

NARRATIVE

NEWSLETTER OF THE NATIONAL ALLIANCE FOR AUTISM RESEARCH

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NEWS FEATURE

CDC & NAAR Co-Sponsor Conference *Autism: Emerging Issues in Prevalence and Etiology* November 6-7, Atlanta

by Micki Bresnahan

By the close of the CDC-NAAR sponsored conference on autism, the momentum of the autism research machinery was in plain view. It was electric. During a break between speakers on the last day I was sitting behind Dr. Godfrey Oakley, a major player at the CDC. I leaned forward and said "exciting enough for 'ya?" He responded "my heart skipped a beat!" That morning represented a brilliant conclusion to an amazing conference. The science was unbelievable and the scientists outstanding. Suddenly, hope was a realistic option.

The initial plan for the conference had been formulated at a meeting in Princeton a year earlier, when three distinguished representatives of the Centers for Disease Control and Prevention (CDC) met with representatives of the National Alliance for Autism Research. The CDC's interest in autism had been stimulated by anecdotal reports of "outbreaks" or "clusters" of autism. They decided to run a pilot study on the feasibility of adding autism to a surveillance program in Atlanta that was already up and running. A surveillance program over time could provide

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SCIENCE FEATURE

The Hunt for Autism Genes: *A Conversation With Researcher Ed Cook, M.D.*

by Catherine Johnson

You have to kiss a lot of frogs to get a prince," Ed Cook says, remembering the time he and partner Eric Courchesne thought they had found the perfect candidate gene for autism. The gene—now known to cause Angelman's syndrome—looked remarkably promising: it expressed itself only in the hippocampus and in the Purkinje cells of the cerebellum, two areas of the brain known to be affected in autism. How could it not have something to do with the disorder?

But so far it hasn't panned out.

For gene-hunters like Cook and his colleagues, brilliant hypotheses that don't work are more the rule than the exception. So it is impossible to exaggerate the excitement generated among autism researchers when, in just the course of the past couple of years, several leads finally began to pay off.

And thus far Ed Cook, of the University of Chicago, along with department chair Bennett Leventhal; Cathy Lord, co-creator of the Autism Diagnostic Interview;

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Editor's Note

Sometimes, in our frantic efforts to work for increased autism research budgets, to raise awareness of autism as an important public health policy concern and to advocate for new autism treatments and pharmaceutical products, we lose sight of those men and women—basic and applied scientists—whose lives and work, day after day, are quietly devoted to solving the mysteries of autism. This issue features a conversation with one of those researchers, Dr. Edwin Cook of the University of Chicago, who, with other colleagues there and elsewhere, has made important progress in the area of genetics. We believe it is important to highlight the work of such innovative and dedicated researchers, and we will do so in future issues.

We would like to welcome, too, two new members to NAAR's Scientific Advisory Board. They are **Dr. William Bunney** of the University of California, Irvine and **Dr. Dante Cicchetti** of the University of Rochester.

Dr. Bunney is Della Martin Chair of Psychiatry and Distinguished Professor of Psychiatry at the College of Medicine at UC Irvine. He has served as President of the American College of Neuropsychopharmacology, is a member of the Editorial Board of the Journal of Psychiatric Research, and has worked both in academia and in government. His major research interests involve psychobiological studies of manic-depressive illness, schizophrenia and childhood mental illness.

Dr. Cicchetti is Professor of Psychology, Psychiatry and Pediatrics at the University of Rochester and Director of the Mt. Hope Family Center. The recipient of many research awards and honors in his field, Dr. Cicchetti's research and writings focus on developmental psychopathology.

We welcome both of these distinguished scientists to the Scientific Advisory Board.

Please Note: In our inaugural issue, we indicated that the first two issues of NAARRATIVE would be complimentary. We will extend that policy to the third issue, expected to come out in June. Further issues will be sent to those who make a contribution, of any amount, to NAAR to help defray the costs of production. If you know of an individual, corporation or foundation that would like to underwrite the costs of producing NAARRATIVE, please contact David Maxson at the NAAR office.

A Message From NAAR's President: *The Gifts We Most Prize*

The gifts we most prize change as we advance in life's journey. In December, on my birthday and in the midst of holiday festivities, I received a letter from Dr. Margaret Pericak-Vance, one of NAAR's 1997 Award Winners. The letter was an update on her genetics research funded through NAAR thanks to the generosity of NAAR Research Partners Audrey Flack and Bob Marcus. "Wrapped" in a plain white envelope, no other gift that week produced as much delight as reading Dr. Pericak-Vance's words. I'd like to share some of them with you since, in a way, this was really an exchange of gifts between NAAR and its supporters and Dr. Pericak-Vance and her outstanding research team.

"Your gift of \$30,000," she wrote, "was used to help us ascertain and collect these (multiplex) Autistic Disorder families that are critical for analysis....Your donation made it possible for us to both identify and study these families. For example, in 1996 we were only able to identify 52 Autistic Disorder families. With your help this number increased to 156 in 1997. Of those families identified, we have now obtained DNA on all members in 93 of these families. This represents outstanding progress."



Karen London with son, Zachary

Dr. Pericak-Vance went on to report that, with her team's ability to work with so many families so rapidly this past year, her researchers were afforded the opportunity to examine high priority candidate regions in the genome that may harbor potential autistic disorder genes. In doing so, they discovered an aberrant pattern on Chromosome 15 in autistic disorder families. These initial findings, reported in November at the American Society of Human Genetics meeting, may provide important clues as to the cause of autism.

Dr. Pericak-Vance, whose lab was successful in identifying the first major susceptibility gene for Alzheimer disease (which, like autism, is a complex genetic disorder), has for several years

wanted to bring her experience to bear on the autism spectrum disorders. NAAR's gift, she wrote, made her involvement in autism a reality.

NAAR's Autism Research Award encouraged Dr. Pericak-Vance to direct her talents to autism, helped expedite the identification and diagnostic work-up of multiplex families, and facilitated new areas of genetic research. And all this is exactly what NAAR set out to accomplish three years ago. So to see it happen and to receive a researcher's letter to this effect was a wonderful gift indeed. And this was only one of NAAR's initial five research award recipients!

As we prepare for NAAR's second Scientific Advisory Board meeting in March, I am filled with gratitude. I am thankful that NAAR received twice as many research proposals seeking NAAR funding as last year. I am grateful that new and accomplished researchers are redirecting their research efforts to autism--perhaps inspired by the availability of funding as well as the increased commitment to autism research by the National Institutes of Health-- and that long-time autism researchers continue in their dedication to

our cause. And I am indebted to NAAR's generous donors who believe that we can, and must, commit ourselves to supporting autism research. Each of your donations, each such commitment, is a gift—not only to NAAR—but ultimately to our children and family members with autism, their siblings and future generations.

It was a wonderful birthday.

With gratitude,

Karen Margulis London

NAAR Moves to New Princeton HQ; Opens 1st Regional Office

Three years after NAAR's "birth," in the basement of the home of NAAR's co-founders, Karen and Eric London, NAAR has relocated to its first office. The new office, located at 414 Wall Street, Research Park, Princeton, New Jersey, offers adequate space for NAAR's Executive Director, David Maxson, Ms. London and administrative assistant April Raush. It will also be the base of operations for the Autism Tissue Program, a joint venture between NAAR and the ASAF (see accompanying article on NAAR/ASAF agreement). The Research Park location has enabled a significant increase in efficiency and productivity as NAAR's efforts have expanded nationwide. Ms. London is grateful to artist Jessie Parks and photographer Rosalie Winard for lending or donating their art to grace NAAR's new headquarters.

NAAR has also recently opened its first regional office! The Southern California Regional Office of NAAR is located at

17383 West Sunset Blvd., Suite 420, Pacific Palisades, California 90272. Los Angeles Friends of NAAR will also operate from this location. If you are interested in obtaining more information about NAAR or would like to join a dedicated group of active NAAR volunteers in the Los Angeles area, please contact Vicki Hennelly, Esq., Coordinator, at (310) 230-3568 or by e-mail at vickih@artsci.net.

"NAAR's new offices in Princeton and Los Angeles are a dream come true," said NAAR's President, Karen London. "It is the physical manifestation of NAAR's growth and success and represents the collaborative efforts of our supporters from coast to coast to advance autism research. We are incredibly grateful to the private foundation whose generous two-year operating grant made our new headquarters possible and to Vicki and John Hennelly, whose contribution of time and office space created NAAR's first regional office." ♦

ASA Foundation Becomes NAAR's First Alliance Member

The Autism Society of America Foundation (ASAF) and NAAR have entered into a renewable two-year agreement to jointly fund and advance biomedical research. The agreement specifies that substantially all of the funds that ASAF annually commits to biomedical research will be contributed to NAAR as a restricted donation to support top-ranked biomedical research proposals and specific scientific initiatives. ASAF will be identified as the "Research Partner" of each NAAR Autism Research Award fully funded by ASAF or as joint Research Partner, with NAAR, of each such Award funded equally by ASAF and NAAR. NAAR has agreed that *every penny* of ASAF's contributions to NAAR will directly support biomedical research. In this way, ASAF will have an effective means to advance autism biomedical research without incurring any related expenses.

The agreement creates a framework for a coordinated and collaborative effort between the two organizations that will maximize resources, minimize duplication, and strengthen the fundraising efforts of both NAAR and ASAF. Karen London, NAAR's President, stated "NAAR's very name was selected to stress the critical importance of establishing a nationwide 'alliance' of families and organizations dedicated to autism research. We are therefore extremely pleased to welcome ASAF as NAAR's first Alliance Member. This important partnership is a model of cooperation between autism organizations. By avoiding duplication of efforts and operating costs, we can maximize the resources available to fund the science

and create a synergy that will substantially advance the cause of autism research." Added John Maltby, Chair of ASAF's Board of Directors, "This collaboration is a major step in mobilizing the resources of ASAF and ASA in demonstrating how serious the autism community is about advancing the cause of biomedical research." ♦

1998 NAAR Autism Research Awards to Be Announced in April

The second annual meeting of NAAR's Scientific Advisory Board will be held on Monday, March 30, 1998 at Harvard University. NAAR Scientific Advisory Board members from all over the country will assemble to review and rank each of the scientific proposals seeking funding from NAAR. This year, for the first time, NAAR has offered up to \$60,000 for two-year awards. The recipients of the 1998 NAAR Autism Research Awards and a description of the autism research to be undertaken with NAAR's funding will be presented in the next issue of NAARRATIVE. "We are thrilled that NAAR is in the position to substantially increase the number of NAAR Autism Research Awards granted this year and that we can also offer two-year awards," commented Eric London, NAAR's Vice President-Medical Affairs. "We are indebted to our Research Partners and to our many supporters who have made this level of autism research support possible." ♦

NAAR Represented at Major Neuroscience Conferences

Dr. C.T. Gordon and Dr. Eric London, both members of NAAR's Medical Affairs Committee, attended numerous conferences on behalf of NAAR throughout the fall and winter months.

Dr. Gordon, together with NAAR President Karen London, presented on behalf of NAAR at the annual meeting of the National Institutes of Health (NIH) Inter-Institute Autism Coordinating Council in September. In the 1980's, before his own son's diagnosis with autism, Dr. Gordon had been engaged in autism research at the National Institute of Mental Health (NIMH). He now provided the more than 50 NIH representatives in attendance with an overview of the research projects NAAR is currently funding and the language, brain tissue, epidemiology and other initiatives that NAAR is sponsoring. The NIH provided NAAR and the other advocacy organizations in attendance with detailed information regarding NIH-funded autism research and the opportunity to learn of plans for increased NIH funding.

In late October, Dr. Gordon attended the Annual Meeting of the Academy of Child and Adolescent Psychiatry, a key meeting addressing the clinical and research issues of autism. A week later, Dr. London and NAAR volunteer Dr. Jonathan Deutsch attended the Annual Meeting of the Society of Neuroscience in New Orleans. At each of these meetings, NAAR had volunteers manning its exhibition display and distributing information regarding the availability of NAAR funding for autism research. In addition, Dr. Susan Hyman, a member of NAAR's Scientific Advisory Board, attended the Annual Meeting of Developmental Pediatricians and distributed NAAR

literature. "Visibility at these meetings is critical to encouraging new scientists to undertake autism research and to making the availability of pilot funding known," said Dr. London. "We are pleased that NAAR received several research proposals from scientists who had never previously considered engaging in autism research but who were encouraged to do so by our discussions at the Neuroscience and other meetings."

In December, Dr. Gordon attended an NIH inter-institute conference on the ethical and legal issues involved in research involving individuals with questionable capacity to provide informed consent. This working group focused on developing policies and guidelines for research proposals that involve individuals with disorders such as autism, schizophrenia or Alzheimer's disease. In addition to ethicists, attorneys, clergy, clinicians and researchers, NAAR was one of four advocacy organizations to participate in this conference (along with the Citizens for Responsible Care in Psychiatry Research, Alzheimer's Association and the National Alliance for the Mentally Ill). There was a consensus that individuals with these brain disorders need to be provided medical treatments based on the same sound clinical research that governs the treatment of non-cognitively impaired individuals. Practical guidelines are being prepared to assess the capacity to consent and to implement a surrogacy system where needed. NAAR will review the forthcoming guidelines and continue to follow the important ethical, legal and practical issues involved.

Finally, Dr. London and Executive Director David Maxson attended a meeting of NIH-funded genetics researchers on January 7, 1998. (See article on page 7.) ♦

Missing Link Discovered

by Richard S. Nowakowski

A major goal of current research in brain function is to understand how genes affect behavior. This is not an easy goal to reach and there are major technical and conceptual problems that remain to be solved. However, an important "missing link" in this effort has been discovered as recently reported* in the journal *Cell*, that establishes the existence of a gene that affects the social behavior of mice. Interestingly, each mouse with this mutation is overtly normal by itself, at least as has been tested so far, but when caged together, the mice exhibit profound disturbances in social interaction.

The work is important for several reasons. First, and perhaps most interesting for NAAR, is the fact that the affected behaviors are related to those affected in autism. Second, this work provides, for the first time, a link in the cascade between genes and whole animal behavior and inter-animal interaction (i.e., social behavior). Third, the method by which this discovery was made reveals the importance of basic research to the development of treatments that may someday help patients.

The behavioral changes were revealed in mice that were "engineered" to lose their copy of the gene *Dvl1* using the recently developed "gene targeting" technology. A group lead by Dr. Anthony Wynshaw-Boris of the National Institutes of Health (NIH) began their work by taking the molecule for the *Dvl1* gene, which is the mouse version of a gene originally found in the fruit fly (*Drosophila melanogaster*). Dr. Wynshaw-Boris' group manipulated the genetic sequence of the *Dvl1* gene and removed the sequences that code for its protein product. Then, this abnormal gene was introduced into cultured "embryonic stem cells" so that the normal *Dvl1* gene was replaced. Next, the "embryonic stem cells" were injected into a "host" mouse embryo at a very early stage (blastocyst) of development. After multiple attempts three mice were obtained in which cells derived from the *Dvl1*-minus cells were incorporated into the germline. This means that these mice could be used for subsequent breeding and the establishment of a new line of mice in which the *Dvl1* gene was absent.

The mice produced are viable, fertile and look completely normal. Moreover, in standard tests of learning and memory, they achieve performance equivalent to the normal mice. What is interesting is that the mice do not interact with each other normally. They trim each others' whiskers, which is an atypical

behavior, they build nests poorly, and they don't like to "huddle" together the way normal mice do. These behaviors can only be demonstrated in tests that involve the social interaction of more than one mouse at a time. In fact, the behavioral deficits were revealed because the sharp-eyed and attentive researchers noted that the mice had shorter whiskers when they were caged together. They followed up on this detail and, as a result, have produced a major new finding.

What happens next? With a gene in hand, a high priority task will be to try to determine what the function of *Dvl1* in the normal brain is. Where in the brain does it act? And, when during development does it act? Next, an effort will follow to determine how the absence of the gene changes the brain and how those changes relate to the observed behavioral changes. Possibly, a direct connection will be found. For example, maybe *Dvl1* will turn out to be important in the development of the part of the brain that is called the "limbic system." It is the limbic system that is generally believed to control the complex behaviors of the sort that are changed in the *Dvl1*-minus mice. It is also possible, however, that the link between the gene and behavior will be indirect and that it will be only the first step in unraveling a complex cascade of events that connect genes with these sorts of behaviors. In either case, however, it is an important first step that will someday help us to understand how these behaviors are controlled and how to help people in which these behaviors are outside of the normal range. And to think it all began with a fruit fly! ♦

Richard S. Nowakowski, Ph.D., a member of NAAR's Scientific Advisory Board, is Director of the Image Enhancement and Analysis Facility and Associate Professor in the Department of Neuroscience and Cell Biology at UMDNJ-Robert Wood Johnson Medical School.



*Lijam, N., Paylor, R., McDonald, M.P., Crawley, J.N., Deng, C.X., Herrup, K., Stevens, K.E., Maccaferri, G., McBain, C.J., Sussman, D.J., and Wynshaw-Boris, A. (1997). Social interaction and sensorimotor gating abnormalities in mice lacking *Dvl1*. *Cell*, 90, 895-905.

The National Alliance for Autism Research notes with deep sorrow the untimely death of Dr. Reed Warren of the University of Utah. Dr. Warren was a dedicated autism researcher and one of the principal scientists investigating immunogenetic susceptibility as a cause of autism. We extend our sympathy to his family.

STUDIES OF THE PHARMACOLOGICAL TREATMENT OF AUTISM: SEROTONIN RE-UP TAKE INHIBITORS

by C.T. Gordon, III, M.D.

The question of how or when to use medications in children and adults with autism is extremely important for many of the families I see in my office. Unfortunately, there is no medication "approved" by the Food and Drug Administration for use in autism because the pharmaceutical companies have not sponsored the extensive testing of medications for this population. Physicians are therefore called upon to "try" different agents to see if they are effective.

At this point, a body of medical literature is emerging which suggests that some medications are quite effective in individuals with autism and should be used in some cases. NAAR's Medical Affairs Committee believes that it is very important to provide parents information about these medications in order to help them engage in informed discussions with their treating physicians. In this issue, I would like to review the serotonin re-uptake inhibitors, a category that includes the medications Prozac, Luvox, Paxil, Zoloft and Anafranil. These medications are now being used widely in autism and, as a general rule, are quite safe.

Medications to Inhibit Obsessive-Compulsive Disorder

Since the time of its first description by Dr. Leo Kanner in the 1940's, autism has been characterized by a high frequency of repetitive, ritualized behavior. These behaviors can take several forms. Repetitive stereotyped body movements such as arm flapping, spinning, or running back and forth are termed "motor stereotypies." Simple rituals, such as lining up objects, opening and closing doors, or insistence upon objects being in a particular place, are also common. In addition, more classic "obsessive-compulsive" rituals, such as hoarding, washing, counting and touching rituals, are frequently seen in autism. These repetitive behavior patterns can be associated with severe anxiety, tantrums, and aggressive behavior toward self and others. They are also highly time-consuming and extremely distractive to learning.

Fifteen years ago obsessive-compulsive disorder (OCD) was where autism is today: there was not a single medication on the market that was directly targeted to OCD. But over the past ten years several pharmacologic agents have been developed that diminish the repetitive, ritualized thoughts and behaviors in children and adults with OCD. The overlapping symptoms between OCD and autism prompted trials of these medications in autism. These medications are called serotonin re-uptake inhibitors. Although they influence several other neurotransmitter systems, their effects on serotonin are theorized to be related to their benefits. Three serotonin re-uptake inhibitors primarily have been studied in autism and found to be helpful: clomipramine (brand name: Anafranil), fluoxetine (Prozac), and fluvoxamine (Luvox). The effectiveness of clomipramine and fluvoxamine has been demonstrated in double-blind controlled studies in individuals with autism (Gordon, et. al. 1993 and McDougal et. al. 1996) and that of fluoxetine in a large open label case series (Cook et. al. 1992).

What Do Serotonin Re-uptake Inhibitors Do in Autism?

All of the studies report that these medications work well in autism to reduce the frequency and intensity of repetitive,

ritualized behaviors including motor stereotypies and more classic compulsive rituals. Somewhat surprisingly, improvements in other autistic symptoms have also been noted. For instance, some children show improvements in eye contact, social initiation and responsivity. Others show decreased withdrawal and an expanded repertoire of interests. Behavior improves, with a decrease in tantrums, aggression, and self-injurious behavior. Improvements in initiating, shifting, and sustaining attention are also observed, with improvements in "connectedness" to the environment and therefore less internal preoccupation. Many of these associated benefits may relate to the potent anti-anxiety effects of these medications. The positive effects seen with clomipramine, fluoxetine and fluvoxamine appear similar both in terms of quantity and quality except that clomipramine seems to have greater ability to decrease motor stereotypies and is generally more "calming" than either fluoxetine or fluvoxamine.

Potential Adverse Side Effects

The three medications differ in their side effect profiles, with clomipramine having a greater frequency and severity of adverse effects compared to fluoxetine and fluvoxamine. The most common side effects of all three are hyperactive, impulsive behavior and sleep disturbance. Both of these side effects are dose-related and can be minimized with careful and conservative dose titration down to the absolute lowest effective amount. This varies tremendously from one individual to another. My experience is that if one starts with a very low dose and increases the amount slowly, these side effects can be minimized. Clomipramine may also cause dry mouth, dizziness, and constipation (so-called "anti-cholinergic" side effects) as well as heart rhythm changes (baseline electrocardiogram monitoring is necessary) and a lowering of the seizure threshold (making it a more problematic medication than fluoxetine or fluvoxamine in individuals with seizures). However, in healthy patients without seizures and with normal heart function, clomipramine is generally safe and well tolerated. Each of these three medications has been studied in children and has been found to be safe, with side effect frequency and severity being similar to those seen in adults. There are no known long-term side effects of these medications, but the longest follow-up has been 10-15 years and further study is therefore necessary.

Who Should Receive a Trial of a Serotonin Re-uptake Inhibitor?

Although this is a complex question, the simple answer is that if a child's or adult's symptoms are severe enough to warrant the risks, then a trial is indicated. A trial of a serotonin re-uptake inhibitor might be considered whenever compulsive behavior, anxiety symptoms or poor joint attention is significantly impeding appropriate developmental, educational or social progress.

As with all medications, prescription of a serotonin re-uptake inhibitor should be done only by a physician experienced with using these medications in the autistic population. The dose should be minimized and there should be a clear list of target symptoms and a well-integrated feedback system of the pa-

NIH-Funded Research Programs Move Forward: Families Needed to Verify Findings

The autism research programs funded by the National Institutes of Health are moving forward actively in their search for better understanding of the causes, development and treatment of autism. In particular, the International Collaborative Network on the Neurobiology and Genetics of Autism, funded by the National Institute of Child Health and Development (NICHD) is reporting its first results. Two research groups announced preliminary genetic discoveries in autism at recent meetings. Drs. Rodier, Hyman (a member of NAAR's Scientific Advisory Board) and Figlewicz from the University of Rochester, and Dr. Bryson from York University in Canada reported their preliminary findings on mutations in early developmental genes at the national Society of Teratology meeting. Drs. Lord, Cook, and Levanthal of the University of Chicago; Drs. Volkmar, Pauls, and Klin of the Yale Child Study Center, and Dr. Smalley of UCLA are part of The International Molecular Genetic Study of Autism Consortium that announced their preliminary discoveries based on the first genome-wide screen for autism susceptibility genes at the national Psychiatric Genetics meeting. The Consortium findings will be published in the March issue of *The American Journal of Human Genetics* and will be reported on in the next issue of NAARRATIVE.

The five-year, \$27 million NICHD collaborative network, co-funded by the National Institute on Deafness and Other Communication Disorders (NIDCD), involves more than 65 scientists and 25 universities throughout the US. It includes outstanding autism scientists and geneticists who have discovered genes for other disorders such as Alzheimer's, Werner's syndrome, and Duchenne's Muscular Dystrophy.

On January 7, 1998, Eric London, M.D., NAAR's Vice President-Medical Affairs, was invited to a meeting at the NIH attended by all of the principal investigators of the NIH-funded autism genetics research sites. These researchers stressed the critical importance of participation in their research by families affected by autism and, particularly, by families with more than one autistic family member (so-called "multiplex families").

NAAR believes that the first priority—and the best way to expedite autism research—is for families, particularly multiplex families, to participate in the NIH funded studies so that they can be completed expeditiously. These research teams are among the best in the world, are already well underway and require additional family participation to be completed. They have met all NIH criteria for safety and confidentiality of information. They have already received NIH funding to undertake the diagnostic work-ups and study the genetic material of over 1,000 multiplex families. This will require an extraordinarily high rate of participation from the autism community. Scientists at the NIH meeting indicated that they need at least 200 multiplex families in order to determine if the encouraging early genetics findings hold up with other families.

The following information is presented as part of NAAR's continuing effort to support the NIH-funded research programs and provide up-to-date information for families to make informed decisions. **It is important to note that you may participate in only one genetics study involving multiplex families.** In other types of studies, participation in more than one study may be possible. Many of these studies provide



patient's progress to the physician, including parents' and teachers' reports as well as direct observation of the child. A good trial of the medication usually takes between 10-12 weeks. A careful weighing of the possible benefits and risks of treatment should always be done and the medication should be viewed as only one component of a multi-modal treatment approach that includes behavioral, educational and other interventions. Medications should be viewed as a method that prepares "the brain's physiology" in such a way that learning can be optimized. It is neither a "cure" for autism nor is it a competitor to or replacement for other modes of treatment. Indeed, if effective, medication enables children and adults with autism to make better use of other modes of treatment.

The field of psychopharmacology has literally exploded in the past ten years in terms of the development of a number of safe and effective agents. Serotonin re-uptake inhibitors are but one example of a class of medications "borrowed" from other brain disorders and found useful for individuals with autism spectrum disorders. In upcoming issues of NAARRATIVE, the role of other classes of medications used in treatment of individuals with autism, such as the atypical neuroleptics and anti-convulsants, will be reviewed. NAAR is committed to spurring the pharmaceutical industry to develop medications that would be specifically "tailored" for autism—taking into account the growing knowledge of central nervous system

biochemical abnormalities. Basic science researchers will need to work hand in hand with clinical investigators to develop more effective, safe medications with the final goal being improvement in the quality of life for children and adults with autism and their families. ♦

Dr. C.T. Gordon is a professor of psychiatry at the University of Maryland Medical School and a child psychiatrist in private practice in Bethesda, Maryland. Prior thereto, Dr. Gordon conducted autism research at the National Institutes of Health. A founding trustee of NAAR, Dr. Gordon serves on the Medical Affairs Committee. He is the father of a nine-year-old son with autism.

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valuable neuropsychological evaluations and other medical testing at no cost to participating families. Travel expenses are typically covered. Information is provided so that you may contact these researchers directly. Alternatively, several of the NIH-funded research teams have indicated to NAAR that they would be willing to travel to you if there are several multiplex families in a particular geographic area. Please contact NAAR at 1-888-777-NAAR if you would like our assistance in arranging this or to find out if there are other families in your area interested in research participation.

Genome Scanning Projects

Yale University, New Haven, Connecticut (Yale -Dr. Fred Volkmar, University of Chicago- Drs. Catherine Lord and Ed Cook, UCLA – Dr. Susan Smalley (with Oxford University, the University of London, plus others in England, France, Germany, Denmark, Greece and the Netherlands)

This program is conducting genome screening studies for autism susceptibility genes in families with more than one child with autism. The overall project focuses on the causes of high functioning autism and Asperger's disorder. Studies include the underlying genetics, neuropsychological profiles, and brain structures and functions for the various autism disorders. A follow-up study of children originally diagnosed at age 2-3 will identify early predictors of autism. Families with more than one child with an autism disorder are needed as are high-functioning singleton patients with Asperger's or autism. At Yale University, contact Kathleen Koenig (203-785-3488, ext.2); at the University of Chicago, contact Linda Lambrecht (773-702-3052), and at UCLA, contact Erin Cantwell (310-825-3414).

• The University of Washington, Seattle. Dr. Geraldine Dawson (with the Universities of Alaska, Florida, Montana, Oregon, and Vanderbilt University.)

In addition to genome screening studies for autism susceptibility genes using DNA from families with more than one child with autism, this program is studying the emergence of speech and language and the brain structure and function that underlie problems of speech and social behaviors in autism. The project is also studying first and second birthday videotapes of children who developed normally then lost speech and social skills during the preschool years. Families with more than one child with an autism disorder are urgently needed. (Contact: Cathy Brock: toll-free 800-994-9701; e-mail: cbrock@u.washington.edu).

• Stanford University, Palo Alto, California. Drs. Neil Risch and Donna Spiker.

The Stanford Autism Genetics Program is a joint effort by researchers from the Department of Psychiatry and Behavioral Sciences and the Department of Genetics who are examining the possible genetic causes of autism. In this project, Stanford is studying families with two or more siblings with autism or pervasive developmental disorder. It is also examining families in which both parents are of Ashkenazi Jewish background with one or more children with autism or PDD. Multiple-incidence families are urgently needed. Participation entails 1-2 days of interviews and observations, typically at the family's home, and obtaining a blood sample from family members. (Contact Dr. Donna Spiker at 650-723-7809; e-mail: ms.dks@forsythe.stanford.edu).

• Collaborative Autism Project (Duke University Medical Center – Dr. Margaret Pericak-Vance, Tufts/New England Medical Center- Drs. Helen Tager-Flusberg and Susan Folstein, University of Iowa-Dr. Joseph Piven, Johns Hopkins University- Dr. Rebecca Landa, Univ. of South Carolina and Vanderbilt University)

This is a collaborative effort by several NIH-funded centers to conduct molecular genetics studies of the genes underlying autism. Each of the centers is seeking families with more than one individual with autism, in either the nuclear or extended family, for participation in ongoing studies. Participation involves several interviews, a brief exam of the children and a small blood sample. Participants will not be expected to travel or to pay expenses incurred due to participation. At Duke University, contact Shannon Donnelly (800-283-4316); at Tufts/New England Medical Center, contact Sarah Svenson (888-217-4935); at the University of Iowa, contact Debra Childress (800-793-5715); at Johns Hopkins University, contact Stacey Barrett (410-614-4948).

Other Genetic Studies

• The University of California, Irvine. Drs. M. Anne Spence and Pauline Filipek

This research team is studying candidate genes in autism and investigating brain structure, especially changes in the brain in adolescence, using magnetic resonance imaging (MRI). They will also document "regression" in language and/or social behavior for children with autism whose early development was normal. Using these methods they will identify subgroups that will help "map" autism genes. Families of children with autism from age two to pre-adolescence are needed. (Contact Dr. Spence, 714-456-8385).

• The University of Rochester. Dr. Patricia Rodier (with York University, Canada, and Cornell U., Ithaca, NY).

This project uses an animal model to test a new theory that autism may be caused by exposure to an environmental toxin very early in pregnancy and/or a genetic susceptibility. The studies also evaluate multiplex families in which the affected relatives are cousins, parents, aunts, uncles or other close relatives for specific genetic mutations expected on the basis of this new theory. Individuals with autism and with physical or neurological differences of the head or face are also of special interest. (Contact Drs. Susan Hyman or Patricia Rodier at 714-275-2986 or through website at <http://www.urmc.rochester.edu/smd/OBGYN/autism/>)

• The University of Utah, Salt Lake City. Dr. William McMahon (with Utah State University and the University of Iowa).

This project tests the idea that autism is caused by an immunogenetic susceptibility to pathogens during pregnancy that might be harmless to others. The other studies in this project are focused on other types of subgroups in autism, including the study of brain structure and function, particularly executive function, and the brain structures underlying the enlarged head sizes reported in autism. (Contact Dr. Wm. McMahon, 801-588-3559; e-mail: pcwmchmah@ihc.com).

Autism as a Complex Information Processing Disorder

• The University of Pittsburgh. Drs. Nancy Minshew and Patricia Carpenter (with Carnegie Mellon University, Pittsburgh, PA and Case Western Reserve University, Cleveland, Ohio).

This project tests the assumptions that autism is a disorder of

complex cognitive abilities that results from abnormal development and dysfunction of neocortical systems. This team will examine evidence of strengths and deficits in complex information processing. A cross-sectional study of adults and a longitudinal study of children will assess maturation of language, cognitive abilities, and the neural circuitry underlying both. The help of 200 non-mentally retarded, verbal individuals with autism between the ages of 8 and 50 is needed for these studies to be successful. (Contact Dr. Nancy Minshew: 412 624 0818; e-mail minshewnj@msx.upmc.edu)

Hearing in Autism

• *Albert Einstein College of Medicine, New York. Dr. Michelle Dunn.*

This project will examine the integrity of auditory processing in children with autism through behavioral (audiometric), physiologic, and electrophysiologic (event-related potentials, ERP) measures, and relate these to later language development. This project may represent the most thorough assessment of hearing yet undertaken in autism. (Contact Dr. Dunn: 718-430-2459; fax: 718-430-8785)

Language and Communication

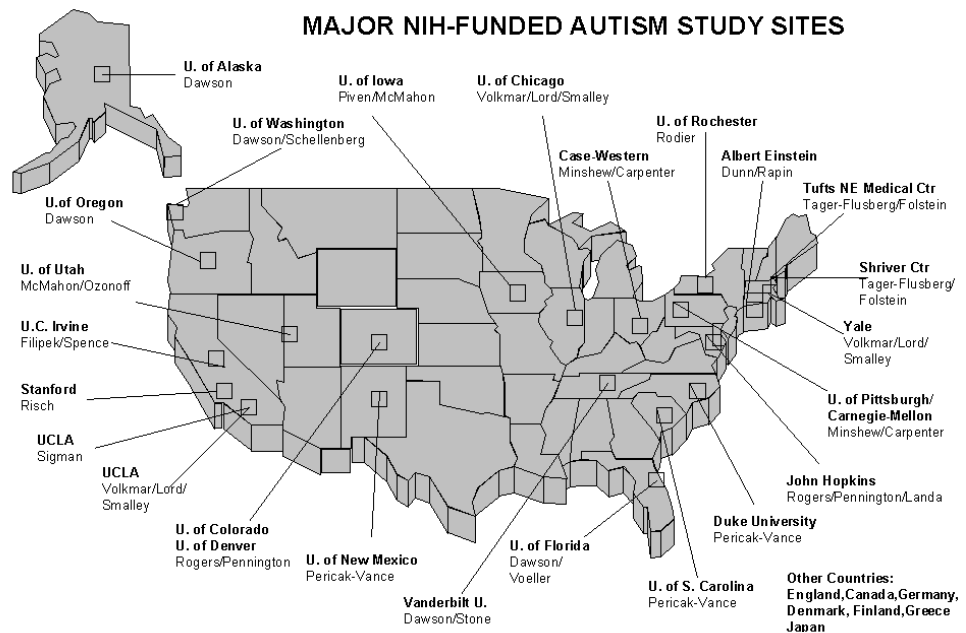
Although the study of language and communication is a part of many of the foregoing research studies, two of the projects are focused specifically on defining the developmental course and brain functions related to language and communication.

• *Eunice Kennedy Shriver Center, Waltham, Massachusetts. Drs. Helen Tager-Flusberg and Susan Folstein (with the University of Massachusetts and Tufts New England Medical Center).*

This program is studying the genetics, behavioral characteristics, developmental course, neural processing, and neuropathology of autism, particularly as they relate to language and social understanding. This will include a study of Theory of Mind in high functioning subjects, an in-depth study of adolescents with autism with IQs below 40, and structural and functional imaging of language-related brain regions. Free language evaluations and travel costs from Massachusetts and surrounding areas to the Shriver Center (10 miles west of Boston) will be provided for eligible families. Families with more than one child with an autism disorder as well as families with one high or low-functioning person with autism are needed. (Contact Cindy Aweimrine: 617/800 642-0180; e-mail: htagerf@shriver.org)

• *University of California, Los Angeles (UCLA). Dr. Marian Sigman.* This program will determine biological and environmental contributors to social communicative competence in autism. It is studying brain functioning in autism in tests of empathy, facial expressions, and prosody (the rhythm and accents of speech); comparing two methods for accelerating language development; and assessing competence in adolescents and adults with autism whose skills were measured at ages 3-5 years. (Contact Margie Greenwald: 310-825-0575; e-mail: margieg@ucla.edu)

MAJOR NIH-FUNDED AUTISM STUDY SITES



Movement and Sensory Processing

• *University of Colorado Health Sciences Center. Drs. Sally Rogers and Bruce Pennington.*

This research effort is measuring sensory processing in adults and young children with autism and Fragile X syndrome. Sophisticated brain imaging technology including magnetoencephalography is being used to test hypotheses regarding auditory memory, cortical hyper-reactivity, and other aspects of brain functioning in autism. A longitudinal study of preschool children will measure early sensory, affective, and motor abilities and relate them to later functioning. A related study will assess language and social functioning in relatives of families with more than one child with autism. (Contact Dr. Rogers: 303 315 8244; e-mail: Sally.Rogers@UCHSC.edu)

Other Non-NIH Funded Autism Research Programs

• *The Mt. Sinai Family/Genetic Study of Autism Project, New York. Dr. Eric Hollander*

This project is actively seeking families with at least one child with autism and a second (sibling, cousin, etc.) with an autism-related disorder (autism, Asperger's Syndrome, PDD) for molecular genetic studies. Families of Irish background are of particular interest. The project involves a detailed interview with the primary caregiver, observation of affected children and the collection of blood samples from all available family members. Members of the research team are willing to travel to the family within the tristate area. The program offers, at no charge, comprehensive neuropsychological and neuropsychiatric assessments, medication treatment studies, social skills training programs, diagnostic imaging and other procedures. (Contact: Christopher Smith, 718-367-5727; e-mail: smithc01@doc.mssm.edu)

(This information is based, in part, on an article by Dr. Marie Bristol-Power, Director of the Mental Retardation and Developmental Disabilities Branch of the National Institute for Child Health and Development, in the Fall/Winter issue of Outreach, published by The New Jersey Center for Outreach and Services for the Autism Community-COSAC.) ♦

(continued from Page 1)

CDC & NAAR Co-Sponsor Autism Conference

answers to the questions coming their way. And, given the newness of this project, they wanted to get input from the very best and brightest minds in autism research. Thus, it was agreed that NAAR and CDC would cosponsor the first U.S. conference on the epidemiology of autism. The target date was set for November of 1997.

If You Build It They Will Come

Although aware of the caliber of scientists slated to give presentations, I was wholly unprepared for the mix of ideas and excitement. From the very beginning, when people gathered in Auditorium A at the CDC, there was a mood of anticipation. Many of the participants were in high gear, having recently returned from other neuroscience or genetics conferences. Now, the CDC conference was an opportunity to focus on autism alone. And there was talk that new findings of tremendous significance might be presented over the two days.

Autism was getting the "CDC-treatment" as described by Dr. Dixie Snider (Associate Director for Science) and by Dr. Godfrey Oakley (Director of the Division of Birth Defects and Developmental Disabilities) in their introductory remarks. Then, stating the purposes of the conference, Dr. Marshalyn Yeargin-Allsopp (Acting Section Chief of the Surveillance and Epidemiology Section and a member of NAAR's Scientific Advisory Board) voiced the "we can do this" attitude that is so critical in a successful approach to "hard to study" diseases. And autism is a hard to study disease from an epidemiologic perspective. Dr. Yeargin-Allsopp not only expressed confidence in the feasibility of epidemiologic research in autism but a commitment to "doing it smart," which was supported by all that followed.

Session I: Operational Definition of the Disorder for Epidemiologic and Surveillance Purposes

Dr. Isabelle Rapin of the Albert Einstein College of Medicine, a neurologist with a long commitment to autism research, chaired the morning session. The speakers included Dr. Catherine Lord of the University of Chicago, whose work in the development of research diagnostic instruments has been crucial to the rapid expansion of autism work and the successes of current research efforts; and Dr. Ami Klin, a key researcher/clinician at the Yale Child Study Center, who has been intimately involved in the study of high functioning individuals with autism and Asperger's Syndrome.

This session was comprised of methodologically driven talks reflecting the "state of the art" in the definition and measurement of autism—the goal being to identify all those with autism, and only those with autism, as having autism. The Autism Diagnostic Interview (ADI) and the Autism Direct Observation Schedule (ADOS), instruments developed by Catherine Lord and colleagues, achieve these goals. Dr. Lord described research showing that, using these instruments, one can reasonably diagnose children over 3 years of age. The significance of this contribution to quality research

cannot be overestimated. To quote Donna Spiker of the Stanford Autism Research Program, "I want to thank Cathy Lord for the development of the ADI and ADOS; we would never have gotten federal funding without the instruments she developed."



Standing: Dr. Godfrey Oakley (CDC), Dr. Eric London (NAAR)
Seated: Micki Bresnahan (NAAR),
Dr. Marshalyn Yeargin-Allsopp (CDC), Dr. Coleen Boyle (CDC)

After reviewing what is known about ADI and ADOS and giving guidance regarding issues that will arise in the use of any instrument for surveillance research, Dr. Lord focused on perhaps the most important issue that must be confronted. If the questions epidemiologists want to answer are prevalence and changes in prevalence, we must first decide if we are interested in a narrow or broad definition of autism. While the broad definition may be closer to telling the "truth" about autism, it is more difficult to measure. Ami Klin, who followed Catherine Lord, extended the discussion and reinforced this point. Reflecting on the experiences of the Yale Child Study Center, he noted both an increase in referrals for evaluations beyond the demand expected given regional births, and an increase in awareness of the pervasive developmental disorders among educators and parents. A breakdown by diagnosis of unsolicited referrals in two time periods, '89-'93 and '94-'97, showed that there was a notable increase in the proportion of PDD-NOS and of Asperger's Syndrome cases. These groups, and others in the autism spectrum which Dr. Klin reviewed, should be carefully considered for inclusion in prevalence/surveillance research. Dr. Klin went on to describe novel screening procedures developed for use in their study of high functioning children with autism. When validation data are summarized, these procedures have the potential to help researchers develop strategies for the inclusion in epidemiologic research of more elusive populations of children with autism and related conditions who are higher functioning.

Session II: Prevalence and Epidemiology: Trends and Risk Factors

The second session of the conference, moderated by Dr. Jane Costello of Duke University, featured presentations by three members of the CDC, and by two international epidemiologists.

Incorporating Autism into the CDC Developmental Disabilities Surveillance Program

The commitment of the CDC Developmental Disabilities Branch to the study of autism was clear in the presentations of Dr. Coleen Boyle, Acting Chief of the Developmental Disabilities Branch, and of Drs. Kimberly Caldwell and Jacquelyn Bertrand. The ongoing Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP),

modeled after birth defects surveillance programs, monitors the prevalence of serious developmental disabilities (including mental retardation, cerebral palsy and serious hearing and vision impairments) among 3-10 year olds in a five county area. The program is a collaborative effort involving reviews of records provided by the departments of Education and Human Resources as well as private sources including hospitals and clinics. The data collected from MADDSP is used in the



Dr. Ami Klin

estimation of prevalence, and in analytic research exploring the etiologies of these conditions.

The goal of the CDC Autism Surveillance Pilot Study was to determine the feasibility of enlarging the existing MADDSP program to include autism. The pilot study absorbed three staff members for one year and involved the review of 15,000 records. The strategy implemented was a multi-stage review of all records of children ages 3 through 10 referred for special education in nine school districts. The main source of information used from these files were psychological reports, which include behavioral observations, testing results, history, diagnostic impressions and recommendations. Records which included a diagnostic impression of autism or other autism spectrum disorder, a standardized instrument diagnosing a spectrum disorder, or behavioral description consistent with the DSM-IV diagnosis of autism spectrum disorder were flagged in the first stage.



Dr. Christopher Gillberg

The second stage of the record review included extracting relevant information from flagged records onto an abstraction form, and preparing case summaries which were then used to determine whether an individual met the study definition of autism or autism spectrum disorders. Two hundred and fifty children were identified using this strategy. The profile of this captured group was similar to published profiles of autistic children: the sex distribution, average IQ and level of functioning (as assessed by the Vineland) were consistent with expectation. This meticulously implemented strategy resulted in a provisional prevalence of 8.6 per 10,000 for spectrum disorders, and 2.6 per 10,000 for core autism. The surveillance mechanism will undergo further revisions and will subsequently include children in private school settings as well. Researchers anticipate that this further work will result in an upward revision of the prevalence estimate. Although the CDC methodology may be overly burdensome for local health agencies, lessons learned through the CDC pilot study may provide insight into ways to investigate clusters in autism.

The Prevalence of Autism and its Spectrum Disorders. Is it going up?

Dr. Christopher Gillberg, the eminent Swedish researcher and clinician whose work in the epidemiology of autism is widely known, placed the CDC work in context. In a historical review of prevalence studies in autism, Dr. Gillberg observed that studies published after 1985 show significantly higher rates of autism than studies published prior to 1985. Before 1985, the prevalence figure was roughly 4 per 10,000, less than half the pooled average of 11.8 per 10,000 in studies published from 1985-1995. Since 1995, studies of prevalence have turned in a pooled mean consistent with the 1985-1995 estimate. Whether or not this represents an actual increase in prevalence is unclear. It may represent an increased ability to diagnose autism in the very lowest functioning group, coupled with an increased ability to identify and diagnose autism in the highest functioning group.

The experience of Dr. Gillberg's own research team represents a case in point. The same team, using the same methods and working in the same area, found prevalences of 4/10,000 in

1980, 7.5/10,000 in 1986, and 11.5/10,000 in 1991. After looking carefully at these findings, the rate of autism in those with mild mental retardation (IQs in the 50-70 range) had not changed over the three studies (excluding immigrants). But, there was an "enormous" difference among the three studies of rates among the severely retarded and among those with IQ's above 70. The ability to recognize autism in lower functioning individuals and to identify higher functioning individuals with autism is clearly contributing to the "apparent" increase in prevalence. Researchers also believe that as "awareness increases, so does prevalence."

At the very least, the evidence weighs in for a higher prevalence over the last thirteen years than previously believed. And what about the U.S. specifically? Interestingly, studies conducted in the U.S. after 1985 have yielded significantly lower prevalence estimates than non-U.S. studies. Dr. Gillberg remarked on the difficulties inherent in conducting studies of this type in the U.S. (due to such factors as the absence of universal healthcare and the mobility of populations), and implied that differences in prevalence findings may have more to do with these difficulties than with actual lower U.S. prevalence. Given that there have been no non-U.S. studies published in the past 15 years that support the prevalence estimate of 4/10,000, Gillberg simply stated it should no longer be used as the standard. Autism is clearly more prevalent than previously reported. Dr. Gillberg safely places the rate in Europe at "1 in 1000 or slightly above that". But whether or not the changed estimates of prevalence represent a true increase or a change in our ability to recognize autism in subpopulations is still unanswerable.

Autism Spectrum Disorders: Prevalence, Associated Characteristics and Policy Implications

The next presenter was Dr. Susan Bryson, a principal investigator in the Nova Scotia Prevalence Study conducted in the mid-1980's. In this study, researchers focused on two regions, targeting all resident children ages 6-14 years old. The prevalence estimate for the mainland Nova Scotia study area was 11.1 per 10,000. In the rural study area, Cape Breton, the prevalence was 13.1 per 10,000. Statistically speaking, these prevalences are not "different." The Nova Scotia sample, collected in the '80s, suggested a higher prevalence rate of autism than earlier studies. Bryson attributed this result to the broadening definition of autism, which extended the diagnosis from cases like Kanner's to lower and higher IQ groups. (Gillberg's talk described the same increase in diagnoses in these groups in other recent studies.)



Dr. Susan Bryson

The Nova Scotia study has not only contributed to our estimation of how common autism is, but has also suggested support for a commonly held belief that early intervention is effective at lessening the severity of the condition. The rural children with autism, as a group, when compared to the suburban/urban children with autism, had lower IQ's (20 points lower) and fewer speech and language skills. These striking differences are possibly the result of the availability of early intervention programs in Nova Scotia but not in the Cape Breton study area.

The richness of the data collected for this study was demonstrated in a second set of findings Dr. Bryson presented. Data were also collected on physical anomalies and a number of other physical measurements in children with autism and in several comparison groups. Posterior rotation of the ear was present in 45% of the children with autism. This anomaly distinguished them from all three comparison groups—typically developing children, siblings, and the matched developmentally disabled controls. Since the ear develops during the third and fourth weeks of gestation, the presence of early biological processes in autism is indicated by these findings.

Dr. Bryson is currently studying individuals with mental handicaps (i.e., IQ 70 or less), ages 14-21, in the Niagara region of Ontario, and she shared some preliminary results. Using the ADI-R to identify the presence of autism, they have found that a full quarter of the mentally handicapped population meets the criteria. Furthermore, among young adults with autism, 45% have at some time had an episode of psychiatric disturbance (most commonly, mood disorders). While it is too early to be certain that the rate of comorbid psychiatric conditions in autism differs from that in a matched mentally handicapped group, the psychiatric disturbances in the autistic may be more intractable.

SESSION III: Etiology: Emerging Issues

Dr. Marie Bristol-Power, a major friend to autism research and coordinator of the Collaborative Programs of Excellence in Autism at the NICHD, moderated the final session which focused on emerging issues in the etiology of the disease. A brief overview of the NICHD Collaborative Programs of Excellence in Autism (funded in the amount of more than \$27 million over a five year period) underscored the expanding commitment of the NIH to supporting research in the etiology of autism. What followed could only be described as an avalanche of findings.

The South Carolina Autism Project - Strategy and Preliminary Results

The first presenter of the morning was Dr. Roger Stevenson, Director of Research at the Self Institute of Human Genetics in South Carolina. The South Carolina Autism Project, he explained, was set up to identify the causes of autism in a subset of the 5-21 year old individuals served by the South Carolina Department of Disabilities and Special Needs. The project is involved in exploring genetic and environmental etiologies. Among the findings Dr. Stevenson presented, two absorbed the most attention. The first, a clinical finding, was that 24% of the autistic study subjects had large head circumference. At birth these individuals had head sizes that were normal; the large head size was acquired during the first four to five years of life. It appears that the observed macrocephaly consisted of excess brain tissue rather than enlarged ventricles. Excess neuron growth can result from two different processes—increased neurogenesis and decreased neuronal cell death. Future research will focus on imaging studies hopefully helping to discriminate areas of excess, longitudinal studies to

follow head growth over time, and assessments of family members for the same characteristic.

A number of cytogenetic studies were pursued in the South Carolina Autism Project. Cytogenetic research focuses on abnormalities in chromosomes, including abnormalities in the numbers and structure of chromosomes. In the case of structural abnormalities researchers examine the impact of parts of chromosomes being lost, gained or moved to new positions. Studies of structural abnormalities have pointed the way to chromosomal locations of genes involved in several diseases. Dr. Stevenson reported that eleven of the one hundred fifty study participants had chromosomal abnormalities. In these eleven, unlike changes normally observed in a population of mentally retarded individuals, the chromosomal changes were balanced appearing, or were very small changes that are easily missed. Five individuals had abnormalities on chromosome 15—all of which occurred on the maternal chromosome.



Dr. Marie Bristol-Power

Prior published reports on 108 cases with duplications/deletions on chromosome 15 include eight cases of diagnosed autism and a greater number with autistic behaviors. The South Carolina findings add to this line of evidence. The region on the chromosome where the common abnormalities have been found include several subunits coding for GABA receptors. (See Science Feature, p. 1.)

Neurobiologic Abnormalities Characteristic of Patients with Autism

Next in the all-star lineup was Dr. Eric Courchesne of the University of California, San Diego. Giving us perspective on what is now known about the neurobiology of autism, Dr. Courchesne noted that ten to twelve years ago there was no neurobiological information concerning this disorder other than the persistent finding of serotonin abnormalities. There was no demonstration of an association between neural substrates and deficits in behaviors that characterize autism, no knowledge of the timing of the biological onset of the disorder, no identification of candidate genes, and no animal model. And, as he later pointed out, studies in autism had never contributed to an understanding of normal brain functioning.



Drs. Eric Courchesne and Catherine Lord

Since that time progress has been rapid. Citing a dizzying array of anatomical evidence from autopsy and imaging studies, Dr. Courchesne began by noting that many of the observed brain abnormalities involve regions and systems whose "principal" neurogenesis is at 4-5 weeks gestation. The disruption in these systems may indicate one "window of vulnerability" for the development of autism. Thus, not only have specific brain regions been implicated, but one possible time for biological onset has been suggested by this evidence.

Pursuing findings of cerebellar abnormalities in autism, Dr. Courchesne's team conducted one of the first studies successfully correlating an abnormal behavior found in autism to an anatomic abnormality found in the autistic brain. Ultimately, this line of research led to further study of the cerebellum in

normal individuals, and to the development of a new theory of the functioning of the cerebellum. Having earlier found a reduction in the cerebellar vermis nodules 6 and 7 among autistic patients, the researchers evaluated the speed of orienting attention and its association with the size of the cerebellar vermis nodules 6 and 7. In a since replicated experiment they showed that the more abnormal the cerebellar vermis, the slower an individual is in orienting attention. Deficits in shifting attention from one thing to another have also been documented. These findings, coupled with studies in normals which have demonstrated cerebellum involvement in an array of activities including working memory, long-term memory, language generation, learning novel skills, speech, complex problem solving, and concept formation—many of which are areas of deficit in autism—led Courchesne to the formulation of a new theory of the cerebellum. He proposes that the cerebellum is involved in prediction and preparation functions which help us to respond to our constantly changing environment. His theory also asserts that a "cerebellum, when active and out of control," might adversely influence the development of related brain structures. Indeed, Courchesne found in autistic subjects (ages 3-8) that a smaller and more abnormal vermis was also correlated with larger frontal lobe volume.

The landscape of our knowledge with respect to the genetics of autism has also changed. A laundry list of findings, something which could not even have been assembled 5 years ago, emphasizes the dramatic progress in the area of genetic research and the potential for future contributions in this area. The work presented by Dr. Stevenson earlier on chromosome 15 q11 to q13 anomalies, along with the findings of other researchers at this location, make it the most consistent site of reports in autism. The finding of maternal origin of the chromosomal anomaly by Dr. Stevenson and his colleagues and by Dr. Edwin Cook and Dr. Courchesne and their colleagues also add the first reports of a *mode of transmission*. Reed Warren's research into the HLA complex on chromosome 6 relating autism and immune profiles, along with Ed Cook's and Lesch's work on the serotonin transporter gene, demonstrate other areas deserving further investigation.

Genetic Studies of Autism

Dr. Donna Spiker of the Stanford Genetic Autism Project, reminding us of a time—only a few years ago—when federal money for genetic studies in autism was nonexistent, also told a story of a dramatically changed picture in autism research. The evidence for a genetic basis for autism is no longer circumstantial. Autism has been linked with chromosomal and genetic abnormalities, with increased risk for a diagnosis of autism to siblings (on the order of 75-fold increased risk), and with concordance for identical twins of 75% for a diagnosis of autism and approaching 100% for a more broadly defined phenotype. Family studies have shown language delays and learning disabilities in unaffected siblings, and milder phenotypes or subclinical phenotypes in first degree relatives. Based on a ratio of concordance rates between identical and fraternal twins, it is thought that more than one gene is involved. Dr.

Spiker described two broad strategies for identifying these genes—linkage studies (which involve a complete genome scan) and candidate gene studies (in which researchers hypothesize that a specific gene is involved, and then test to see whether it is). Both strategies are being vigorously pursued both nationally and internationally by a large number of research teams. Dr. Spiker's update of the Stanford Genetic Autism Project's work illustrated the complexity of conducting these studies. In its affected sib-pair linkage study, the Stanford group is currently genotyping 90 families. The genotyping plan involves reviewing 381 individuals and identifying 422 markers which will give us 161,000 genotypings. The Stanford team is roughly halfway through the process. In communicating the urgency of their mission, Dr. Spiker stated the importance of getting at causes, rather than symptoms, so as to understand the biological mechanisms and to develop rational treatments.



Dr. Donna Spiker

The Embryology of Autism

The much anticipated presentation of Dr. Patricia Rodier from the University of Rochester followed. Dr. Rodier is a stellar representative of researchers with expertise in basic science who are new to the field of autism research. The excitement her work has generated is obvious and, according to Eric Courchesne, is perhaps the "most exciting evidence that I've heard in the last 10 years of autism research". As a developmental biologist, her approach to understanding autism or any developmental disability is to describe the embryology in the period in which the developmental disability is initiated. Through a convergence of prior information on the timing of toxic exposures and minor physical and structural abnormalities associated with autism, she hypothesized that the biological age at onset for autism falls during days 20-24 after conception. She further hypothesized, based on her work in animal studies and in her autopsy study of an autistic individual with Moebius syndrome, that certain observed factors (structural abnormalities found in the facial nuclei, the absence of superior olive, and an associated shortening of the brainstem) implicated a specific set of genes responsible for the segmentation of the neural tube at this time of embryogenesis. Her subsequent work has focused on this set of genes which, by great good fortune, are well described because of their biological significance to embryologic development.



Dr. Patricia Rodier

She then turned to the preliminary results of her candidate gene research. For this study, Dr. Rodier selected families which might have a higher probability of having genetic defects of this sort—multiplex families, and those with defects in the face or in the neurology of the muscles of the face. She looked for polymorphisms of the primary candidate gene, and found a single-base change in the sequence which was significantly more common in children with autism spectrum disorders than in controls. A paralogous gene on another chromosome—a kind of back-up gene which shares a common function—also was found to have a previously unsuspected polymorphic form. Data from three generations

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Los Angeles Benefit Features John Lithgow and Kathy Bates

Almost 600 people packed the auditorium at Los Angeles' Directors' Guild of America Theatre last October for "An Evening of Commitment, Compassion and Hope," NAAR's first West Coast benefit. NAAR partnered this wonderful evening with the Achievable Foundation, a Los Angeles-based organization that serves the needs of the developmentally disabled. The benefit featured a series of dramatic readings by acclaimed actors John Lithgow (Emmy award winning star of "Third Rock from the Sun") and Kathy Bates (Academy Award winning actress most recently in "Titanic")--both of whom donated their time and incredible talent to the cause of autism and developmental disabilities. NAAR Honorary Board members Joe and Arlene Mantegna and Aidan and Elizabeth Quinn served as Honorary Co-Chairs for the event.

The evening opened with introductory videos on NAAR and Achievable featuring actor Joe Mantegna, who spoke about his daughter, Mia, who has autism. Lithgow and Bates then performed scenes from *The Glass Menagerie*, *Who's Afraid of Virginia Woolf?* and *Of Mice and Men*. The performances were brilliant and riveting. Most touching was the conclusion of the evening, where Lithgow and Bates read the winning entries of a writing contest that had been conducted in the weeks before the event.

"Usually a benefit is just a benefit, but this one was different" commented one guest. "It was magic. People go to the movies to laugh or cry, and during this evening of commitment and compassion, we did both." ♦



Above:
Kathy Bates and John Lithgow acknowledge the applause of a grateful audience



Above:
NAAR President Karen London (left) and Achievable President Kent Graham (right) presenting plaque of award winning art and writing entries to Lithgow and Bates



Right:
Lithgow and Bates with Winners of the Writing Contest



NAAR President Karen London (left) with NAAR supporters Ed Berenson (center) and Connie Lapin (right) following the theatrical readings



NAAR Research Partners Norma and Malcolm Baker (center), with Carey Zuckerman (left) and NAAR Trustee, Catherine Johnson (right) enjoying the post-performance reception

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 or two years; however, special opportunities to sponsor autism fellowships and multi-year and multi-site collaborative projects are also available. 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 that 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 genetics 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.

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 414 Wall Street, Research Park, Princeton, NJ 08540."

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 414 Wall Street, Research Park, Princeton, NJ 08540."

(continued from page 1)

The Hunt for Autism Genes

Valerie Lindgren, the team's cytogeneticist; and Courchesne and his group are central figures in the tale. Cook and his colleagues are the first to report a gene—not just a region on a chromosome, but a single gene—related to autism. This is the famous (or infamous, considering how slippery the thing has been so far) serotonin transporter gene, located on chromosome 17. Now, with his new findings concerning a connection between chromosome 15 and autism, Cook and his colleagues have published another paper that has placed the field of autism research squarely within one of the hottest areas of genetics research today.

Genetics 101

Autism is now known to be one of the most genetic of all genetic disorders. To many of us this news has come as a shock; in my own family's case my husband and I were told, in 1991, that although "statistically" our chance of having a second child with autism was approximately 3%, in actual practice, none of the genetic counselors on staff at the major urban hospital handling our case had ever seen a family with more than one child with autism. Needless to say, we weren't happy when, just a couple of years later, we started to hear that autism was not only "genetic" but that it was among the most strongly genetic disorders known to the scientific community. Today, depending upon whom you ask, parents are told that the chance of having a second child with autism varies anywhere from 5 to 10%—with a roughly 25% chance of having children with related problems. In the meantime we had gone on to have twins, one of whom—surprise—is indeed autistic. We parents need the science to be moving a great deal faster than it is.



Ed Cook, M.D.

Still, these percentages are not quite as bad as they sound. To begin with, Susan Folstein, the first researcher to study identical twins with autism, believes that the 10% figure will turn out to be wrong; her work tells her that the correct figure will probably be 7 to 8% (Cook uses a range of 5 to 9%). Still too high, but not 10%. And of course this also means that a family's chance of the next child *not* being autistic is 90 to 95%; the odds are in parents' favor that it won't happen again.

Perhaps more importantly, the 25% figure for related problems does not mean that 25% of a family's non-autistic children will have severe and life-altering problems. Some of these kids will have problems with spelling, for instance, and that will be the end of it. Some of them will be poor readers who will improve with age, as almost all dyslexics do with proper intervention. Only about 15% will show social reticence, and this won't be social reticence at the level of HFA or Asperger's. And some of these "differences" in the siblings of children with autism will actually be beneficial.

In Folstein's words, "I think that some of these various traits are valuable traits—or at least they are not in themselves bad things. A case of autism results when you get all of them together. They don't just add up; instead, whatever negative effects they have multiply."

In other words, the real problem for parents of a child with autism is the 7 to 8% chance of having a second child with autism—not the 25% chance of having a child who can't spell, or who isn't the life of the party.

One last note. As parents, you will continue to see the 3% figure cited as the "prevalence rate" in siblings. What this means is that when researchers go out and simply *count* how many families have more than one autistic child, they find that approximately 3% (some say 3 to 5%) of families with one child with autism also have another child with autism. However, from the perspective of family planning, the 3 to 5% range underestimates the danger. The true risk of having a second child with autism should be the "recurrence rate," which is 7 to 8% (or 5 to 9%, depending upon the source). The reason there are fewer "multiplex" families than we would expect is that families who have a seriously handicapped young child—any handicap, not just autism—frequently stop having children. Researchers call this phenomenon "stoppage," and it obviously lowers the number of autistic siblings in families. If you stop having children after having a child with autism—or choose to have fewer than you would have otherwise—you limit the population. Sadly, the real risk of having a second child with autism is the higher figure.

We know that autism is highly genetic through studies of identical twins in which the index twin has been diagnosed with the disorder. Recent studies, such as that of Bailey, et. al., (1995), have found that the odds of a "co-twin" also having autism are as high as 73%; that is, if the index twin is autistic, there is a 73% chance that his or her co-twin will be, too. This is the "concordance" rate.

Schizophrenia, by contrast, which is understood by all to be a genetic disorder, has a 46% concordance rate. And diabetes, another complex disease passed down through generations, has only a 30% to 50% concordance rate, with a risk to siblings of 6%. So 73% clinches it, particularly when you compare this figure to the rate in the studies of fraternal, or *non*-identical, twins which is extremely low. (In both the original group of fraternal twins, studied by Folstein, et. al., and the group recruited later by Bailey, et. al., none of the fraternal twins were concordant for autism.)

But as it turns out, the 73% concordance rate for autism is not the whole story. When researchers went back to revisit the original twins from the very first twin study, who were now grown, they discovered that the typical twins were no longer quite so typical. Most of them, in one researcher's words, had "something genetic" going on. They were not autistic; they would not even qualify for the label "high-functioning autistic" or "Asperger's." But only 1 of 7 had married and was living independently, and just 3 had managed to achieve full-time employment.

Looking at these grown non-autistic twins of index twins with autism, the researchers concluded that the concordance rate

for this group was 60% for a diagnosis of autism—but 92% for “a broader spectrum of related cognitive or social abnormalities.” Thus, autism may well be more strongly influenced by genetic makeup than schizophrenia, possibly even more strongly genetic than manic depression, which was previously thought to be the most powerfully genetic of all the mental illnesses.

This much makes sense, but for parents confronting such data the immediate question is: if our child inherited his autism from us, why aren't we autistic?

The simple answer is that autism is a “complex disorder”; in many or most cases it is “oligogenic,” meaning that it takes more than one gene to develop the disorder. Say autism requires a precise combination of 5 genes: if a husband has three of these genes and his wife has two, their child can be autistic while they themselves are not. Moreover, some of the 5 genes may be dominant, others recessive—which would mean that for the recessive gene the child would have to inherit two copies, one from each parent.

Alternatively, either husband or wife—or both—*could* have some symptoms of autism, but not enough to actually be autistic. One spouse might have had a language delay as a child, one spouse might be obsessive, one might be anxious or depressive—any or all of these traits might signal the presence of a gene or genes for autism. A student of Cook's recently constructed a Venn diagram with five intersecting circles, each circle representing a gene for autism. She showed that at the point where all five circles intersect you get autism, but at the point where only 3 circles intersect you get something else, at the point where two circles intersect you see a different symptom, and so on.

But Cook says what is most interesting to him is that you can also show that it would be possible to have *four* of the intersecting circles and yet show no symptoms at all. This is a particularly intriguing possibility in terms of what it would take to treat or to cure some cases of autism: if it is possible to have four autism genes with no symptoms, theoretically all you would need to treat is the one gene that “tips” the person into the disorder. A child or adult with autism, after having just this one gene remediated, could—with proper education and behavioral support—climb out of his autism even though four of his autism genes are still fully functional.

Which brings us to another critical point concerning “bad” genes and the mischief they work in human beings: the very same gene can have variable “expression” from one person to another. A really bad gene, for a progressive, wasting disorder, say, might send one child to an early death, while leaving another child only minimally affected.

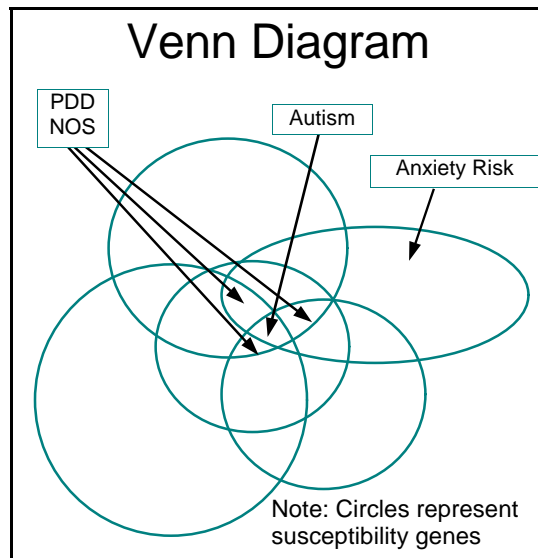
This is why you can have such incredible variation in identical twins, who share the same genes. Identical twins are essentially clones, and yet one twin can suffer from a terrible genetic disorder while the other does not (although this is rare). Cook cites the even more startling case of identical octuplet mice who have had a critical gene “knocked out” or removed from their genotype. When you have eight genetically identical baby mice, they are all phenotypically different—they come out looking different. Cook recalls a set of identical octuplets who had a genetic mutation that should have caused the mice to be born with malformed ears. Some of the mice had no ears, but others had just one ear missing, on one side; still others had one ear missing on the other side; and another one or two had some deformities to the ear, but only very mild. “What this tells us,” says Cook, “is that there's something that's not genetic about even very simple developmental biology—it could be as simple as where the mouse was carried in the womb, but we often don't know. This is an example where genetics may provide focused approaches to studying environmental effects.”

In fact, data on non-concordant identical twins *may* one day tell us how to use the environment to prevent autism in the first place. Most of us, when we hear the word “prevention,” think “abortion”—but abortion is a drastic and tragic means of preventing a genetic disorder. Down the line we may be able to use the environment to protect children with autism genes in the same way the environment may have protected Folstein's non-concordant twins. Remember: these are children who

carry *all* of the genes for autism—who are genetically identical to their co-twins who *do* have autism—and yet they themselves are not autistic. When we know why, we may be able to use this knowledge.

Getting back to parents: a parent could have all kinds of autism genes, and yet have been lucky enough that they were not expressed in him or her. Instead, the bad luck hits his child. Even more intriguing: a parent might carry autism genes that have actually benefited him in his own life—given him special skills or talents he would not have had otherwise. Cook himself pointed out, after reading this paragraph, that he wouldn't have been able to spend his weekend finishing the team's latest updated analysis without being willing to give up social contact and focus on the details of his work “in a somewhat repetitive manner.” This is easily the kind of useful and productive ability that could come from an autism gene that *doesn't* result in autism.

Last but not least, the parents could have few to none of the autism genes themselves, and yet still end up with an autistic child because of random mutations that take place during the complicated and sometimes perilous process of recombination that unites the mother's DNA with the father's. (And of



In this Venn diagram, each circle represents an autism susceptibility gene. It is possible to have one or even four genes, yet have no autism traits.

course the reality of environmental pollutants and toxins adds another dimension to the story: a child can become autistic because of a spontaneous mutation in his parents' genes caused by a virus or a toxin.)

Why We Need to Find the Genes

Most of us were taught, in high school or college, that genes are the blueprint for the human organism. Every middle-aged college graduate remembers the drill for eye color: you inherit a gene for blue eyes from your father, a gene for brown eyes from your mother (or vice versa) and bang: you've got brown eyes, end of story. In fact, eye color is more complicated than that, but this is what our college professors described to us as the one-gene-one-trait law of "Mendelian" genetics. In the popular view of genetics, a baby is conceived, its genes make it who it will be, and that's it.

As a result, most of us don't immediately see what is to be gained by discovering the genes for autism other than a prenatal test like the one for Down syndrome. What good does it do, for that individual child, to find out that a gene located on chromosome 15 may have caused him or her to be born autistic?

The answer is that finding the genes for autism may well mean finding treatments or cures for autism.

This is why. Broadly speaking—very broadly—there are two different classes of genes: "developmental" genes, and "operating system" genes. Developmental genes are the genes that guide the baby's development in the womb (though some are active throughout life). The genes that determine eye color are developmental genes. Developmental genes turn on, do what they were designed to do, then turn off and are not heard from again (except, interestingly, in cases of cancer which some researchers believe result from old developmental genes accidentally becoming active again and causing out-of-control cell growth).

Operating-system genes are different: operating system genes are the genes that are operating all day long; they are the genes that underlie and make possible everything we do. My own "operating system" genes make it possible for me to write this page; your operating-system genes make it possible for you to read this page. Other "system" genes make it possible for our lungs to breathe air, our hearts to pump blood, and our muscles to maintain a seated position in the meantime. Everything we do in life is "run" by genes.

This is where the possibility for treatment comes in. But first: another basic principle. Each gene "codes for"—or creates—one or more proteins. These proteins then go out to do their job: they might foster a chemical reaction in the brain or gut or heart or anywhere in the body; they might serve as receptors to allow one cell to receive a message from another cell; they might turn on another gene, which will produce another protein. But whatever they do in the body, proteins have to be

shaped correctly in order to work. Just one tiny flaw in the gene can result in a fatal flaw in the structure of the protein. (It doesn't have to; a gene can undergo mutations that are entirely harmless. But some mutations are deadly.) Babies born with PKU, for instance, are missing one enzyme, the enzyme that metabolizes phenylalanine, an ordinary amino acid found in food. Enzymes are made of proteins, and for PKU babies, that one missing enzyme, due to one mutated gene, causes profound mental retardation unless identified early so that dietary changes can prevent this fate. (For the sake of accuracy I should mention that PKU can be caused by either one of *two* different genes. But both genes cause the disorder alone, neither requiring the presence of the other.)

This is why knowing which genes are affected in autism has such an enormous potential payoff: once scientists have identified an affected gene, and have figured out what that gene does, pharmaceutical companies have a target. They can learn the structure of the protein that the affected gene, in its normal form, manufactures, and they can work from there. They might try to develop a "designer protein," a drug that looks and acts like the missing or mutated protein. Or they might try to create a medication that will affect gene expression—turning on a gene that is currently turned off, turning off a gene that is currently turned on, or speeding up or slowing down a gene that is presently operating too quickly or too slowly.

Or—and this has been covered extensively in the press—they might take the route of creating a gene therapy that would replace the bad gene with a new, good one. However, what is not often reported is the fact that gene therapy is currently the least attractive of these options, because it is the most complex—needlessly complex, in the view of many. Because genes not only produce proteins, but can also be turned off or on or slowed down or speeded up by proteins, most biotechnology companies are instead trying to create medications that will, like proteins, modify the gene's action. As Ed Cook says, "Gene therapy is something you turn to when you don't think you'll find an orally administered, more typical medication."

In all likelihood, autism will involve both mutated operating system genes and mutated developmental genes. Patty Rodier of the University of Rochester is looking into a connection between the Hox genes and autism (her work is covered in the Summer 1997 issue of NAARRATIVE.) A mutation in a developmental gene is more worrisome, because the developmental genes guide the creation of the brain in the first place, determining its structure. When a developmental gene is damaged, the brain ends up misformed—essentially, the baby is born with a birth defect of the brain. Many of the "thalidomide" babies of the 1960s were born not only with birth defects of the limbs and ears, but also with birth defects in the structure of their brains that caused them to have autism. This is not reason to lose hope, however, because structural differences in the brain can be, and have been, treated with



Bennett Leventhal, M.D.

medication in other brain disorders like schizophrenia and Parkinson's disease. More on this later.

The Serotonin Gene

The serotonin transporter gene has been a puzzler.

Cook and his team looked at genes controlling serotonin in the first place because one of the most robust findings in the biochemistry of autism has been that approximately one quarter to one third of people with autism show abnormally high levels of serotonin in the blood. And sure enough, Cook and his team found, in three separate studies, a statistically significant association between autism and a shortened version of the promoter of the serotonin transporter gene, HTT.

However, while it was no surprise to find a serotonin gene involved in autism, it *did* surprise everyone involved that the short form of HTT turned up in all three studies. In simple terms, the "transporter" portion of the gene transports serotonin inside blood cells—and the long form is better at doing this than the short. Thus if people with autism have more serotonin inside their blood cells than average, which they do, you would expect that people with autism would also have higher levels of the long transporter than typical people. But this is not what Cook's three studies found.

The precise relationship between serotonin in the blood and serotonin in the brain is complicated, of course, but basically blood cells are analogous to brain cells—which means that the long form of the transporter would lead to *more* serotonin *inside* the brain cells, and *less* serotonin *outside* the brain cells. Generally speaking (and again this is a simplification) we want good levels of serotonin *outside* our brain cells where it is free to work its magic. All of the "SSRIs" (selective serotonin reuptake inhibitors), —Prozac, Paxil, Zoloft and Luvox—are thought to work by increasing the level of serotonin in the spaces, or synapses, between brain cells.

HTT was the first susceptibility gene for autism found using appropriate family-based controls, and it was big news. Without consulting Cook, the University of Chicago dispatched a press release to EurekaNet asking them to post it on May 1, the day of the paper's release. Just days before the release was to be posted, word reached Cook that Fritz Poutska, Annemarie Poutska, and K. Peter Lesch's group in Germany had found no evidence either way, for short *or* long form being associated with autism. Cook contacted Eureka at once, but it was too late; for some reason the service did not have a provision for altering an announcement just before it was scheduled to be posted, and thus all the world was given the impression that Cook and his team considered their finding to be absolute. Cook has been trying to explain the provisional nature of published research to parents and journalists ever since, causing his wife, in their Christmas letter, to call him "the boy who cried gene." (Though Cook fondly points out to his wife that she said the same thing about a gene for ADHD he and his colleagues identified a few years back which has now been replicated twice, albeit after a two-year delay . . .)



Catherine Lord, Ph.D.

Naturally, these conflicting reports have led to confusion among parents trying to follow the science: is the HTT gene involved in autism or not? The answer, for the time being, is "maybe." Eric Courchesne speculates about where these findings may lead down the road:

"We're uncertain whether there is an association between autism and the short variant, or whether the short variant is a signpost that there is something somewhere else on that gene that is the real problem. Both groups are wondering whether these two findings may be telling us that it's not long vs. short that matters; maybe it's not the promoter region, but somewhere else in the gene that we should be looking. "

In other words, for parents, clinicians, and researchers alike the message is: stay tuned.

In the meantime, it is possible to draw some useful, although tentative, conclusions from work on HTT. To begin with, the HTT gene is probably normal; it is not a mutation. This means that it does not cause autism in and of itself, but may instead amplify the effects of mutations that do cause the disorder. The good news is that since the HTT gene is a normal variant (also called an "allele") we can use data collected from non-autistic people to think about people with autism.

In the normal population the short form is extremely common: over 60% of the general population carries at least one shortened form; 16% carry two. Furthermore, generally speaking, the short form is dominant over the long form: if you have one short and one long, behaviorally you'll act more "short" than "long." (Though researchers do not yet know whether the short is always dominant in all tissues of the body, or whether having two shorts is different behaviorally and emotionally from having one long and one short.)

In any case, the extremely common short form is associated with higher levels of *normal* anxiety. That is, on average, people who have the shortened form are more anxious than people who have two longs, but they are not pathologically anxious; they do not qualify for a diagnosis of generalized anxiety disorder (GAD), unless of course they do for other reasons. Ask a room filled with 500 people, half with the short form and half with the long, how they feel about speaking in public, and the group with the short form is going to be more anxious *on average*—though of course there will be plenty of "short-form" people with low anxiety, as well as "long-form" people with high anxiety. Nothing is absolute.

At this point, of course, any parent reading this account may be feeling confusion setting in for real, since many of us do see a great deal of anxiety in our autistic children—why shouldn't the short form, associated with higher anxiety, be exactly what researchers expected to see?

The answer is that, for the time being, there is no answer. That's the difference between designing a hypothesis according

to behavioral data (autistic people have high anxiety) versus designing a hypothesis according to physiological data (autistic people have high blood serotonin). As we've said: the research is extremely complex.

For his part, Cook, who is a clinician as well as a geneticist, has given a great deal of thought to what these findings may mean directly, in day to day life, for the children he sees:

"My latest hunch is that the short/long distinction may be related to aggression. Aggression is one aspect of autism we don't currently have ratings of in our samples, because as a group we've been appropriately focused on whether our kids did or did not have autism, and there is nothing about aggression that is diagnostic of autism. The most aggressive people in the world, the kids with childhood onset conduct disorder, don't have a touch of autism."

Fortunately, we know that medications that affect the serotonin system—the SSRIs, the older antidepressant Desyrel, and atypical antipsychotics like Risperdal—treat anger, irritability, and aggression in many clinical populations, including people with autism, and this is where Cook sees the HTT gene findings as eventually being useful:

"What I'm most interested in with this gene is whether it will give us a way to predict what dose of an SSRI a child needs. Some of these drugs are metabolized by enzymes that vary a great deal in the population. So in 90% of children and adults with autism the usual administration dose may make sense, but the other 10% might be completely different. There isn't a real predictable relationship between blood serotonin levels and clinical response, and I think there's a good chance we'll get some practical clinical data from this research soon."

Apart from this, the serotonin-autism connection may give us clues to other aspects of autism quite apart from anger and aggression. Cook again, "In broad strokes, if there's more mental retardation, there's higher serotonin—though we do see high-functioning kids with high serotonin as well."

Which points to the very real possibility that serotonin may be involved in autistic learning and social deficits as well as in mood and aggression. This is an exciting possibility given that the large pharmaceutical companies (which smaller start-up biotechnology companies call the "big pharmas") are spending billions trying to develop new and better serotonin medications. Cook explains:

"Right now there are limits to how high you can push the serotonin system. If you push the dose too high you get a worsening of symptoms—in depression, autism, or any problem you're treating—and that's usually because you're triggering the 'autoreceptors.' The autoreceptors are like a thermostat in the system: they say, 'Oh-oh, there's too much serotonin, I have to shut the system down.'"

In other words, push the dose too high and you end up with *less* serotonin in the synapses, not more. Up to a point, an SSRI like Prozac will increase the amount of serotonin in the synapse; after that point the autoreceptors turn on and start pulling serotonin back out of the synapse.

Fortunately, the big pharmas are working feverishly to find a way around this barrier—not on behalf of people with autism, but in order to help people with depression, schizophrenia, obsessive-compulsive disorder, and other anxiety disorders. Cook says:

"A lot of people are trying to figure out how to get around the autoreceptors, either to get a faster antidepressant

response or to treat resistant depression. One model of doing this that has been shown to reduce the time to antidepressant response and treat non-responders is to add pindolol to the SSRI. Pindolol is a beta blocker normally prescribed for hypertension, but it has the 'impure' effect of also blocking the serotonin autoreceptors."

Unfortunately, when Cook has tried this combination in a few of his patients with autism, he has not seen any improvement. But he's confident that sooner rather than later we'll have something that can block the serotonin autoreceptors in our kids:

"It's possible that our understanding of the serotonin system is insufficient, but I'm very excited because Prozac is coming off patent this year or next, so Eli Lilly has to come up with something else. And when they

do, we could start to see medications that can treat social and learning issues, too." [Editor's note: See C. T. Gordon's article on page 6 for another view on SSRI treatment of autism]

"...serotonin may be involved in autistic learning and social deficits as well as in mood and aggression. This is an exciting possibility given that the large pharmaceutical companies...are spending billions trying to develop new and better serotonin medications."

Trouble on Chromosome 15

"This is the hottest story in autism genetics," says Eric Courchesne, speaking of the recent confirmation of a link between autism and chromosome 15—a connection that has now been found by two separate teams in three separate studies. With chromosome 15, we move directly into genes affecting the cerebellum, one of the main brain structures that UCSD's Courchesne (as well as, in Boston, Margaret Bauman, and earlier, at UCLA, Ed Ritvo) has found to be affected in cases of autism.

First off, it's important to remember that with chromosome 15 we are talking about a *chromosome*, not a *gene*. Chromosomes are the squiggly lines expectant parents see on their amniocentesis reports; the baby's 100,000 separate genes lie on these 46 chromosomes (which are arranged in 23 pairs, one from the mother, one from the father).

The new finding on chromosome 15 is of an affected region on that chromosome—a region that does not "look right." This

puts the chromosome 15 finding in a different category from HTT: as Courchesne puts it, "I would bet a dinner at the nicest restaurant in San Francisco that this is a mutation, not a normal variant."

He and Cook looked at Chromosome 15 because Christopher Gillberg, author of *The Biology of the Autistic Syndromes*, suggested that 15 would have problems. In 1991 he reported several cases of autistic people with duplications of genetic material on 15. Sure enough, Gillberg was right. And while often in the history of "behavioral" genetics initial findings have not been replicated, so far this one has.

The biggest news about chromosome 15—the finding that suddenly places autism research in one of the hottest areas of all genetics research—is that children who develop autism due to an anomaly on chromosome 15 do so only if they received the anomaly from their mothers. In other words, for the first time ever, researchers have established a *mode of transmission* of autism—in this case, through the mother, not through the father. (Cook says fathers will get equal time once all the genes are discovered; it just so happens that this first anomaly comes from the mom.)

In the science of genetics this phenomenon is called "imprinting," and it is one of the most exciting—and most active—areas in the field today. Courchesne explains: "Imprinting refers to the concept that the gene will become differentially active—or "expressed"—based on whether it came from the father or the mother. Some genes remember where they came from; they care whether they came from the mother or whether they came from the father. And that "memory" determines whether or not they are expressed in the child."

With a maternally-expressed gene (or mutation) the gene has to come from the mother in order to be expressed in the child. If the child gets the exact same mutation from his or her father, nothing happens; the mutation is not expressed. With a paternally-expressed gene it's the opposite. The child has to inherit the gene or mutation from his father in order to have the traits that gene causes. Otherwise the mutation remains silent.

This is exactly what Courchesne and Cook found in the first family with the chromosome 15 abnormality whom they studied closely. There were three children, a girl with classic autism, a boy with atypical autism, and a third child, a girl, who was developing typically. (The unaffected sister was actually a step-sibling; the mother had remarried before conceiving her.) Both of the affected children had a duplication of material on chromosome 15. When Cook looked at the mother and the father of these two children he found that the father's chromosome 15 was normal; it was the mother who had the duplication.

But the mother herself was completely average; she showed no signs of autism at all, not even subtle ones. Cook then went

back to *her* parents, and found that she had inherited the abnormal chromosome from her father—whose own version of 15 was normal. In the transmission of 15 from father to daughter, the chromosome had undergone a spontaneous rearrangement, which the daughter then passed on to her own children. The mom was normal because she had received the mutation from her dad; if she had received it from her mother, in all likelihood she would have been autistic, too.

Cook and Courchesne have now looked at 140 children with autism in all, and have found one more, a boy, with a duplication on 15. He inherited the duplication from his mother—who did not have the mutation herself. In this case the duplication arose "de novo" when the *particular egg* that was to become this boy was originally formed many years ago. (Which means that this mother's chance of having a second child with autism is near zero, since the duplication on 15 cropped up simply as a random mutation in a random egg.)



Eric Courchesne, Ph.D.

The 2-out-of-140 rate may be low, of course, because at this point researchers are dealing with anomalies on chromosome 15 so large they can be seen under a microscope—or picked up by having 3 alleles at a locus instead of the normal 2. Any of the other 138 children could also have duplications on 15 that are too small to be picked up in this way. (One note: in all, Cook and his group have found 3 children with the chromosome 15 duplication: the brother and sister from the first family, and then the boy whose mother did not have the duplication. But the official figure is 2-out-of-140 instead of 3-out-of-140 because the one very high-functioning boy was too mildly affected to meet the diagnostic

criteria for inclusion in the 140. The research team picked him up by accident, after they found the duplication in his sister and so decided to look at the whole family.)

Interestingly, further evidence for maternally-imprinted duplications on chromosome 15 has just come from Browne's team in England, which has been studying the genetics of language disorders. They, too, found that the genes they were looking at had to come from the mother in order to produce a language disorder in the child. When their paper recently appeared in the December 1997 issue of the *American Journal of Human Genetics*, the authors mentioned Cook and Courchesne's paper and said that while they hadn't been looking for autism, now they would.

And finally, Cook's work has been duplicated and extended in the laboratory of Margaret Pericak-Vance (an expert in gene-mapping and 1997 NAAR Research Award winner) at Duke University. Previously Pericak-Vance had also found anomalies on 15; she has now replicated the maternal inheritance, and has added two important pieces to the puzzle:

1. Pericak-Vance found an "increase in recombination" on chromosome 15 in families with autism. "Every time people have a baby," Pericak-Vance explains, "it's like a deck of cards being shuffled." Say you have a deck of cards with all four suits separated out from each other, and the numbers put in order. Then you shuffle that deck of cards once. The families

that end up with an autistic child will show a much more pronounced "reshuffling" than the families that end up with a non-autistic child. In physical terms, Pericak-Vance and her team found that the autistic person's markers on chromosome 15 appear further apart than they are in the typical person. And: this difference came from the mother.

2. Having confirmed Cook's findings, Pericak-Vance then looked at chromosome 15 in families with a different neurological disorder, unrelated to autism. She found that in these families, this region of chromosome 15 was normal, further evidence that the duplication on chromosome 15 is specific to autism—not a general genetic anomaly you might find in many brain-based problems. More evidence for 15. (Cook, too, has a paper in press in which his team looked for duplications on 15 in over 250 non-autistic children with moderate to profound mental retardation, and did not find any duplications on chromosome 15, although they did find 4 cases of Angelman syndrome in which there was a *deletion* of the same portion of chromosome 15 that is *duplicated* in autism.)

Pericak-Vance notes that there are a number of different possibilities as to what could cause this anomaly. You might see perfectly normal genes that for some reason have been duplicated, giving the child an extra copy. Having extra copies of otherwise normal genes can be very damaging to the organism. This is the problem in Down syndrome. Or you might see some kind of incorrect rearrangement of otherwise normal genes; you might see a mutated gene that is causing the chromosomes to break and reshuffle. There are other possibilities as well.

Time will tell—and most researchers feel we'll know sooner rather than later. The next step is to pinpoint a *narrower* region on the chromosome, or a single gene within this region that is key to the disorder. Ed Cook's prediction: "Within the next two years there's going to be some very hot and definitive information about specific genes involved in autism."

Where Does Your Child Fit In?

At present we can't tell the autistic children who have chromosome 15 duplications from the ones who don't simply by looking at them. However, there do seem to be characteristics specific to these kids. "The one I'm sure of," Cook says, "is increased epilepsy and epileptiform EEGs. One autistic woman we studied didn't have her first seizure until her late teens, but she had abnormal EEGs as a child in the way autistic kids often do."

The chromosome 15 children studied so far also show regression. Between 12 and 24 months in their development, they lost skills. As well, these children have low muscle tone. "They walk on time," Cook says, "and they can eat OK; it's not severe. But they might have a little trouble holding their heads up as infants, and show a history of low tone in other ways. Most kids with autism aren't like that, so the floppy ones stand out a little bit." He continues: "A lot of them visually look like Fragile X, with hyperextensibility of the joints, double-

jointedness, and ears that may be a bit longer than normal, and incorrectly 'rotated' backward."

As preliminary as these impressions are, they are extremely significant for any parent of an autistic child who is contemplating having another baby. Cook gives this advice to parents:

"You can find this on an amnio, but most labs don't do it. You have to look very carefully. But people who are trying to get pregnant now, and already have one autistic child, should look for it. It's much more important than looking for Fragile X, though we still recommend checking for Fragile X, too."

Bear in mind, of course, that any lab that agrees to look for a duplication on chromosome 15 is going to come up with a large number of "false negatives," since at this point all anyone can look for is an anomaly large enough to be seen under a microscope. Bear in mind, too, that we don't know what a chromosome 15 duplication found on an amniocentesis is going to look like in the actual *child*. Of the two original children Cook and Courchesne studied, the sister was much more severely autistic than her brother, who was so mildly affected that the school system did not want to provide him with services. His IQ, language, and academic performance were normal, and the school system was not concerned with his narrow interests or poor social skills.

This is the mystery of gene expression, the mystery of why a gene mutation can be devastating in one person, only mildly troublesome in another, and silent in yet a third. Ed Cook comments:

"Even in this family the little girl probably has a second gene involved. So here is a major finding and you can't even use it to distinguish a child who is mildly retarded and has classic autism from a child who has normal intelligence and is only mildly autistic."

Parents of children with autism who are contemplating having another child and would like to check for duplications on chromosome 15 should tell their physicians that a possible region may be 15q11-q13, so that the chromosomal analysis will be done with attention to this region as well as to the other chromosomes. Be sure to discuss this very early on in the pregnancy, since locating a lab that can do this test may take time.

Other Hot Spots: Chromosomes 7 and 16

The results of the first full genome-wide screen of autism were published this March in *Human Molecular Genetics* (which can be found on the internet at http://www.oup.co.uk/hmg/Volume_07/Issue_03/.) This study, by the International Molecular Genetics of Autism group, reported linkage for chromosomes 7 and 16. Previously, Sue Smalley of UCLA had suggested a connection between autism and tuberous sclerosis (TS) that excites people; one of the genes for TS is on 16, though it looks as if this gene is not going to be the same one the International group is looking at on 16. Nevertheless, researchers feel there is fairly strong evidence for an autism

**Ed Cook's prediction:
"Within the next two
years there's going to
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gene on the long arm of chromosome 7, weaker evidence for an autism gene on the short end of chromosome 16. Geneticists are in the stage of working across groups to find out which gene hypotheses hold up and which do not; we'll report their discoveries as they emerge.

At this point we have no idea how many autism-susceptibility genes researchers will eventually identify. Assuming it takes a combination of 5 genes to produce the disorder, there is nothing to say that these 5 genes will be the same 5 genes in every person with autism. There could be 20 autism-susceptibility genes, with some people having one combination of 5, other people having other combinations of 5. And of course, it is likely that there also exist dominant genes for autism, genes that can cause autism acting entirely on their own. We just don't know yet. As Clarence Shutt, a structural biologist at Princeton and Executive Vice President of NAAR, says: "In science, everything's a mystery until it happens."

Can Chromosome 15 Lead Us to a Treatment?

The prospects for chromosome 15 leading to a biomedical treatment for autism—not a "cure" (or not necessarily) but a genuine treatment—are high. This is so because the affected region on chromosome 15 contains three genes that code for the neurotransmitter GABA—and the pharmaceuticals are already pouring buckets of money into the GABA system, and have been for years. GABA, or gamma-aminobutyric acid, is the neurotransmitter involved in anxiety. Alcohol, anticonvulsants like Gabapentin and Vigabatrin (note that the drug companies have been helpful enough to include "gaba" in the names of these medications like Xanax and Valium all work by attaching to the GABA receptor.

GABA is an "inhibitory" neurotransmitter; it prevents cells from firing. Some call it the brain's "braking system." This brings us to another line of converging evidence: in the cerebellum, the Purkinje cells—which Margaret Bauman has found to be diminished in number in the autistic brain—release GABA.

The problem with antianxiety drugs like Valium and Xanax, as anyone who has taken either for sleep knows, is that although they can work wonders at first, the effects do not last. Shortly before last Christmas, Cook used a GABA medication to treat a severely behaviorally disordered young man with autism, and it helped. But the effect was fleeting.

As a result, the pharmaceuticals are engaged in an ongoing quest to develop a GABA drug that can work over the long term—the financial payoff would be enormous. And the chances that one or more of this new generation of improved GABA drugs could be helpful to our children are good. It is

also possible that an existing compound—a medication that has already been developed and tested for safety but never marketed—could work for autism. Drug companies cannot legally test medications in humans without having a biological "target," and until now it was not known that GABA was involved in autism. As a result, none of the GABA medications has ever been formally tested in people with autism; the tests were all run on people with anxiety disorders. A medication that does not work for an anxiety disorder in fact *might* work for autism. It's possible.

As Ed Cook says, "Now we need to think about the GABA system as much as we think about serotonin." Happily, more work on GABA is being done all the time. The Cook team's findings on GABRB3—a gene for one part (or subunit) of the GABA receptor—are in press, and will appear in May in the American Journal of Human Genetics, (web site <http://www.journals.uchicago.edu/AJHG/journal/>).

Other Paths to a Treatment

As to the question of whether the missing Purkinje cells are the "real" problem, as opposed to a "chemical" anomaly in the GABA system—it is at least theoretically possible that an autism-specific GABA medication could compensate for missing cells by drastically increasing the GABA production of the Purkinje cells that are present. This has been done in other brain disorders like Parkinson's disease. Or, eventually, the structural differences in the autistic brain may be treated by "neurotrophic factors" or "nerve growth factors"—chemicals that cause new brain cells to grow. (See related story on p. 10 in the Summer 1997 issue of NAARRA-

"I think the differences between the autistic brain and the normal brain are relatively subtle. Of course a structural difference can be small but critical, but even so I don't see anything in the neuroanatomical studies that says autism is untreatable."

TIVE.)

But Cook believes—and here there is disagreement among researchers—that the structural flaws we see in the autistic brain are not drastic enough to be insurmountable:

"There's nothing that's that abnormal in the brains of people with autism. If you compared a young autistic person's brain to the brain of his healthy 60-year old grandfather, the grandchild would have the better looking brain." [Editor's note: Men's brains shrink with age—as do women's, though to a lesser degree.]

"I think the differences between the autistic brain and the normal brain are relatively subtle. Of course, a structural difference can be small but critical, but even so I don't see anything in the neuroanatomical studies that says autism is untreatable. With the right nerve growth factor, you might get maturation of those structurally different parts of the brain."

The fact is, it is possible to treat autism now: both Anafranil and the SSRIs have been shown to diminish core symptoms of the disorder, not just behavioral "add-ons." (see article, p. 6.)

In Ed Cook's words: "The SSRIs are very exciting. With these medications we can treat something we couldn't touch just 10 years ago. I think there's a lot of excitement about where we can go with autism treatment medically, and in general I see SSRIs as giving us 5 percent of what we'd like to be able to do. Say we get 5% every five years—that doesn't sound like a lot. But there are going to be a number of kids out there who, with just a 5% bump up in functioning, will have their lives significantly changed. Then you keep adding onto that, and adding on, until you get as far as you can go.

"Will we eventually be able to cure autism? I don't know. Maybe there would always be something left over; maybe you could never give an autistic person the fluidity of thought and movement normal people have. But I don't see anything about the neuroanatomy that says we can't bring everybody up to Temple Grandin's level, except that the rest of us aren't as bright as Temple.

"But we're very far away from that today. "

This is where parents come in. What we can do—what we must do as parents—is to push the science forward. Raise the money, raise the awareness, make it happen. That is our job, and our hope. ♦

A Note From Ed Cook: We would like to thank the NIMH, NICHD, NINDS, the University of Chicago Brain Research Foundation Seed Grant Program, the Jean Young and Walden W. Shaw Foundation, the Irving Harris Foundation, the Daniel X. and Mary Freedman Academic Psychiatry Fund and the MRC in the UK. None of what has been done in our laboratories would be possible without this support.

*Catherine Johnson, Ph.D., co-author with John Ratey, MD, of **Shadow Syndromes**, is a member of NAAR's Board of Trustees and the mother of two children with autism.*

(continued from page 13)

CDC & NAAR Co-Sponsor Autism Conference

of an extended family with many cases of developmental disabilities suggest that both genes may play a role in autism spectrum disorders, but the coincidence of the two polymorphisms in the same individual is particularly hazardous to early brain development. Genetic and behavioral investigation of the remaining members of the study families are needed to confirm the importance of these candidate genes, but the initial results are promising.

Two unscheduled short presentations followed. Margaret Pericak-Vance of Duke University presented preliminary findings from the Duke/University of South Carolina linkage



study data. Dr. Pericak-Vance examined 50 multiplex families for linkages in the region of chromosome 15. Previous studies have implicated the 15q11-13 region in mostly sporadic cases of autism. After examining their multiplex families, however, linkage analyses also implicate 15q11-13 in familial cases of autism. Added to this important linkage finding, complex maternal mechanisms in this region are also implicated. The second unscheduled presenter was Jonathan Haines of Vanderbilt University. Working with Susan Folstein on a subset of the Tufts/Hopkins/Iowa linkage study families, they have also found some significant indications of linkage in this region (15q11-13). These results are being followed up. Although these are preliminary findings, replication of this sort is highly significant.

Uses of Epidemiology in Facilitating the Search for the Etiology and the Mechanisms of Autism

Dr. Susan Folstein of Tufts University, in the final presentation of the conference, commented on how epidemiology can be used not only to study prevalence, but to further recent advances in the understanding of the causes and mechanisms of autism. In closing, she stated: "That we need a new epidemiological study of autism using modern sampling schemes and incorporating biological measurements is not in question. There will need to be careful planning to assure that the design allows us to illuminate the most etiologies and mechanisms of this heterogeneous syndrome."

In the rather rushed closing moments of the conference my thoughts turned to the opening comments made by Dr. Eric London, Vice President-Medical Affairs of NAAR, calling for the epidemiologic study of autism. The passion of Dr. London's call for research was fueled by the bare facts of the disease and its enormous cost to society. The utility of epidemiologic research was clearly laid out by the many unanswered questions of prevalence, increasing prevalence, and non-genetic risk factors, which can only be addressed through epidemiologic study designs.

Dr. Godfrey Oakley's conviction that the epidemiologic approach can be "applied to improve the lives of children" has been supported by striking contributions of epidemiology to the understanding and prevention of a number of other disabilities in children. Perhaps the biggest success story is the epidemiological finding that roughly three-quarters of spina bifida is preventable with the consumption of a simple vitamin, folic acid. Dr. Oakley's vision, shaped by such experiences, seems to have grown to include autism. He is convinced that an epidemiologic approach will contribute to an understanding of the causes of autism, and that "hopefully we can find modifiable risk factors or causes, and actually do some primary prevention." This is a hope, I believe, we can all commit to and share with equal conviction. ♦

Micki Bresnahan, M.P.H., M. Phil., is a NAAR volunteer and the mother of a 15-year-old boy with autism.

Because Of Alex...Only Connect

By Clarence E. Schutt, Ph.D.

Autism is the Rosetta Stone of human neurobiology. Deciphering autism will lead us to new insights into the origins of language, personality, and artistic vision. The very characteristics that define us as human beings—affability, communication, and intelligence—are cruelly dimmed in an autistic child. Yet, in compensation, these children seem to glimpse the world in ways shared by great artists. How else can their delightful responses to running water, spinning backgrounds, and flowing hair be understood? We must find ways to bring autism research to the forefront of modern brain science, not just to help our children, but to be able to unwrap the gift of philosophical truth these mute angels bear.

One of the most remarkable discoveries of modern neurobiology is the concept of "neuronal plasticity." The brain literally "wires itself up" during development, with neurons seeking out connections with other neurons, often situated hundreds of cell diameters away, by sending out long axonal projections tipped with highly sensitive and motile "growth cones" that can sense the subtle structural and chemical cues along the way. When they reach their target cells, growth cones restructure themselves into the receiving ends of neuronal synapses, effectively establishing direct physical communication links between neurons.

Almost a half century ago, the brilliant Canadian psychologist E. O. Hebb theorized that networks of connected neurons might store memories by strengthening frequently used synapses, while weakening those not carrying information. "Use it or lose it" expresses the idea. Today, scientists have discovered some of the protein molecules and signals that underlie the physics of synaptic strength. In my "Scenarios for a Future without Autism" lectures to parent groups, I like to refer to this phenomenon because I imagine that someday we might use this knowledge to find the means to strengthen synapses in the brains of autistic individuals. Maybe the connections continually form, but are broken down too quickly in this complex jungle of competing synapses to contribute to learned memories. Perhaps we could find a medication to shift the balance of competing influences to favor strengthening over weakening. But, can we go from mere scenarios such as this to realistic research programs that will help our children? My answer is "Yes."

There is a remarkable confluence of knowledge from many investigators supporting the notion that similar molecular mechanisms have been used over and over again during evolution to solve functional problems. For instance, the proteins actin and myosin, which generate force and movement in muscle fibers, are also found in crawling amoebae, in neuronal growth cones seeking their contact sites, and at the surfaces of macrophage cells actively ingesting foreign invaders. It appears that once Mother Nature hit upon a means of moving things around, she passed the secret on.

The tremendous power of molecular genetics to reveal, not only patterns of gene expression, but the effects of mutating or deleting particular genes, enables us to learn about human



disease directly from studies on flies, worms, and mice. These studies are necessary for the important "target validation" data required by the FDA before a new drug can enter into clinical testing.

An apt example of the power of human genomic research comes from the search for the cause of congenital deafness. Several genes have been identified recently from mapping the genomes of extended families where deafness is prevalent. In one case, the gene responsible for deafness codes for a protein that was previously discovered to be essential for the correct development of wings in the insect *Drosophila*. What is the connection between fly wings and human hearing? It turns out that, at the molecular level, the protein encoded by the deafness gene is a kind of "assembly factor" that directs the incorporation of actin molecules into extended structures. In the inner ear, there are thousands of actin-containing hair cells that convert the energy in sound waves into nerve impulses. Without the actin assembly, these hair cells fail to form, and deafness results.

What about autism? Several promising leads have been reported recently, among them the exciting news that chromosome 15 contains a genetic "hot spot" for autism. The gene responsible for Angelman's syndrome, a disease in which children exhibit many autistic-like behaviors, is also located in this gene cluster. The point, from my perspective as a structural biologist, is that we know a lot about the protein encoded by the genes in this cluster. Furthermore, GABA receptor subunits, which bind the most potent inhibitory neurotransmitters, are found in this cluster. Pharmaceutical companies have studied this "target" extensively (Valium, for example, is known to bind to GABA receptors). There is a wealth of pharmacological, toxicity, and behavioral data for thousands of promising chemical compounds that were not useful for their original purposes but could spark an idea in a mind prepared to think about autism.

New connections are being made to the pharmaceutical world, and our children are ready and waiting for them to be strengthened. When I was preparing to meet an important pharmaceutical executive recently to tell her about chromosome 15, I happened to tell my son Alex that I was going to meet someone who might help him get a medicine enabling him to talk. Alex, who cannot say much more than "Hi," went over to a drawer where vitamin tablets are hidden (from him!) and brought me a bottle to open. My wife remarked: "He wants it now."

We need to see that young scientists are trained and motivated to undertake careers in autism research. They will be the connectors that may find the way to strengthen the connections between neurons in our children's fantastic minds.

Clarence E. Schutt, Ph.D., is Executive VP and Secretary of NAAR. 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.

Glossary of Selected Scientific and Medical Terms

allele. A normal variant of a gene. Both the long form and the short form of the serotonin transporter gene are normal variants, or alleles.

birth cohort. A group of individuals born in the same year who share a common characteristic.

brain stem. One of the oldest parts of the brain in evolutionary terms and the lowest section, serving as a highway for messages between other parts of the brain and the spinal cord. The activities of the brain stem—control of vital functions, such as breathing and blood pressure—are largely below the level of consciousness.

cerebellum. The “little brain”; sits just above the brain stem. Was previously thought to control movement and coordination, but is now known to be involved in “higher functions” as well, particularly shifting and orienting attention, and predicting and preparing biologically for upcoming movements (e.g., by altering cerebral blood flow levels).

chromosome. Linear sequence of genes. Human beings have 46 chromosomes, arranged in 23 pairs, one from each parent.

concordance rate. The number or percentage of members of a study group that share a common trait, e.g. the number of identical twins in which *both* twins have autism.

cytogenic. Producing or forming cells.

dominant gene. An allele (normal gene variant) that is expressed instead of the “recessive” allele for that same trait. In eye color, the allele for brown eyes is dominant over the allele for blue eyes: if you inherit one allele for brown eyes and one allele for blue eyes, you have brown eyes.

embryogenesis. Formation and growth of the embryo.

epidemiology. The study of the distribution and determinants of diseases in populations.

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

15q11-q13. Instructions telling other geneticists how to locate this region in the DNA. The number 15 stands for chromosome 15; the letter “q” stands for the long end of the chromosome (“p” stands for the short end); number 11 is the particular area on the long end. (“P” is short for *petit*; geneticists use “q” for long because it is the letter after “p”.)

GABA (Gamma-aminobutyric acid). A neurotransmitter involved in anxiety. GABA is an inhibitory neurotransmitter now known to be involved in autism. It is also the neurotransmitter Xanax and Valium affect.

gene. The smallest physical unit of heredity. Geneticists estimate that we have 100,000 genes, all of them arranged on the 46 chromosomes. Each gene codes for one or more proteins.

genotype. An individual’s unique arrangement of his or her 100,000 genes.

hippocampus. A part of the brain that is involved in learning and memory. Margaret Bauman has reported that, in autistic brains, the cells of the hippocampus are small and closely packed—possibly implying that they have not fully matured.

macrocephaly. Excessive head size.

neurogenesis. The development of nervous tissue.

neuron. Also called “brain cell” or “nerve cell.” Major cell type in the brain and spinal cord.

neurotransmitter. Neurons release tiny amounts of neurotransmitters into the synapse to communicate with each other. Some neurotransmitters are “excitatory,” causing the next cell to fire. Some neurotransmitters are “inhibitory,” preventing the next cell from firing. Serotonin, dopamine, acetylcholine and GABA are all neurotransmitters.

phenotype. The *expression* of an individual’s genotype—this is the way the person actually looks and acts because of his or her genes. With HTT, the “genotype” is the tiny biological unit of DNA that makes up the gene; the “phenotype” is a slightly higher level of normal anxiety.

promoter. A substance that, in very small amounts, can increase the activity of a catalyst.

Purkinje cells. One of two major cell types in the cerebellum. Eighty to 85% of people with autism show a reduction in Purkinje cells.

recessive gene. An allele (normal gene variant) that is only expressed when both chromosomes have that allele. For a child to have blue eyes, he or she has to inherit the allele for blue eyes from *both* parents.

selective serotonin reuptake inhibitor (SSRI). A medication that blocks the “reuptake” of serotonin back inside the cell that has released it into the synapse. By blocking reuptake, SSRIs increase the amount of serotonin free and available in the synapse. There are currently four SSRI’s: Prozac, Zoloft, Paxil, Luvox.

serotonin. A major neurotransmitter involved in depression and anxiety. A quarter to a third of people with autism show abnormally high levels of serotonin in the blood.

serotonin transporter gene (HTT). A normal gene that is involved in transporting serotonin into the cell. Ed Cook’s team has found an association between autism and the short form of this gene.

target. A term used by pharmaceutical companies to denote a protein or nucleic acid molecule that can potentially bind a drug molecule. Since the protein or nucleic acid acts as a control or checkpoint in some biochemical cascade, the binding of a candidate drug molecule can influence or modulate the disease-related process of interest. Serotonin reuptake inhibitors, for example, are drugs aimed at modulating the proteins responsible for serotonin transport across cell membranes.

Thank You!

Although they are too numerous to list here, we would like to express our gratitude to all of NAAR's supporters. The following people need to be particularly recognized:

With respect to NAAR's benefit in Los Angeles last October, special thanks to our stars, John Lithgow and Kathy Bates, who graciously volunteered their time and remarkable talents to our event, our honorary co-chairs, Joe and Arlene Mantegna and Aidan and Elizabeth Quinn, Joe and Arlene's daughter, Mia, for creating our benefit invitation, our many friends at The Achievable Foundation and Westside Regional Center in Los Angeles, and NAAR trustee, Catherine Johnson, without whom this special evening would not have been possible.

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