "real" increase in the amount of autism (i.e. an epidemic) or whether it can be explained by the improved methodology of the studies.

Since 1995, more evidence continues to suggest that the prevalence of autism is still being underestimated. Interestingly, the better the methodology of the study, the higher the numbers have been. One study in Sweden found a prevalence of 6/1000 for autistic disorder. This was a very small study of a total population of only 826 and uncovering 5 autistic individuals. *Aside from that small study, the Brick Township study found the highest prevalence ever recorded anywhere in the world.* In Brick, the study population was 8,896; 36 children were identified using the strict definition of "autistic disorder" and a total of 60 children were identified on the autism spectrum.

Other very recent studies have also shown higher than expected numbers. Since 1995 one study from Japan found 2.1/1000, another study in Sweden found 3.1, and in an as yet unpublished study using the CHAT (Checklist for Autism in Toddlers - a screening tool) in England, the number reported was 3.08. In the Brick Report, the CDC has released some preliminary numbers from its ongoing Atlanta Surveillance study, and the prevalence is 2 to 3/1000. Reports of service utilization from California, Florida, Maryland and elsewhere have found rapidly increasing numbers.

The Meaning of the Results in Brick

The obvious question that needs to be addressed is whether Brick is typical or whether there is in fact a "cluster" there. The responsible reply is that we do not know. A definitive answer requires at least surveillance data from other surrounding areas in New Jersey; preferably data from all over the United States, as well as the world.

Since 1995 NAAR has been calling on federal agencies to undertake prevalence studies. Last year, in a bill introduced by Congressman Chris Smith (the representative of Brick Township), there was a call for an appropriation to fund the CDC. While this bill passed the United States House of Representatives (as part of the Children's Health Act 2000), it has yet to pass the Senate. There is however movement. The CDC has (in addition to its Atlanta surveillance) received another \$500,000 to study autism and has recently issued a call for proposals. The review process will occur this August and funding will begin this fall. The CDC is also funding a surveillance project in West Virginia. At NAAR, in order to continue the momentum of determining autism's prevalence, we are funding Dr. Ira Cohen to conduct a study in Staten Island, NY similar to that in Brick. Lastly, there is in the preliminary planning stage, a prospective longitudinal cohort study of 100-150 thousand individuals. Many federal agencies will be involved and the CDC, EPA and NIH have been designated lead agencies. The study anticipates tracking participants beginning in pregnancy to learn about the causes and evolution of many diseases. Because of the tremendous costs of such a study, many diseases and dis-

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Gene Identified for Rett Syndrome: MECP2 !

by Dawna Armstrong, M.D., FRCP

Rett Syndrome, along with autism, is a pervasive developmental disorder which affects girls. It is primarily a sporadic condition with about 1% of cases being familial. Until last October, when a mutant gene was found in some Rett girls, there was no way of making a definite diagnosis of Rett Syndrome, and there were few clues about its pathogenesis.

The syndrome begins with subtle clinical signs in infancy; a slowing down of the rate of head growth, a delay in the attainment of motor milestones, and an awkwardness of gait and hand use. Into the second year of life the symptoms become much more apparent; hand stereotypies develop, and there may be seizures, irregular breathing, teeth grinding and agitation. This period culminates with an outburst of irritated behavior, restlessness and inconsolable crying. Following this distressing "regression period" the little girls can no longer use their hands in a purposeful way, and have no meaningful speech. Rett girls survive for many years, requiring complete care, and frequently developing additional medical complications related to their underlying neurodevelopmental disorder.

The neuropathology of Rett Syndrome reveals a brain of decreased weight with small neuronal dendritic trees in selected parts of the cerebral cortex. There are some minimal alterations in most of the neurotransmitters that have been examined. There is no recognizable pathologic process which explains the decreased size of the brain and the neurons, but abnormal development has been suggested.

There is some overlap in the symptoms of autism and Rett Syndrome, so that early in the disease the differential diagnosis of Rett Syndrome includes autism and several other genetic and metabolic disorders. Autism and Rett Syndrome are also similar in their lack of a specific pathology and diagnostic test. Thus, the identification of a genetic alteration in Rett Syndrome is of great importance providing the first clue about

the biologic defect that is responsible for the profound clinical phenotype that we recognize as Rett Syndrome. If we can learn how this gene interrupts development in Rett Syndrome, we may begin to understand the pathogenesis of other pervasive developmental disorders.

MECP2 is a gene which encodes for the protein methyl-CpG-binding protein-2. This is a *regulator* protein which represses the transcription of CpG dinucleotides. That is, MECP2 prevents DNA from coding for proteins. This is an essential biologic function in the cell, acting to "silence" the genes which code for enzymes and structural proteins at times when they are not required for cell growth or maturation. We can speculate, then, that in those cases of Rett Syndrome where a genetic mutation has been identified in the MECP2 gene, there will be some genes which will be allowed to code for proteins. These proteins must then influence brain development adversely and produce the developmental disorder recognized as Rett Syndrome.

All of this is speculation, and there is a great deal of research that will have to be done in order to understand how MECP2 is involved in the normal development of the brain. It is fortunate that the sciences of molecular genetics and neurobiology are poised and prepared with the techniques needed to explore the function of MECP2 in brain maturation. The understanding of the role of MECP2 will provide new insights into mechanisms of epigenetic control of development. This knowledge will be important in our understanding of other pervasive developmental disorders such as autism. ♦

Dr. Dawna Armstrong is a pediatric neuropathologist with teaching, service and research responsibilities at the Baylor College of Medicine and the Texas Children's Hospital in Houston, Texas. She serves as a member of the Tissue Advisory Board of the Autism Tissue Program.

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orders, including autism, will be targeted. This study could shed much light on all developmental brain disorders and could be used to address issues that are very difficult to study in autism, such as environmental components (toxins, vaccines, etc.).

The ATSDR Report

One of the reasons that Brick received such prompt attention was its proximity to a Superfund (toxic waste) site. ATSDR studied the possibility of toxic exposures in Brick Township. ATSDR did not find a correlation between the toxic site and the indexed cases. However, it did note the presence of three classes of substances that were, at times, abnormally high in the Brick water supply. Although ATSDR could not establish a connection between autism and these substances, it did raise some interesting questions that may deserve some further investigation. The most interesting is a class of compounds known as trihalomethanes (THMs). These compounds are formed when organic matters (i.e. leaves) combine with chlorine (which is used to disinfect the water supply). In two separate reports, also done in New Jersey, THMs in the range found in Brick were associated with a twofold increase risk of neural tube defects, although a third study in Nova Scotia

found a smaller increased risk. Neural tube defects is the proposed mechanism that Dr. Patricia Rodier at the University of Rochester has been studying as a possible cause of autism. (See "An Embryological Approach to Autism: The Thalidomide Connection" *NAARRATIVE* 1, Summer 1997).

Clearly, this finding should be viewed as highly speculative. The reality of the situation is that even if we found a compound that could cause autism, at this time we may not know enough about the neurobiology to prove this. It is possible that compounds even at EPA acceptable levels may cause abnormalities in the developing fetus. The toxicology research that has been done has not been focused either on the fetus or on brain development.

More Research

The study done in Brick Township was a great contribution to our scientific understanding of autism. It is clear that the CDC/ATSDR study poses more questions than it answers. However, it makes the need for further research that much more compelling. Research is needed both in the area of epidemiology as well as the neurobiological underpinnings of the disorder. ♦

The Scientist

Karen B. Nelson is a highly respected clinician-scientist, whose work was a cornerstone of my child neurology education at New York Hospital-Cornell Medical Center. Her landmark 10,000 infant, collaborative multi-center study, published in the *New England Journal of Medicine*² twenty years ago, demonstrated that cerebral palsy was not due to obstetrical accidents (difficulties during labor and delivery of infants), except perhaps in 5-8% of births. Instead, the causes of CP were yet to be identified, but clearly occurred prior to birth and likely represented abnormalities of development. As a consequence of her work on CP, a period of ceaseless litigation against physicians came to an end, and the health care profession turned its attention to discovering what problems in development might underlie congenital diseases like CP. Dr. Nelson has also earned a reputation as a very careful epidemiologist.

Given her important contributions over the years, we should rightly take notice of her new work. She is a very careful scientist; in fact, when I spoke to Karin last month I was impressed by her personal level of caution regarding the methods she had used, and what the results might mean.

She remains cautious because at this stage her work is preliminary, and not yet “peer-reviewed.” The public learned of her findings when she presented an abstract at the American Academy of Neurology. An abstract is a formal presentation to a professional audience from an established investigator (in most cases) of work considered accurate because proper methods have been used. Such work reflects well-planned experiments, using reliable methods, and results that the investigator has reproduced several times.

Usually these abstracts are presented in the form of posters. The academy rents a convention hall room the size of an airplane hanger—the kind of room that normally houses car shows—and hundreds of researchers put up rows and rows of posters 8 feet wide by 6 feet tall describing their work. Each poster follows the standard format of an academic article: Introduction, Method, Results, Discussion. On the day of the convention hundreds or even thousands of “conventioners” mill through the room studying the posters and taking notes. It’s quite a scene.

While a presentation at the American Academy of Neurology sounds important to those outside the field, in fact the selection process for presentations is very liberal or even open. The Society for Neuroscience, for instance, has no selection process; any reputable researcher with a poster can put it up. I don’t know what the selection process is for the American Academy of Neurology, which is one of the most prestigious forums in the field, but at most they would be relying on an advisory board, not on a formal peer review process. Of course, Dr. Nelson delivered her presentation orally, rather than on a poster, which indicates that her work was reviewed and chosen in some way by a selection committee.

Not surprisingly, many poster presentations never see publication. At the Society for Neuroscience, with whose workings I’m more familiar, perhaps only one in three presentations make it into print; the ratio could be as low as one in eight. In other words, as a parent or non-medical professional, whenever you read the term “presentation” you should know that

there is a strong likelihood the researcher’s results will not hold up. Science is a supremely difficult and frustrating undertaking, and the most beautiful and precise work can fail to bear fruit.

The odds begin to change with the peer review process, which Nelson’s work will be undergoing very soon. Nelson will submit her work to a journal, which sends it on to anonymous experts in the field who examine it in detail. Typically, assuming the reviewer thinks there is something to the work, an article will go back and forth among reviewers, editor and author several times. The editor will ask the author to respond to each criticism, objection or comment the reviewer makes; the author can choose to write a rebuttal explaining why the criticisms are untrue, or he or she can present further data, or new methods of analysis, to strengthen his or her conclusion.

In other words, peer review is a painstaking process, taken seriously by everyone involved. Once an article has been through peer review it has been thoroughly vetted—and even then 60 or 70 percent of journal articles add little new information because the research is incomplete or will not be replicated. In order to evaluate a new finding reported in the media you need to know both whether the finding was published in a peer-reviewed journal *and* whether that journal is respected within its field.

Even then you don’t know. What any field may believe today can be overturned tomorrow, not because today’s work is sloppy but because it is incomplete. The great butter-versus-margarine debate is a perfect example. We had 10 years of well-done studies stacked up showing that cholesterol caused heart attacks, and that butter was a source of cholesterol. Then all of a sudden we discovered triglycerides, which are raised by margarine, and are dangerous *to more people* than cholesterol. In this case it wasn’t that the cholesterol studies were wrong; cholesterol did cause heart attacks in a small group of people. It was their interpretation by the medical establishment—cholesterol is bad for everyone—that was wrong.

Other times a study itself is wrong because the premises shared by many members of the field are wrong and the premises dictate the methods chosen to examine the question. Within my own field the most glaring example of this is the recent discovery of neurogenesis, the growth of new brain cells, in the human brain. For many, many years neurologists believed that the human brain does not grow new neurons.

And, in fact, the studies that looked for new growth, mainly performed in monkeys closely related to humans, found no new growth. But it turned out that one reason these studies found no new growth was that the new growth was happening so quickly that it was gone by the time the researchers looked. They were looking at monkey brains six months after introducing a substance that could identify new DNA (and thus new cell growth) when they should have been looking after six weeks. They chose the six month period because neurogenesis in the monkey brain seemed so unlikely that they wanted to make sure they gave the brain as much time as possible to grow any new cells it was going to grow.

Worse yet, as it turned out, the tracer for new cells—which was standard at the time—had a weaker signal than more recent tracers, which meant that it was poorly seen after 6 months anyway.

Dr. Nelson's work could face a similar issue, as she herself pointed out when we spoke. The technique she used to measure these small and large molecules in the blood is brand new and has not itself been peer-reviewed and published. Given that there is a long, long history of researchers trying to find markers in the blood for psychiatric illness—a history famous for its abject failure—this is a real concern.³ Over and over again researchers believed they'd finally found a marker they could develop into a blood test for depression, say, or schizophrenia, only to discover with further work that all kinds of non-depressed and non-schizophrenic people had the same "funny blood" themselves. At this point we simply can't know whether the brand-new method of measuring proteins used in Dr. Nelson's study measures what it says it is measuring.

Last but not least, since abstracts are very short (Dr. Nelson's was 265 words), other scientists can't evaluate the necessary relevant information, nor come to their own conclusions based on a thorough reading of the researcher's methods and data.

All we really know now is that Dr. Nelson is a superior scientist who has made major contributions to the field. Apart from that we must now wait as her work goes through the peer review process. Even then her research won't be "true." *Findings* do not become *facts* until they've been replicated numerous times by other groups of scientists studying other patient populations.

What She Did

Dr. Nelson and her colleagues examined frozen and stored samples of blood from babies born in the state of California 15 to 17 years ago. The samples were collected as part of the California Birth Defects Monitoring Program, which was established almost 20 years ago and mandates preservation of blood samples from one in seven babies born in California. The program has already paid off by allowing researchers to establish a link between cleft palates and mothers who smoke.

Nelson's children were born between 1983 and 1985 and lived in the northern part of the state. Samples came from four groups of approximately 65 children each. One group was identified as having autism, another had mental retardation (MR: I.Q. below 50), a third had cerebral palsy, and the fourth group, the control group, had no nervous system problems at all.

Nelson and her team analyzed these archived blood samples for chemicals or proteins associated with the brain. The word "protein" invariably confuses people when we're talking about genes and the brain. The last thing most of us heard about

protein, before high-protein diets came into vogue again, of course, was that it was something your mother worried you weren't eating enough of.

The important thing to know, for those who don't already, is that we ingest three basic molecules through food: proteins, fats and carbohydrates. Of these, proteins are the molecules that *do something* in our bodies. Enzymes, neurotransmitters, immune molecules—all are proteins. Carbohydrates and fat simply store energy. (RNA and DNA store information, another function altogether.)

To return to Dr. Nelson's work: Dr. Terry Phillips, an immunologist at George Washington University and at the Office of Research Services at the National Institutes of Health, analyzed the blood samples for eight different molecules—all of them proteins, either large or small (small proteins are called peptides—see Glossary):

- 3 small proteins called neuropeptides [see Glossary] These were vasoactive intestinal peptide (VIP), substance P (SP), and calcitonin gene related peptide (CGRP).

- Growth factors [see Glossary]: brain derived neurotrophic factor (BDNF) and the related neurotrophin 4 (NT4)

- 3 immune molecules, all of which are antibodies to structural proteins in the brain: an antibody to neuron-axon filament protein (NAFP), an antibody to glial fibrillary acidic protein (GFAP) and a third to myelin producing cell protein or myelin basic protein (MBP)

Dr. Nelson's reasons for choosing these 8 illustrate how new this field is—assuming it becomes a field at all, of course. VIP, BDNF and NT4 all appear to be important during early development; they are also significant after birth, in the normal cognitive functions of the brain. Since cognitive functions are affected by autism, these molecules might be involved.

The peptides VIP, SP and CGRP are present in sensory nerves so, since sensory function is disturbed in autism, they seemed like good candidates, too. And finally, damage to the brain is one model for the cause of autism, and antibodies to brain proteins may indicate that brain damage occurred; thus their inclusion in the study.

In short, all eight molecules are involved in nerve cell production and survival, communication and learning and memory, which meant logically that any or all of the group could be involved in autism and/or mental retardation.

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Alphabet Soup: VIPs, CGRPs, Substance Ps, etc.

Three of the molecules Dr. Nelson measured were **neuropeptides**: vasoactive intestinal peptide (VIP), substance P (SP), and calcitonin gene related peptide (CGRP). VIP, SP and CGRP occur in the brain, the peripheral sensory and autonomic nerves that contact most body tissues to sense the world and regulate functions, and in the gut. (Secretin, a member of the VIP family, is an example of a neuropeptide located in the gut.)

The **neurotrophins** are much larger molecules, around the size of insulin. They play major roles in brain development and function, but also occur in the tissues to which the nerves connect, such as muscles and salivary glands. Neurotrophins include brain derived neurotrophic factor (BDNF) and the related neurotrophin 4 (NT4), both of which Nelson measured.

Finally, Dr. Nelson measured 3 **antibodies** to brain proteins: antibodies to neuron-axon filament protein (NAFP), antibodies to the supporting glial cell filament, called glial fibrillary acidic protein (GFAP), and antibodies to myelin-producing cell protein or myelin basic protein (MBP).

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"We chose eight of them," Dr. Nelson told the New York Times, "and went on a fishing expedition."

What She Found

She came up with quite a catch.

By report of my colleague, Dr. David Mandelbaum, chief of Child Neurology at Robert Wood Johnson Medical School, who attended the presentation, the findings were striking. Members of the audience were struck both by the clear cut nature of the differences, and by the fact that what she discovered was somewhat counterintuitive.

Children with autism and MR almost universally had elevated levels of at least two or more of four factors—VIP, CGRP, BDNF and NT4⁴—compared both to typical children and to those with CP. In other words, children with autism and children with MR tested the same, whereas children with cerebral palsy and typical children tested the same.

In contrast, two proteins, SP and antibodies to MBP, were no different among any of the four groups.

Finally, antibodies to NAFF and GFAP were significantly lower in those with autism or MR than in those with CP or those who had developed typically.

On the face of it this data is complex, and that very complexity is actually encouraging because no simple "artificial" process can easily explain Dr. Nelson's findings. In a scientific experiment an artifact is anything outside the question being asked that could have caused—or in fact did cause—the findings. For instance, if all of the smaller molecules Dr. Nelson looked at had been present in smaller amounts, with the larger molecules all occurring in larger amounts, this would make us suspect an artifact since small molecules would be expected to degrade faster in the blood than large ones. But, in fact, she didn't find this; instead, different molecules of different sizes turned up in different levels. Similarly, if all eight molecules had been elevated, or all eight depressed, this would make one suspect some physical chemical process of inappropriate handling or storage—not the possibility of real biological markers for autism and MR.

That said, what is so remarkable about Nelson's findings is that her markers appear to identify children who will develop problems in the thinking process itself. In contrast, children with cerebral palsy who suffer from defects in the motor control regions of the brain did not show differences in these markers; their blood profiles were the same as those from typical children.

The differences in these molecules are distinct and appealing, since they confirm neuroscientists' belief that diseases like CP are produced by different abnormal events or processes than diseases like MR and autism. One model of autism and MR suggests that the brain is essentially *built correctly* from the beginning, but that certain functional components that underlie nerve cell communication, such as the synapses, may not work correctly.

Cerebral palsy is different: with CP it is clear that many or most cases of CP are due to damage to a normal brain by physical and thus frequently discrete injuries, such as a stroke before birth. While this disorder can be devastating to the child and family, CP is a *focal process*—the part of the brain that has been damaged functions badly, but the rest of the brain, including the thinking regions, functions well.

Colloquially neurologists speak of a "hole in the brain" when discussing disorders like CP, not because people with CP have an actual hole in their brains, but because there is a specific, circumscribed *place* that is not working. Of course, if much of the brain is involved in a prenatal stroke—if you have a lot of holes in the brain—eventually thinking will be disrupted, too, leading to CP-plus-MR. But even when a tremendous amount of the brain has been affected by CP, the parts that were not hit function properly—and that is reflected in Dr. Nelson's finding that teenagers with CP who also had MR *still* had the same levels of these chemicals as typical teenagers.

Thus Dr. Nelson's data correlates with our current models for how these diseases occur—and how brain-injury-based disorders like CP differ from disorders like MR and autism which may reflect disturbed function.

In terms of specifics, four of the proteins Dr. Nelson studied were very high in nearly all of the teenagers with autism as well as in the teenagers with mental retardation:

- vasoactive intestinal peptide (VIP)
- calcitonin-related gene peptide (CGRP)
- brain-derived neurotrophic factor (BDNF)
- neurotrophin-4 (NT4)

Yet another striking finding: not one of the controls (the typical teenagers) showed elevated levels of any of these proteins, and, according to the New York Times, fewer than 10 percent of the CP group had elevations. Given the complexity of the brain, such remarkably clear-cut findings are rare.

Building Models

If Nelson's findings are confirmed and we learn that these proteins are in fact elevated in the blood of newborns, what might this mean?

This is the fun part for us scientists, building models after the grueling work of chemical analysis and data crunching has been done. The challenge, of course, is to create a model that explains how these particular proteins relate to the processes of nervous system development or function such that, if disrupted, the disruption would result in a "broken brain."

I can think of a couple of possible models, neither of which may be true; many more could be proposed, and will. As I am a pediatric neurologist I'm going to build models that make sense in terms of what we currently know about child neurology; I'll leave models concerning the immune anomalies to neuroimmunologists.

For now, suffice it to say that the significantly low levels of antibodies to the brain proteins NAFF and GFAP in babies

with MR and autism are intriguing. In theory, no one should have antibodies to brain proteins, though obviously we do find them in typical people. Antibodies to NAFF and GFAP form when some aspect of brain cell structure has broken down, allowing these two proteins, which are normally “hidden” *inside* the cell, to become “visible” *outside* the cell, where they are exposed to the immune system.

Thus these antibodies, when present in large quantities, are an indication that something terrible has gone wrong in the brain. It’s important to point out that the NAFF/GFAP finding neither supports nor disproves an autoimmune theory of autism.⁵ With these molecules the brain damage comes first, the antibodies second: the antibodies are the *sign* of damage, not the *cause* of damage in and of themselves.

I want to emphasize that antibodies to brain proteins are always considered a bad thing: you don’t want to have them in your blood or anywhere else. That is why Dr. Nelson’s finding of unexpectedly low levels of antibodies to brain proteins in infants with MR and autism is counterintuitive⁶—it ought to bode well for these babies that their levels are low. And yet their brains do not function well.

One more observation: antibodies in the newborn reflect mainly the mother’s immune status, with the infant’s immature immune system influencing the reading to only a small degree. Nevertheless, Dr. Nelson’s finding does imply that there is something different about the immune function of this mother-infant unit.

The low levels also imply, very strongly, that these 130 newborns did not sustain *gross* damage to the brain in utero—gross meaning massive damage affecting every area of the brain, or nearly so, as we see in illnesses like encephalitis. (CP does not involve gross damage to the brain, and hence does not produce high levels of antibodies to brain proteins.) If the infants had undergone severe brain injury in the womb surely the many antibodies to their own brain proteins created as a result would have registered in the blood readings taken by Dr. Nelson.

Model #1: Built Wrong

In terms of my own specialty, pediatric neurology and neuroscience research, the first model suggests that in autism the brain is abnormally built from the very beginning.⁷ In all human beings the initial patterning of the nervous system is complete at the third week of gestation, days 20-25. (This is day 20 after fertilization of the egg, not 20 days after the first day of the last menstrual period, as obstetricians define a pregnancy.) A current theory proposed by Dr. Patricia Rodier suggests that autism may be due to differences occurring at this time, with the rest of the nervous system developing incorrectly as a consequence. Dr. Rodier’s work was based on the discovery of high rates of autism in adults who had been exposed to thalidomide, a morning sickness medication that caused deformed limbs in babies whose mothers had taken it during their pregnancies. Of 15 infants exposed between days 20-24, five emerged with symptoms consistent with autism, a tremendously high rate that strongly implicated thalidomide as the cause.

Rodier tested and extended her model in rodents leading to one possible model in which a gene that controls formation of the

hindbrain, Hoxa1/2 is abnormal. Studies of Hoxa1/2 in autism are now ongoing.

Significantly in terms of Dr. Nelson’s findings, the proteins VIP, BDNF, and NT4 all play important roles in these very same developmental events. They control the number of nerve cells that are produced, which ones live or die, and how they differentiate into specific kinds of neurons that do different tasks, such as moving and thinking. So this is a model in which the very earliest processes, from the very beginning of the brain’s formation, are abnormal, *due to abnormal levels of these proteins*.⁸

Of course, Dr. Nelson did not look at these molecules during days 20-24 of a pregnancy; nor did she look at their levels in the brain itself. Both undertakings were beyond the scope of what she was attempting to do, not to mention what she could do given the materials available to her. She measured her eight molecules nine months past the day 20-24 period, at the point of birth, and she examined them in the blood, not the brain. Since no one yet knows what the connection is, if any, between levels of these molecules at early gestation versus birth, or between levels in the brain versus levels in the blood, we can only say that Dr. Nelson’s findings may support Dr. Rodier’s hypothesis, and certainly do not contradict it.

Model #2: Sound Structure, Poor Function

My second model has nothing to do with initial brain formation, but instead assumes that the autistic brain is essentially normal in structure, as a number of researchers believe. Dr. Nelson’s findings fit nicely with this model because the molecules she found to be elevated, in particular BDNF, have been found to be released at the synapse during learning and memory.

BDNF is released on a moment-to-moment basis to control the nerve cell⁹ as it learns new information. Abnormalities in BDNF function result in animals who learn poorly. Adding back BDNF corrects these defects, which is powerful evidence that the animals’ learning problem is an ongoing deficiency in function, rather than a faulty construction of the cell in the first place.¹⁰

It is entirely possible that abnormal functioning of these proteins may cause normal cells to function abnormally. Under this scenario the brain is entirely well at birth, and the problem is an ongoing deficiency in one or more proteins critical with learning.

Stumbling Blocks

While other models could be generated, what do the reported elevated levels of Nelson’s four proteins tell us about the two I’ve just described?

In fact, that might be a big problem. As we’ve seen, no one has ever successfully identified blood markers for any brain disorder, so the possibility that we are going to be able to do so now requires a leap of faith. The brain and body are separated by the blood-brain-barrier (BBB), which keeps most molecules from crossing from one space into the other. Because of the BBB, the levels of any given substance in the brain may have

(continued on page 22)

(continued from page 21 ~Autism in the Blood~)

no relationship at all—or no quantifiable relationship—to its levels in the blood.

This is especially true of large proteins, such as the neurotrophins, which do not cross the BBB in animal studies. However, recent evidence suggests that when it comes to the blood-brain-barrier all of the large brain proteins may have to be examined individually. PACAP, for instance, which is a peptide closely related to VIP, *does* cross the barrier in newborns and adults, as does another growth factor, FGF, in both animals and humans even though both are large enough that we would not expect them to do so.

The upshot of our present uncertainty is that it is entirely possible that the elevated VIP levels Nelson discovered have nothing to do with VIP levels *in the brain*. We simply don't know whether VIP crosses the BBB (although we do have evidence that it crosses the blood-placenta barrier in the womb.) Making matters even more uncertain is the fact that we only have evidence concerning blood-to-brain crossings; we know nothing as yet about passages from brain to blood.

Another issue: VIP, as well as the other 3 molecules Nelson found to be elevated in MR and autism, can come from other parts of the body apart from the brain. VIP and CGRP are released from sensory and gut nerves as neurotransmitters; they also participate in immune cell function. The neurotrophins, including BDNF, are made by tissues with which spinal cord neurons make contact.

For all kinds of reasons, Nelson's findings may have nothing to do with the brain or brain function at all. Elevated levels may not reflect primary causes of disease, but may instead reflect what goes wrong when you have a disease, period. Or, perhaps children with autism or MR are more active than other infants, or have a different metabolism, leading to greater accumulation of these substances. In that case the markers would still serve to identify them, but would have nothing to do with the cause of autism or MR *per se*—or with what can be done about it one day after birth.

Last but not least, at present we have no way of knowing whether these proteins even come from the infant. Maternal proteins are known to cross in the child's bloodstream before and during delivery: Nelson could have identified elevated levels in the mothers, not the babies.

Next Steps? Treatments?

So where do we go from here?

For one, we anxiously await the full research paper's publication after it has undergone peer review.

Then, we hope others will repeat and confirm these findings.

Meanwhile, we may consider what else we want to know. For example, are these same molecules still elevated several days after birth? How about the parents; what are their levels like? (If the parents run high levels, but do not have autism or MR themselves, this may lead us to a quirk of genetics in those particular family trees.)

What about levels in and around the brain, as reflected by cerebrospinal fluid: if Nelson's blood measurements hold up researchers will certainly want to measure these substances in the spinal fluid, which is a direct measure of brain levels.

And: are the genes for any of these 4 molecules located on chromosomes currently being considered as harboring mutations associated with autism?

If Dr. Nelson's work is confirmed, and answers to the questions her work raises all seem to indicate that these four substances are intimately involved in autism and MR, what will this knowledge do for us? All of the medical treatments we use for autism and MR today have been borrowed from other disorders—could we be glimpsing the possibility of the first treatment created specifically for autism and mental retardation?

As always, there are different ways of thinking about this question. Obviously, if it is confirmed that levels of any or all of these molecules are abnormal in autism and MR, then the cause(s) will need to be determined. It could be that too much BDNF is harmful to the forming brain, resulting in too many neurons—or the wrong kind of neurons—being made. In that case, reducing levels of BDNF might help.¹¹

On the other hand, perhaps the increase reflects a compensation by a system that is too insensitive to BDNF.¹² This could occur if BDNF receptors were deficient. In that case lowering BDNF would actually make things worse, because the body would need extra BDNF to flood its faulty BDNF receptors. Obviously, simply knowing that these molecules are elevated (assuming we do know this eventually) is not sufficient; we must understand how the system works.

One of the main methods scientists will use to answer these questions will be to create animal models in which the gene for each one of the molecules, individually, has been deleted, or “knocked out.” Researchers will study a set of animals who have no VIP, another set with no CGRP, another with no BDNF and a fourth with no NT4. By looking to see what happens to an animal without a particular substance, we can begin understanding what this molecule does in normal animals (and perhaps humans). Of course we would not be able to determine whether these animals have any core symptoms of autism.

Fortunately this has already been done for BDNF. It was from the BDNF knock-out mouse that we learned that adult mice lacking BDNF learn more slowly, and that they can be helped (at least their living brain cells in a laboratory dish can be helped) by squirting BDNF back onto the nerves (or brain cells). Others have found that these mice do not make all the right nerve cells in the first place.

And, interestingly, when they grow older these mice become obese and exhibit some of the behaviors the pharmaceutical industry uses as mouse analogues to human depression when they are in the animal testing

phase of drug development. In other words, when pharmaceutical companies test new medications in animals, they have to rely upon certain behaviors in these animals as the mouse equivalent of depression (or anxiety or any other disorder) in people. The BDNF knock-out mice, when they age, begin to show “mouse depression.” They do not build the right nerve cells to begin with, they have trouble learning throughout life, and late in life they gain weight and appear to develop depression. (Unfortunately, of course, we do not as yet know what behaviors in rodents, if any, may relate to autism.)

As to the other three molecules, one of my collaborators is studying the effects of deleting the VIP gene. Many others continue to examine all of these proteins in cell culture dishes, studying effects in isolated nerve cells. Indeed, it was evidence from this body of work that led Nelson and her colleagues to choose the eight proteins they did. If Nelson’s work is confirmed, it will be this kind of work that helps us discover what it means.

While all of this may sound like a tall order (it is) we should be grateful for how far we have come. Just a few years ago you could say the word autism, and scarcely a scientist or lay person would know what you



Dr. Emanuel DiCicco-Bloom is a child neurologist in the Departments of Neuroscience and Cell Biology and Pediatrics at Robert Wood Johnson Medical School, and is a member of the Scientific Advisory Board of NAAR and of the New Jersey Governor’s Council on Autism. He spends much of his time in the laboratory examining the effects of VIP, PACAP, and the neurotrophins on still-developing as well as mature neurons both in cell culture models and in the whole animal. His studies are supported by both the neurological and child health institutes of the NIH.

were talking about. Private as well as national funding for autism research is stronger, and we have succeeded in bringing many bright and talented scientists and physicians into the field. By one count, as recently as seven or eight years ago there was only a handful of scientists studying autism; today there are, in this country alone, as many as 200 to 250. We should be encouraged by the magnitude of effort, and sustain our support.

And in our greatest hopes for our children we must do our best to learn all we can, to provide treatments that are safe and proven, and to proceed judiciously and cautiously as each new piece of information is revealed. Sooner, not later, we can hope to have meaningful treatments for our children. ♦

Endnotes

¹ See glossary

² The New England Journal of Medicine is the most prestigious medical journal in the United States.

³ Editor’s Note: A famous ADHD researcher used to open lectures by putting up a slide of 30 or so empty swimming pools and telling the audience that this was the amount of urine he had processed looking for markers.

⁴ That is, one child might have elevated levels of VIP and CGRP, another might have elevated levels of BDNF and NT4, a third might have elevated levels of VIP and BDNF, and so on. The children weren’t identical in their biochemical profiles; instead they showed an overall elevation in levels of these four factors compared to levels in typical children and children with CP.

⁵ An autoimmune theory of autism would hold that the body is producing antibodies to its own nervous system, as in diseases like multiple sclerosis.

⁶ There is no established “normal” level of antibodies to brain protein.

⁷ A brain that is built differently from the beginning is completely different from a brain being built properly for several months in utero and then being damaged by, say, a stroke. In

other words, the model I’m proposing is not the “hole in the brain” model we have for CP.

⁸ Genes produce proteins, and when a gene is faulty it may produce a faulty version of the protein that cannot perform its proper function, or no protein at all.

⁹ Nerve cell: also called brain cell or neuron.

¹⁰ This work has been done “in vitro,” meaning it has been done with living brain cells in a laboratory dish. When these cells are given BDNF, “long-term potentiation,” or LTP, which is a measure of the learning ability of a cell, goes up to normal. I’m unaware whether this is now being done with living animals who are low in BDNF, but that is the logical next step. This work has been done using hippocampal cells, which are thought to be different in autism.

¹¹ There is no way to speculate, currently, as to how long in an individual’s life such a treatment might be helpful: before age 3? Throughout childhood? Throughout all of adult life? We have no idea.

¹² Readers may be familiar with this process in Type II diabetes, in which “insulin resistance”—the body’s insensitivity to insulin—leads the pancreas to over-produce insulin. (In Type I diabetes the body does not create enough insulin from the outset.)

Because of Alex—Notes on Trailblazers

by Clarence E. Schutt, Ph.D.

Last weekend, Alex, my 14 year old son with autism, resumed a project of building his own swimming pool in our back yard. He had begun last summer by directing a jet of water from the garden hose into an ever-expanding mudhole. Every so often, he would step into the ankle deep muddy water to check his progress. After several days, he had a breakthrough. He discovered that by planting our pet dog's stainless steel water dish in the middle of the mudhole he could create a clear water pool. He quickly realized that his eighteen inch "pool" didn't measure up to his expectations and redirected his attention to jumping into the small (6 foot) plastic pool he normally uses.

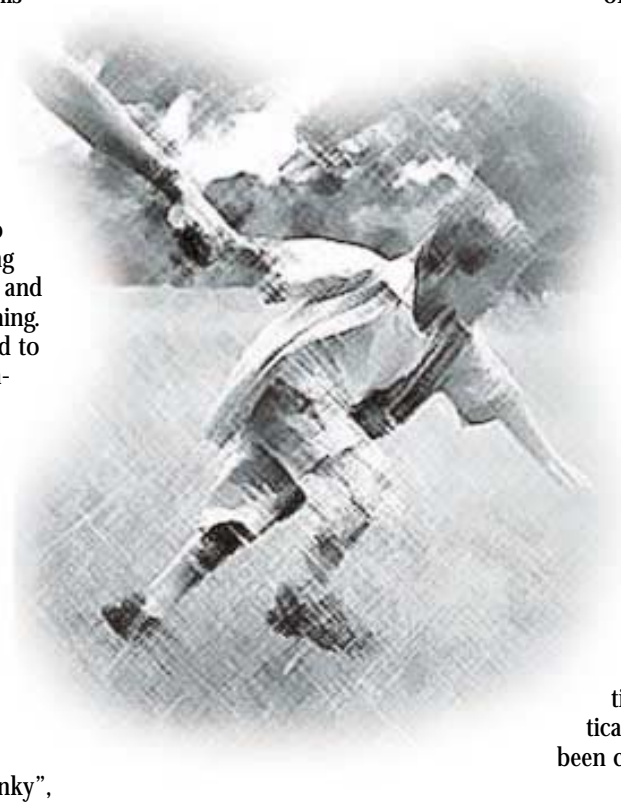
As I watched him stepping into his self-made pool, my memory took me back more than ten years to when I first established serious eye contact with Alex. I had been trying to catch his attention at the edge of the pool at our swim club by waving my arms and trying to get him to jump to me and, for just a fleeting moment, he looked into my eyes and jumped. That was just the beginning. Later that summer, we progressed to the point of diving to meet open-eyed under water, where we would begin to laugh and hug as we rose to the surface. Parents of "normal" toddlers asked me what my secret was in teaching him to dive with such confidence. I never knew where to begin.

My NAAR-related work often takes me to New York City to meet with potential donors or to attend meetings. A one-car train, affectionately known as "The Dinky", shuttles passengers between the Princeton University campus and the main line running along the Eastern Seaboard. It is not unusual to recognize someone at the station, a former student or fellow faculty member. A brief nod of recognition or exchange of pleasantries is enough to maintain our distance as we seek out separate seats on the train. I like to use the hour-long trip into the City to read recent issues of *Nature* or *Science*. Often some article sets me to musing about cures and treatments for autism - Alex is never far from my mind. Indeed, in the past few months I've spent the time on the train reading about sensational discoveries reported by some of my Princeton colleagues.

Once I get off the train at Penn Station in New York and begin to make my way through the crowd, it is rare that I spot anyone I know from among the hundreds of persons I pass. It is a curious and generally unremarked fact of human nature that in the instant it takes to scan a face we immediately real-

ize that we *don't* know someone. Some researchers believe, based on recent brain imaging data, that individuals with autism find it difficult to perform this everyday act of magic and avert their gazes to avoid trying. Maybe so.

Occasionally in one of New York's many museums or galleries, or along Park Avenue, a "celebrity face" will jump out and a little shot of adrenaline surges through my body. Recently, near Broadway, I unexpectedly ran into two well-known Californian advocates for services for adults with autism. Their faces were instantly recognizable, even though we see each other only once per year and I had no reason to suspect that they would be in New York. No brief exchange of pleasantries on that occasion!



Trailblazing...

Several lines of research suggest that the hippocampus in individuals with autism may not be functioning properly, perhaps because the number of neurons is reduced, or available neurons are not able to sprout "mossy fibers" of high enough density for high speed processing of complex inputs (like faces or sentences). But, I've never had much worry about Alex's spatial memory or ability to plan.

One winter's day, when he couldn't have been more than six years old, he took my hand and headed out across nearby Springdale Golf Course, through the Einstein Woods, all the way to the chained gates of our summer swimming club, a half mile away, where he had first learned to swim. It amazed me that he charted a course quite different from the route traveled in the reliable old 1953 Buick Special that usually carried us down the short dusty road to the pool. I should have anticipated that Alex wouldn't understand the chains and locks at the gate keeping him from the water on this cold

Professor Charles Gross, a distinguished colleague of mine in the Psychology Department, has spent many years studying the mechanisms in the brain responsible for face recognition and for perceiving one's place in space. He recently published an article in *Science* demonstrating that neurons in the hippocampus, the region of the brain required for associating immediate sensory information with long-term memory, can be replenished, contradicting the long-held view that brain cells do not divide. This pioneering discovery offers hope that damaged brains might be repaired by stimulating natural restorative processes by the application of growth factors or pharmaceuticals. The hippocampus has sometimes been called "the gateway to the mind".

winter's day and the image of him violently shaking at the gates haunts me still.

Scientists are beginning to understand at the biochemical level how the connections between cognition and emotion are mediated by hormones, and surely this knowledge will help our children. Charlie Gross co-authored the *Science* paper on neuron rebirth mentioned above with another Princeton colleague, Professor Elizabeth Gould, a rising star in the neuroscience firmament. Liz was one of the first scientists to demonstrate that neurons in the hippocampus respond to steroid hormones by increasing or decreasing the number of potential sites on their surfaces that can synapse ("join with") other neurons in the "nets" of neurons that capture and refine our thoughts and memories.

This important discovery reveals one of the ways in which our brains respond to stressful situations and how emotional states may affect learning. Conceiving or fixing a plan in our minds seems to require hormonal stimulus to maintain or strengthen active memory and learning circuits. We all learn better when we're excited. There is an excellent book by Antonio Damasio on the "mind-body" problem (*The Feeling of What Happens*) in which he argues that "consciousness"

itself, the sense we have that we are here, may be just another emotion.

On that cold day at the gate, Alex just couldn't adjust to the fact that his plan had been thwarted. It must have been hard for him to drop it, not that he didn't understand, but because his powerful determination was sustained by strong neural-hormonal circuits that he couldn't control. I sometimes wonder if sometime ten thousand years ago, when the human population dwindled to a dangerously small number, whether some autistic person led our species to safety, or to a fresh water supply, because they had the determination and clear-headedness to blaze a new trail. ♦



Clarence E. Schutt, Ph.D. is Chairman of the Board of NAAR. He is Professor of Chemistry at Princeton University, where he is also Associated Faculty of the Molecular Biology Department and a Member of the Program in Neuroscience. He is the parent of a 14-year-old son with autism.

Editor's Note: Thoughts on Karin Nelson's Preliminary Findings

by Catherine Johnson, Ph.D.

Dr. Nelson's study raises interesting questions concerning early versus late onset autism. It would be interesting to know whether there were "regressive" children in her study, and if so how many.

Assuming she did have late onset children in her sample (you'd expect 20 or so in a group of 65) it would be interesting to know whether their levels of these brain proteins, though apparently higher than those in typical newborns, differed in any way from those in the early onset kids. If not, if the early onset and late onset children showed roughly the same elevated levels, this might tell us that the relationship between late and early onset autism may be different than what many had believed.

For a number of years, of course, clinicians assumed that parents of late onset children simply missed the signs that their children were different. But that view may be changing. A recent "Brief Report" from the University of Washington, published in the *Journal of Autism and Developmental Disorders*, found that researchers could retrospectively identify "autistic" 8 to 10 month olds with a high degree of accuracy from home videotapes—but only when they removed late onset children from the analysis.

The question of regressive versus nonregressive children has gained more attention of late not only due to the controversy over vaccines, but also with increasing knowledge of Landau Kleffner Syndrome, or LKS, a regressive epileptic disorder similar to autism in many ways. Work on LKS has led many researchers to believe that regression in early onset children is more widespread than clinicians realize. Roberto Tuchman, a member of NAAR's Scientific Advisory Board and a pediatric neurologist who is an authority on LKS as well as on epilepsy in autism, observes that many nonregressive children *do* show regression in "communica-

tive intent." An early onset child who was talking at 12 months will continue to talk—he won't lose his words as regressive children do—but he may stop seeming to *want* to talk. He does not lose skills, he loses intent to use his skills.

Is it possible that a similar genetic and/or environmental event "tips" all children with autism either from normal to autistic (in the case of regressive autism), or from "slightly" autistic to "severely" or "full-blown" autistic, as parents of nonregressive children often report when describing the developmental history of their children?

In a future issue of NAARRATIVE we hope to examine the issue of regressive versus nonregressive autism, and to bring you Dr. Tuchman's discoveries and clinical approach to treating language in children with severe language loss.

On another subject, it would also be interesting to know what the levels of these chemicals are in babies with Asperger's syndrome. Even more intriguing, what might the levels of these proteins look like in children like Temple Grandin who begin life with classic autism but progress to high-functioning autism?

We all, parents, teachers and researchers alike, have a great deal to think about. At least we *will* have a great deal to think about if Dr. Nelson's findings are confirmed. And we hope that we learn the validity of her results soon, one way or the other. ♦

* "Brief Report: Recognition of Autism Spectrum Disorder Before One Year of Age: A Retrospective Study Based on Home Videotapes." Emily Werner, Geraldine Dawson, Julie Osterling, and Nuhad Dinno. *JOURNAL OF AUTISM AND DEVELOPMENTAL DISORDERS*. Volume 30, Number 2. April 2000. pp. 157-162.

Glossary of Selected Scientific and Medical Terms

(Biologic) Marker protein. A protein molecule that is strongly associated with a biologic process or condition. For instance, insulin is a biologic marker of diabetes.

Nerve growth factors. Also called neurotrophins. "Trophe" is Greek for nourishment. Neurotrophins are survival-promoting molecules that nourish and maintain nerve cells.

Neuropeptide. A peptide that has functions to do with nerves, or nerve cells. Neuropeptides differ from "neurotransmitters" in that when a neurotransmitter locks onto a cell receptor it either causes that cell to fire, or inhibits that cell from firing. In contrast, a neuropeptide may only increase or decrease the chance that a cell will fire or be inhibited from firing. All neurons have an electrical charge, called "a resting potential"; neuropeptides modulate electrical potential. Thus they are neuromodulators, as opposed to neurotransmitters. There are up to 40 different neuropeptides.

Peptide. A small protein consisting of a very short string of amino acids.

Structural or cytoskeletal proteins. These proteins maintain the three-dimensional structure of the cell, and include microtubules and microfilaments among others. They are akin to two-by-fours inside the cell, holding it open.

Target. A pharmaceutical term meaning a biological or chemical aspect of the body you are trying to affect in one way or another. For instance, if you are attempting to block a receptor for serotonin, that receptor is the "target."

Triglycerides, or triacylglycerols. A fat composed of one glycerol molecule bonded to three fatty acids. Glycerol is related to sugar, making triglycerides a "sugar-fat" that is common in adipose tissue (body fat) and in the blood.

(continued from page 10 ~Research Awards~)

tioning in social situations. The anatomic and behavioral data this study generates may lead to the development of pharmacologic treatments.

Development of Measurement Tools

Two other research projects that NAAR is funding have important clinical relevance. One serious, ongoing problem is the inability to make an early diagnosis of autism spectrum disorders. In order to facilitate this, various investigators have recently developed quick and easy-to-use instruments to make a presumptive diagnosis and to use to refer a child for more extensive evaluation. The "CHAT", a screening instrument that was developed in Great Britain, was a major advance but has certain flaws. Among them is its inability to identify the higher functioning children on the spectrum. **Deborah A. Fein, Ph.D.** of the University of Connecticut will study a modification of the CHAT instrument ("**Early Detection of Pervasive Developmental Disorders**"). This modified instrument samples a much wider range of behaviors, is given to 24 month old children (as opposed to 18 month old children), and has a lower threshold for identification, thereby "catching" higher functioning children. With her NAAR grant, Dr. Fein hopes to validate this new instrument by testing it on 4000 children. If successful, this may become the standard screening instrument that could be used by all pediatricians, general practitioners and early intervention centers.

Although we are all aware of the social difficulties in autism, at the present time it is very difficult for scientists to "measure" them. The ability to do so could be very important especially for genetic studies looking at social difficulties or perhaps later on if a substance such as oxytocin can be used to treat social deficits. **John N. Constantino, M.D.** of the Washington University School of Medicine in St. Louis has devised such a scale, known as the "Social Reciprocity Scale." Dr. Constantino's research ("**A Quantitative Genetic Measure of**

Autistic Traits") is to validate this scale which can then hopefully be used as a tool in clinical and genetic studies of autism.

The Prevalence of Autism

Since NAAR was established, it has had an ongoing commitment to epidemiological studies in autism. Using the state-of-the-art research diagnostic tool, the ADOS, the Centers for Disease Control and Prevention (CDC) recently found a prevalence of autism of 4 per 1000 and prevalence for the broader autism spectrum, including PDD-NOS and Asperger's Syndrome, at a rate of 6.7 per 1000 in Brick Township, NJ. This is about four times the prevalence rate cited in recent studies. In their preliminary findings in Atlanta, the CDC is also finding very large numbers of autistic children (2-3/1000). These numbers demand more study. NAAR is therefore funding **Ira Cohen, Ph.D.** of the Institute for Basic Research in New York who will undertake an autism prevalence study in Staten Island using similar methodology to that utilized by the CDC in Brick Township ("**Epidemiology of Autism on Staten Island**"). This will enable us to have two comparable prevalence studies that we anticipate will provide solid documentation regarding the underestimate of autism. It is our hope that this NAAR-funded research on autism prevalence will help underscore the need for a federally funded nationwide surveillance of autism as well as for significantly increased NIH-funded autism research investigating causes, prevention and cures. ♦



Eric London, M.D., is a founder of NAAR and its Vice President-Medical Affairs. He is a psychiatrist in private practice with a special interest in developmental disorders and an Adjunct Assistant Professor in Psychiatry at the University of Medicine and Dentistry of New Jersey. Dr. London is the father of a twelve year old son with autism.

Thank You!

It would be impossible to thank all of the volunteers whose efforts contribute to NAAR's achievements and promise. However, the following individuals are owed a particular debt of gratitude over recent months:

Michael Alessandri	Jennifer Fulton	Sue and Scott Mellanby
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And to NAAR's Scientific Advisory Board for their generous donation of time, energy and expertise and for another superb and stimulating Scientific Advisory Board meeting

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