NAARRATIVE

The Journal of the National Alliance for Autism Research

SPRING 2004

Breaking New Ground in Funding Biomedical Research

NAAR Makes Largest Single-Year Non-Governmental Commitment to Autism Research

NAARRATIVE is published by the National Alliance for Autism Research (NAAR).

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Established in 1994, NAAR is the first organization in the country dedicated to funding and accelerating autism research that seeks to determine the causes, prevention, effective treatments and, ultimately, cure for autism spectrum disorders. To date, NAAR has committed $14.9 million to directly fund 169 autism research projects worldwide - more than any other non-governmental organization.

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NAARRATIVE
Spring 2004

What's Inside

Science & Research

Progressions - Development & Fundraising News

A Letter from Prisca Chen Marvin
Chair, Board of Trustees

Prisca with her youngest daughter, Helen.

Like you, I am often asked, by the curious and the concerned, "How is Helen?" or "What is she like?"

And more often than not, I find myself answering, almost by rote, that "She is 11 years old and that she has no functional language, no social inhibitions but she is very purposeful, destructive and happy." But no one sentence can capture what our children are really like.

Indeed, no one hundred sentences can even begin to describe how different they are from typical children and from each other. Helen adores Disney as do children around the world. But like so many children with autism, it means watching a particular segment over and over, and, for Helen, at the highest volume that her little portable TV can generate, for weeks on end - at all hours of the night. Currently, in the Marvin household, 101 Dalmatians is once again, the featured presentation. My husband, Kim, came into our bedroom the other night as I was just drifting off to sleep and in his best "Pongo" voice informed me, "They are going to keep all the puppies! Every one!"

All of us have stories that are funny, scary, sad and bizarre. Whenever I am with fellow parents, there is an instant bond. Our daily routines are never "ho-hum". We are all overwhelmed at times by details and concessions to the characteristics of our children that impact the entire household. It's exhausting to contemplate and I rarely attempt to explain it to the uninitiated.

We have all lost something extraordinarily precious, but we have all made a commitment to effect a change. I thank you for letting NAAR be that vehicle for change. Its steadfast concentration on biomedical research, transparency and integrity makes NAAR the vanguard and ally of parents world-wide and generations to come.

NAAR has brought about a sea-change in the field of autism research. It has created more awareness, more focus, and most importantly, a genuine excitement amongst the scientists that an understanding of the disorder and a treatment or prevention is on the horizon.

Today, we find ourselves at an unprecedented convergence of clinical insights, technological advances and increased governmental responsiveness. We have an obligation to maximize this opportunity.

I invite you to join us.

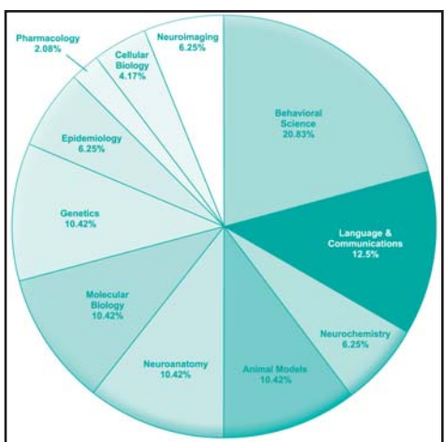
Prisca

Research Review: A Closer Look at NAAR's 2003 Research Awards

By Eric London, M.D.
Co-founder & Vice Chair, Scientific Affairs

For the seventh time since our organization's first announcement of NAAR's research awards, I have the pleasurable task of summarizing the latest projects NAAR is funding. Over the years, I have come to recognize that with these awards, NAAR is laying the groundwork for the science headlines of the future.

In prior years, we established a tradition of describing each and every grant that NAAR funds. In NAAR's initial year, this consisted of only five awards for a total commitment of $150,000. This funding cycle - only six years after our first - we are reporting on an unprecedented 35 grants, 13 pre- and post-doctoral fellowships and two training programs, for a total commitment of over $4.9 million. In order to facilitate this overview, I will describe the grants by topic and also try, wherever possible, to present them in the context of other research.



The above graph illustrates what percentages of scientific disciplines are represented in NAAR's 2003 Research Awards.

Research on Language and Communication Issues in Autism Spectrum Disorders

Auditory Systems

Since its earliest funding years, NAAR has maintained a special interest in research investigating language and communications issues in individuals with autism spectrum disorders. At the time of our founding in 1994, we observed that there was virtually no research and no scientific literature on this topic. Scientists could not even offer an educated guess as to the neurobiologic underpinnings of the language impairments observed in individuals with autism. To stimulate scientific investigations in this area, NAAR began issuing special requests for proposals ("RFPs") to scientists to investigate language/communications issues in autism spectrum disorders in 2000 - and continues to do so today. In the initial year of this RFP, NAAR received only a handful of research proposals in response to this unprecedented call. This funding cycle, however, no less than one fourth of our funded proposals that we received were in response to the special language/communications RFP. NAAR is thrilled that a new cadre of scientists have been stimulated to study the diverse language and communications issues that affect so many of our family members.

The language issues observed in autism are indeed varied in nature. Some individuals with autism spectrum disorders never develop any spoken language; some acquire just single words. Some can express their thoughts and needs through written language while having no expressive speech, while others cannot.

Amongst those individuals with autism spectrum disorders who do develop spoken language, some have problems articulating words while other articulate perfectly. Some have problems with prosody (intonation), while for others this is much less of a problem. There is even scientific debate as to whether the problem stems from impairments in the mechanics of speaking and hearing or if it represents a much more subtle problem involving comprehension of the spoken word.

Regardless of this debate, the answers to these questions are critically important to determining how to best educate children with autism spectrum disorders and, more profoundly, how to best "connect" with them and maximize their potential throughout their lives.

A fundamental question that needs to be answered is whether the auditory systems in individuals with autism are functioning adequately. In order to process language there needs to be a complex set of neuronal processes which not only need to function

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individually, but also in synchronicity with all the other systems in the brain.

In the 2003 funding cycle, NAAR is funding three studies that focus on the auditory systems. **Dr. Timothy Roberts**, of the University of Toronto, is continuing his NAAR-funded studies on the auditory system in autism using a technique called magneto-encephalography or "MEG". MEG is a very sensitive system that can measure fine changes in the magnetic field emitted by the brain based on the electrical activity generated by the brain's functioning. MEG allows us to measure certain aspects of the brain's functioning which other imaging techniques do not. In earlier NAAR-funded research, Dr. Roberts found that autistic subjects have a significant abnormality in their ability to process sound. He used a technique called "mismatched negativity." This technique involves a series of sounds in sequence such as: a a a a a u a a.

When the brain perceives the change in the sound "u", it registers electrical activity. The exceptional value of this technique is that the brain will react whether the subject is "listening" or not. It is a "passive" task that requires no response or even attention on the part of the subject. This is extremely valuable insofar as one can never be certain that individuals with autism spectrum disorders will cooperate with a research requested task and, therefore, whether the ability to pay attention is the problem rather than the actual sound processing. By eliminating these factors, this technique permits a greater degree of confidence that what we are measuring is truly the functioning of the brain's auditory system. In his previous work, Dr. Roberts demonstrated that the autistic subjects took significantly longer time than controls to register the recognition of this difference of vowel sounds in the mismatched negativity test.

In his new study, entitled MEG Correlates of Linguistic Processing At and Below the Word Level in Autism, Dr. Roberts will try to determine whether individuals with autism have a problem in processing pure sound or whether the sound is accurately received but the brain is unable to process those sounds into language recognition. His method to separate these two functions is to examine the brain's responses to various sounds and words. The brain is known to show a spike of electrical activity at about 170 milliseconds after a sound is generated. This is believed to be related to the brain's processing of pure sound awareness. Abnormalities at this level suggest a deficit in "hearing." Another spike in electrical activity at 350 milliseconds is believed to represent brain activity that relates the sound to the meaning of the word, which is already stored in the brain. This is what would generally be called "language processing." Abnormalities therefore found at the 350 millisecond range would suggest not a hearing problem but a language problem.

Various strategies will be used, such as presenting sounds that exist in English versus other combinations of sounds not part of the English language. The typical brain is "surprised" by unknown combinations of sounds. If this is found not to be the case in autism, it would suggest that the brains of individuals with autism have a deficit in the recognition of the language sounds. Another experiment will use the fact that "high frequency" or commonly utilized words are processed faster in neurotypical listeners than are words which not frequently heard. If this is different in individuals with autism, it will also suggest that there is a primary language processing deficit.

While Dr. Roberts was undertaking his language studies in autism funded by his initial NAAR grant at the University of California at San Francisco, he mentored **Dr. Nicole Gage.** Dr. Gage has since moved to the University of California at Irvine where she is continuing her work on the auditory system and autism. Dr. Gage will also use MEG in a project entitled MEG Investigations of Cortical Auditory Processing in Children with Autism. This work is more focused on the "hearing" function than the language function described in Dr. Roberts' work above. Dr. Gage intends to study the brain's response to many of the mechanical issues of speech production and to measure the ability of the individual with autism to hear under several variables. For example, she intends to study sounds that are made with different parts of the mouth and with different amounts of opening of the windpipe. She will also look at the variables of frequency and the ability to discriminate "gaps" in speech. These issues will also be tested with the subjects hearing them

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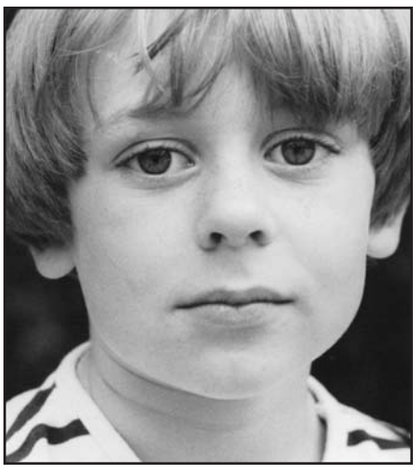
against a silent background as well as a noisy background, suggesting that any deficits in hearing may be related to the autistic individual's inability to filter out noise and process more significant sounds.

Dr. Michelle Dunn, of the Albert Einstein College of Medicine in New York, has been studying the auditory systems in autism for many years. Her previous research has found that the peripheral auditory system-that is, from the ear to the brain--is intact in the autistic children tested. There has been controversy over the past 20 years as to whether the brainstem auditory functioning is impaired in individuals with autism. Dr. Dunn's data is that a relatively small subgroup (about 13%) of such individuals has abnormal functioning in that area. The early cortical functioning, as described in her previous research, also appears intact in these subjects. She has found, however, a marked abnormality in the later electrical activity that is called the "N1c component". This is thought to be a reflection of the functioning of the auditory associating area of the cortex. The association areas are responsible for the communication of the auditory part of the brain with the other brain areas such as those needed to provide meaning to the sounds produced.



In her NAAR-funded project, Understanding Cortical Auditory Processing Abnormalities in Children with Autism, Dr. Dunn will use electrical measurements to further explore these findings. She and her colleagues will measure the timing of the brain's response and see if varying the task affects the brain's speed in responding to sounds. For example, they will use English words vs. nonsense words (backwards words) and they hypothesize that, when hearing an actual word, the association areas of the brain need to work to understand the word and that this slows down the brain's ability to process the word. The results of this research on cortical auditory processing may help guide educational methods as well as potentially lead to future development of pharmaceutical agents that can improve the timing of the brain's auditory response system.

The Brain's Language Processing Systems

One of the parameters of language is its intonation and emphasis. This is called "prosody". Since the earliest descriptions of autism, it has been noted that, even in those individuals with good expressive language skills, there is often a deficit in prosody.

Although it may seem to many that prosody is the "icing on the cake" in language acquisition, **Dr. Mirella Dapretto** at the University of California at Los Angeles (UCLA) hypothesizes that abnormalities in prosody may actually represent a much more fundamental problem in language development in autism. There is some mounting evidence that when a neurotypical toddler is first acquiring language, the acquisition appears to be a stream of sound. One word follows the other closely in time so that it may sound like one big word. One of the first tasks for the toddler is to discern the individual words in that stream. If you listen to a foreign language being spoken rapidly, it is clear that this is no easy task. One way the brain might learn to discriminate individual words is through "statistics" - by hearing that sound repeatedly one recognizes it. Another way is through clues given in the prosody of the speaker. If there is a deficiency in the ability of toddlers with autism to perceive these prosodic cues, then it might be much more difficult to start the process of deciphering language, thereby placing the children at a distinct disadvantage.

In her project, Language and Prosody in Autism: Evidence From fMRI, Dr. Dapretto will test this hypothesis by creating a nonsense language and studying the ability of autistic individuals and controls to pick out the new words out of the stream of sounds. She is also using functional magnetic resonance imaging ("fMRI.") to study the brain mechanisms used by these two groups. This understanding could lead to speech and language interventions to maximize autistic individuals' abilities to learn language.

In a second NAAR-funded project, **Dr. Michelle Dunn** will study a model of how the language system works. This model has been called the "mental

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lexicon." In a nutshell, the brain has formed a system that has been compared to a dictionary containing all of the words known to that person. This dictionary is, however, infinitely more complicated than the list of words we have in Webster's. Each word gets weighted in many subtle ways. The weight is really a measure of the ease of the electrical connection between neurons containing information.

For example, if I say "I have a pen", the typical listener understands that I mean a writing device and not a pig pen or the University of Pennsylvania. Very young children learn word associations by experience. If we tell the toddler that it is "bed time" and she always gets a bath before being put into bed, she may at first understand "bed time" to mean "bath". However, neurotypical children will soon learn the concept of bed time and realize that the bath is only incidental.

In children with autism, the conceptual understanding of words seems to come much harder. There is evidence that there is an abnormality in the mental lexicon. In her project, Mapping the Lexical Organization in Children with Autism, Dr. Dunn will use evoked electrical potentials to study the brains' functioning in undertaking these associational tasks. She hopes not only to demonstrate more precisely where individuals with autism break down in their lexicon's functioning, but also to create a model for the neuronal networking responsible for the system's failure.

Dr. Michael Ullman, of Georgetown University, in his project Neurocognitive Correlates of Language in Autism, is investigating the language deficit in autism from a different angle. He proposes that there are two language systems in the brain that work together. One is called the "declarative system" and is analogous to the mental lexicon discussed above. It is responsible for the memorized rules of language including the meaning of words. This is largely a function of the temporal lobe in the brain's cortex.

The other system is called the "procedural system", a computational system responsible for the more sophisticated process of stringing words together in the right order and with the right grammar so as to provide meaning. The anatomic systems that accomplish these tasks are completely different and Dr. Ullman believes that the procedural system is more responsible for the deficits in autism. The researchers will test their subjects with several cognitive tasks to try to document the exact nature of the language deficits.

Other Language Studies

It is not clear whether the language impairments so typically found in autism spectrum disorders are due to genetic abnormalities. Besides autism, there is another diagnosis in which there is a severe language impairment, also called "SLI." In this disease, there is severe language disability in the absence of the other symptoms found in autism. There is some scientific evidence that there is an overlapping genetic predisposition to the language impairment in autism and SLI. At issue, therefore, is whether the language abnormality should be considered integral to a diagnosis of autism. The alternative hypothesis is that other core symptoms in autism-- such as social deficits-- adversely impact language development and that language impairment is a resulting or "secondary" problem.

To study these issues, **Dr. Patrick Bolton**, of the Institute of Psychiatry at King's College in London, England will be funded for his project, Speech and Language Impairments and Autism Spectrum Disorders: A Twin Study of the Links. Dr. Bolton will utilize a collection of over 16,000 school age twins available in England in a prospective longitudinal study to ascertain the relationship between language delay and autism . He and his colleagues will then compare the heritability of language disorders comparing identical and fraternal twins. The data compiled will be the basis for further genetic studies.

Scientific evidence demonstrates that autism is a neurobiologic disorder with a genetic predisposition. It is also widely believed that the clinical outcome of a child diagnosed with autism is partially determined by the intensity and scope of early interventions.

One topic which has received scant investigation is the role that parents play in this outcome. Due to the tragic misconception in past decades that "refrigerator mothers" were to blame for causing their children's autism, there has been a particular sensitivity at looking at the mother's role in the child's progress. Nevertheless, there is some evidence that autistic children achieve better language acquisition when the

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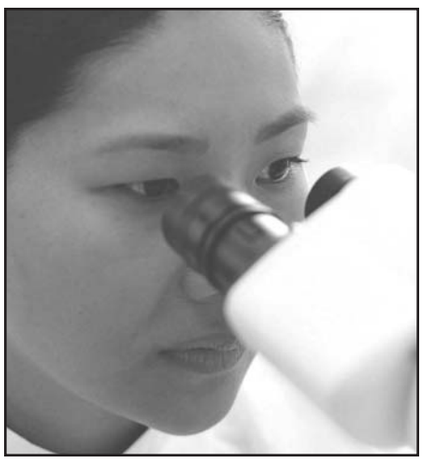
caregiver is able to establish better joint attention. Although there have been many intervention programs which include the parent in home programming and train parents to utilize interventions based on applied behavioral analysis or "floor play", there has been no attention given to the factors which may make the caregiver more effective.

Dr. Alice Carter, of the University of Massachusetts in Boston, as part of a large prospective study, is looking at the family and environmental factors that predict better outcomes in autistic children. In her study, Maternal Sensitivity, Joint Attention and Gains in Language Acquisition in Toddlers Diagnosed with Autism, Dr. Carter will study "maternal well-being" and its impact on the child's prognosis. At the same time that a family - and, most frequently, the mother - of a newly diagnosed child is being called upon to provide many hours of intensive early intervention, the family is also going through perhaps the greatest emotional trauma they have ever experienced. Dr. Carter will also study those factors that provide support to the mother and correlate that also with the child's outcome. By studying these factors, there is likely to be a greater awareness and sensitivity among clinicians as to how to better treat issues affecting the whole family and support a better outcome for the child with autism.



Brain Development and Neuroscience

Since autism is a developmental disorder, it is crucial to better understand the abnormal developmental course that has taken place. When NAAR was established in 1994 this was not even a topic of investigation. There were no neurobiologic hypotheses being discussed, this despite the fact that the 1990's was the so-called "decade of the brain." Over the ensuing years, NAAR began "seeding" the field and encouraged many "brain" scientists to focus their research on autism spectrum disorders. Our challenge remains to find that basic developmental error, model it and prove that this is the origin, or one of the origins, of autism spectrum disorders.

In the 2003 funding cycle, NAAR is supporting eight new research proposals - all on different topics - any one of which could provide the needed clues to understanding the origins of the disease.

In the spring 2003 issue of NAARRATIVE, we highlighted the research of **Dr. Manuel Casanova**, who recently joined the faculty at the University of Louisville. In brief, Dr. Casanova's previous work has demonstrated the presence of abnormalities in individuals with autism in the brain cortex's minicolumns. Dr. Casanova found the minicolumns to be smaller and more numerous in individuals with autism than in controls. As minicolumns are believed to be the most fundamental processing unit in the brain, this abnormality could have far reaching effects and be a central finding in understanding autism. In his 2003 NAAR-funded study, Macroscopic Correlates of Minicolumnar Abnormalities in Autism, Dr. Casanova will utilize the collection of 26 autism brains secured through the Autism Tissue Program - a brain tissue donation program established by NAAR in 1998 and now co-funded by the M.I.N.D. Institute - that have received postmortem MRI scans. He intends to study many anatomic areas and also correlate the anatomy with the microscopic features of the minicolumns in these same brains. This could lead to a greater understanding of the developmental mechanisms that produce these abnormal findings.

When structural abnormalities are identified in the brains of individuals with autism, it begs the question of how the brain developed that way, or, as any parent might ask, "what went wrong?" It is only when this question is answered that scientists will be able to investigate ways of potentially interrupting the development of abnormal pathways. **Dr. Susan Birren**, of Brandeis University in Walthan, MA, advances the hypothesis that the cholenergic nervous system may be involved in this abnormal development. Four areas of the brain that are known to be anatomically abnormal in autism-- the cerebral cortex, the cerebellum, the amygdala and the hippocampus-- are all connected to and influenced by the cholenergic system. There has also been research evidencing abnormalities in the

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2003 Research Partners

Each year, NAAR benefits from the generous support of many individuals and organizations who, as Research Partners, take a leadership role in supporting biomedical research. NAAR's Research Partners provide major funding for pilot studies, mentor-based fellowships and collaborative programs.

Autism Coalition for Research & Education

NAAR is once again grateful for the support of the Autism Coalition and their embrace of biomedical research. In 2003, the Autism Coalition sponsored the following pilot studies:

Poul Thorsen, M.D. Ph.D.
NANEA at Department of Epidemiology and Social Medicine/Aarhus University (Denmark)
"Exposure to Pharmaceuticals in Pregnancy & Development of Autistic Disorder"

Karl Herrup, Ph.D.
Case Western Reserve University, Cleveland, OH
"The Engrailed-2 Mutant as a Model of the Neuropathology of Autism"

James Millonig, Ph.D.
University of Medicine & Dentistry of New Jersey/Robert Wood Johnson Medical School, Piscataway, NJ
"Studying Mouse Cerebellar Development as a Tool to Identify Autism Susceptibility Genes."

Autism Coalition & Solving the Mystery of Autism Foundation

This year, the Autism Coalition teamed up with the Solving the Mystery of Autism Foundation to co-sponsor the following study. NAAR greatly appreciates their support.

Susan Christian, Ph.D.
University of Chicago, Chicago, IL
"Identifying Small Chromosomal Rearrangments in Autism Using Microarrays"

Dan Marino Foundation

The Dan Marino Foundation has been a solid supporter of NAAR for years, especially in the area of infant siblings research. NAAR is again grateful for their support.

Lonnie Zwaigenbaum, M.D.
McMaster University, Hamilton (Ontario)
"Investigating the Emergence of Familial Traits in Autism"

Nancy Lurie Marks Family Foundation

The Nancy Lurie Marks Family Foundation has been one of NAAR's longest and biggest supporters and has been instrumental in the organization's growth. NAAR is grateful for their support and guidance. In 2003, the NLM Family Foundation sponsored the following projects:

John Welsh, Ph.D.
Oregon Health & Science University, Portland, OR
"Inferior Olive & Autism: Electrical Synapses, Neuronal Synchrony & Cognition"

Michelle Dunn, Ph.D.
Albert Einstein College of Medicine, Bronx, NY
"Understanding Cortical Auditory Processing Abnormalities in Children with Autism"

Timothy Roberts, Ph.D.
University of Toronto, Toronto (Ontario)
"MEG Correlates of Linguistic Processing at and Below the Word Level in Autism"

Manuel Casanova, M.D.
University of Louisville, Louisville, KY
"Macroscopic Correlates of MiniColumnar Abnormalities in Autism"

Richard & Susan Smith Family Foundation

NAAR is fortunate to have been a long-time beneficiary of the Richard & Susan Smith Family Foundation and is honored that the organization is a supporter of autism research. NAAR is again very grateful for their support.

Susan Birren, Ph.D.
Brandeis University, Waltham, MA
"Regulation of Cortical Synaptogenesis by Basal Forebrain Cholinergic Neurons"

The Michael & Cynthia Moran Family & Friends

NAAR is grateful for the support of Michael and Cynthia Moran and for their decision to become Research Partners in 2003.

Michael Cuccaro, Ph.D.
Duke University Medical Center , Durham, NC
"Retrospective Association Analysis of Children with Idiopathic Autism Spectrum Disorders Treated with Fluoxetine"

Canadian Research Partnership

Collaboration with NAAR and the CIHR Fosters Next Generation of Autism Researchers

by Remi Quirion, Ph.D.
Scientific Director, Institute of Neurosciences, Mental Health and Addiction

A promising partnership for funding and developing an international research agenda that encompasses all aspects of autism research has recently been initiated by the National Alliance for Autism Research (NAAR) and the Institute of Neurosciences, Mental Health and Addiction, one of the Canadian Institutes of Health Research (CIHR). The objective is to train the next generation of autism researchers.

Together, these organizations will invest approximately $2.4 million (USD) over the next six years for two collaborative training programs in autism research - the first of their kind in Canada.

The mentor-based programs, based at McGill University in Montreal and Queen's University in Kingston, take a multi-disciplinary approach to foster investigations into the genetics underlying autism and the epidemiology of the disorder. They will also address the importance of delivering effective treatment options to those who suffer from autism spectrum disorders (ASDs) and their families.


Dr. Remi Quirion

A mysterious brain disorder that affects people of all racial, social and economic backgrounds, autism displays a wide spectrum of symptoms and disability. So far, there is no cure. People who suffer from autism are often robbed of the ability to communicate, to form emotional bonds and to engage in normal social interactions.

In addition, they often engage in repetitive behaviors and are dependent on rigid daily routines.

For autism, making a timely diagnosis is a challenge. No blood test, brain scan or physical measurement exists that can identify ASDs. They are largely genetic disorders and strike males about four times more frequently than females.

The Autism Society Canada (ACS) estimates that 105,000 Canadians suffer from an autism-related disorder, costing Canada an average of over $3 billion (CDN) annually.

Queen's University Site

Dr. Jeanette Holden is a principal investigator with the Autism Spectrum Disorders - Canadian-American Research Consortium (ASD-CARC) and a professor cross-appointed to the departments of Psychiatry and Physiology at Queen's University. She has studied ASDs for 21 years and is leading one of the training programs funded by NAAR and CIHR. The program led by Dr. Holden, which is called the "Inter-Institute Interdisciplinary Training Program in Autism Spectrum Disorders," is designed to provide interdisciplinary research training related to ASDs to the students, post-doctoral fellows and clinicians who will comprise the next generation of autism researchers.

"We hope that introducing trainees to faculty in different locations will help them develop a sense of belonging to a research community and they will choose to continue doing research on ASDs after their formal training periods are finished," said Dr. Holden.

The trainees will be led by a group of 45 mentors from 17 institutions across Canada and the US. Collectively, their expertise ranges from ASDs to other fields such as neuropathology, imaging and immunology. Although the training program will focus on ASDs, Dr. Holden hopes it will act as a model that may be applied to other complex neuro-developmental disorders.

"With this interdisciplinary approach we are creating a novel learning environment," said Dr. Holden.

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"In academia many of us tend to be monodisciplinary, but the dissemination of knowledge is very important and you can't learn it early enough."

The program is multidisciplinary on many levels, from the nature of the supervisory committees to the nature of the research. Trainees will pursue two inter-related research projects with two different supervisors. The first project will investigate a topic that is most appropriate to their training, whereas the secondary project will provide an introduction of a complementary approach to the same topic. So, while a Ph.D. student may do a genetic study as part of his or her main project, the second project may be related to eye-tracking or communications research.

Trainees will also be required to take a new course on ASDs, being developed from experts from among the mentors and other participants, and will communicate on a regular basis using videoconferencing and electronic technologies. Bi-monthly research seminars and work with local autism societies are also part of the curriculum.

"We want to foster close ties with the ASD community and ensure that trainees are able to speak to lay audiences," said Dr. Holden.

Trainees will be required to give a seminar on their research to members of local autism societies and write short articles for the ASD-CARC's newsletter. They will also be encouraged to volunteer with local autism societies for special events and attend special presentations at their meetings.

Dr. Holden has a personal connection with autism - her brother has autism, as do some of the children of her many research assistants. She is examining physical commonalities among people with ASDs to subgroup and phenotype families. Dr. Holden and her team are planning to use three-dimensional imaging techniques in order to look for facial landmarks.

Like any disorder for which there is no cure, there is a wealth of opinion and information available on the Internet, not all of which is from a reliable source. For Dr. Holden, it is also important that the trainees in her program learn to evaluate information published by all communities.

"Parents of children with ASDs are understandably anxious to try something that might change their non-verbal children into verbal ones," said Dr. Holden. "We feel it is important that families be provided with up-to-date information on the scientific validity of new 'cures' or treatments, so that they can make informed decisions about using or considering such treatments."

McGill University Site

Developing the future of autism research and addressing the lack of an integrated curriculum for future ASD researchers is also a pressing objective for Dr. Eric Fombonne, the head of Psychiatry at the Montreal Children's Hospital site of the McGill University Health Centre. Dr. Fombonne is leading the other training grant in autism research from McGill University and the Montreal Children's Hospital. In addition to funding from NAAR and CIHR, this grant is also supported by Le Fonds de la recherche en santé du Québec (FRSQ).

"I became concerned with the lack of proper understanding and services for these children and their families in the mid 1980s when I worked in France," said Dr. Fombonne, who is also a Canada Research Chair in Child and Adolescent Psychiatry. "At that time, professionals still held obsolete views on this disorder, based on Freudian theories, despite the growing evidence for the neurobiological basis of autism."

Through the program, Dr. Fombonne says he hopes to attract trainees from multiple disciplines in autism research, to develop a training track for autism and to boost Canada's research capacity in autism.

The program focuses on laboratory and clinical research and will be led by 22 mentors from seven Canadian universities, specialists in molecular genetics, neuroimaging, neuropsychology, brain pathology and epidemiology. Other experts work in biological, clinical and assessment studies, as well as early screening and detection.

Dr. Fombonne's trainees will develop their projects under the guidance of two supervisors, one who will direct the lab where the trainee will be based and an external supervisor preferably chosen in a different discipline. The yearly curriculum will include a 10-day summer school, a new national autism research conference and two invited international speaker events.

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Dr. Fombonne also plans to encourage trainees to develop careers as independent researchers in autism.

"Until now there was no training on autism per se in Canada," he said. "Someone who wants to do research on autism has to get bits and pieces of training here and there, on the psychosocial aspects, on neuroimaging, genetics, neuropsychology and epidemiology."

In six years, Fombonne and his team anticipate training at least 50 new investigators.

CIHR forged successful and rewarding collaborations with both NAAR and the Autism Society Canada in 2002.

Along with other supporters such as NAAR, CIHR contributed financial support to the Canadian Autism Research Workshop, hosted by the Autism Society Canada. The workshop provided a forum by which to present the latest information on ASDs and develop a Canadian autism research agenda to ensure funding and increase the quantity and quality of autism research.

As a result of the workshop, the Society published the White Paper, a strategic plan for guiding the implementation of the research agenda, soon to be published on the Society's website, which is located at (www.autismsocietycanada.ca).

Our partnerships with NAAR, ASC, and the other institutes comprising CIHR have built a strong and robust foundation for a unique, groundbreaking autism research agenda in Canada.

We gratefully acknowledge the dedication of these partners to the field of autism research and have been the fortunate recipients of their enthusiasm and boundless knowledge and experience base in this initiative.

We at CIHR are also proud of our scientists and their innovative approaches to health research. Researchers such as Dr. Holden, Dr. Fombonne and their teams have demonstrated a high level of expertise and long-standing commitment to autism research.

Together, we will continue to work together to position Canada as a leader in autism. ❖

What is the CIHR?

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

The Canadian Institutes of Health Research is Canada's premier agency for health research. Its objective is to excel, according to internationally accepted standards of excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened health care system. A governmental agency, the CIHR is similar to the National Institutes of Health in the U.S.

The Institute of Neurosciences, Mental Health and Addition supports research to enhance mental health, neurological health, vision, hearing, cognitive functioning and to reduce the burden of related disorders through prevention strategies, screening, diagnosis, treatment, support systems and palliation. Associated research supported by the Institute is designed to advance our understanding of human thought, emotion, behavior, sensation, perception, learning and memory.

NAAR expresses its sincere thanks to Dr. Quirion for contributing the article on the Autism Training Programs for NAARRATIVE.

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cholenergic receptors in autism. A third data point is that there has been one study in autism showing very high levels of BDNF. BDNF is a neurotrophic factor - a growth factor that guides the brain in development. There is evidence from Dr. Birren's lab to show that BDNF is important in the growth and development of the cholinergic system. Combining all of these clues, Dr. Birren's NAAR-funded project, Regulation of Cortical Synaptogenesis by Basal Forebrain Cholinergic Neurons, intends to investigate the effects of BDNF and the cholenergic system on brain development and to investigate if this could be a model for the abnormalities found in autism.

Although there have been tremendous advances in neuroscience over the past decade, there remains much that scientists do not understand. Until quite recently, many of the areas of the brain that are affected in autism received little attention by neuroscientists. One brain area that is emerging as very important for autism spectrum disorders is the amygdala. The amygdala is a very small structure but one that has great importance especially for social skills. Various lines of investigation, including behavioral, structural scanning, brain tissue and animal models, all point to the amygdala as an important area to study in autism. As with the cholenergic system, there has been scant research about the neurodevelopment of the amygdala, even in the typically developing brain. **Dr. Kenneth Campbell**, of the Children's Hospital Research Foundation in Cincinnati, will study the development of the amygdala in his study, Genetic Control of Mammalian Amygdalar Development. This is a crucial step if we wish to understand the developmental abnormalities that cause autism.

The cerebellum is another area of the brain that has been implicated in autism spectrum disorders. In his project, Studying Mouse Cerebellar Development as a Tool to Identify Autism Susceptibility Genes, **Dr. James Millonig**, of the University of Medicine and Dentistry of New Jersey, proposes to use three different mouse models to study abnormal cerebellar development. He further will investigate the genes that have a role in cerebellar development. At last fall's annual meeting of the Society for Human Genetics, Dr. Millonig reported an association with a mutation in the "Engrailed-2" gene in individuals with autism. Through these three lines of research - the cerebellar abnormalities found in autism found through the study of post-mortem brain tissue, the abnormalities found in animal models and human genetic findings - a strong case for the neurodevelopmental cause for autism spectrum disorders can be established.

In the 2003 funding cycle, **Dr. Karl Herrup**, of Case Western University in Cleveland, is being funded for his second NAAR grant. This is a follow-up to his initial project which was to study the cerebellar patterning found in a mouse model lacking the Engrailed -2 gene. The Engrailed -2 gene is a very early developmental gene and the same gene that Dr. Millonig has associated with autism. "Patterning" refers to how the cells line up in space. For example, imagine the difference between a nice formal arrangement of patio tiles versus patio tiles that are bunched up one on top of the other in a seemingly scattered fashion. Dr. Herrup has recently found that, in addition to the cerebellum, there are similar patterning abnormalities in the amygdala of individuals with autism. This would suggest that two brain areas with abnormalities in autism can both be affected by the Engrailed-2 gene. In his new NAAR grant, The Engrailed-2 Mutant as a Model of the Neuropathology of Autism, Dr. Herrup will advance his preliminary work on the patterning in the amygdala.

Rather than focusing on one particular part of the brain, **Dr. Peter Scheiffele**, of Columbia University in New York, will research synapse formation - one of the functions of brain development. When one neuron needs to communicate or send a message on to the next neuron it communicates through a close junction called a synapse. In early childhood the brain is very active forming-and also destroying-- synapses. The brain "rewires" itself during that period of time when autism is typically first diagnosed. The later onset of the illness (rather than being noted from birth) may be attributable to an alteration in this synapse formation processing. Recently, two families with autistic children in Europe were noted to have mutations in a gene responsible for producing a protein called neuroligin. Neuroligins are responsible for regulating the formation of synapses and the dendritic spines. In his study, Frequency and Functional Characterizations of Neuroligin Mutations, Dr. Schieffele will study a population of autistic subjects genetically to look for the frequency of mutations of the genes for neuroligins.

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He also will study the developmental effects on neurons of genetic mutations of this protein.

Dr. John Welsh, of the Oregon Health and Science University in Portland, is undertaking another study focusing on synapse functioning called, Inferior Olive and Autism: Electrical Synapses, Neuronal Synchrony and Cognition. In the brainstem, there is a structure called the "inferior olive," which has been found to be abnormal in autism. This structure seems to have a very important function in sensory perception. The cells of this structure produce an occilation that is thought to be a "cognitive clock". In other words, it is responsible for the brain's ability to perceive individual events that happen very quickly in time. If this system is not functioning correctly, some scientists believe that the brain cannot separately perceive events that occur faster than 500 msec (one half second) apart. Studies have shown that 6-month-old babies, in communicating with parents, interact at about one event per second. However, as the child matures, this becomes faster and exceeds the half second per event speed. Perhaps the "lack of interest" in responding to social cues that is noted in individuals with autism is really a manifestation of their brains' inability to process cues that are happening too rapidly in time. Dr. Welch's research bears a similarity to Dr. Roberts' research on the auditory system in autism that was discussed earlier. That research also demonstrated an inability in individuals with autism to process sounds that occur too fast.

Using rats, Dr. Welsh will use a novel model to disrupt the synaptic functioning in the inferior olive and then will test the rats' ability to perceive rapidly occurring stimuli. If his hypothesis is substantiated, this research could point to new targets for treatment for the cognitive and social impairments noted in autism.

There have been many reports documenting various abnormalities in the immune system in individuals with autism. Despite this, there has been no research regarding how the immune system might be affecting the brain in order to cause the problems characteristic of autism.

Dr. Payam Rezaie, of the Open University in England, proposes to do this in his project, Assessment of the Glial Response Within the Cerebral Cortex in Autism. Although the vast majority of brain research focuses on neurons (nerve cells), which appear to be the main functioning cells of the brain, there is another very significant and numerous type of cell in the brain called "glial cells". Glial cells are associated with the immune system and, in the brain, are thought to play a role of supporting the neurons. Glial cells, however, can take on the immunologic role if needed. Dr. Rezaie will study these cells in depth using tissue from the Autism Tissue Program. He will be collaborating and sharing tissue with Dr. Christoph Schmitz who was awarded a NAAR Research Award last year to produce a "brain atlas" of autism.

Social Impairments

Although, by definition, there is a deficit in social skills evident in individuals with autistic disorder and Asperger Syndrome, it is not clear what exactly those social deficits are. Furthermore, there may be many types of social skills deficits and it is not known whether all of the affected individuals have similar social problems. One reason for the lack of knowledge in this area is the absence of a good measuring tool for social deficits. To date, the tests tend to be rather specific and cannot measure the broad range of deficits. A new instrument has been developed in Germany and has been tested on schizophrenic subjects.

Dr. Antonio Convit and his collaborators at the New York University School of Medicine in Manhattan, propose to test this instrument on a group of individuals with Asperger Syndrome. In the project, Social Cognition and Brain Volumes in Asperger Syndrome, Dr. Convit and his team will use this new instrument. The subjects are tested with a naturalistic video-based test that has the breadth to measure many social parameters, including the ability to read emotions, thoughts, intents, nonverbal and literal speech, and other parameters. The group will also measure various brain regions involved in social awareness using structural MRI. They hope to correlate particular areas of the brain with specific deficits in social awareness.

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One of the social parameters that Dr. Convit will study involves "Theory of Mind." Generally, people understand that other individuals have minds and can, to some extent, put themselves "in the other person's shoes" to anticipate what they are thinking. Without this ability to "mind read," it would be very difficult to function in the world. Individuals with autism spectrum disorders are notoriously lacking in this skill. In fact, this "mind reading" ability seems to have very little correlation with other parameters, such as intelligence.

It appears somewhat counterintuitive that there would be a discrete neurologic function to mediate this very complex ability to know others' minds. **Dr. Elise Temple**, of Cornell University in Ithaca, NY, intends to study "theory of mind" using fMRI. In her project, Neural Mechanisms Underlying "Theory of Mind": fMRI Studies of Normally Developing and Autistic Children, Dr. Temple will study typical children's ability to do "theory of mind" tasks and to determine which parts of the brain are typically utilized to perform such tasks. Thus far in autism, this has been studied primarily in adults. Interestingly, neurotypical three-year-olds cannot perform "theory of mind" tasks but neurotypical four-year-olds can. By developing the methodology to study "theory of mind", Dr. Temple hopes to gain insights into what could be a very important developmental abnormality in autism spectrum disorders.

Another mysterious characteristic that is disproportionately present in young children with autism is the failure to imitate. One of the first interventions undertaken with newly diagnosed autistic children is to "teach" them motor imitation. Although this function generally improves as the child gets older, many continue to learn better by using "hand over hand" teaching. This pre-empts the need for imitation skills and allow the skill to be learned through a different neurologic pathway. Little is known about the neurobiology of imitation, but recently a type of cell called the mirror neuron has been identified. These cells seem to respond equally to both seeing an action and doing an action. It seems as if these could be the link between observing and actually undertaking an action. Further, much like with the auditory system discussion above, there appears to be a more sophisticated brain system called the “cognitive representational system,” which mediates more sophisticated imitation skills. This may be close to the analogy between sound processing and language.

In his project, Functional Neuroimaging Studies of Action Facial and Object-directed Imitations, **Dr. Justin Williams**, of the University of Aberdeen in Scotland, will study the neuronal correlates (mirror neurons) of several different types of imitation-based tasks using fMRI. In one component of the study, Dr. Williams will lower the serotonin levels in the brain and document imitative skills to see if that neurotransmitter is involved with imitative systems. Imitation may be more important than it appears at face value in that it may be the brain's way of creating a "language" for social understanding.

Another striking finding which appears specific to autism is the difficulty in facial recognition. There is widespread agreement that individuals with autism utilize unusual brain pathways when looking at faces. To further understand the cause and significance of this finding, **Dr. Patrick Bolton,** of King's College in London, in his second NAAR award in 2003, will study children with tuberous sclerosis. A sub-population of patients with tuberous sclerosis also have autistic-like presentation. Dr. Bolton has found that the patients with tuberous sclerosis and autistic characteristics have abnormalities in facial recognition and an unusual brain mechanism to process faces. He believes that the group with autistic symptoms uses a neuronal mechanism also used in very young neurotypical infants (4 months old). As infants mature, they develop more sophisticated neuronal pathways. In this project, Event-Related Potential and Behavioral Investigations of Face Processing in Individuals with Tuberous Sclerosis and Autism, Dr. Bolton will study various face processing tasks using evoked electrical potential. By differentiating the subtypes of tuberous sclerosis, Dr. Bolton will study the development of autistic symptoms and facial recognition deficits in a very young sample who are at high risk of autistic symptoms.

Another hypothesis which might explain the social difficulties typical in individuals with autism spectrum disorders is that there are abnormalities in vagus nerve functioning. There are two types of "autonomic," or involuntary, nerves in the body.

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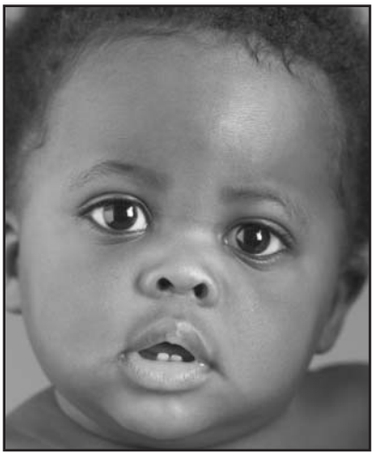
One is the "sympathetic nervous system" well known to control the "fight or flight" response.

The other is the "parasympathetic nervous system". This system is engaged to undertake our more "sustaining" functions, like digestion. The theory is that the parasympathetic nervous system needs to be functioning at an optimal level in order for an individual to engage in social contact. The most important nerve in this system is called the vagus. This nerve needs to function properly in order to have successful functioning of the digestive system, the immune system and the cardiac system, among others.



In his project, Vagal Tone and Social Behaviors in Children with Autistic Disorders, **Dr. Stephen Sheinkopf**, of Brown University in Providence, will - for the first time -measure vagal tone in individuals with autism to determine if the parasympathetic system is functioning normally. If the system is malfunctioning, it could be a cause underlying the lack of social awareness and attention observed in autism. Vagal tone can also be easily measured in very young children and infants and could help us understand the developmental course in autism.

Pregnancy Risk and Early Infant Development

There is strong evidence that the abnormal brain development in autism may occur as early as the first trimester of fetal life and continues through the first year after birth. Since 1997, when we first started supporting infant research in autism, NAAR has continuously expanded its funding commitment to this critical early period in human development. Since autism is typically not diagnosed until at least the second year of life, researchers had little opportunity to study children prior to diagnosis. NAAR has therefore committed to funding research of "baby siblings"- the infant siblings born into families who already have an affected child. Since these families have an estimated 5-10% chance of having a second child with autism, they present a unique opportunity to study a "high risk" population prospectively from birth.

NAAR will continue to support the research of **Dr. Lonnie Zwaigenbaum**, of McMaster University in Hamilton Ontario. In 2003, NAAR is funding his pilot study entitled, Investigating the Emergence of Familial Traits in Autism. Dr. Zwaigenbaum and his collaborators in Toronto and Halifax have already enrolled 140 baby siblings of autistic children and are expected to enroll a total of 250 siblings. The unprecedented evaluation of hundreds of high risk, but undiagnosed young children presents new opportunities, such as determining whether certain traits of the older diagnosed sibling make it more or less likely that the infant sibling will also receive a diagnosis. In addition, the researchers will attempt to more accurately create subtype categories of autism, given their ability to observe and evaluate the children from infancy and to secure DNA to genetically correlate these potential subtypes.

In another "baby sibs" project, **Dr. Jana Iverson**, of the University of Pittsburgh, has been funded for her project, Early Identification of Autism: A Prospective Study. In this study, Dr. Iverson will focus on the motor skills of the infant siblings as well as their ability to vocalize. Hand movements are highly correlated with verbal language. In very young children, meaningful hand gestures predate spoken language. New to autism research, Dr. Iverson is interested in studying whether there is a link between the malfunctioning of these two systems in autism. As Dr. Iverson has been awarded an NIH grant to study motor skills and vocalization in children who are not at risk, she will already have a "control group" against which to compare the high risk siblings of autistic children.

The underpinnings of social competencies are believed to be related to some of the very basic and early developing neurologic functions. One example of this is a baby's ability to shift focus. In a social context, shifting focus in a perfectly timed way is needed to observe facial gestures and to relate them to events occurring in the environment. Deficits in "shared attention" are a well described and somewhat unique finding in autism. Unfortunately, little is known about the development of these brain skills in typical children and we therefore

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have a hard time characterizing where autistic children diverge. In their study, The MESA Project: Modeling the Emergence of Joint Attention, **Dr. Jochen Triesch** and his colleagues at the University of California at San Diego, will use sophisticated technology to study these phenomena in detail. They will study infants age 3 months to one year old using "high tech" recording devices to investigate the timing and sequence of even subtle movements of the children in relation to their mothers and their environment.

Dr. Triesch hypothesizes that autistic children "need" a greater degree of predictability than other people can offer in a social situation. In order to test this, they will have a robot which will interact with autistic children in the 3-4 year old range. The robot will act either in a highly predictable or in an unpredictable fashion. The response of the children will be studied. The underlying deficit which leads to social impairments could be of great importance if treatments are to be targeted efficiently.

The above studies on very young children can prove extremely valuable in providing important clues as to what is going awry in early brain development. We face a problem, however, in that there are so many parameters which need to be researched. Obviously, for ethical reasons, there is a limit to the amount of research which can be done on children. Consequently, scientists like **Dr. Laura Hewitson**, of the University of Pittsburgh, in her study, Autism in Primates: Genetics vs. Environment, use animal models-in her case, the rhesus monkey-- to study early development. Dr. Hewitson intends to make genetic models based on the candidate genes which have been reported in autism. Using these models, Dr. Hewitson and her colleagues can do a great deal of in-depth study. Specifically, they will monitor nervous system development (autonomic, motor and sensory), learning abilities, social emotional development, immune system development and skeletal growth. In addition, they will using scanning techniques including PET and very high resolution MRI (which can visualize down to single cell) to study brain development. Their findings may provide a guide as to how to design human studies in order to test and confirm their genetic models.

Epidemiology

In addition to studying the single organism for evidence of disease, another powerful research approach is to look at whole populations. By identifying trends and associations among large numbers of individuals, it is possible to prove causality. As part of our 2003 awards, NAAR is funding three such studies.

Dr. Hill Goldsmith, of the University of Wisconsin at Madison, is the investigator on a study entitled, A Birth Register-based Twin Study of Autism Spectrum Disorders. This study will "piggy-back" on to an already funded twin study in which researchers are tracking all twin births in the state of Wisconsin. They intend to use their sample for many studies, including genetics and brain functioning. Previous twin studies provided scientists with the most convincing evidence of a genetic component to autism. Dr. Goldsmith and his colleagues will attempt to replicate that data on a new sample and extend the result to fit new broader diagnostic criteria, including what is known as the "broader phenotype". The study of twins, including "discordant twin" (that is, genetically identical twins only one of whom has a diagnosis of autism) provides a very important method for separating the genetic from the environmental causes of the disease.

Dr. Poul Thorsen, of Aarhus University in Denmark, will again be funded to use his enormous population-based sample to study another important issue in autism. Dr. Thorsen previously reported on his earlier research evidencing a lack of correlation between the measles, mumps, rubella (MMR) vaccine and the prevalence of autism in Denmark. In his new project, Exposure to Pharmaceuticals in Pregnancy & Development of Autistic Disorder, Dr. Thorsen will focus on prescription drugs taken before and during pregnancy. In his population sample of over a half a million subjects, he will have more than 400 children with autism and approximately 600 children with autism spectrum disorders. This will be the first study of its kind and may lead to the identification of contributing environmental factors in autism spectrum disorders.

There have been two previous studies that found a higher incidence of autism in births in which the mother and child had Rh blood factor incompatibility.

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In his project, Maternal-Fetal Incompatibility and Autism Risk, **Dr. Peter Zandi,** of the Johns Hopkins School of Public Health in Baltimore, will further investigate this issue by examining genetic issues which might be a confounding factor. This methodology was recently used in schizophrenia research and suggested that, in that disease, Rh incompatibility does appear to be a risk factor.

Pharmacology Interventions

Although we hope that an ultimate treatment or cure for autism emerges from research efforts, at the present time families and affected individuals are in need of immediate relief from its symptoms. Over the past decade, there have been tremendous advances in psychopharmacology; however, these advances have not encompassed the autism spectrum disorders. Currently, there is still not one medication approved for use in autism. At this point, the pharmaceutical industry has given little indication that they intend to study and develop medications specifically for autism. Nonetheless, there are medications available which could have immediate and, at times, dramatic and beneficial effects for individuals with autism spectrum disorders. There is an enormous need to rigorously test the risks and benefits of various medications rather than continue to rely on the individual physician's best judgment as to which medications work and which do not.

NAAR is therefore funding three research projects focusing on pharmacology interventions.

Dr. Sherie Novatny, of Mt. Sinai School of Medicine in New York, is being funded for her project, Galantamine vs. Placebo in Childhood and Adolescent Autism. Galantamine works on the cholenergic system and there previously have been two studies of brain tissue which suggest that individuals with autism evidence abnormalities in the cholenergic system. There have also been three previous studies of cholinergic medications in autism. Two of them were small, "open" studies (that is, the medication was not compared to placebo by raters who were "blind" to who was receiving medication and who was receiving placebo) and the third study was a "double-blind" study. Since all three studies evidenced some benefit to the recipients, there is a need for further high quality research to assure the benefits of these medications in autism.

Some of the most commonly used medications in autism are the class of medications known as the SSRIs ("select serotonin reuptake inhibitors").These are medications that enhance the functioning of the serotonin system in the brain. Some children and adults with autism spectrum disorders benefit significantly from these medications (like Prozac, Paxil, Zoloft and others) while others seem to secure little or no benefit from these same medications. **Dr. Michael Cuccaro**, of Duke University in Durham, NC, in his study, Retrospective Association Analysis of Children with Idiopathic Autism Spectrum Disorders Treated with Fluoxetine, proposes to try to better understand these divergent responses by studying the genetics of autistic individuals who respond to fluoxetine (better known as Prozac) in comparison to those individuals who do not. The ultimate goal of such research is to be able to appropriately select the right medications for each individual. This type of research, however, also offers the potential to better characterize autism "subtypes". Dr. Cuccaro and his colleagues hypothesize that there is a subtype of autism which responds to SSRIs and that those individuals will evidence different genes than those who do not similarly respond.

Another project which seeks to understand the role of serotonin in autism is being led by **Dr. Xiaoxi Zhuang**, of the University of Chicago, in his study, Behavioral Effects of Hyper and Hypo Serotonergic Function in Transgenic Mouse Models. Although there is ample evidence of abnormalities in the serotonin system in autism, the exact nature of the abnormality remains unknown. In fact, it is not entirely clear whether there is too much serotonin or too little. To further complicate the situation, at different developmental stages serotonin levels will have varying effects on the brain. In order to further investigate this very complex problem, Dr. Zhuang will use mouse models which will have a gene manipulated to both over and underproduce

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serotonin. The gene is called SERT and is responsible for the serotonin transporter. Dr. Zhuang will research under which serotonin conditions the mice will simulate the pathology seen in autism.

Environmental Factors in Autism Spectrum Disorders

Although it is generally accepted that genetics play a role in the causation of autism spectrum disorders, twin studies also suggest that environmental factors may also be implicated.

In his study, Placental Metabolism and Fatty Acid Homeostasis in Fetal Imprinting of Autism and Autism Spectrum Disorders, **Dr. Thomas Cook** of Rutgers University will utilize an innovative model to test the hypothesis that a toxin could interrupt the proper functioning of enzymes in the placenta. Dr. Cook hypothesizes that this would have the direct effect of altering the metabolism of "essential fatty acids." There has been one prior study linking abnormalities in essential fatty acids with autism. Dr. Cook and his colleagues will be using a chemical known as DEHP (a plasticizer) which is found widely in the environment as a model for such placental derangement.

2003 Roland D. Ciaranello, M.D. Memorial Award in Basic Research

Laura Hewitson, Ph.D.
University of Pittsburgh
Pittsburgh, PA

"Autism in Primates: Genetics vs Environment"

While limited scientific evidence exists that demonstrate essential fatty acids as an etiologic agent for autism, this proposal presents an interesting and valid hypothesis for examining a potential cause. NAAR remains committed to aggressively funding research that addresses a wide variety of research, including proposals examining environmental risk factors, when our Scientific Advisory Board determines the proposals are promising and scientifically rigorous.

Genetics

Of all the etiologic hypotheses of autism, a genetic contribution continues to be the one with the most credible and substantial scientific evidence. For this reason, NAAR recently announced the launch of an international genetics collaboration, the NAAR Autism Genome Project (a related story on this project is featured in this issue of NAARRATIVE). In addition to this research partnership with the NIH, NAAR is funding three pilot studies which comprise work that is specific and complementary to that larger project. The search for "autism genes" comprises both whole genome scans as well as the search for specific "candidate genes" premised on our knowledge of the biology of autism.

One such candidate gene is the FOXP2 gene. This gene is intriguing in that it is known to have a role in brain development and is located on chromosome 7 - an area of interest defined by prior genome screens. Research has also shown that a mutation of this gene has been associated with language impairment. Thus far, studies have failed to show an association of the FOXP2 gene with autism. In his study, Genetic Mutations Associated with Autism in Unexplored Regions of FOXP2, **Dr. Russell Margolis**, of Johns Hopkins School of Medicine in Baltimore, will search for mutations in this gene in autism by investigating previously unknown parts of the gene.

Although DNA is a miraculous substance largely responsible for life as we know it, it is also a chemical subject to routine insults similar to other substances. For example, DNA can break or chip or come apart and then recombine incorrectly. These events are called "chromosomal abnormalities" and are the known cause of several brain diseases. There have been many identified cases of chromosomal abnormalities in individuals with autism. The problem is that - thus far - no consistent pattern in the chromosomal abnormalities has been identified and, until recently, only relatively large abnormalities could be detected. With recent techniques, much smaller abnormalities can be discerned.

NAAR is funding two projects in this area: **Dr. Susan Christian**, of the University of Chicago, and her study, "Identifying Small Chromosomal Rearrangements in Autism Using Microarray" and **Dr. Eli Hatchwell**, of Cold Spring Harbor Laboratory on Long Island, NY and his study, "Genomic Copy Number Variation in Autism". It is hoped that these newly refined methodologies will identify chromosomal abnormalities that may cause some subtypes of autism. ❖

Science & Research: 2003 Mentor-Based Fellowships

MENTOR-BASED FELLOWSHIPS - In addition to the foregoing awards for pilot studies, NAAR also provided funding in 2003 for the following fellowships, continuing its unprecedented commitment to training the next generation of autism experts and attracting the brightest young investigators to the field.

PRE-DOCTORAL FELLOWSHIPS

Centre for Molecular Medicine & Therapeutics, Vancouver, British Columbia

"Mouse Models of Autism: Behavior and Genetics"

Mentor: Elizabeth Simpson, Ph.D.
Fellow: K.Y. Bibiana Wong

Using a genetic mouse model, information derived from this study is designed to offer a potential window of insight into the genetics of autism not found in human studies. Dr. Simpson and her fellow intend to establish a battery of tests that accurately characterizes autistic-like behaviors in mice and test specific hypotheses about known genes and gene combinations. The project will examine whether quantitative trait loci (QTL) mapping analysis can identify new genes involved in components of autistic-like behavior. The study aims to establish standardized high-throughput tests of affect in mice, a better understanding of genes leading to autism, and the confirmation and identification of autism candidate genes.

Vanderbilt University, Nashville, TN

"Genetic Analysis of Serotonergic and GABA-ergic Genes in Autism"

Mentor: James Sutcliffe, Ph.D.
Fellow: Jacob McCauley

This fellowship will perform a thorough, systematic genetic analysis of select candidate genes to test the hypothesis that variation or mutation in one or more of these genes contributes to risk for development of autism and related disorders. Dr. Sutcliffe and his fellow are identifying and screening genetic markers (single nucleotide polymorphisms) spaced throughout each of the genes selected for study. Using genetic data from these markers, alone and in (haplotype) combinations, they will test whether affected individuals in autism families more frequently inherit a particular version of the gene in question than you would predict by chance. Such a scenario would define genetic association, suggesting the particular version of the gene contains DNA sequence changes that affect the function of the protein product or expression of the gene.

University of Massachusetts, Boston, MA

"The Impact of Parental Autism-related Cognitions on Interventions"

Mentor: Alice Carter, Ph.D.
Fellow: Chantal Jennifer Kuhn

The goal of this fellowship is to learn more about mothers' experiences parenting young children with autism to develop more effective early intervention programs. Dr. Carter and her fellow are examining mothers' knowledge of autism, their insightfulness or the ability to take the perspective of the young child with autism (or the ability to explain his or her motivations, behaviors and emotions), and their sense of confidence in parenting as well as feelings of responsibility and of being an important and helpful agent in the child's development.

Johns Hopkins School of Public Health, Baltimore, MD

"Epidemiology of Autism Spectrum Disorders"

Mentor: Craig Newschaffer, Ph.D.
Fellow: Keely Cheslack-Postava

This project marks one of the first formal training programs in the U.S. to prepare doctoral students in epidemiology to study autism spectrum disorders. Dr. Newschaffer's fellow will work in the Maryland-Delaware Autism and Developmental Disabilities Monitoring (ADDM) Project, one of twelve CDC-funded autism public health surveillance projects. The fellow has the lead responsibility in the analysis of parental stress and will provide analytic support to the analyses of the autism screening questionnaire. In addition, she is responsible for administering one of the data collection components (data collection will include multiple interviews, clinical exams, record review, and biologic sampling) and will participate actively in all study meetings on site and across sites.

Universidad Miguel Hernandez, San Juan de Alicante (Spain)

"Immuncytochemical and Morphometrical Analysis of Double Bouquet Cells Microcircuitry in the Cerebral Cortex of Autistic Patients"

Mentor: Jorge J. Prieto, M.D., Ph.D.
Fellow: Edith Lopez Hurtado

This fellowship involves studies of brain tissue from the Autism Tissue Program with a focus on the anatomical and neurochemical basis of the impairments seen in autism. Dr. Prieto and his fellow will study possible changes in the cortical circuitry involving pyramidal cells and neurochemically identified interneurons in cortical areas of the brain. This approach would hopefully elucidate the controversy on the existence of morphological changes that could be responsible for the functional alterations and behavioral impairments seen in autism. Specifically, the project addresses the question of the overstimulation of the cerebral cortex seen in autistic individuals, as an alteration of the inhibitory cells that normally gate such excitation. Furthermore, the precise identification of the neuropathological substrate for the deficits in cognition and communication of the autistic individuals is an essential prerequisite to search for the genetic and/or environmental causes of the disease.

Princeton University, Princeton, NJ

"Multiphoton Investigation of Sensory Encoding in the Mammalian Cerebellum"

Mentor: Samuel Wang, Ph.D.
Fellow: Megan Sullivan

This project utilizes fluorescence imaging of the output axons of granule neurons, parallel fibers and seeks to understand how parallel fibers encode natural sensory stimuli. Dr. Wang and his fellow will examine both single parallel fibers and groups of parallel fibers. They will search for spatial patterns of parallel fiber activity, a phenomenon that has previously generated spreading synaptic effects, and

continued on page 21

which may play a role in sensory integration. Finally, they will search for conditions that modulate parallel fiber activity. By characterizing sensory encoding in the typical cerebellum, Dr. Wang hopes to gain a better understanding of sensory processing in the autistic cerebellum.

POST-DOCTORAL FELLOWSHIPS

Cambridge University, Cambridge (England)

"Social Emotional Processing"

Mentor: Simon Baron-Cohen, Ph.D.
Fellow: Christopher D. Ashwin, Ph.D.

This fellowship is investigating social-emotional information processing at different stages of cognition in adult participants with autism who are high-functioning and/or diagnosed with Asperger Syndrome as compared to a control population. The stages of cognition being examined include the preconscious stage, the early attention stage, and at memory/recall. Dr. Baron-Cohen hypothesizes that the multiple methods will show deficits that people with autism have in processing social-emotional information, and how this affects cognition and behavior in autism spectrum disorders.

University of Michigan, Ann Arbor, MI

"Quantitative Neuroanatomical Training: New Methods to Reveal Structural Changes in the Cortex of Individuals with Autism"

Mentor: Jeffrey Hutsler, Ph.D.
Fellow: Hong Zhang, Ph.D.

This fellowship involves using stereological and computer-assisted techniques in the process of collecting data regarding fundamental questions that explore the organization of the cortex in autism. These questions include whether there is a clear relationship between increased cell densities found in autistic individuals and other aspects of cortical organization, such as neuropil volume and cell size; whether changes in neuropil volume reflect an underlying change to the morphology of individual cell types within the cortex; and whether claims of deficits in cell migration in individuals with autism are evident in the subplate zone of the cortex.

University of California at San Francisco San Francisco, CA

"The Primary Auditory & Visual Cortex in Children with Autism and Animal Models"

Mentor: Michael Merzenich, Ph.D.
Fellow: Haruka Nakahara, Ph.D.

This fellowship plans to test the hypothesis that autism stems from inherited weakness that results in a degradation of signal-to-noise conditions in the self-organizing brain that strongly impacts the normal course of early post-natal brain development. Three parallel experimental paths will be used to test this hypothesis, including the development of an animal model designed to further define the impact on the developmental process where the signal-to-noise ratio is degraded in several different alternative (and realistic) ways; a second set of experiments focusing on behavioral and neuroimaging studies of ASD children, geared towards testing their signal processing abilities relative to noise; and the application of training software designed for language-impaired children, to create a new set of tools for children.

University of Medicine & Dentistry of NJ/ Robert Wood Johnson Med. School, Piscataway, NJ

"Neurodevelopmental Origins of Autism Brain Abnormalities"

Mentor: Emanuel DiCicco-Bloom, M.D.
Fellow: Kristina Sennvik, Ph.D.

This fellowship focuses on the suggestion that abnormal levels and functions of growth factors may result in the wrong numbers and kinds of neurons in autism-related brain regions. To begin understanding how these growth factors control the generation of specific neurons, Dr. DiCicco-Bloom and Dr. Sennvik will define the effects on neuronal cell production and differentiation in developing embryonic rat brain in utero. This study may provide insight into signaling pathways disrupted by genetic and environmental factors to elicit disordered brain growth leading to aspects of the autism phenotype.

Yale University School of Medicine, New Haven, CT

"Symbolic Understanding in Children with Autism"

Mentor: Paul Bloom, Ph.D.
Fellow: Melissa Allen Preissler, Ph.D.

This research will examine the relationship between theory of mind and the understanding of symbols, including words and pictures, and investigate whether the symbolic domains of pictures and words are linked and correlated with theory of mind. The results of this research may impact how we think about the kind of information children with autism use to learn about the world around them, and elucidate whether children with autism are learning associatively or referentially.

Columbia University College of Physicians and Surgeons, New York, NY

"Regulation of the Purkinje Cell, Dendritic Growth, Spine Formation and Synaptogenesis"

Mentor: Carol Mason, Ph.D.
Fellow: Phillip Buttery, Ph.D.

This project examines cellular mechanisms relevant to the late postnatal period of brain development with a focus on Purkinje cells in the cerebellum. Purkinje cell loss is a consistent pathological feature of autism. Dr. Mason and Dr. Buttery will examine the interactions and regulation of a group of molecules called the Rho GTPases and concentrate on one specific regulator of the Rho GTPases called Chimaerin. They will use the morphological maturation of Purkinje cells as a neuro-developmental model through which to address and further define the molecular-cellular foundations of autism, concentrating specifically on a candidate autism gene, Chimaerin.

Vanderbilt University, Nashville, TN

"Autism Screening in Children Under Two Months"

Mentor: Wendy Stone, Ph.D.
Fellow: Lynnette M. Henderson, Ph.D.

This fellowship aims to develop an interactive screening measure for identifying children under 24 months who are at risk for autism. This project builds on Dr. Stone's past research on early identification by developing a downward extension of the Screening Tool for Autism in two-year-olds (STAT). The project has the potential to direct children to early intervention programs at as young as possible and provide valuable information to parents who already have one child with autism. ❖

NAAR and the NIH Form Major Autism Research Partnerships

Initial Collaborations Focusing on Genetics and Behavioral Science Announced at Autism Summit Conference

by Andy Shih, Ph.D.
Director of Research & Programs

E Pluribus Unum.

Out of many, one.

It is often said that there is strength in numbers.

This is applicable in many arenas, from politics to barn-raising. In many respects, it is also true of research.

Consider autism.

Even though autism was first described by Dr. Leo Kanner more than 50 years ago, autism continues to baffle the medical and research communities. It is highly unlikely, if not impossible, that one researcher or laboratory has the resources and expertise required to make the major breakthroughs required to solve the many mysteries of autism. Our best opportunities for understanding the etiologies of autism and developing more accurate diagnostic techniques, specific medical treatments, preventions and cures, will occur by working together and sharing our collective resources and data.

(from left) NINDS Director Dr. Story Landis and NIMH Director Dr.Tom Insel discuss research partnerships between the NIH and NAAR during the NAAR Luncheon at the Autism Summit Conference in Washington, D.C.

This is the inspiration behind the innovative research partnerships between NAAR and the National Institutes of Health (NIH). These collaborations, focusing on genetics and behavioral science, are designed to enable doctors for the first time to biologically diagnose autism and gain a detailed understanding of the cause of the disorder, which continues to elude the medical field.

The new public/private collaborations between NAAR and the NIH focus on building partnerships and research consortiums - a major theme of the recently announced NIH Roadmap Initiative for Medical Research. The partnerships, which represent a joint commitment of at least $5.2 million, were announced at the opening session of the Autism Summit Conference on November 19 by Prisca Chen Marvin, chair of NAAR's Board of Trustees, and NIH officials.

The first of the partnerships is the NAAR Autism Genome Project, the largest research collaboration ever assembled that seeks to determine the genes associated with autism spectrum disorders. The project involves four institutes partnering with NAAR: the National Institute of Mental Health (NIMH), National Institute of Child Health & Human Development (NICHD), National Institute of Neurological Disorders & Stroke (NINDS), and National Institute of Deafness and Other Communication Disorders (NIDCD).

The institutes have collectively committed $2.5 million towards this project and NAAR, which began co-funding one of the largest autism genetics consortiums with the Nancy Lurie Marks Family Foundation in 2000, has committed $2 million.

"Unraveling the complex genetics of autism spectrum disorders will require the kind of statistical power afforded only by a pooling of DNA samples and data from ever larger numbers of affected families," said NIMH Director Thomas R. Insel, M.D. "This ambitious task calls for the model embodied in our new collaboration with NAAR."

The second partnership is the High Risk Baby Siblings Autism Research Project, which focuses on early diagnosis of autism spectrum disorders and identifying biological markers, and involves the NICHD. NAAR, which began funding baby sibling research in 1997, has committed $700,000 to the collaboration. Part of this commitment includes a $100,000 gift to NAAR from the Dan Marino Foundation.

"This partnership will enable us to move into this important area of research much faster than if we had

please see **Research Partnerships** on page 23

Research Partnerships (continued from page 22)

to start it on our own, and to complete it sooner," said Duane Alexander, M.D., director of the NICHD.

These unique projects have the potential to enable clinicians to biologically diagnose autism and definitively diagnose autism earlier than ever, which improves the prognosis of children and their families affected by autism. Providing a definitive, biological diagnosis will make it easier for more parents to seek early intervention.

Prisca Chen Marvin, chair of the NAAR Board of Trustees, announces the NAAR Autism Genome Project at the Autism Summit Conference.

While autism is largely considered one of the most heritable neurological disorders, the causes of autism are not known and there are no ways to biologically diagnose the disorder. Also, there are no specific medical treatments for autism and no cures for the disorder.

Only when we understand what causes autism can we seriously begin to focus on biologically diagnosing the disorder, developing medical protocols that help children and adults effectively manage autism and, perhaps prevent it from happening in the first place. Gaining a thorough understanding of the genetic underpinnings of autism may lead to a way to prevent some causes, especially if it is determined that autism is caused as the result of genetic and environmental factors.

The collaborations are unique examples of how the federal government is working with a national parent-led organization to fund and advance research.

"NINDS has supported a collaborative genetics project in autism in the past and is delighted to contribute to this significantly expanded effort. This public/private partnership should make it possible to move much more quickly to find answers to the genetic puzzle that autism presents," said Story C. Landis, Ph.D., director of NINDS.

NAAR provided the initial support and infrastructure that fostered a collaborative atmosphere in both the NAAR Autism Genome Project and the High Risk Baby Siblings Autism Research Project. The NIH has now brought its support and expertise to both partnerships, which has elevated each project to the next stage and illustrates how the public and private sector can work together to enhance investments in medical research.

Not to rest on our laurels, NAAR is currently working on developing two additional partnerships with the NIH, including a collaboration focusing on language and communications research that is being planned with the NIDCD; and a brain development research initiative with the NINDS.

These partnerships, both current and future, between NAAR and the NIH may pave the way for a broader understanding of behavioral science in general. Advanced knowledge on how genes control human behavior will likely further our understanding of human biology and the role genes play in developmental, language and communications, and emotional disorders and other neurological conditions. ❖

Senator Clinton Speaks at NAAR Luncheon

Senator Hillary Rodham Clinton (D-NY) was the keynote speaker at NAAR's Luncheon at the Autism Summit Conference on Wednesday, Nov. 19 at the Washington, D.C. Convention Center. Senator Clinton was greeted with a standing ovation by the more than 600 people who attended the event and praised NAAR's efforts to accelerate the pace of research.

"The National Alliance for Autism Research has come so far since its inception in 1994," she said. "The parents who began this organization have truly demonstrated their dedication to children and a commitment to unraveling the devastating mysteries of autism spectrum disorders."

NAAR would like to extend its sincere thanks to Senator Clinton and her staff for doing a remarkable job at the event. NAAR also extends a special thank you to NAAR Trustee Richard Cohen and his wife, Laurie, for their assistance and support in inviting Senator Clinton to speak at the luncheon and for their participation in the event.

To view Senator Clinton's complete speech from the event, visit **www.naar.org** and click on *"In the News."*

Spotlight On: NAAR Autism Genome Project

Bringing Together the World's Leading Genetics Researchers Focusing on Autism

Who:

The NAAR Autism Genome Project is a partnership between NAAR and four institutes of the National Institutes of Health (NIH): the National Institute of Mental Health (NIMH), National Institute of Child Health & Human Development (NICHD), National Institute of Neurological Disorders & Stroke (NINDS), and National Institute of Deafness and Other Communication Disorders (NIDCD). Initially, the institutes have collectively committed $2.5 million towards this project and NAAR has committed $2 million.

What:

The NAAR Autism Genome Project is a large-scale, collaborative genetics research project designed to map the human genome in the search for autism susceptibility genes - the genes responsible for the inherited risk for autism. This unprecedented endeavor is the largest research collaboration ever to focus on the genetics of autism and includes more than 170 of the world's leading genetics researchers from over 50 academic and research institutions focusing on autism and approximately 1,200 multiplex families (two children with autism spectrum disorders and their parents) from all over the world who are directly affected by autism spectrum disorders.

At the core of the NAAR Autism Genome Project are the investigators bringing it to life - a "collaboration of collaborations" composed of four main research teams:

The Autism Genetics Cooperative (AGC)

The International Molecular Genetic Study of Autism Consortium (IMGSAC)

The Collaborative Programs of Excellence (CPEA)

The Autism Genetics Resource Exchange (AGRE)

The first phase of the NAAR Autism Genome Project currently includes the completion of the largest genome screen for autism to date.

A genome screen is a genetic analysis designed to identify intervals in the human genome that show the highest priority for further investigation. Intervals are like "genomic neighborhoods" that appear to be the most likely places where the genes believed to be involved with autism exist.

To date, there have been several genetic analyses completed for autism, however results have varied and none have been performed on such a large scale as the NAAR Autism Genome Project.

This initiative's unprecedented convergence of the largest sample set ever assembled, a consortium of leading researchers in the field and cutting edge genetics technologies offers the autism community the best opportunity to date to elucidate the genetic underpinnings of this devastating disorder.

Why:

Autism is considered one of the most heritable neurological disorders. Locating the genes responsible for autism will likely enable researchers for the first time to gain a thorough understanding of what causes autism. Having a detailed understanding of the cause will better enable researchers to develop specific, more targeted medical treatments, preventions and a cure.

In addition, autism is a disorder with symptoms that are associated with other brain-based conditions. Determining the genetic causes of autism spectrum disorders has the potential to yield significant advances for other disorders involved in schizophrenia, social anxiety disorder, various learning disorders, language impairments and some forms of mental retardation. ❖

Spotlight On: High Risk Baby Sibling Autism Research Project

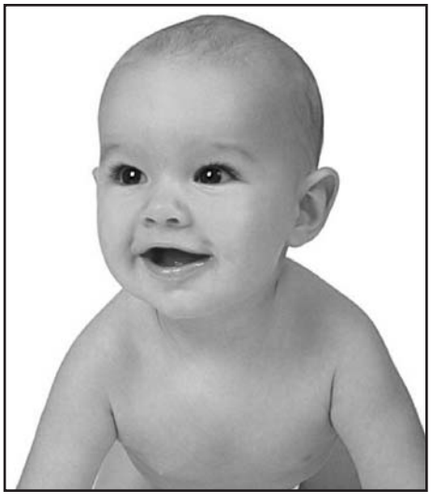
Examining the Infant Siblings of Children with Autism for Clues to Earlier Diagnosis

Who:

The High Risk Baby Sibling Autism Research Project is a partnership between NAAR and the National Institute of Child Health & Human Development (NICHD). NAAR, which began funding baby sibling research in 1997, has committed $700,000 to the collaboration. Part of this commitment includes a $100,000 gift to NAAR from the Dan Marino Foundation.

What:

The High Risk Baby Siblings Autism Research Project is a multi-site project designed to identify behavioral and biological markers for autism and eventually enable clinicians to make a more definitive diagnosis earlier than ever before.



In addition, the project also focuses on determining and developing specialized behavioral early interventions specifically designed for infants and very young children.

The genesis of this partnership originated with pilot studies funded by NAAR over the past several years that focus on a population at high-risk for developing autism: the infant siblings of children with autism. This research is commonly known as "Baby Sibs" studies.

In an effort to enhance this research, NAAR approached the NICHD in 2003 to discuss the possibility of transforming the initiative into a large, collaborative effort with an expanded size and scope. The NICHD recognized and welcomed the opportunity to partner with a national, parent-led research advocacy group on a topic that is a high priority at the Institute: early diagnosis of autism spectrum disorders.

It is a collaboration that the NIH plans to integrate with two ongoing NIH-funded autism research networks: the Collaborative Programs of Excellence in Autism (CPEA) and Studies to Advance Autism Research and Treatment (STAART) programs.

NICHD and NAAR have met with various researchers conducting infant sibling studies to identify priorities as well as potential challenges that such a collaborative effort may face.

Why:

Autism has a recurrence rate of between 5 - 10% in families with one autistic child - a rate about 50 times higher than the general population. By tracking the early development of siblings of children with autism, it is hoped that clinically predictive behavioral and biological markers can be identified and correlated with the potential onset of autism.

Before the first infant siblings studies were conducted, there was little or no information about children with autism prior to their diagnosis, which typically was made at age two or three years of age. Since then, however, high risk baby sibling research has contributed to clinicians' ability to diagnose much earlier - between 12 - 18 months.

The High Risk Baby Siblings Autism Research Project has the potential to enable clinicians to diagnose autism even earlier, which will further improve the prognosis for children and their families affected by autism. Providing definitive diagnosis (i.e. biological) will make it easier for more parents to seek early intervention and may also provide important clues to autism's etiology. ❖

Hilibrand Foundation Makes $1 Million Pledge to the NAAR Autism Genome Project

The Hilibrand Foundation, longtime supporters of NAAR, have recently made a $1 million pledge to the NAAR Autism Genome Project.

Glenn R. Tringali, NAAR's chief executive officer, announced the gift at a luncheon sponsored by NAAR at the Autism Summit Conference in Washington, D.C. on November 19.

At the luncheon, NAAR Trustee Debbie Hilibrand talked about her family's inspiration for making the pledge and for supporting NAAR.

"A decade ago, the outlook for medical advances for autism was bleak," she said. "But in the past few years, we have witnessed a revolution in terms of both advocacy and funding for research. NAAR has been instrumental in this revolution."

NAAR Trustee Debbie Hilibrand discusses her family's inspiration behind making a $1 million pledge to the NAAR Autism Genome Project.

NAAR's efforts to accelerate the pace of research, elevate the caliber of the science and form strategic partnerships with government health agencies as well as research and academic institutions is a key example of the progress that has been made, said Debbie.

"No project is more worthy of our support than the efforts of NAAR to create the systems change that we have so desperately needed in the scientific community," she said. "Now is the time that we can harness the latest technologies, fast-track our research initiatives and count on the support of the National Institutes of Health to foster our efforts."

Debbie and her husband, Larry, are strong advocates for research and have also supported many other autism-related programs in the Westchester/Fairfield community.

Debbie served as co-chair of the 2002 and 2003 Westchester/Fairfield Walk F.A.R. for NAAR events. She is also a member of NAAR's Lay Review Committee, examining the Scientific Advisory Board recommendations for funding grants and fellowships, as well as NAAR's Development Committee. The Hilibrands are also active supporters of the JCC of Midwestchester, where they played a key role in establishing the Technology Learning Center; and of the Greenwich ARC, where they were instrumental in the development of the Greenwich Autism Program.

The Hilibrand Family was recently awarded the Greenwich Volunteer of the Year Award for their distinguished service to the autism community. The Hilibrands were nominated by their child's school principal, who is a team captain for the Westchester/Fairfield Walk F.A.R. for NAAR and found the event to be inspirational for the community.

"We are honored and fortunate to have the support of the Hilibrand Foundation and for Larry and Debbie's commitment to the NAAR Autism Genome Project," said Karen London, NAAR's co-founder and vice chair of Development. "Their leadership and passion exemplifies the spirit and enthusiasm that NAAR was founded on." ❖

NAAR Receives $1 Million Gift from Anonymous Donor

NAAR has recently received a gift of $1 million from an anonymous donor. NAAR is extremely grateful to the donor and their family for this extraordinary support of the organization and its mission to accelerate the pace of biomedical research.

Progressions: 2004 Spring Walk Schedule

2004 Spring Schedule

Cumberland/Tri-State Area Walk FAR for NAAR
Allegany College of MD
Saturday, April 3
NAAR's First Walk in 2004 Has Great Turn Out!

Atlanta Walk FAR for NAAR
Piedmont Park in Atlanta, GA
Saturday, May 1
To register, call 404-344-3229

National Capital Area Walk FAR for NAAR
Montgomery County Fairgrounds in Gaithersburg, MD
Sunday, May 8
To register, call 301-519-0770

Carolinas Walk FAR for NAAR
Bank of America Stadium in Charlotte, NC
Saturday, June 5
To register, call 704-333-0051

San Diego Walk FAR for NAAR
Qualcomm Stadium in San Diego, CA
on Saturday, June 5
To register, call 858-597-9300

Pittsburgh Walk FAR for NAAR
Heinz Field in Pittsburgh, PA
Sunday, June 6
To register, call 412-487-6851

Westchester-Fairfield Walk FAR for NAAR
Manhattanville College in Purchase, NY,
Sunday, June 6
To register, call 203-552-8980

Greater Seattle Walk FAR for NAAR
Marymoor Park in Redmond, WA
Sunday, June 6
To register, call 206-464-5182

Greater Delaware Valley Walk FAR for NAAR
Cooper River Park in Pennsauken, NJ
Saturday, June 12
To register, call 856-755-0330

Iowa Walk FAR for NAAR
Gray's Lake in Des Moines, IA
Saturday, June 12
To register, call 888-777-6227

Chicago-land Walk FAR for NAAR
Soldier Field in Chicago, IL
Sunday, June 13
To register, call 312-832-9900

For more information on any of the events listed above, please visit WWW.NAAR.ORG and click on the Walk F.A.R. for NAAR logo located on the homepage.

Thank you for your support!

T.J. Maxx Launches Footprints Program to Benefit NAAR & Autism Research

"You Should Go" is Not Just a Slogan -- It is a Call to Action

The National Alliance for Autism Research is honored to announce a new partnership that has been formed with the national retailer T.J. Maxx, which included an in-store fundraising campaign that benefits NAAR and promotes the need for increased funding for autism research.

T.J. Maxx, a division of The TJX Companies, Inc. based in Framingham, MA, which also owns Marshalls, HomeGoods and A.J. Wright in the United States, launched the "Footprints" program in more than 750 of its stores throughout the country. The campaign ran from March 21 to April 10, 2004, and invited T.J. Maxx customers to purchase NAAR Footprints at check-out for a donation of $1. All proceeds benefit NAAR and all Footprints purchased will be displayed in the stores. In the program's first week, more than 200,000 Footprints were sold!

T.J.'s CaRes about KIDS®
Helping Kids Helps Us All

Every T.J. Maxx store in the United States participated in the campaign and featured window posters, postcards and general information on autism and NAAR that educated customers and store associates about the disorder and the need for increased funding for biomedical research.

Ted English, president and CEO of The TJX Companies, and NAAR Honorary Board Member Doug Flutie, taped a special message for a video that was shown to all T.J. Maxx associates and introduced them to NAAR, the challenges of autism and this new campaign.

"T.J. Maxx is proud to support NAAR in their commitment to funding autism research and raising public awareness. The new "Footprint" initiative gave both our associates and customers the chance to show their enthusiasm and generosity for this important cause," said Mr. English.

NAAR's partnership with T.J. Maxx is largely the result of the work of NAAR Trustee Margie Pascetta, chair of the New England Walk F.A.R. for NAAR in 2001, co-chair of the 2002 Walk and president and founder of NAAR's New England chapter. Over the past two years, Margie developed a relationship with the company, which became a major sponsor of the New England Walks. The relationship has led to this exciting, new partnership with T.J. Maxx.

"We feel extremely lucky to have T.J. Maxx signed on as a partner that shares NAAR's vision of funding and advancing biomedical research," said Margie. "In addition to raising critically needed funds, the promotion increased public awareness of a cause that has been sorely neglected. We are deeply grateful for the support of Ted English and the associates of T.J. Maxx, who have all made this promotion possible."

For more information on T.J. Maxx, or to find a store in your community, please visit www.tjmaxx.com.

T.J.maxx you should go®

Leave a Lasting IMPRINT...
Support Autism Research.

Office DEPOT
Caring... and making a difference

Office Depot Promotes Awareness During National Autism Awareness Month

Campaign Educates Customers in 900 Stores Throughout North America

In honor of National Autism Awareness month in April, Office Depot, Inc., has teamed up with the National Alliance for Autism Research for a second year to launch an awareness campaign in Office Depot's 900 retail stores across North America.

Office Depot's awareness program educates customers with informational brochures and posters in the stores about autism and the need for increased research. The program runs through the month of April.

(from left) Palm Beach/Broward Walk chairs Julie Guzy, Grace Rodriguez and Dianne Orr receive a $50,000 check from Bruce Nelson, Chairman and CEO of Office Depot at the 2003 Palm Beach/Broward Walk.

"Despite the strikingly high prevalence and significant national interest in autism, research remains considerably under funded," said Bruce Nelson, Chairman and CEO of Office Depot. "We are pleased to lend our support to NAAR as they seek to find a cure for autism and improve the quality of life for those struggling with it."

In 2003, thanks to the support of Office Depot, other corporate sponsors and many dedicated volunteers, NAAR committed a record $4.9 million to fund 50 pilot studies and fellowships focused on autism research - the largest single-year autism research commitment ever made by a nongovernmental organization.

NAAR's partnership with Office Depot is the result of the work of Dianne Orr and Tim Paull, both Office Depot employees, parents of children with autism and NAAR supporters. Dianne served as co-chair of the 2003 Palm Beach/Broward Walk F.A.R. for NAAR and is serving as co-chair of the 2004 event. Last year, Dianne and Tim worked with their colleagues at Office Depot and NAAR staff to bring the organizations together. The 2003 promotion marked NAAR's first national retail partnership.

As part of last year's campaign, Office Depot produced a video hosted by Mr. Nelson that features employees of the company who are parents of children with autism. The segment was used as an educational tool for store employees and customers.

In addition, Office Depot hosted the 2003 Palm Beach/Broward Walk F.A.R. for NAAR at the company's corporate headquarters in Delray Beach, FL and Mr. Nelson served as honorary chair of the event. At the Walk, Mr. Nelson presented NAAR with a $50,000 check.

Office Depot is a major sponsor of the Palm Beach/Broward Walk and will host the 2004 event at their corporate headquarters for a second consecutive year.

"We are excited to be partnering with Office Depot again in 2004 with this important initiative that educates the general public about autism spectrum disorders," said Prisca Chen Marvin, Esq., chair of the NAAR Board of Trustees. "We are grateful for the outstanding support Office Depot has given to NAAR as we continue to search for answers to this devastating disorder."

Mary Wong, Office Depot's Director of Community Relations, said the company feels strongly about supporting research and providing hope to the many families facing autism who are looking for answers to a baffling disorder.

"For parents of children with autism, it can seem like everyday living is a puzzle. Fortunately, NAAR is helping to find the cause and a cure for autism - and once again this year, Office Depot is pleased to partner with this extremely worthwhile organization," she said.

For more information on Office Depot, or to find a store in your community, please visit www.officedepot.com.

TGI Friday's Bartender Event Benefits NAAR

More Events to Benefit NAAR & Autism Research Planned for 2004

TGI Friday's has blended the perfect concoction of spirit and good will to support autism research, raising more than $65,000 at its Eastern New York Division's Shake, Rattle & Pour Regional Bartender Championship, a charity event benefiting the National Alliance for Autism Research (NAAR).

The championship, held last Sept. 17 at the TGI Friday's restaurant in Wallkill, NY, attracted hundreds of patrons and raised significant awareness for autism and the need for increased research funding. Proceeds of the event benefitted the Long Island Walk F.A.R. for NAAR.

"We are truly honored by the support of TGI Friday's and especially the employees and patrons of the restaurants that took part in this year's competition," said NAAR Trustee Marty Schwartzman, president of NAAR's Long Island chapter.

The genesis of the TGI Friday's benefit can be traced to the 2001 Long Island Walk, which was attended by Jim Mazany and his family. Jim is director of operations for Carlson Restaurants Worldwide's Eastern Division, which includes nine New York area TGI Friday's.

Jim is also the father of a child with autism. He and his family and friends comprise Luke's Troops, named after his son, Luke. Jim recalled his impressions of first taking part in the Walk in 2001.

"When we did our first walk, we saw all of the families and all of the people and it just hit me," he said. "I began to think about what I could do to benefit research and possibly make a better future for families and children faced with autism."

In 2003, Jim decided to make NAAR the beneficiary of this year's contest. In addition, he asked a fellow regional manager to consider naming NAAR as the beneficiary of another Shake, Rattle & Pour Regional Bartender Championship on Long Island, which his colleague agreed to do. Jim is now helping NAAR establish relationships with other regional managers.

For 2004, Jim is interested in planning a golf outing to benefit NAAR and implementing the Footprints campaign in the nine restaurants located in his district, which include sites in Brooklyn, Forest Hills, Rockville Center, Manhasset and Wallkill.

NAAR thanks TGI Friday's and Jim Mazany for their support of autism research!

St. Louis Area Melting Pot Restaurant Supports NAAR

For the second consecutive year, The Melting Pot restaurant of West County, located in Town & Country, MO, is hosting fundraising events to benefit the National Alliance for Autism Research in April, in honor of National Autism Awareness Month.

On Monday, April 26, the fondue restaurant will host an invitation-only benefit dinner and silent auction. Reservations for the dinner can be made by calling (636) 207-6358. The Melting Pot will also donate $10 to NAAR for each "Big Night Out' four-course fondue meal purchased Sunday through Thursday during the month of April. Guests can also make donations to benefit NAAR at the restaurant.

"We are excited to have the opportunity to raise funding for much needed autism research. As a parent of a child with autism, we know first hand the devastation of this disorder, " said Karen Barnett, owner of The Melting Pot in Town & Country. "Our management and staff are excited to be a part of autism awareness for the second year, where each of our guests has an opportunity to make an impact on finding a cure for autism."

NAAR extends its grateful thanks to the Barnett Family, the Melting Pot staff and all their customers.

Board Update

NAAR is honored to announce that the following key volunteers and supporters have joined NAAR's Board of Trustees to help shape and guide the development of NAAR.

Michael Alessandri, Ph.D., is a Clinical Associate Professor of Psychology and Director of the Center for Autism and Related Disabilities (CARD) at the University of Miami and has worked with individuals with autism and their families for nearly 20 years.

Richard Cohen, is President and CEO of Ermenegildo Zegna North America. Under his leadership, Zegna has become the premier men's luxury brand in the U.S. Mr. Cohen has helped raised awareness and funds to benefit the development of children and is the father of a child with autism.

Adrian Jones, is a Managing Director in the Principal Investment Area at Goldman Sachs in New York. He served as an officer in the Irish Army and served as part of a U.N. Peacekeeping Force in southern Lebanon. He is the father of a child with autism.

Marjorie Woolf Pascetta, has worked for 25 years with AT&T, In recognition of her outstanding performance, she was selected for AT&T's prestigious Leaders Council in 2003. She is the mother of a teen-age son with autism.

Dolores Rezendes, is a Graphic Artist and promotions and Marketing Manager for Herald Media Inc., supporting 139 weekly and daily newspapers in Eastern Mass. She is the mother of a child with autism.

Bernard Rosof, M.D., is Senior Vice President for Corporate Relations and Health Affairs at the North Shore-Long Island Jewish Health System; clinical associate professor at SUNY - Stony Brook; and an attending physician at Huntington Hospital in Huntington, N.Y., where he also serves on the Board of Directors.

Dame Stephanie Shirley, is a highly successful entrepreneur turned ardent philanthropist. She started what is now Xansa in 1962, and developed it into a leading business technology group. She founded the Shirley Foundation in 1996, which focuses mostly on autism and using IT in the voluntary sector. Her late son, Giles, had autism and passed away in 1998.

Here is Something to Cheer About

Tickets to Your Next Sporting Event or Concert Can Benefit Autism Research

The National Alliance for Autism Research presents a new way to support autism research: by converting unused tickets to sporting events and concerts into donations. NAAR's new partnership with **www.StubHub.com,** provides the opportunity to buy or sell tickets for any event, anywhere in the country.

Season ticket holders can allocate their unused tickets to NAAR and receive a tax deduction while NAAR receives critically needed funding for research. In addition, NAAR can receive a commission whenever tickets are purchased through StubHub and the buyer includes NAAR's fan code: **NAAR.**

For more information on the program, call (888) 777 - NAAR, or visit www.naar.org and click on the StubHub link in the Support NAAR Now section of the website.

Enroll Today to Receive NAAR's New E-Newsletter

Visit Website to Receive NAARRATIVE and NAAR Research News Online

The National Alliance for Autism Research invites you to receive the new NAAR E-Newsletter, which includes the online version of NAARRATIVE. To receive NAAR's new E-Newsletter, visit **www.naar.org** and click on the NAARRATIVE icon. Along with NAARRATIVE, you will receive timely information about autism research, NAAR-funded investigators, development and government relations news and biomedical research. In addition, **www.naar.org** contains the NAARRATIVE archives, including current and past editions of the newsletter as well as research news, information on autism, *Walk F.A.R. for NAAR* and other initiatives supporting NAAR's mission.

Hard copies of NAARRATIVE will continue to be mailed to our current and active supporters. To learn how you can support NAAR and advance research, visit **www.naar.org** and click on "Support NAAR Now", or call (888) 777-NAAR.

Thank you for your support!

NATIONAL ALLIANCE FOR AUTISM RESEARCH

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