

NARRATIVE

NEWSLETTER OF THE NATIONAL ALLIANCE FOR AUTISM RESEARCH

NEWS FEATURE

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NIH Announces \$27 Million Funding of Multi-Site Autism Research Network

Two institutes of the National Institutes of Health recently announced that they will put into place a five year, \$27 million, international collaborative network to study the neurobiology and genetics of autism. This autism research network will combine scientists at 24 universities with families in 13 states and four foreign countries (Canada, Britain, France and Germany) to study the causes of autism, including its genetics, the underlying biological mechanisms, and the developmental course.

The effort is co-funded by the National Institute of Child Health and Human Development (NICHD) and the National Institute on Deafness and Other Communication Disorders (NIDCD), with additional funds provided by the Office of the Director of the National Institutes of Health and the Office of Alternative Medicine.

"This is the largest commitment to a single autism research venture in history", said Duane Alexander, M.D., Director of NICHD. "Autism is a major pediatric health problem in the United States, with health care costs exceeding \$13 billion per year."

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SCIENCE FEATURE

An Embryological Approach to Autism: The Thalidomide Connection

By Patricia M. Rodier, Ph.D.

Edited by Catherine Johnson, Ph.D.

I became interested in studying autism after a parent asked me to think about the disorder. He had just heard me talk about injuries to the embryo's developing nervous system during early pregnancy, and he thought an embryologist might have new insights into the causes of autism.

Even though I had never studied autism, I was intrigued. So I went to the library and dug in. I read about 200 papers before concluding that there was simply not enough information to suggest how an embryologist like me might approach the problem. The causes of autism appeared to be multiple, the time of causation was not established, "morphologic" studies were few and often negative (meaning that the researcher had found nothing different about the basic shape or size of the various parts of the brain in autism), and the genetic studies, while interesting, were difficult to interpret as far as early development during pregnancy goes, which is what I study.

The behavioral studies were fascinating, but autistic behaviors are not ones we can easily relate to particular brain regions or systems. We have no idea what part of

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NATIONAL ALLIANCE FOR AUTISM RESEARCH

66 Witherspoon St., Suite 310
Princeton, New Jersey 08542

Toll Free: (888) 777-NAAR

Website: www.naar.org

Email: naar@naar.org

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Editor's Note

Our goal in publishing this newsletter is to inform readers of activities of the National Alliance for Autism Research and of the broader biomedical research community. We hope to convey, in addition to the information itself, the same sense of excitement and hope we ourselves feel as we pursue our mission of advancing an autism biomedical research agenda.

Because we believe that our readership will be broad and diverse—ranging from individuals whose first exposure to autism is through this newsletter to individuals who have lived with autism since birth—we have tried to adopt a tone and style that will speak to a broad spectrum of readers.

We anticipate that effective treatments and cures will come after the body of knowledge about autism has been dramatically deepened as the result of intensive research by many scientists in an array of disciplines. We can never report on all of the research being done, but we can illuminate the scientific process by publishing articles that provide in-depth looks at particular scientists or particular research projects. This issue's science feature is on the fascinating work of teratologist Dr. Patricia Rodier, and we think that it illuminates the scientific process beautifully. Future issues will include feature articles on scientists working in other exciting areas.

We will also publish summary articles that provide some of the background needed to better assess research issues. Dr. Rebecca Landa's article on genetic research is our first such offering.

This inaugural issue of NAARATIVE is provided on a complimentary basis to all interested readers, as will be the planned Fall/Winter 1997 issue. If you feel that your friends and colleagues would enjoy reading this publication, please give us their names and addresses and we will send them complimentary copies.

Please give us your comments on this newsletter. We want to hear from you!

In Future Issues

Exciting and informative articles are in preparation for future issues, including:

- ***The Discovery of an Autism Susceptibility Gene.*** A profile of important work by Dr. Edwin H. Cook's research team, featuring interviews with Dr. Cook and his major collaborator, Dr. Eric Courchesne.
- ***What Are Your Chances of Having Another Child With Autism?***
- ***Is Autism On the Rise?***
- ***Guidelines for Evaluating Autism Treatment Options.***

A Message From NAAR's President

nar~ra~tive *noun.* A story or description of events

naar~ra~tive *noun.* The story of NAAR and biomedical research in autism

NAAR~RA~TIVE. The newsletter of NAAR (the National Alliance for Autism Research)

I want to welcome you to this inaugural issue of NAARATIVE. For many, this newsletter will also be an introduction to the National Alliance for Autism Research itself. It is my hope that NAARATIVE will not only be a source of information regarding autism biomedical research, but also about NAAR's mission and philosophy and what you can do to participate and strengthen our cause.

Permit me to share with you the beginnings of this *naarative*. In the months following our own son's diagnosis with autism in 1989, my husband and I noticed that, despite innumerable requests to fund medical research from all sorts of disease-specific charities, we had never received a similar request for autism. Why was this? Nonetheless, with a newly diagnosed two year old and an infant daughter, I did not make any effort to find out.

Five years passed. There still was no such effort for autism research--this despite dramatic breakthroughs in the neurosciences. Gradually, the idea took hold that an organized effort to help fund autism biomedical research was a critical and unmet need.

In the spring of 1994, a small group of parents began to investigate and research the possibility of forming an organization to advance autism research. We spoke with a number of autism researchers throughout the country. They confirmed our impression--there was no US autism organization comparable to the MS Society, Juvenile Diabetes Foundation, Cystic Fibrosis Foundation, National Alliance for Research on Schizophrenia and Depression or any one of a dozen other nonprofits who promote medical research for specific disorders. They explained to us that the impact of this vacuum was enormous. These nonprofits raise millions and millions of dollars annually for their diseases (many of which have no higher or even lower prevalences than the autism spectrum disorders!). Even more critically, the relatively small grants that these nonprofits disburse are very significant in that they enable scientists to obtain the preliminary or pilot data essential to securing larger and longer-term funding from the National Institutes of Health (the NIH). In the absence of pilot study funding, autism research applicants just couldn't be competitive for funding at the NIH.

Within two months, in July 1994, the National Alliance for Autism Research was born. The new organization's name was selected with great care. We literally hoped and prayed that it would be exactly that--a nationwide alliance of families, autism organizations, researchers and concerned others united in and supportive of a common purpose: to advance and accelerate biomedical research into the causes, prevention, treatment and, ultimately, cure of the autism spectrum disorders.

Over the course of its first year, NAAR expanded its initial Board of Trustees and developed a wonderful honorary board comprised of noted actors, musicians, authors and others whose lives have been touched by autism. We also completed the federal and state legal requirements prerequisite to initiating our fund-raising efforts. Most important, however, we

secured the volunteer participation of one of the finest Scientific Advisory Boards in the country. Our Scientific Advisory Board (SAB) is the jewel of this organization and has been called by one autism expert "a review board without peer." Its distinguished members are recognized experts in every discipline relevant to autism biomedical research. NAAR's SAB reviews and ranks competitively each research proposal seeking funding from NAAR according to the highest scientific standards. NAAR can assure its supporters that no dollar is spent unwisely and that only the most promising and meritorious projects are funded with their contributions.

As we approach NAAR's third birthday, we can point with pride to many accomplishments, some of them detailed in this inaugural issue of NAARATIVE: the first NAAR Autism Research Awards, the first NAAR-sponsored conference; the first of several scheduled NAAR scientific working groups. NAAR has now raised **nearly \$900,000** in gifts and pledges. These accomplishments are due to the members of its SAB, the continued efforts of many, many volunteers and an incredibly dedicated and talented Board of Trustees. I am indebted to all of them for volunteering their time and professional talents for this organization and to this mission.

All of this, however, is only an introduction. Succeeding chapters of this *naarative* will be determined by the efforts and commitment of all of us, individually and collectively. We can make this commitment by donating, and encouraging others to donate, to NAAR in order to assure that NAAR can each year fund as many excellent proposals as its SAB recommends should be funded. We must not turn away any outstanding proposal for lack of funding. We must be determined in our efforts to support the best research, to attract the brightest new scientists to the field and to continue to support those who have previously dedicated themselves to our cause. We must have our collective voices heard by relevant governmental agencies, Congress and the scientific community and be viewed by them as partners engaged in a common mission. We must do so by having our families participate, where appropriate, in funded and peer-reviewed research studies: **it is especially critical that the NIH's important new funding commitment to autism research be matched by our commitment to participate in those funded studies.** Finally, and no doubt most difficult, we must consider tissue donation in the event of death--as this is truly the most precious gift of hope one can make to advance our understanding of autism.

I am the mother of a beloved nine year old son with autism. I harbor no illusions that this will be a short story. However, I have no doubt that, with the support of the autism community and concerned others, NAAR is positioned to make a significant impact on autism research. For our children, siblings and grandchildren with autism, and for their siblings, I invite you to join with us and dedicate ourselves to that effort.

With appreciation,



Karen Margulis London

NAAR Holds Conference on Biomedical Research in Autism

Family members and professionals attended a full-day conference on autism research on April 12, 1997 at the Crystal City Marriott in Alexandria, Virginia. The conference, sponsored by The National Alliance for Autism Research, was titled "Biomedical Research in Autism: A Conference on the State of the Science, Future Directions and Treatment Implications".

The conference presentations, made by seven leading experts in the field of autism research, covered many topics of immediate concern to parents and professionals. The objective was to inform attendees of current research in autism and provide some of the background necessary to understand and evaluate it. Care was taken by the presenters, however, to connect research to everyday practical issues, such as how to choose from among various pharmacologic and therapeutic treatment options and how to decide whether or not to take part in particular research projects. Three of the presenters were themselves parents of children with autism.

After the conference one attendee remarked: "What was unusual and special about this meeting was that the speakers, though they were scientists who work at the highest levels, did not seem to talk down to the audience. Using common language to express complex ideas, they seemed to regard parents and professionals as partners and peers."

The first speaker was Marie M. Bristol, Ph.D., a well-known expert on autism who currently serves as Health Scientist Administrator of the National Institute of Child Health and Human Development of the National Institutes of Health. Dr. Bristol spoke from her perspective both as an experienced autism professional, who for nearly fifteen years was on the faculty of the UNC Medical School and a participant in TEACCH, and as administrator of the largest funding source for research in autism. She reviewed recent research in autism and discussed its implications for intervention. Dr. Bristol expressed her view that ongoing and proposed autism research showed great promise and that the current climate seemed ripe for significant increases in public and private funding of autism research.

Susan L. Hyman, M.D., a developmental pediatrician and faculty member at the Strong Center for Developmental Disabilities at the University of Rochester School of Medicine and a research partner of Patricia Rodier (see article on page one), reviewed the scientific evidence behind the many different treatments and tests for autism spectrum disorders. Her remarks included practical advice for parents and professionals on how to evaluate proposed treatments, including "alternative" treatments. Dr. Hyman serves on NAAR's Scientific Advisory Board.

Judith M. Rumsey, Ph.D., a researcher in the Child Psychiatry Branch of the National Institute of Mental Health and a faculty member at Georgetown University Medical Center, spoke about an area in which she is a leading expert: the use

of brain imaging techniques, such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), to understand the structural and functional brain abnormalities in developmental and child psychiatric disorders. She illustrated her presentation with many PET and MRI brain images, and provided the audience with the basic tools to understand how and why the interpretation of such images can provide clues necessary to the understanding of autism. Dr. Rumsey is a member of NAAR's Scientific Advisory Board.

Barry Gordon, M.D., Ph.D., a professor in the departments of neurology and cognitive science at the Johns Hopkins University School of Medicine and a renowned expert in language and memory, spoke of his personal experiences as the father of a pre-school child with autism, and the methods he has recently developed to evaluate speech perception and comprehension in children with autism. Dr. Gordon is the recipient of a 1997 NAAR Autism Research Award.

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Rebecca Landa, Ph.D., CCC-SLP, Director of the Center for Autism and Related Disorders at the Kennedy Krieger Institute of The Johns Hopkins University and a principal investigator in the Collaborative Linkage Study of Autism, spoke about evidence that autism and a set of related characteristics have a genetic etiology in many cases. She provided an informative overview of how good genetic linkage studies are designed and implemented. She also described the research project for which she won a 1997 NAAR Autism Research Award, a prospective study of siblings of autistic children which will form the basis for a larger-scale, longitudinal study. An article by Dr. Landa appears elsewhere in this newsletter.

Charles T. Gordon, III, M.D., a member of the clinical faculty at the University of Maryland School of Medicine and a child psychiatrist with a private practice which specializes in developmental disabilities, reviewed the scientific studies of medications currently used to treat symptoms and behaviors of autism, and discussed their side effect profiles. He described in detail his own much-cited study of the use of Clomipramine in children with autism, conducted while he was a researcher at the National Institute of Mental Health. Dr. Gordon is a member of NAAR's Board of Trustees and the father of a son with autism.

Eric London, M.D., a member of the clinical faculty at the University of Medicine and Dentistry of New Jersey and a psychiatrist, is co-founder of NAAR and its Vice President-Medical Affairs. Dr. London provided an overview of the state of autism research in the U.S. and discussed in detail the many components of NAAR's strategy to accelerate its pace.

This was the first of many scheduled autism conferences for parents and professionals. Please contact NAAR if you would like to help organize a conference in your community. ♦

NAAR Grants \$150,000 in Autism Research Awards

The National Alliance for Autism Research is pleased to announce that it has awarded the first NAAR Autism Research Awards. NAAR made grants of approximately \$30,000 to each of five outstanding scientists to fund their promising autism research projects. This is the culmination of a process which began in July 1996, when an RFP (Request For Proposal) was sent nationwide to universities and medical research centers. NAAR received thirty proposals from scientists from eighteen universities, all of which were carefully reviewed and ranked by NAAR's distinguished Scientific Advisory Board (SAB) at its December 1996 meeting at Harvard University. The meeting was chaired by SAB member Martha Bridge Denckla, M.D., who is Director of Developmental Cognitive Neurology at the Kennedy-Krieger Institute and Professor of Neurology at The Johns Hopkins University School of Medicine.

"We were gratified to have received such a large group of excellent and diverse autism research proposals from highly qualified scientists across the United States," said Eric London, M.D., NAAR's Vice President—Medical Affairs. "Our only disappointment was that we didn't have the funds to support more of them. Our hope and expectation for the next funding cycle is that we will attract even more quality research proposals and be able to fund a significantly higher percentage of them."

The 1997 NAAR Autism Research Award winners are:

Pauline A. Filipek, M.D., Assistant Professor in Residence of Pediatrics & Neurology at the University of California-Irvine, for her study "*Autism: A Model of Anomalous Neural Systems Development*". Human brain growth extends into the second decade of life, with the most rapid rate occurring in utero and in the first postnatal years. By school age, the growth rate has declined sharply, but these final phases are especially critical to the maturation of motor, linguistic, cognitive and social aptitudes. Previous magnetic resonance imaging (MRI) studies by Dr. Filipek have suggested that children diagnosed as having developmental disorders have unexpectedly larger brain volumes, owing to increased amounts of white matter localized to certain areas of the brain. Dr. Filipek will test the hypothesis that anomalous developmental events affect neural systems responsible for the communication and neurobehavioral deficits in autism. She will apply the state-of-the-art neuroimaging techniques used in her previous pioneering studies on autistic individuals.

Barry Gordon, M.D., Ph.D., Professor of Neurology and Cognitive Science at The Johns Hopkins University School of Medicine, for his study "*Training of Speech Perception and Speech Comprehension in Autistic Children: A Combined Behavioral-Neurophysiological Pilot Study*". This innovative pilot study,



Martha Bridge Denckla, M.D., Chair of the Scientific Advisory Board meeting, with Eric London, M.D., NAAR's Vice President—Medical Affairs.

focusing on training speech perception and single-word speech comprehension with selected children with autism, will use objective brain wave measures to determine what aspects of speech the child does not understand and also what he or she is learning with training. Dr. Gordon's study is expected to have important implications for the development of effective treatments for the language impairments so common in individuals with autism. Dr. Gordon is not only a world renowned expert in language and memory but also the father of a child with autism.

Rebecca Landa, Ph.D., CCC-SLP, Associate Professor of Psychiatry at Johns Hopkins University, Director of Research and Education with Autistic Children at Hopkins (REACH), and Director of The Kennedy-Krieger Center for Autism and Related Disorders, for her study "*Core Deficits of Autism: Evidence from Infant Siblings of Autistic Probands*". This is a case-control pilot study that will employ innovative, state-of-the-art procedures in infant/toddler research to produce the first *prospective* study of siblings of autistic children ever undertaken. It will form the basis for a larger-scale longitudinal study addressing important clinical and theoretical questions about the causes, core symptoms and course of autism. This work has important implications for early intervention.

W. Ian Lipkin, M.D., Professor of Neurology, Anatomy & Neurobiology, Microbiology & Molecular Genetics, at the University of California-Irvine, for his study "*Bornavirus Infection and Autism Pathogenesis*". This pilot study uses recently developed molecular detection methods to investigate the possibility that Borna disease virus (BDV), a newly described RNA virus that infects the brain and causes behavioral disturbances, may be linked to autism. If a link were found, this discovery could have a profound impact on the management and prevention of autism. NAAR's *Research Partner* for this study is The Harold Broitman Foundation.

Margaret A. Pericak-Vance, Ph.D., Chief, Section of Medical Genetics and Professor of Medicine and Neurology, Duke University, for her study "*Genetic Studies in Autistic Disorders*". Taking advantage of resources developed through the Human Genome Initiative, as well as recent advances in molecular technology and statistical genetic methodology, this study will help to uncover the genetic etiology of autism. Dr. Pericak-Vance has led many successful gene mapping endeavors. She was the first to map Alzheimer's disease to chromosome 19 and, more recently, has been involved in a major study to map Multiple Sclerosis susceptibility genes. This study is a component of a multi-site collaborative effort with investigators at the University of South Carolina, Tufts University, University of Iowa, Mt. Sinai School of Medicine and Massachusetts General Hospital. Technology developed in Dr. Pericak-Vance's laboratory, such as the PEDIGENE data base, will be applied to autism. NAAR's *Research Partners* for this study are Audrey Flack and H. Robert Marcus. ♦

NAAR Sponsors Five Scientific Initiatives

by Eric London, M.D., NAAR Vice President-Medical Affairs

NAAR's mission is to stimulate and accelerate autism biomedical research toward prevention, treatments and cures. While the principal component of our agenda is to provide direct funding for specific research projects, we have also adopted a strategy of accelerating the science by facilitating communication among researchers and by recruiting new talent to the field. To accomplish this, NAAR will sponsor five Scientific Initiatives over the next year. Our Scientific Initiatives are meetings organized and funded (or co-funded) by NAAR that bring autism researchers together with relevant experts outside the field of autism so that both groups share perspectives, coordinate efforts, and brainstorm regarding the difficult research challenges posed by this disorder.

We devoted our first Initiative, held May 10 at New York University Medical School, to the pressing issue of increasing the availability of brain tissue for research purposes. Representatives from NAAR's Scientific Advisory Board, the National Institutes of Health, and several preeminent brain banks met with invited autism researchers, clinicians, and neuropathologists. All present agreed that collecting brain tissue from newly deceased individuals with autism is vital to the cause. We cannot hope to attract more basic neuroscientists—researchers who work at the cellular level—to autism research if they do not have brain tissue available to study. Because producing an animal model for autism is extremely difficult, the tiny number of autistic brains collected to date poses an enormous obstacle to progress. Where many other human disorders can be recreated in an infinitely replenishable supply of laboratory animals, creating an animal with autism will have to be an approximation, given that language impairment is a key component of the condition. If we hope to make progress in autism research we must find a way to collect more human brain tissue.

Workshop participants concluded that a first order of priority is to undertake an outreach program to affected families, and NAAR hopes to begin such an effort this year. Other more technical issues discussed included clinical evaluations, medical-legal issues, and neuropathological methodologies. These are difficult topics, and further meetings addressing each one in turn are being planned with the goal of ultimately creating a standardized Research Protocol that could be implemented nationally.

Our second Initiative will take place in October 1997, and will address the language impairment in autism. Much of the knowledge we have about autism has been "borrowed" from research conducted on other brain diseases. But the language disorders characteristic of autism are unique even among the major psychiatric illnesses. As a result, there has been far less biomedical research regarding developmental language abnormalities than on psychiatric symptoms such as obsessive behavior, sleep disturbances, mood issues, and so on. Given the tremendous importance of language and communicative ability, NAAR has determined to make this an area of high priority.

We have made plans to assemble language experts from both

inside and outside the field of autism for a two-day meeting chaired by NAAR Award Winner and expert in language disorders, Barry Gordon, M.D., Ph.D. This initial language workshop will focus on treating young, nonverbal children with autism. The question of what is preventing language development will be explored. The panel will focus upon attention problems, receptive and/or expressive aphasia (the loss of or defect in language comprehension and/or power of expression), intentionality, apraxias (the inability to make one's body do what is intended) and preverbal cognitive issues. We hope that through a series of such language-oriented workshops, NAAR will stimulate research efforts in these areas, develop pilot projects, and pave the way to the creation of more effective language interventions and treatments. In the future, biological assessment tools such as scans or electrical potentials will be used to evaluate the effectiveness of teaching methods or medications developed to treat language.

Our third Initiative addresses the epidemiology of autism. Epidemiology is the study of the distribution and determinants of diseases in populations; epidemiologists use sophisticated statistical techniques to estimate the numbers of people with a disease or disorder, and what characteristics these people have. By examining such issues as affected individuals' geographical location, age, co-morbidity (other diseases they may have), and so on, these researchers detect clues to possible causes of the disorder. For instance, a confirmation of geographic clusters (regions in which numbers of cases are far higher than would be expected) can give epidemiologists leads concerning the possibility of viruses or toxins that may have caused the condition.

Another critical question confronting epidemiologists is the issue of whether the incidence of autism is rising, as many parents and clinicians believe, or whether increased case loads are due simply to greater awareness and more accurate diagnosis. Certainly if it were to be established that the occurrence of autism spectrum disorders is increasing, this would be a powerful incentive to government funding bodies to increase the research budget for autism—and this issue can only be resolved through epidemiological research.

Over the course of the last year, representatives from NAAR met twice with experts from the Centers for Disease Control and Prevention (CDC) to discuss these issues. We found a very receptive group at the Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, under Director Dr. Godfrey P. Oakley, Jr. Indeed, the Division has already initiated a pilot surveillance project for autism spectrum disorders. In addition, the CDC, acting in conjunction with NAAR, is assembling a group of world-renowned experts in autism and epidemiology to address these issues. We will report on this Initiative in a future newsletter.

Our fourth Initiative, to convince the pharmaceutical industry to take a more active role in developing treatments for autism and related disorders, will be launched in December 1997. NAAR is planning a symposium on relevant issues in autism research to be given at the prestigious American College of Neuropsychopharmacology (ACNP), with Dr. Edwin Cook of



Researchers Discover First Autism Susceptibility Gene

A multi-center research team headed by Edwin H. Cook, Jr., M.D. of the University of Chicago Medical Center has found preliminary evidence of a significant association between autism and a shortened version of the promoter of the serotonin transporter gene, HTT. This discovery, if replicated and confirmed by other researchers, should speed the search for additional genes that increase susceptibility to autism and should enhance understanding of the disorder. This finding may eventually contribute to the development of improved diagnosis and medical treatment of autism.

In this study of 86 families with at least one autistic child and two parents, it was found that autistic children are much more likely to have inherited a shortened form of the HTT promoter. "This is just one of at least three to five genes whose interactions result in autism," said Dr. Cook. "But nailing the first one confirms the value of the genetic approach and may provide clues about where to look for others."

This finding, reported in the May 1997 issue of *Molecular Psychiatry*, provides evidence that the serotonin transporter gene, which codes for a protein that reabsorbs the neurotransmitter serotonin back into the neuron that has released it, may serve as a susceptibility locus in autistic disorder.

Serotonin abnormalities in autism were first noted by Schain and Freidman over thirty-five years ago. Elevations in whole blood serotonin in a subgroup of autistic patients have been

the most consistently observed biochemical abnormality in autism although the precise mechanism causing the elevation is unknown and has been the subject of study for many years. Recent findings that serotonin reuptake blocking medications such as fluoxetine (Prozac), fluvoxamine (Luvox), and clomipramine (Anafranil) help treat several of the features of autism support the hypothesis that serotonin dysregulation is associated with autism spectrum disorders.

Responding to news of the discovery by the Cook team, NAAR Trustee C.T. Gordon, III, M.D., a Medical Affairs Committee member and expert in psychopharmacology commented, "It wouldn't be surprising if a genetic cause of autism is related to serotonin regulation. The serotonin transporter gene finding, though preliminary, is exciting. It is the first result from a new type of genetic research in autism whose time has come."

"Given the present state of genetic technology as well as increasing scientific interest and funding support in autism," said Dr. Gordon, "the discovery of the causes and contributing factors of autism is likely right around the corner."

Other members of the research team include Rachel Courchesne, Catherine Lord, Nancy J. Cox, Shuya Yan, Alan Lincoln, Richard Haas, and Eric Courchesne. The research was conducted at the University of Chicago, the Children's Hospital Research Center in La Jolla, California, and the University of California at San Diego. ♦



the University of Chicago (see related article above), Dr. Christopher McDougal of Yale University, and NAAR Medical Affairs trustees Dr. C.T. Gordon of the University of Maryland and Dr. Clarence Schutt of Princeton University presenting. ACNP is a highly regarded conference in the field of neuropharmacology that is attended by academic researchers as well as representatives of the pharmaceutical industry. In addition to ACNP, NAAR plans a second meeting on pharmacological interventions in collaboration with the NIH.

The pharmaceutical Initiative is vital to the development of treatments for the autism spectrum disorders because currently there is no FDA-approved medication available for the treatment of autism (nor is there one for the mental retardations or learning disabilities). Although several medications developed for other diseases are sometimes effective in treating certain autistic behaviors, to date there has been only limited systematic evaluation of these medications in individuals with autism.

In our presentations to the industry we will aim to dispel the myth that autism is a rare disorder and to encourage pharmaceutical sponsorship of research testing the efficacy and safety of medications already on the market, as well as those still under development. A longer-term goal is to persuade the pharmaceutical industry to undertake product development specifically for autism.

In order to develop autism medications, however, scientists need to know more about the exact abnormalities in the brain that could be targeted by medication. This is the focus of our fifth and final Initiative on early brain development in autism. We are inviting experts in autism research, embryology (the study of first trimester development in the womb) and brain development (several of whom are members of NAAR's Scientific Advisory Board). This Initiative will address developmental genetics—the study of the genes that guide the embryonic brain through its developmental sequence. As in the case of the pharmaceutical industry, our goal is to encourage these experts to undertake research in autism, to outline scientific questions that need to be investigated, and to help NAAR prepare a specific Request for Proposals (the "RFP"—the notice of funding availability we send to selected scientists each year) to solicit research to answer these questions.

Reports on these Initiatives will appear in future issues of NAARATIVE. We are extremely pleased to be sponsoring and co-sponsoring these efforts, and are gratified that such prominent experts have volunteered their time to chair or participate in them. It is important to emphasize that each of the Initiatives is only the first step in a series designed to target specific issues critical to autism research—and that NAAR's ability to implement these Initiatives, and to plan subsequent ones, depends upon having adequate financial resources to do so. Your continued support is vital to our efforts, and we thank you. ♦

Studies on the Genetic Bases of Autism: An Update

By Rebecca Landa, Ph.D.

Autism is a complex disorder that affects up to 12 children per 10,000. Autism places enormous financial and emotional stress on families as they embark on the perilous journey through diagnostic and treatment processes. Any individual touched by autism recognizes the need for effective educational, behavioral, and biological (e.g. nutritional, pharmacologic) interventions. One of the most promising ways to identify effective interventions for a disease or disorder is to determine its cause. Autism is sure to have a number of different causes, but twin and family studies have yielded strong evidence for a genetic etiology in many cases. Researchers believe that identifying the genes causing autism will lead to explanations about how brain function and development go awry. By identifying the action of the genes contributing to a disorder, researchers will eventually be able to look for ways to correct the genetic error through medications, dietary changes, etc. Genetic research in autism is imperative to reach a full understanding of the treatment of and cure for autism.



What are the best research methods for determining whether a disorder is genetically based?

Adoption studies are the most powerful tool for investigating genetic bases of disorders. Here, adoptees with the disorder of interest are matched with control adoptees, and a comparison is made between the incidence of the disorder in their biological and adoptive relatives. When a disorder has a genetic cause, biological relatives will have higher rates of disorder than expected even if they have never lived with or had contact with their affected relative. This method controls for environmental influences (e.g., toxins, stress factors) that may have caused a trait to occur within family members.

Another research strategy is to conduct a twin study. Twin studies compare the similarity of identical (monozygous, MZ) twin pairs and fraternal (dizygous, DZ) twin pairs for the trait in question. On the assumption that both types of twins have an equal degree of common environment, greater resemblance between MZ twins (who are genetically identical) than between DZ twins (who share 50% of their genetic material) points to genetic effects. Powerful indication that the trait is genetically based occurs when twins who were separated at birth and raised without contact have resemblances.

Methods used to explore the underlying genetic mechanism of a disorder include family history studies, family studies, and linkage studies. In family history studies, one or more informants in a family are interviewed regarding the presence of traits or disorders in themselves and other family members. This method is most useful when the trait is clearcut, with unmistakably present symptoms that persist over time (e.g., Huntington disease). It may provide an underestimate of the presence of the trait in a family when

the informant is unable to recall whether a relative had the trait (as in childhood language delay), or is not able to make the necessary discriminations about whether an individual presents with traits, especially if the traits in question are subtle or the relative in question is not seen often.

Family studies involve direct measurement of a trait(s) in patients and their relatives. A comparison is made between how often the trait is present in relatives of the patient compared to the general population or a control group. Family studies are important

for defining what aspects of a disorder are genetically based. This is especially important in complex disorders such as autism, which have numerous facets (e.g., language, social, and behavioral differences). As researchers identify what traits run in families, they look for patterns of inheritance across generations. Statistical methods are used to determine pattern of inheritance (e.g., is there evidence for a single major gene or is it likely that multiple genes are contributing to the disorder?). Laboratory studies are completed to compare the genetic material (DNA) of 'affected' and 'unaffected' family members to locate the gene or genes contributing to the disorder (see description of linkage studies below).

This strategy has led to identification of at least one gene, for colon cancer. That is, when the 'disorder' was narrowly defined as colon cancer, there was no clear evidence that it 'ran in families' (e.g., was 'familial'). However, when the disorder was defined more broadly as 'cancer', rather than only colon cancer, a genetic basis was identified.

What research has been done in autism to determine a possible genetic etiology?

Although the adoption study method has not been used in autism, several twin studies have been completed. One such study showed that autism as well as a set of milder impairments (e.g., language delay) occur more often in MZ than in DZ co-twins of a child with autism (Folstein & Rutter, 1977). A more recent twin study has confirmed this finding, concluding that the impairment in the non-autistic co-twins may involve social, language, and/or repetitive/stereotyped behaviors and interests (LeCouteur et al., 1996). Family history and family studies have found that autism, as well as specific types of language, social characteristics, psychiatric (e.g., depression, anxiety), and personality features occur more often in adult siblings and parents of individuals with autism than in controls (Bailey et al., 1996; Landa et al., 1997; Piven et al., in press). This information is now being used to inform linkage studies of autism.

What is a linkage study and is this methodology being used in autism?

Linkage studies employ statistical and lab procedures to determine genetic mechanisms that may cause a disorder. That is, linkages between genetic material (DNA) and traits





associated with a disorder are sought. The statistical methods used in linkage studies are becoming more powerful as are the mathematical models and computer programs. New discoveries about genetic mechanisms also benefit the linkage studies. Linkage studies are completed on families in whom a genetic basis for the disorder is likely (e.g., families having more than one member with autism). In order for linkage studies to be successful, several essential criteria must be met:

- Large numbers of families (at least 200 with two autistic children) are needed;
- The individuals with autism must be carefully diagnosed by experts in the diagnosis of autism (based on interviews with parents, review of medical records, and an interview with the individual(s) with autism);
- Must have careful definition of which family members have the traits of interest; and
- Must have expert lab and statistical researchers. This requires a highly expert team of researchers and collaboration among researchers. Collaboration is especially important after a 'finding' has been made so that replication of the finding on different families may be completed.

Researchers studying autism are highly motivated to answer questions about the cause of this disorder. Yet, for the protection of the participants in the research and to ensure high quality research methods and procedures, painstaking steps must be taken, such as:

- Getting institutional review board approval to conduct the requested research with human beings, developing methods to safeguard the well being of the participants and confidentiality issues.
- Writing detailed research justifications and methods which are submitted to funding agencies to request funding. These applications are rigorously reviewed by highly trained and judicious researchers from the same or related fields.
- Making sure that all staff are well trained on all methods and conducting reliability trials to make sure that everyone is doing things the same way now and across time.
- Collaborating with other experts to tap their expertise and replicate findings. Entering data, checking data entry again and again for accuracy.
- Conducting statistical analyses and writing manuscripts.

Linkage studies have been ongoing since the late 1980s in autism, and some of the major linkage study sites include: (1) the Collaborative Linkage Study of Autism (Johns Hopkins, University of Iowa, Tufts/New England Medical Center, Duke University); (2) Stanford University; (3) University of Washington and associated collaborators; (4) University of Chicago, Yale, and UCLA; (5) Mount Sinai Hospital; (6) two European collaborative projects; (7) Australian project. There may be other linkage studies ongoing as well. The linkage study sites listed above may use different approaches, but all will contribute to our understanding of the genetic basis of autism.

Although the technology for doing this work is quite sophisticated, there is no 'quick and dirty' way to find the answer to our questions. Findings relevant to the causes and treatments for autism are occurring everyday, both within labs directly

studying autism and those of other fields. Judging from the course of events in genetic research with other diseases, we have to have patience in the case of autism. We expect that multiple genes are contributing to the disorder, and there may be different sets of genes in different subtypes of autism. Once the markers, then the genes are identified, we need to identify the gene action. This is a multi-step approach, with the goal of helping individuals affected with autism and their families as quickly as possible.

Families having more than one child with autism may benefit science greatly by participating in one of the linkage studies of autism listed above. Families may call any of the groups to get more information (see listing on next page). There is no cost to families who participate; researchers will travel to families' homes to complete interviews and to collect blood samples. What is needed more than anything else is a willingness on the part of families to work closely with researchers who have established scientific rigor and expertise in the areas of genetics, autism, statistics, and related fields. ♦

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- Rebecca Landa, Ph.D., CCC-SLP, a 1997 NAAR Autism Research Award Winner, received her Ph.D. in Speech and Hearing Sciences from the University of Washington and completed her post doctorate in Psychiatric Genetics at The Johns Hopkins University. She is the director of The Kennedy-Kreiger Center for Autism and Related Disorders and the director for REACH (Research and Education with Autistic Children at Hopkins). Her research focus is in the genetics and neuropsychological basis of autism. Dr. Landa and her research team are involved in multiple international research collaborations.

Researchers Develop Experimental "Brain Repair" Compound

Researchers at Guilford Pharmaceuticals in Baltimore, Maryland are working on the development of immunophilin compounds, a novel class of medication that is proving to exert potent protective and regenerative effects in the brains of laboratory animals.

The first such compound to be effective, GPI-1046, was administered to rats and mice with Parkinson's Disease. Parkinson's disease is a form of brain damage in which the brain cells that produce the neurotransmitter (or "brain chemical") dopamine die. Once these cells are gone, the brain no longer manufactures enough dopamine to create smooth body movements, and patients develop tremors and stiffness.

In the GPI-1046 experiment, researchers exposed healthy animals to brain toxins that selectively destroy nigrostriatal dopamine neurons, the neurons (or brain cells) that die in Parkinson's. When the team gave GPI-1046 simultaneously with the toxin more than twice as many neurons remained alive as survived in animals who did not receive the compound. More importantly for eventual use in treating brain damage, when GPI-1046 was administered after maximal damage to the brain had already occurred, it produced a regenerative effect. The few nigrostriatal dopamine neurons left alive sprouted new connections to each other, resulting in a 30% restoration of dopamine levels. Even more encouraging, this partial regrowth of nerve connections resulted in nearly full recovery of function: with neurotransmitter levels restored to only 30% of normal, the animals could move well. Researchers characterized their behavior as "near-normal".

Experimenters also reported that GPI-1046 did not promote aberrant brain growth when given to normal animals, an essential requirement of any drug being developed with the goal of ultimately treating brain damage in humans.

NAAR Scientific Advisory Board member Solomon Snyder, M.D. of the Johns Hopkins University School of Medicine, who presented these research results at the annual meeting of the American College of Neuropsychopharmacology, was quoted in *Psychiatric Times* (April 1997) as saying that these compounds "represent the first instance of agents that make damaged nerves grow back with restored function".

Based on these promising results, researchers at Guilford Pharmaceuticals are moving forward with further research and development of neuroimmunophilin compounds as potential treatments for a range of neurodegenerative disorders such as Alzheimer's Disease, multiple sclerosis, traumatic head and spinal cord injuries, stroke and peripheral neuropathies.

Reacting to news of GPI-1046's development, Eric London, M.D., Vice President-Medical Affairs of NAAR, commented: "The development of these neuroprotective and neuroregenerative compounds is tremendously exciting, and provides a basis for hope that eventually treatment agents can be developed for all neurological disorders, including autism. Although these results are preliminary, we must work to insure that researchers at Guilford and elsewhere include autism as a target disorder in their research and development focus." ♦

A Partial Listing of Genetic Research Sites Needing Participants

Collaborative Linkage Study Sites

Duke University Medical Center
Contact: Chantelle Wolpert
Tel: 800-283-4316; Fax: 919-681-7043
chantell@dnadoc.mc.duke.edu

University of Iowa
Contact: Debra Childress
Tel: 800-793-5715; Fax: 319-353-4987
childres@blue.weeg.uiowa.edu

Johns Hopkins University
Contact: Stacey Clark
Tel: 410-614-4948; Fax: 410-955-8691
sclark@welchlink.welch.jhu.edu

Tufts/New England Medical Center
Contact: Brian Winklosky
Tel: 888-217-4935; Fax: 617-636-8318
brian.winklosky@es.nemc.org

NAAR encourages family participation in high-quality, peer-reviewed biomedical research projects in autism.

While NAAR cannot evaluate and/or recommend individual projects, we are pleased to publish contact information as a service both to researchers and to families considering participation.

This is only a partial listing of research sites that are recruiting families for participation, and the information provided here for listed sites is limited. Each site has different research objectives and different parameters for participation. Some of these sites have collaborative sites which are not listed.

For additional information please contact the sites directly or call NAAR at (888) 777-NAAR. This listing will be updated and expanded in future issues of NAARATIVE.

Other Research Sites

University of Chicago Medical Center
Contact: Linda Lambrecht
Tel: 773-702-3052; Fax: 773-702-9929
llambrec@yoda.bsd.uchicago.edu

Mt. Sinai School of Medicine
Contact: Christopher Smith
Tel: 718-367-5727; Fax: 212-849-2505
cjsms@cunyvm.cuny.edu

The College of New Jersey
Contact: Lynn Waterhouse, Ph.D.
Tel: 609-771-2363
lynwater@tcnj.edu

Stanford University Medical Center
Contact: Donna Spiker, Ph.D.
Tel: 415-723-7809; Fax: 415-723-5531
ms.dks@forsythe.stanford.edu

Principal Sites of the NIH Autism Research Network

University of California at Los Angeles
Contact: Marian Sigman, Ph.D.
Tel: 310-825-0180; Fax: 310-825-2682
msigman@ucla.edu

University of Colorado HSC
Contact: Sally J. Rogers, Ph.D.
Tel: 303-315-6497; Fax: 303-315-6844

Albert Einstein College of Medicine
Contact: Michelle Dunn, Ph.D.
Tel: 718-430-2130; Fax: 718-430-8786

University of Pittsburgh
Contact: Nancy J. Minschew, M.D.
Tel: 412-624-0818; Fax: 412-624-0930

University of Rochester
Contact: Susan Hyman, M.D. (phone)
Patricia M. Rodier, Ph.D. (fax & email)
Tel: 716-275-2986; Fax: 716-244-2209
rodierp@ehsct7.envmed.rochester.edu

Eunice Kennedy Shriver Center
Contact: Helen Tager-Flusberg, Ph.D.
Tel: 617-642-0180; Fax: 617-642-0185
htagerf@shriver.org

University of Utah/Utah State
Contact: William McMahon, M.D.
Tel: 801-588-3559; Fax: 801-588-3585

University of Washington
Contact: Cathy Brock
Tel: 800-994-9701; Fax: 206-685-3157
c.brock@u.washington.edu

Yale University Child Study Center
Contact: Kathleen Koenig
Tel: 203-785-3488 ext. 2
Fax: 203-737-4197

(continued from page 1)

NIH Funds Autism Research Network

The collaborative network came about as a result of a congressionally mandated Conference on the State of the Science in Autism, which took place in April 1995 to identify gaps in the knowledge of autism and directions for future research. Dr. Marie Bristol of NICHD, coordinator of the 1995 NIH conference and of the autism network, said: "This network will begin to make the research recommendations from the NIH conference a reality. The collaborative project responds to a request from Congress for more research on autism."

The network will bring together premier autism researchers as well as outstanding scientists who have never before worked in autism research to find out how the disorder develops. Among those new to the field is a geneticist, Dr. Gerard Schellenberg, who discovered genes for Alzheimer's and Werner's syndromes; Dr. Martin Reite, a nationally known expert in magnetoencephalography, a sophisticated brain imaging technique that will be used to study sensory processing in autism; Drs. Patricia Carpenter and Marcel Just, experts in the study of brain functions, particularly executive function and working memory; Dr. Patricia Kuhl, renowned for her electrophysiological research on infant processing of language; and Dr. William Eddy, a statistician who has developed software for analyzing the complex digital data generated by functional magnetic resonance imaging (fMRI), a technique that allows researchers to observe the physical changes that take place in the brain during various mental activities.

The network involves nine multisite projects and more than 65 scientists. The nine project leaders are: Geraldine Dawson, Ph.D., University of Washington; Michelle A. Dunn, Ph.D., Albert Einstein College of Medicine; Nancy J. Minshew, M.D., University of Pittsburgh School of Medicine; Patricia M. Rodier, Ph.D., University of Rochester Medical Center; Sally J. Rogers, Ph.D., University of Colorado Health Sciences Center; Marian Sigman, Ph.D., University of California at Los Angeles; Helen Tager-Flusberg, Ph.D., Eunice Kennedy Shriver Center; Fred R. Volkmar, M.D., Yale University; and Reed Warren, Ph.D., University of Utah.

The European Consortium, linked to the network through the Yale project, is funded independently by the British Medical Research Service and the Wellcome Fund. It is headed by Sir Michael Rutter of the University of London and Dr. Anthony Monaco of Oxford University.

Universities involved in the research network as subcontractors are Case Western Reserve, Carnegie Mellon, Johns Hopkins, Tufts/New England Medical Center, Utah State University, the University of Iowa, and the University of California at Los Angeles. Additional scientists are collaborating with the network at Vanderbilt University, the Universities of Florida, Montana, and Oregon, and York University in Canada.

"Each of the nine multisite projects is focusing on some unique aspect of the problem, but all will study various causes of autism, brain development, and behavior in autism", Dr. Bristol said. "They will all use a common diagnostic system, family history, and will share aspects of procedures and protocols. Researchers in the network have complementary or sometimes even competing ideas as to the nature of autism and will be vying with one another to confirm their particular hypothesis about its cause and development. Plans are being considered to immortalize DNA cell lines for use in future research by these and other researchers."

Genetic studies will include studies of hundreds of families with more than one child with autism at the University of Washington and the Yale University project. Molecular genetic studies are underway at the University of Chicago site of the Yale project, and family genetic studies comparing autism and Asperger's syndrome will be conducted at Yale and UCLA. The project at the University of Rochester is headed by Dr. Patricia Rodier with the collaboration of NAAR Scientific Advisory Board member Dr. Susan Hyman. This project is studying possible genetic mutations related to exposure to toxic substances before birth and the possible role of the HOX gene in autism. The University of Utah/Utah State project is examining the possibility of an immunogenetic cause of autism.

Across these varied projects, the brain development and behavior of children and adults with autism will be compared to those with mental retardation, megalencephaly, fragile X syndrome, Asperger's syndrome, childhood disintegrative disorder, obsessive-compulsive disorder, specific language impairment, or other developmental disorders. State of the art techniques in measuring brain structure and function will be used in all projects including electrophysiological techniques at the University of Washington, the University of Colorado, and The Albert Einstein College of Medicine.

Brain functions in autism will be examined using fMRI at the Pittsburgh, Yale, UCLA, and Shriver Center projects. An animal model of autism is being used at Rochester to investigate how brain connections develop after very early loss of key elements of the brain stem. The University of Colorado project will focus on sensory and motor development in autism and its role in later cognitive and social development and performance. The Albert Einstein project will provide the most thorough study of hearing in autism to date.

The University of Washington project will use home videos of first and second birthdays to try to identify early indicators of which children will regress after apparently normal development. Communication, emotion, affect, and brain responses to linguistic and social stimuli will be studied at the University of Pittsburgh, the Shriver Center, the University of Washington, and UCLA. The Shriver Center will investigate Theory of Mind in autism, the hypothesis that complex, flexible, functional language requires the ability to infer what others in the conversation are thinking. This project also will identify communication and symbolic representation in very low functioning persons with autism using computerized learning/teaching techniques.

The UCLA project will compare two interventions to accelerate language development. Both the UCLA and Yale groups will follow children diagnosed in the preschool years to determine the accuracy of the early diagnosis and to assess how outcome relates to age and intervention. A follow-up conference on implications for treatment from these and other neurobiological studies is planned for 1998.

NAAR has expressed its appreciation to the NICHD and the NIDCD for this significant commitment to autism research, and has indicated its willingness to help recruit the more than 1,000 persons with autism needed to make it a success.

Families are strongly urged to participate. A listing of principal research sites of the NIH Autism Research Network appears on page 10. ♦

NAAR Receives \$500,000 Expansion Gift

A private foundation has pledged \$500,000 over a two-year period to enable the National Alliance for Autism Research to dramatically expand its efforts to advance biomedical research in autism in the United States.

Acknowledging the gift, Karen Margulis London, NAAR's President, said: "This extraordinarily generous grant will give a tremendous boost to our efforts at a critical time. It will enable us to hire professional staff, set up our first permanent offices and strengthen our partnerships with families and the scientific community.

"Our ability to raise money to fund and otherwise promote biomedical research in autism will be significantly enhanced, particularly since our administrative costs will be covered for two years and we will be able to tell contributors that more of every dollar of their donations will be used in direct support of autism research. We are grateful to the donors for their confidence in NAAR and their commitment to our work."

A representative of the foundation said: "Our foundation has a long-standing commitment to autism and autism research. The vision we and others share is the hope that we may someday understand the mystery of autism and significantly help individuals with autism. Over the years, we've realized that while private support of individual autism researchers and projects is worthy and important, to truly put autism research on the map requires mounting a national mobilization of efforts garnering the broadest possible scientific and financial resources. We believe that NAAR is poised to become just such a national organization. Its determination to advance autism research and its dedication to a high level of organizational and scientific quality prepare NAAR to serve in this crucial mission. In giving this pledge for expanding NAAR's professional operational capacity, it's our hope to help enable NAAR to build itself into the kind of large-scale, dynamic and enduring public organization which autism research deserves and needs. We hope that our commitment will inspire others to join in supporting NAAR." ♦

Wynton Marsalis Attends NAAR Benefit Reception

Musician Wynton Marsalis, a member of NAAR's Honorary Board, attended a reception following a performance at Princeton University's McCarter Theatre. Addressing a large group of NAAR supporters, Mr. Marsalis said:

"Many times, as we grow and mature, we find different ways to extend ourselves past our immediate surroundings. Community service used to be something abstract to me, but we come to realize that if something affects one person's child, it affects all of us. This is a great cause and autism is a serious thing."



Above: NAAR President Karen Margulis London welcomes Mr. Marsalis to the benefit reception

John Lithgow and Kathy Bates to Perform in NAAR Benefit



Emmy award winner John Lithgow (*Third Rock from the Sun*) and Academy award winner Kathy Bates have graciously offered to perform in an exciting benefit for NAAR and the Achievable Foundation, a charity that provides support services to the developmentally disabled community in the Los Angeles area. The benefit, entitled "An Evening of Compassion and Commitment", will be held on Friday, October 24, 1997 at the Directors Guild of America in Los Angeles. Mr. Lithgow and Ms. Bates will perform a number of scenes from their favorite plays. Honorary Chairs of the benefit are NAAR Honorary Board members Joe and Arlene Mantegna and Aidan and Elizabeth Quinn, as well as Achievable President Kent Graham, partner in the law firm O'Melveny & Myers.

We hope that our L.A. supporters will "save the date" for what is sure to be a wonderful evening. For more information about corporate sponsorship and tickets, please call NAAR at (888) 777-NAAR.

Research Partners Program

A Unique Opportunity

NAAR has established a unique opportunity for significant donors to sponsor research projects that have been recommended for funding by NAAR's Scientific Advisory Board. The Research Partners Program provides donors the opportunity to sponsor specific NAAR awardees. A NAAR Research Angel (\$100,000+) or Research Partner (\$30,000+) provides the entire funding for one or more researchers. Grants typically will be in the amount of \$30,000 per annum and for one year; however, special opportunities to sponsor autism fellowships and multi-year and multi-site collaborative projects are also needed. The award may be named in honor of the donor or a person designated by the donor.

An Opportunity for Collaborative Efforts

Research Angels and Research Partners may be individuals, families, foundations, corporations, institutions or other autism organizations or chapters which wish to advance biomedical research. Some donors may be interested in sponsoring a particular research project because of a specific interest in one area of autism research, such as immunology or neuroimaging. Other donors may be interested in funding autism research in honor, love or memory of a child or grandchild with autism, distinguished autism researcher, or other special person. Organizations or support groups that undertake a specific fund-raising benefit for NAAR, such as a Golf Tournament or Benefit Concert, may contribute the proceeds to provide full support of research grants and have the award named after the organization, group or benefit.

Research Partner Awards Go 100% to Awardee

Each donation of a Research Partner is considered a dedicated gift, i.e. a donation specifically to fund a NAAR Award. As such, Research Partners are assured that their entire donation goes to supporting a Research Award. Research Angels and Research Partners will work with NAAR's Medical Affairs Committee to review and select one or more specific SAB-approved projects for funding. They will receive all scientific and financial reports prepared by the researchers so sponsored and will, wherever possible, meet with the researchers to review prospective projects and be updated on scientific results. Research Angels and Research Partners will also, wherever possible, be recognized for their generosity in publications authored by the sponsored scientists with respect to the research funded by such benefactor. They will also receive an invitation to attend NAAR's Scientific Advisory Board meeting.

We are deeply honored by the commitment to autism research evidenced by NAAR's first Research Partners, The Harold Broitman Foundation and Audrey Flack and Robert Marcus. If you or your organization would like to become a Research Partner, please contact David Maxson or Karen London at 1-888-777-NAAR.

Opportunities for Giving

The autism research sponsored by NAAR is made possible by the generosity of donors. To acknowledge other pacesetter contributions to NAAR and also to encourage others to participate in a significant way to the advancement of autism biomedical research, NAAR has specified the following other leadership categories:

Research Patrons (\$10,000+)

Research Benefactors (\$5,000+)

Research Leaders (\$2,500+)

Research Associates (\$1,000+)

Research Supporters (\$250+)

All NAAR supporters will be recognized in NAAR's Annual Report. Supporters may select a variety of ways to contribute to NAAR's mission:

Gifts of Cash or Securities—Gifts of cash or securities may be eligible for a matching gift from your employer.

Gifts to United Way—NAAR can be designated as the charity of choice for donors who participate in a United Way program through their place of employment. Please remember NAAR when United Way selections are made!

Memorial Gifts and Gifts for Special Occasions—A memorial or special occasion gift creates a thoughtful remembrance of someone you love. Upon receiving your gift, NAAR sends an acknowledgment that a memorial or special occasion gift has been made.

Bequests—A bequest is a special way to support NAAR research and can be a permanent memorial in your name or that of someone you love. Through a will you might consider gifts greater than may have been possible during your lifetime.

To remember NAAR in your will, the following forms are suggested for discussion with your attorney:

For a specific amount:

"I give, devise and bequeath the sum of \$____(or ____%) of my estate to the National Alliance for Autism Research with headquarters at 66 Witherspoon St., Suite 310, Princeton, NJ 08542."

For a residuary amount, after satisfying other bequests:

"I give, devise and bequeath all (or a specific portion of) the rest, residue and remainder of my estate, both real and personal to the National Alliance for Autism Research with headquarters at 66 Witherspoon St., Suite 310, Princeton, NJ 08542."

(continued from page 1)

An Embryological Approach to Autism

the brain might produce echolalia, or resistance to change, or just about any of the other behaviors parents see in their children. Knowing what part or parts of the brain are affected is essential to an embryologist. If this parent had asked me to study a syndrome that caused blindness, for instance, I would have had a place to start, since we know exactly what parts of the brain are necessary for vision—and I could have looked immediately at the periods when these parts of the brain are forming in the womb. But the research on autism told me very little about where in the brain the extremely varied problems in autism were being caused. So I wrote to the parent, saying I was discouraged. Given the state of knowledge at the present, I didn't see any way an embryologist could study autism until a great deal more was known.

But shortly after that, purely by happenstance, I stumbled across some new results that changed my mind completely about the possibility of studying the causes of autism, and I have been hard at it ever since. The editors of NAARATIVE have asked me to describe the findings that gave me the clue I needed—as well as some of the studies we have completed or initiated over the past three years since then.

Eureka!

Shortly after I had written back to the parent, I went to the annual meeting of the Teratology Society ("teratology" means birth defects). Usually I don't go to the clinical talks because they are rarely about the nervous system, which is what I study. (Clinical presentations in teratology often focus on heart defects, limb defects and other structural malformations. Not defects of the brain.) That day a clinical talk called, "Thalidomide embryopathy: An insight into autism?" was scheduled for 4:30 in the afternoon. Unexpectedly, the speakers were two pediatric ophthalmologists. I was sleepy, and I remember debating whether to go to the talk or take a nap—and since I couldn't imagine what an ophthalmologist would have to say about autism the nap seemed like the better idea.

Today I am very happy I decided to skip the nap. The presenters, Marilyn Miller and Karin Strömmland, were discussing eye motility in thalidomide babies—all of whom were now of course grown to adulthood. I was dumbfounded when Miller described her data. In fact, as I have told many people, I felt as though a curtain were being lifted, allowing me to "see" the disorder at last! I was literally hyperventilating.

What Miller and Strömmland had discovered was that a large and significant number of thalidomide babies also had autism. As many readers will recall, thalidomide, which women were prescribed by their physicians for morning sickness, caused an epidemic of birth defects in Europe in the 1960s. Of course as a scientist studying birth defects, I was familiar with thalidomide (many readers over 40 will remember the LIFE magazine photographs of tiny children with terribly stunted limbs). But until that instant I had had no idea that these children also had extremely high rates of autism.

It was a Eureka moment. Because the researchers knew when the mothers of these babies had taken thalidomide, they had for the first time ever conclusively identified the time or origin for some cases of autism.

The story of how Miller and Strömmland made this discovery is a fascinating case history of serendipity's role in the progress of knowledge. There they were, investigating eye motility in thalidomide adults, when they began to notice that a number of these subjects also had an obvious "mental" syndrome involving deficits in language, social skills, and other areas. This came as a surprise to them; they hadn't been aware that thalidomide victims had behavioral problems in addition to their obvious physical issues.

But they didn't know what they were looking at. They knew they were seeing something, but since neither of them had been trained to diagnose any kind of brain disorder, they had no idea what it was. So they called in Christopher Gilberg, a Swedish psychiatrist who also just happened to be the author of a well-known textbook on autism, to take a look. Of course Gilberg saw at once that in addition to having defects in eye motility, these thalidomide victims also had autism. In

my view this story makes Marilyn Miller and Karin Strömmland pretty special clinicians since very few physicians can pick up on a syndrome in which they have received no training at all. Miller and Strömmland certainly were not looking for autism, and yet they found it. Many researchers would not have.

Miller and Strömmland discovered that the rate of autism in thalidomide babies was extraordinarily high—far higher than that found in the general population. Clearly, the thalidomide had caused the autism. But even more interestingly, they found that the rate of autism in thalidomide babies exposed to the drug between the 20th and 24th days of gestation (counting from the day of conception, not from the first day of the last menstrual period) was 33 percent. The rate of autism in thalidomide-babies exposed to the drug at other times in the pregnancy was 0 percent. Their research told them exactly when in the pregnancy—exactly which days—the autism injuries occurred.

They were able to nail down the precise days because all of the thalidomide adults had minor external defects (such as ear anomalies) in addition to their autism. We know when the various birth defects occur in pregnancy, because we know exactly which parts of the embryo are developing on each day of pregnancy. Since autism was associated especially with anomalies of the ear—which develops very early—this meant it had to happen at an early stage in a baby's embryonic life.

It would be impossible to exaggerate the importance of Miller's and Strömmland's discovery to autism research. Because we know the time when most of the brain cells (or "neurons") form to within a few days, knowing the time of injury in autism tells us which neurons were injured. And the answer to this question has turned out to be completely

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unexpected: between days 20 and 24 of development, the structure being formed is neither the cerebellum nor the temporal lobes (structures reported to be damaged in autism), but rather the brain stem tegmentum. This region is a transitional zone between the spinal cord and the rest of the brain. Evolutionarily, it is the oldest part of the brain, and it is rather similar in many animals, from fishes and frogs to humans. Developmentally, it is the first part of the brain to form. The brain stem tegmentum is crucial to a person's level of alertness, as well as to such basic functions as breathing and heart rate, both essential to survival.

Because the brain stem is vital to sustaining life, researchers have been shocked to learn that the initiating injury in autism might be an injury to the brain stem: we have always assumed that any significant injury to the brain stem would simply kill the developing embryo, just as very serious injury to the brain stem in an adult (through stroke, say, or brain tumor) kills that adult. We can live with damage to many parts of the brain, but if the brain stem is massively impaired, we die. So to learn that we have an entire population of healthy young children who suffered brain stem injuries very early in the womb: no one was expecting this.

What happened in the thalidomide victims with autism, it seems, is that they were "fortunate" to suffer brain stem damage mild enough to allow survival, but serious enough to affect motor and sensory functions. Some of them had malfunctions of eye movement; others had malfunctions of the muscles of facial expression; some had both. All had hearing deficits. These neurological symptoms agree with what we know about the brain stem cells that form on days 20 to 24. Thus, the symptoms of the thalidomide cases support the idea that these individuals were injured during this period of embryological development, just as indicated by their ear malformations.

I am not suggesting that every child with autism has ear and hearing abnormalities, or that every child has problems with eye movement or facial movement. I am only suggesting that some do—including the thalidomide cases—and that these cases tell us something that is important for figuring out what part of their brain was damaged and when the injury occurred. However, since "thalidomide autism" could be different from other forms of autism, we should ask how common it is to find evidence of early injury among the whole population of people with autism.

Evidence that autism arises very early in pregnancy in many cases of autism

In fact, the idea that autism might arise very early in pregnancy was suggested long ago, but never really took hold. Steg and Rapoport noted a significant number of minor physical anomalies among children with autism as far back as

1975, and quickly realized that the nature of these anomalies indicated brain injuries occurring during the first trimester of pregnancy. Moreover, virtually every study of minor malformations and deficits in autism since then has also pointed to a very early "originating" injury. In all, five separate strains of evidence support this conclusion:

1. ear malformations in autism

Several studies of minor physical malformations in autism have found the ears to be the body part most commonly affected. This finding points to an early injury to the embryo since the ear forms very early in development, starting at Day 23. Our own team has recently completed an analysis of minor malformation data from Bryson's Nova Scotia prevalence study, and we also found that ear malformations are far more common in children with autism than in children without. (The Nova Scotia study is one of the most ambitious "prevalence studies" ever undertaken in autism research. In prevalence studies researchers look at an entire population in order to find out how many members of that population have any particular condition—in this case, autism. Bryson and her team interviewed over 65,000 Nova Scotian children, and found that 67 of them had autism.)

Forty-two percent of the children with autism in Nova Scotia had "posteriorly rotated" ears—ears in which the ear lobe is moved forward, and the top of the ear is tilted back, making the ear look as if it has been twisted, or "rotated," backwards. Only 18% of the children without autism had posteriorly rotated ears, as well as 13% of a control group of children with other developmental disabilities apart from autism. Ear development is closely tied to brain development, which means that whenever we see a malformed ear on an infant we have to worry that that child

may have suffered brain damage. Certainly not all babies with ear malformations have brain damage—as we noted, 18% of the normal children in Nova Scotia had these malformations, too. But ear malformations are always a red flag.

2. eye movement in autism

Many, many people with autism whose mothers had perfectly healthy pregnancies show the same eye anomalies Miller and Strömland found in the thalidomide adults. A recent study of eye motility in autism found that 7 of 34 subjects had strabismus. ("Strabismus" is any deviation in the position of the eyes, such as being cross-eyed or having one eye that moves more to the side.) As well, 31 of 34 subjects showed abnormal optokinetic nystagmus, a condition in which the eyes jiggle excessively as they pursue a moving target.

3. anomalies of facial muscle movement in autism

This was a major finding of the thalidomide study, of course, but other studies have found facial muscle movement problems in people with autism whose mothers certainly did not



The Rodier team examines a sequencing gel in which the nucleic acid sequence of DNA from a subject is displayed.
 Standing: Susan Hyman, M.D. (NAAR SAB member), Patricia Rodier, Ph.D.
 Seated: Denise A. Figlewicz, Ph.D., Jennifer L. Ingram





take thalidomide during pregnancy. Interestingly, children with Moebius syndrome, a congenital syndrome that causes a lack of facial movement, have a very high rate of autism. (Many readers know of Moebius syndrome through the young girl in California who couldn't smile; this was a case of an otherwise normal child who suffered from the syndrome.) As many as 20% to 50% of children with Moebius syndrome have been reported to have autism spectrum disorders.

It makes sense that children with Moebius syndrome would also have autism: like the thalidomide adults, some of these children must have suffered an injury to the brain cells that work the facial muscles. In essence, these children have faces that are paralyzed; they cannot move their facial muscles in order to form a smile. The muscles are there, but the connection to the brain is not. Whenever you see a child with autism whose face is "expressionless" the explanation could be as simple as a failure of normal function in the motor neurons controlling the muscles of the face. It is not that some of these children with autism do not want to smile; it is that they can not smile.

Of course, some children have odd facial movements, rather than no movement at all. We don't know what causes this, but one possibility is that during the embryonic stage of development their facial muscles became connected to (or "innervated" by) the wrong neurons. The general phenomenon of neurons being miswired is known to occur after some kinds of early brain damage in animals, so this is certainly a reasonable hypothesis to investigate in autism.

4. hearing deficits in autism

Finally, hearing deficits are common in people with autism, with as many as 30% to 50% of people with autism showing evidence of a hearing deficit according to one study. While hearing involves many neural and other structures that develop over a long period, the thalidomide studies demonstrate that very early injury can result in hearing deficits.

5. autopsy evidence

Our team has had the good fortune to be able to study the brain stem of an unusually well-documented human case of autism. (Again, this was a "normal" case of autism, not one caused by thalidomide). This patient, a grown woman with autism, died in Rochester and her autopsy was performed at The University of Rochester 20 years ago. Fortunately for us the tissue samples had been saved, because the patient's psychiatrist—John Romano, a brilliant physician—was so interested in her case. He was 85 years old when he gave me the samples, and still working every day; he and I pored over his thousands of pages of notes together.

I am thankful he lived to see this woman's brain provide a big clue to the cause of the disease. While much of her brain had already been used in other studies—and had appeared to be completely normal—most of the brain stem remained intact.

And of course, that was the part we were interested in. When we looked, we found exactly what the thalidomide studies led us to expect: her facial motor neurons were almost completely absent (as was the superior olive, a brain structure involved in hearing.) Not surprisingly, the notes of her caregivers always described her as expressionless—though some of her pictures show grimaces that suggest her facial muscles still had some remaining connection to the brain. Most photographs of her show the slack jaw, drooping lower lip, and downturned mouth corners of Moebius syndrome.

We also found a marked shortening of her brain stem that could only have occurred very early on in development.



In all, we have evidence that autism occurs very early in pregnancy from five quite different sources. This is what scientists call "converging evidence," and it is especially convincing because it comes from so many different sorts of studies. When you get the same answer from an epidemiological study, evaluation of autism cases in clinics, a study of exposure to a toxic agent (thalidomide) and studies of brain tissue (our autopsy case)—it becomes almost impossible to imagine an error of execution or interpretation that could have occurred in all of these studies. Scientists love converging lines of evidence, because when research from completely different fields begins to come together, that is the moment we know we are on the right track.

“Scientists love converging lines of evidence, because when research from completely different fields begins to come together, that is the moment we know we are on the right track.”

By now, of course, you may be wondering why people who are interested in autism have not picked up on these assorted findings that identify the time and

location of injury. While some of this research is too new to be familiar to most researchers, scientists in the field probably missed the importance of the older studies because they didn't have enough information to understand what those findings meant. It was not until the thalidomide study that we had the necessary context in which these other scattered findings of ear and hearing anomalies finally made sense. Moreover, the parent who first steered me toward autism research was right: what had been missing from the field was the developmental perspective—knowing when the autism developed in an embryo's life was the clue that tied the other findings together.

Apart from this, in all likelihood researchers, clinicians, and parents alike probably overlooked the data concerning eye and ear anomalies in autism simply because they were too busy dealing with the far more obvious problems with which an individual with autism struggles. That is why it took thirty years to notice the high rate of autism in thalidomide victims—the limb malformations were even more dramatic than the nervous system deficits. By the same token, a child born without the capacity to relate normally to other people has a problem so serious that ear rotation and jerky eye movements seem like no problems at all.





Experimental evidence

Once sufficient evidence accumulates that a certain disorder happened in a certain way at a certain time, it becomes possible to turn the question around. We can ask ourselves: if we purposely injure the brain stem early in development, will we produce a case of autism?

We can do something close to this in rats, whose brain structures are very similar to ours. And we find that when we expose the developing rat brain to a teratogen (a substance that causes birth defects) very early in pregnancy we do indeed produce permanent reductions in the number of eye muscle motor neurons, just as in the autistic brain. We also produce the exact shortening of the brain stem found in our autopsy. And last, but far from least, these damaged rat brains also reveal a form of damage to the cerebellum similar to that found in the brain autopsies performed by Margaret Bauman and her team, as well as in Eric Courchesne's MRIs.

Of course, the first question that springs to mind is: are the rats autistic? The short answer is, we don't know. Diagnosing autism in humans is already tricky enough—is there anything that children with autism do that normal children never do? Probably not.

So while we do not see any obvious behavioral oddities in these brain-damaged rats, that doesn't mean that there aren't any behavioral abnormalities there to see. We wouldn't be able to see behavioral oddities in rats whose IQ s have been reduced by 50%, or in rats who are completely blind, without having specific tests to run: just "eyeballing" a rat doesn't tell even an experienced researcher much.

In order to know whether these "autism-brain" lab rats are in fact autistic, we would need to test them for autism—and how do you test an animal for autism? In humans autism is diagnosed in entirely human terms: speech, smiling, eye contact, imaginative play, and so on. I have racked my brain trying to think of analogous animal behaviors, but so far I've come up with nothing at all. For instance, take eye contact. Most animals only make eye contact as a threat gesture—so does this mean that rats sniffing each other would be more like eye contact? Maybe, but it would take a great deal of research to decide.

Before we can figure out the question of autism in animals, we need to work very hard to find some simple behavioral measures that distinguish human cases of autism from humans without autism. None of the official diagnostic criteria do this. Repetitive behaviors are seen in all kinds of other conditions, speech delay occurs in mental retardation as well as in autism, social deficits appear in many kinds of brain damage, etc., etc. It may be that there are no measures that are truly discriminating, but I think there probably are, and we just haven't looked for them.

Susan Bryson, at York University in Toronto, has been studying a task that may be a good discriminator. She is interested

in the kind of attention that is "automatic"—the kind that is operating when you focus on something new in your environment. In her studies, a child sits in front of a screen while a video camera records his face. When lights appear on the screen, the gaze of all children, even infants, goes to the part of the screen where something is happening. Children with autism seem normal at this.

A variation is the introduction of a second set of lights. If the first lights disappear, and new flashes begin in another spot, the eyes move to the new lights. Children with autism may be a little slow to shift to the new lights, but they usually shift fairly well. What seems to discriminate children with autism from others is a second variation: the first flashes appear and then stay on while a second set is introduced. The normal response is to "disengage" from the first set, and shift the gaze to the second. Children with autism are decidedly impaired on this version. It is as though their attention, once captured, is "stuck" on the first stimulus.

Notice that the two variations require the same eye movements, so the problem is not caused by any eye motility problems children with autism may have. Further, because

the task requires no instructions or practice, it can be done with children who have no language at all. Very young or severely disabled children can succeed. In fact, Dr. Bryson has found that young children with Down syndrome behave like normals on this task, while autism seems to interfere with disengagement even in older children with high IQ s.

We don't know whether this particular behavioral measure will end up distinguishing all children with

autism from all children without autism, but this is the kind of "symptom" we're going to need to find in order to test animals for autism. We need a simple, readily observable behavior like this that we can test in our "autism brain" animals.

Back to the brain: the rats with the autism-brains are interesting, because while we exposed rat embryos to a teratogen well before the cerebellum was forming, we still saw damage to the cerebellum as well as to the structures that were forming at the exact moment of toxic exposure. This paradox had bothered Miller and Strömland: they were puzzled as to why a serious brain injury appeared to be occurring before the brain even existed! If there isn't any cerebellum in existence between Days 20 and 24, how can a dose of a toxic agent taken then damage it??

What we think happens, and this is speculation, is a "downstream" effect in which damage to one structure leads to damage to another structure, down the line. There are many examples of this kind of "chain reaction" injury in the developing nervous system. So far I've been talking about injuries in which brain cells are actually lost, but there is another kind of brain injury as well: cells being wired to the wrong cells. Brain cells are assembled like the parts in electrical circuits, with signals being passed from one cell to another. These circuits are set up during development.

“Diagnosing autism in humans is already tricky enough---is there anything that children with autism do that normal children never do? Probably not.”





Young cells in the embryonic brain shoot out projections to other cells, forming contacts that will persist throughout life.

One of the mysteries of brain development is how these tiny wire-like extensions of cells find their way to the correct targets. In some cases it appears that they use pre-existing cells as "landmarks." Our theory is that the loss of some early-forming cells, as we see in autism, not only deprives the individual of the function of those cells, but may also eliminate the landmarks other cells need to make their connections. If this is true, then some cells that are perfectly healthy may end up with the wrong connections. This might explain some of the strange sensory problems that so many parents, therapists, and people with autism themselves describe: crossed wires in the brain.

We are now studying what happens in the subsequent development of the brain after an early injury to the motor neurons. We suspect that loss of these early-forming neurons will create disturbances in the sensory pathways associated with hearing, balance, touch, and sensations from the internal organs. To take one interesting example: Donna Williams writes of not knowing that she needed to go to the bathroom—not getting the sensory signal—until the situation was a true emergency. She solved the problem by setting a watch alarm to remind herself. We'd like to know whether this is common to many or most cases of autism, and if so we think this would indicate damage to the particular sensory pathway from the bladder or the bowel to the brain.

The future

In science, the value of a finding is based not only on how many issues it settles, but also on whether it suggests new hypotheses to be tested. To us, one of the most exciting aspects of our embryological findings is that they suggest some very new ways to study the genetics of autism.

Many previous studies have had no hypothesis at all. That is, they were attempts to screen for mutations in all the genes of people with autism. This is a tall order. But while no one has any idea which genes are abnormal in genetically-caused autism, many of the genes controlling brain stem development are well-known. But of course, until now, studies of these genes were not directed at understanding autism—instead, early development genes have been of special interest primarily to cancer researchers! (Their idea is that the same genes that cause growth in the embryo may also cause tumorous growth in the adult if they somehow become reactivated later in life. In essence, cancer specialists believe, a tumor can be thought of as a group of cells that have "regressed" to an embryonic state.) Fortunately for autism researchers, because there is so much interest in cancer, and so much money available for cancer research, a great deal is known about the genetic control of early development, including that of the brain stem tegmentum.

Once we know that autism begins with a disturbance of brain stem development, the genes involved in that development become prime candidates to play a role in the disease. Mutations in some of these critical developmental genes already have been studied in mice, and the brains of the resulting animals are quite similar to that of our autopsy case! Thus, one of the major projects in our lab is to investigate these genes in human cases of autism. We hope that "piggybacking" on the studies of early developmental genes that have already been done by cancer researchers will allow us to find the genetic causes of autism more quickly.

Where we are now

Today, converging evidence from many different lines of investigation puts the initiating injury of autism in the brain stem. This idea will be surprising to some clinicians, because many researchers believe that the damage occurs in "higher" centers of the brain—because "higher" orders of behavior, such as language and social intelligence, are so impaired in autism. But the fact that higher levels of the brain are not functioning properly does not imply that the higher brain has actually sustained damage. Even a perfectly normal cerebral cortex (and thus far researchers have found the cerebral cortex to be normal in autopsies of autistic brains) would have to function quite abnormally if it receives abnormal input from lower brain structures.

“...some cells that are perfectly healthy may end up with the wrong connections. This might explain some of the strange sensory problems that so many parents, therapists, and people with autism themselves describe: crossed wires in the brain.”

And in fact, many symptoms of autism are most easily explained by brain stem malfunctions. Eye motility abnormalities, hyper-acute hearing, lack of facial expression, unusual sensitivities to food taste and texture, hypersensitivity to touch, oddities of gait, hearing deficits and synesthesias (sensory crossings-over, such as a sound being perceived as a color)—all have been cited as characteristics more common in autistic than in non-autistic populations. While each of these symptoms could be effected by damage to several different levels of the nervous system both "high" and "low," the simplest explanation is that they result from an injury to the brain stem.



Our results up until now do not come close to solving the mysteries of autism, but I think they should be cause for great optimism. They have told us quite a bit about the kind of injury from which autism originates, and this suggests that developmental studies in particular have the potential to answer many of our questions.

Parents of disabled children have to be adept at searching for something "good" in every misfortune. Now that scientists have found something "good" for autism in the tragedy of thalidomide, I hope—and I believe—that bold new insights into the puzzle of autism are, at last, within our reach. ♦





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Dr. Rodier earned her Ph.D. in Experimental Psychology at the University of Virginia, and then did postdoctoral work in embryology. She taught at the University of Virginia in the Department of Anatomy for six years before moving to The University of Rochester in 1980, where she is a Professor of Obstetrics and Gynecology. Her research has focused on birth defects of the brain, and how they affect its structure and function. She has served on advisory groups for the NIH and the National Research Council, and is presently a member of the Scientific Advisory Boards for the Food branch of the FDA and for the National Toxicology Program. Her research on autism has been funded by grants from NIH and EPA, and she is one of the nine project leaders of the recently announced NIH Autism Research Network (see the News Feature article which begins on page one).

A Note from Catherine Johnson, Editor of Dr. Rodier's Article

On a personal note, I will always remember the day I learned that autism was a form of brain damage—that Jimmy's problem was not just a "chemical imbalance", but a structural difference in his brain. We had been told by our doctor that the structure of his brain was fine, it was just the "connections" that were wrong. I had been holding on to this idea as a source of hope.

That hope was dashed by Eric Courchesne in a lecture on his MRI studies showing structural differences in the autistic brain. I had driven down to Long Beach with my friend Orly to hear him speak, and as we listened to him describing the many abnormalities in his subjects' brains our hearts sank. It was a low point in our lives with autism.

But since then I have learned that many if not most of the various mental disorders and mental illnesses, schizophrenia and bipolar disorder among them, also involve structural differences in the brain. Yet often these disorders can be treated by medication—which gave me hope that one day structural differences in the autistic brain might also become treatable by a drug developed specifically for our children's condition.

Then, a few years after the Courchesne lecture, I attended another conference where I heard Margaret Bauman explicitly state that *structural differences in the brain may be treated through chemistry*. Her message cheered me immensely. When another team of researchers recently announced that even clinical depression—the "common cold" of mental illness—in some cases involves a difference in brain *structure*, not just a chemical imbalance, I knew that finding an effective treatment for autism is possible.

While it can be disheartening to read about "injuries" to our children's brains, it is not a reason to abandon hope. Knowing what is wrong is the first step toward finding the help our loved ones need.

Catherine Johnson, Ph.D. is co-author, with John Ratey, M.D. of Harvard Medical School, of Shadow Syndromes, published in February 1997. She is author of two other books, has been a Contributing Editor to New Woman Magazine for twelve years, and has published in numerous other magazines. She has taught at UCLA and at UC-Irvine. Dr. Johnson is a member of NAAR's Board of Trustees and the mother of a child with autism.



Photo by Cindy Cassutt

Because of Alex....My Odyssey from Denial to NAAR

By Clarence E. Schutt, Ph.D.

My son Alexander is eleven years old. It was not until he was about four that I ceased thinking that he was 'just like me'—bull-headed and slow-to-speak as a toddler, disruptive and inconsiderate in grade school—and accepted his diagnosis.

The long process of arranging for schooling and adapting our family and home to Alex's needs and behaviors helped us appreciate the achievements of those pioneers whose autistic children are now adults. They generously shared their experience, even as they continued to exhaust themselves in giving primary care.

Although Alex was benefiting from the programs and rights for which they had had to fight, I couldn't imagine how I could give even a fraction of the time so many of them gave to improving the lives of our children. As a scientist, I was committed to spending many long hours in the laboratory, and I wondered how my wife could cope, not only with Alex, who "was a handful" (as my mother used to say of me), but with our raising his three older and very talented sisters.

Like many parents, I read everything I could about autism and its causes. I also read broadly in the scientific literature, looking for a way in to the problem. But I couldn't find any sure touchstone within the modern sciences of molecular and cell biology. I knew that many diseases could be understood in terms of specific protein molecules, such as the insulin receptor in the case of diabetes, or a certain dopamine-producing enzyme that was absent in patients suffering from Parkinson's disease. What the cold phrase "autism has no known etiology" meant to me was that we didn't have a clue.

Worse, understanding autism seemed tantamount to grasping the secrets of the brain itself, probably the most complicated structure in the universe. At a minimum, to solve the riddle of autism is to explain our ability to use language in social communication, a task as daunting as trying to find out what it means to be human. Where to begin?

Pharmaceutical companies employ very smart people in important positions, such as Vice-President of Discovery, to define new markets, and to think of strategies for developing new drugs. As a Professor of Chemistry in a university situated at the epicenter of the world's greatest concentration of pharmaceutical research laboratories, I have the opportunity to meet with these influential people. I ask them: "Why not autism?"

The answer, never unsympathetic, is invariably: "We don't know the targets". *Targets* are molecules that control the flow of information, energy, and material through cells. The storied development of antihypertensives (by Ondetti at Squibb and Patchett at Merck) flowed from the discovery that inhibiting a single protein molecule, ACE (angiotensin converting enzyme), could reduce blood pressure. Ondetti and Patchett knew the target they were looking for, the ACE protein. These drugs have saved countless lives. In the field of mental health Prozac works by binding to a class of proteins known as serotonin reuptake transporters...again, the target was known.



These drugs would never have been developed without clearly defined protein molecules for the medicinal chemists to target. So, the question for me, as a parent and a scientist, was: How do we find targets in autism, and thus engage the major pharmaceutical companies in our quest for a cure?

My field of specialization is structural biology, a branch of structural chemistry that aims at discovering and "seeing" (with x-ray detectors and computers) the molecules of life. With these instruments, we can discern the arrangements of atoms on the surfaces of

protein targets of interest. Armed with this knowledge, medicinal chemists can use powerful computer algorithms to design molecules that fit neatly into the atomic crevasses and valleys forming the molecular landscape. In some cases, these designed molecules will occupy these sites, substituting for a missing signal — or competing with a signal that appears in excess, perhaps over-exciting a nerve cell.

Eventually the best ones can be optimized into drugs ready to meet the strict requirements of the FDA. The price of developing a drug is estimated to be about \$400,000,000, roughly one thousand dollars for each person suffering from autism in this country, small when compared to the annual costs of care and schooling.

I began to speak with my fellow structural biologists about autism and the need for targets. About five years ago, Dr. Florante Quiocho of Baylor Medical School drew my attention to a protein he was working on called "the memory enzyme". I was stunned! An individual protein molecule, important for long-term memory, perhaps for learning as well! Could this be the target?

After all, some autistic individuals learn slowly, others remember practically everything. Maybe autism was all about memory and its control and access. The more I read about this protein (CAM-Kinase-II), the more intrigued I became. I found studies describing experiments where mice, trained to carry out complicated spatio-temporal tasks, would easily get confused if the *single* gene encoding for this protein was inactivated. (A major advance in molecular biology is the discovery of how to breed "transgenic mice"—normal except that they lack one or two specific genes.) More specifically, the inactivated or mutated gene was located in cells of the hippocampus, considered to play an important role in conscious memory. The hippocampus seems to integrate our senses and produce "maps" of our surroundings. It is thought by some neurobiologists that these interior "maps" of what we perceive are continuously compared with maps of what we expect to see. In this way, memory and perception become intertwined during the earliest stages of cognition.

Imagine my astonishment, then, at first hearing that Margaret Bauman's celebrated autopsy studies had showed less well-developed arborizations (connections) of nerve cells in the hippocampi of autistic individuals! (In a future column, I will discuss "neuronal plasticity" and other ideas, such as neuronal migration, that are the basis of my private hopes that more





and more useful targets will be discovered in autism, especially as the Human Genome Project unfolds.)

I impulsively told Dr. David Holmes, the Director of the Eden Programs Serving Children and Adults with Autism, where Alex attends school, about these developments. He said, "Why don't you tell our parents and staff about this at our next Membership Meeting?"

To make a long story short, these "messages of hope, scenarios for a future without autism" gave rise to the annual Princeton-Eden Lecture Series, to which we invite leading scientists and service providers to speak each year at Princeton University. My lecture "Because of Alex...", opening the Eden Lecture Series, was a call for more research, for parent involvement in fund raising and advocacy at the National Institutes of Health.

At the end of that lecture, Karen London approached me and introduced herself. The National Alliance for Autism Research was still in embryonic form, but her vision for it perfectly matched the organization I had dreamed about but could see no way of starting myself. Most important for me was the quality and integrity of the scientific review process. Without peer review, no pharmaceutical executive or NIH program officer would ever take us seriously at the next stage.

My wife and I discussed whether I could make the time commitment that a Board position on NAAR would entail. I thought of my son Alex, working "bull-headedly" to make sense of the world from the prison of autism. Could I do anything less? I recalled Jesse Jackson's stirring speech to the Democratic National Convention on the homeless – "They work hard. They work hard everyday. They get up. They look for a job. They work hard. They work hard everyday" – and I reflected on the staggering effort expended everyday by autistic children to open the doors and windows of their imprisoned minds. Maybe NAAR could provide the keys to unlock the closed gates—and I knew where to find the locksmiths.

At some point during NAAR's first Scientific Advisory Board meeting last December at the Harvard Faculty Club, my eyes suddenly welled up in tears at the sight of these world-class scientists, some of whom had encountered the mystery of autism only because of NAAR, applying the wisdom of their years to autism. After relieving Martha Denckla as Chair of the SAB for the evaluation of a particular proposal, I returned the gavel to her with the observation "Now I know what it's like to drive a Maserati!"

As the SAB meeting was ending, and all of these great scientists were rushing back to their labs, energized as I was, I thought back to the day two years before when I first met Karen London at the end of my "Because of Alex..." lecture. She had said then, as she now does almost every day "I have something very interesting to discuss with you." ♦

Clarence E. Schutt, Ph.D., is Executive Vice President and Secretary of the National Alliance for Autism Research. Dr. Schutt is Professor of Chemistry at Princeton University, where he is also Associated Faculty of the Molecular Biology Department, Director of the Graduate Programs In Molecular Biophysics and Chemistry, and a Member of the Program in Neuroscience. His column, "Because of Alex...", will be a regular feature of this newsletter.

Reflections on Shadow Syndromes

By Catherine Johnson, Ph.D.

I first heard about shadow syndromes from the doctor who diagnosed our son. Jimmy had just turned four, but, in a classic case of the parents being the last to know, we could have had a diagnosis much earlier. The reason we *hadn't* seen an autism professional was that every time my husband and I read the list of symptoms in the DSM¹, we couldn't find our child in it. Jimmy was loving, affectionate, connected; he liked other children and badgered me to take him to their houses to play. "Go see baby's house," he would say, tugging at my hand on walks.

We thought Jimmy's problem was language, nothing more. My brother had not talked as a small boy; he was 6 years old before he could express himself well. Today he is fine. A married man with two children, a nice wife, a house, and a good job. (OK, yes, he works in computers. But he is not a microserf². He's your basic Midwestern guy, normal, outgoing, lots of friends, loves basketball and fishing.) Jimmy is like my brother, we told ourselves. He'll grow out of it.

But we were wrong. Still, we were wrong for the right reason: what we were seeing in Jimmy, at that age, was a milder form of autism than the one the DSM seemed to describe. It was autism alright, but, as Dr. Edward Ritvo of UCLA told us, it was *mild* autism. My husband and I sat there on Dr. Ritvo's faded office couch, dumbfounded. Mild autism. What could mild autism possible mean? Was it like mild cancer?

Flash forward six years, and now we know—though unfortunately, in our case, "mild" turned out to be wildly far off the mark. Our situation is moderate-to-severe, depending upon the day, or the hour. But while we are not ourselves living with mild autism, we have now met a number of children and adults with very mild forms of the disorder (and in fact are fairly certain we are intimately related to one or two people who fit the profile...)

As it turned out, Dr. Ritvo was exactly the person for the parents of an outgoing four year old with autism to be seeing in 1991, because he was at that time trying to persuade the autism community that autism was a spectrum disorder ranging from the very severe to the very mild. During our visit, he produced his now-famous Letter to the Editor, published in the *Journal of Autism and Developmental Disorders* in 1988, which had run under the title "Eleven Possibly Autistic Parents". While surveying every single known person with autism in the state of Utah, Dr. Ritvo and B.J. Freeman and their team had discovered some interesting quirks in some of the parents—eleven of whom later proved to meet DSM criteria for the syndrome. And yet there they were, leading independent if difficult lives, getting married, having children, holding jobs. As Dr. Ritvo said to us, "If you had told me 10 years ago there were married people with autism I would have told you you're crazy, they're all living in institutions."

¹Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association. The current edition, published in 1994, is known as DSM-IV.

² See Douglas Coupland's novel *MICROSERFS*.





That moment changed my life. My vision of Jimmy and of our family's future were altered forever, of course; but within the year my career had changed as well after a friend gave me a newsletter containing a one-page article called "Paying Attention to Attention" by John Ratey, M.D. I recognized John's name; he was one of Temple Grandin's physicians and had written an article about her in the *Harvard Mental Health Letter* that I had saved for my files. Now, in "Attention to Attention", he was talking about another category of high-functioning DSM-types: grown men with attention deficit disorder.

I had never heard of such a thing—an adult with a child's diagnosis—and as I read I felt the shock of recognition that would eventually lead to John's and my writing our book *Shadow Syndromes* together. In his short article John was talking about my bread-and-butter as a Contributing Editor to a women's magazine: the man who can't be intimate. Probably half the articles I'd written for *New Woman* over the years had dealt with this fellow, always in strictly Freudian terms: single women everywhere considered it to be a self-evident truth that men who had problems with intimacy suffered from *fear of commitment*. Now here was John Ratey, my future coauthor and friend, saying that a man who had "problems" with intimacy might have no trouble with commitment at all—that often the *real* problem might be instead an inborn flaw in the neurological basis of attention. The ADD adult could not be intimate simply because he could not focus well enough to *stay with* an intimate conversation. His brain, and thus his mind, were all over the place.

When I finished reading I called my editor, pitched her an article on hyperactive men, and within days John and I were talking.

A shadow syndrome is a mild and normal form of an otherwise serious disorder; it is a "normal variant." A person can be mildly anything: mildly depressed, mildly obsessive-compulsive, mildly manic, even, as we now know, mildly autistic. The simplest way to think of a shadow syndrome is in DSM terms: where a full-blown clinical depression might require that the sufferer show 8 out of 10 symptoms to meet the threshold for diagnosis, a person with a shadow depression might report only 4 or 5. In recent years clinicians and researchers have become increasingly interested in these "subclinical" or "subsyndromal" cases (they are also called *formes frustes*), perhaps because they offer a window onto the intriguing question of: what does "normal" look like?

Once you begin to think about life in terms of shadow syndromes you reach the conclusion that Freud was right: normal is not especially normal. The only study I've seen that

has tried to count subthreshold symptoms in a general population found that fully one quarter of 1001 patients in a primary care setting in fact had shadow syndromes. Moreover, the research team discovered that for each of the six common disorders they investigated—panic, major depressive, generalized anxiety, obsessive-compulsive, alcohol abuse or dependence, and drug abuse or dependence—the subsyndromal forms were at least as common as (or far more common than) the classic severe forms. Contemplating these figures, it's fair to wonder what would happen if someone were to test for shadow forms of all 410 diagnoses listed in the DSM-IV. Would there be anyone at all who does *not* have a shadow syndrome?

Quite possibly not, which brings me to one of the central messages John and I hope we've expressed in our book: shadow syndromes are not all bad. "Flaws" in brain function

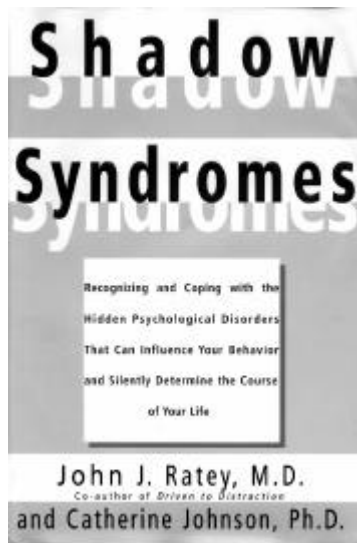
bring gifts as well as troubles: the mild manic-depressive can be creative and charismatic, the mild ADDer enterprising and open to life, the mild depressive more perceptive than normal folk, and more honest with himself and those he loves. As for mild OCD, our editor tells us that in her experience only an obsessive can write a book.

What good does mild autism bring to those of us who see symptoms in ourselves or in people we love? In light of the news that autism is an inherited disorder—and that at least some of us have autistic qualities of our own—this is a question each of us will have to answer for himself. Personally, I take heart from the entirely unscientific observation that faculty children at one major university have roughly a *one percent* rate of autism—ten times the rate found in the general population, or one-child-in-a-hundred at this university versus one-child-in-a-thousand in the rest of the world. And according to publisher Illana Katz, even

Albert Einstein met 20 out of a list of 27 symptoms for Asperger's syndrome.

Scientifically speaking, of course, such observations may mean something, or they may mean nothing. But for me, when it comes to making peace with the fact the I might have autistic shadows of my own, they are a comfort. In my life the old Samuel Clemens line about how it doesn't pay to worry because the worries you have are never the worries you get has always turned out to be true, and I figure it holds for autism genes, too. There's no point worrying how my own share of the family genes might hurt me in the future, or how they may have tripped me up in the past. I figure they've brought me as much good as bad, and I expect they always will.

I hope one day Jimmy will be able to say the same. ♦



Shadow Syndromes, co-authored by NAAR Trustee Catherine Johnson, has received considerable acclaim since its publication in February, 1997.

Glossary of Selected Scientific and Medical Terms

brain stem tegmentum. The brain stem tegmentum is a transition zone from the spinal cord to the rest of the brain. Evolutionarily, it is the oldest part of the brain; developmentally it is the first part of the brain to form. Information from many senses—taste, hearing, balance, plus senses of touch, pain and temperature from the inside and outside of the body enters the brain in the brain stem tegmentum, while motor impulses exit the tegmentum to control the eye muscles, facial muscles, larynx, tongue, and chewing and swallowing muscles. The brain stem tegmentum also controls levels of alertness as well as such basic functions as breathing and heart rate, both essential to survival.

developmental genes. Genes that turn on inside the embryo for a specific period in development, guide the formation of a structure or system, then turn off. Some of these resume activity later in life. They may be active in different regions of the body from those where they are active in development, and they may perform different functions from those served in the embryo. Other developmental genes are permanently inactivated after their brief period of expression in the embryo.

embryology. An embryologist studies development in the womb, and sometimes shortly after birth as well, but especially in the womb. The word "embryo" refers to the growing baby during the first trimester of development; "fetus" is used during the second and third trimesters.

etiology. The causes or origin of a disease or disorder.

eye motility. The movement of the eye by the eye muscles. Eye motility requires an amazingly elaborate system of neural control involving many reflexes (automatic responses) as well as volitional control.

innervation. In the case of muscles, this refers to their connection to nerve cells from the brain or spinal cord that signal the muscle to contract. Muscles deprived of their innervation cannot act. Similarly, skin deprived of its sensory connections to the nervous system sends no messages back. Thus, it is numb.

motor neurons. The neurons that work the muscles. "Motor neurons" are so called because they are the motor of the muscle.

neuron. The technical term for a brain cell (also called "nerve cell").

neurotransmitters. Neurotransmitters are chemical substances that nerve cells use to communicate. Parts of the neuron specialized for communication release the neurotransmitter which then affects the activity of another cell—usually a nerve or muscle cell. Examples of neurotransmitters are serotonin, dopamine and norepinephrine.

optokinetic nystagmus. Whenever normal eyes move, they do it in a slightly jerky, rather than completely smooth, motion. This is called nystagmus. The nystagmus that occurs when the eyes are following a moving target is called "optokinetic." Some people with autism appear to have abnormalities of optokinetic nystagmus.

strabismus. Any deviation of the eyes from normal in position. Strabismus includes crossed eyes, or eyes in which one eye moves more to the side or not to the middle or vice versa. The gaze of the two eyes is not parallel.

teratogen. Any substance that causes birth defects.

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