The UC Davis Center for Children’s Environmental Health

What causes autism? Many scientists, health professionals and parents are concerned that prenatal and postnatal exposure to toxic environmental factors, like xenobiotics (such as mercurials, halogenated aromatics and pesticides) and biotic factors (such as vaccine antigens), may act synergistically to alter the expression of as-yet unidentified genetic factors to cause autism spectrum disorders.

With funding from both the National Institute of Environmental Health Sciences (NIEHS) and the Environmental Protection Agency (EPA), the UC Davis Center for Children's Environmental Health (CCEH) was established in 2001 to address these concerns. Neurotoxicologist Isaac Pessah, CCEH director and M.I.N.D. Institute faculty member, explains that the goal of the CCEH is to understand common patterns of dysfunction in autism and elucidate mechanisms by which chemicals known to be toxic to the developing nervous and immune systems contribute to abnormal development, thereby leading to strategies for prevention and intervention. The CCEH brings together a truly multi-disciplinary team of research scientists dedicated to understanding the complex etiologies that contribute to autism risk.

CCEH project participants represent several basic-science and clinical fields, including neuroscience, toxicology, immunology, epidemiology, pediatrics, molecular biology, and statistics.

“The idea that both genetic and environmental factors work in concert to influence autism susceptibility, severity.
and treatment outcomes was not mainstream science when we established the Center. We were thinking well “outside the box” in 2000, or perhaps you could say we were making a new box to test innovative hypotheses. This could only be accomplished with an integrated multidisciplinary approach encompassing multiple fields,” reflects Pessah.

In 2003 the CCEH launched the CHARGE Study (Childhood Autism Risks from Genetics and Environment), and in 2006 launched MARBLES (Markers of Autism Risk in Babies-Learning Early Signs), headed by epidemiologist Irva Hertz-Picciotto and described elsewhere in this newsletter (page 3).

Since its inception, the CCEH has also supported several mechanistic investigations into environmental triggers of autism using molecular and cellular approaches, as well as animal models. For example, CCEH investigators pioneered investigations into maternal and childhood autoantibodies that appear to contribute to autism risk. CCEH immunologists Judy Van de Water and Paul Ashwood have made significant contributions to our understanding of how peripheral immunity differs in both children diagnosed with autism and their mothers. In addition, the CCEH has fostered investigations of the effect of maternal autoantibodies to fetal brain protein, antibodies unique to some women who have given birth to a child with autism, on neurodevelopmental outcomes in animal models.

CCEH investigators have also investigated how thimerosal, a mercury-containing preservative, influences essential signaling functions of a set of cells whose role is to perceive bacterial invaders and other antigens and activate the body’s T cell defenses. They were the first to show that these dendritic cells (DC) are exquisitely sensitive to dysregulation by mercury, including that found in thimerosal. This is significant since DC dysfunction is emerging as one of the immunological outcomes from the CHARGE Study. However, CCEH investigators also found that mercury levels are not necessarily higher in children with autism compared to those with typical development. Moreover, no overt behavioral consequences were detected in newborn mice exposed to thimerosal. However, more recent studies pursued by Frank Sharp, an expert in transcriptional genomics, indicate that children with autism exhibit very different patterns of gene expression with respect to mercury and lead levels in their blood compared to those with typical development.

Pessah’s laboratory is studying persistent organic pollutants that dysregulate calcium signaling mechanisms common to muscle, neurons and immune cells. Why focus on calcium? Virtually all healthy cells in our bodies tightly regulate the calcium ion concentration (Ca$^{2+}$) within their cytoplasm and organelles. How tightly? Outside of the typical mammalian cell the blood has approximately 20,000 times higher Ca$^{2+}$ than that found within the cell, just molecular distances away. It is clear that cells have evolved elaborate ways to limit their cytoplasmic Ca$^{2+}$, most likely because of its high degree of toxicity. Today we Continued on page 5

“Our investigators are clearly making critical contributions to our understanding of autism.”

— Isaac Pessah
The goal of the CHARGE (CHildhood Autism Risk from Genetics and the Environment) Study is to discover the environmental causes of autism, and the genetic backgrounds in which their effects are strongest. Study researchers are targeting environmental exposures that can be modified, so as to reduce risk, or actually prevent future children from developing autism in the first place.

Directed by Irva Hertz-Picciotto, an epidemiologist with the M.I.N.D. Institute and the Department of Public Health Sciences, the CHARGE Study was launched in 2003. This study has provided several new clues to the environmental causes of autism, and identified mechanisms that could lead to abnormal brain development and health issues more commonly experienced by children with autism spectrum disorders (ASDs). In short, the CHARGE Study is helping to unravel the mysteries of this disorder and to devise ways to intervene, eliminate the factors that are contributing to high incidence rates, and improve outcomes for children already affected.

Initially, the study team focused on known or suspected neurotoxins in the environment. One of these is mercury. CHARGE Study children with ASDs were found to have levels of mercury in their blood that were similar to levels in typically developing children, after taking into account their fish consumption. Fish is a major source of mercury in humans, and the typically developing children were more likely to eat fish, and ate fish more often. When the researchers adjusted for this difference, the two groups were remarkably similar. Also, the blood mercury levels in both groups resembled those of children examined in a nationwide survey. It is important to recognize that fish is beneficial to brain development, particularly in the prenatal and early childhood years. Thus, families are encouraged to select fish that are low in mercury, like catfish, sardines, mackerel, perch and sole.

A group of chemicals, the polybrominated diphenyl ethers or PBDE, that are used to reduce flammability of household products was also measured in a subset of CHARGE Study participants. While PBDE levels were higher than reported in previous studies of populations outside California, the CHARGE investigators did not...
see any differences between children with autism and controls.

Despite these negative findings, it cannot be assumed that mercury or PBDE are safe for children, or that they play no role in causing autism. Before drawing firm conclusions, measurements will need to be made before the symptoms of autism appear. Hertz-Picciotto hopes to publish the results from early measurements for mercury soon. For PBDE levels, early measurements will rely on two sibling studies (MARBLES: Markers of Autism Risk in Babies — Learning Early Signs and EARLI: Early Autism Risk Longitudinal Investigation) that are currently collecting specimens prenatally and during the first few years of the child’s life.

Besides studying environmental exposures, the CHARGE Study has discovered several biochemical differences between affected and typically developing children. For example, those in the ASD group tend to have lower levels of total IgG (immunglobulin G), and also TGF-beta, a cytokine that regulates the immune response. Furthermore, mothers of children with autism are more likely to produce antibodies that react to fetal brain tissue. Thus, the CHARGE Study has generated substantial evidence that the immune systems in some children with autism are not functioning appropriately.

Children with ASD also exhibit metabolic deficiencies. First, they tend to produce more leptin, a chemical with complex functions, including appetite suppression and immune regulation. Second, they have lower concentrations of DHA (docosahexanoic acid), a critical compound for neural development. Other mechanistic hypotheses being pursued by CHARGE Study investigators include mitochondrial dysfunction, with a new report due out soon, and epigenetics, with a recent report on a locus of low DNA methylation in males with autism.

In other work, CHARGE Study children with ASD showed elevated prevalence of difficulty falling asleep and of night waking, and a higher rate of regression, i.e., loss of language or of social skills, than previously reported in scientific
The CHARGE Study from page 4

know of thousands of enzymes and receptors whose activities are tightly regulated by Ca\(^{2+}\). We have learned that spatial and temporal changes in cytoplasmic Ca\(^{2+}\) represent a fundamental means by which cells coordinate their normal functions, including their ability to grow and divide, rates of metabolism, gene transcription and protein expression, and secretion of neurotransmitters and hormones. Thus Ca\(^{2+}\) can be thought of as a common currency in cell regulation. Without Ca\(^{2+}\) cells cannot function, dysregulated Ca\(^{2+}\) causes cells to do strange things, unregulated Ca\(^{2+}\) causes cells to die.

In the early 1990s, Pessah’s lab was among the first to show that certain receptors that are essential for regulating Ca\(^{2+}\) signals in muscle are also broadly expressed in the mammalian brain. Given their fundamental contribution to normal brain development and function, Pessah asked if environmental chemicals of concern to childhood developmental health could directly modify the structure and function of these receptors. In 1996 Pessah and his graduate student showed that a group of persistent organic pollutants, the polychlorinated biphenyls (PCBs), had direct and unprecedented effects on the major forms of this receptor found in the mammalian brain.

Subsequent collaborative studies, with faculty from UC Davis, the University of California, San Francisco, the University of Iowa and Harvard University, have further defined which of these PCBs are most active, and the effects of these neurotoxicants on neural networks. Of particular concern are their dramatic and long-term negative effects on the ability of neurons to adapt in response to learning or auditory cues.

Over the last nine years, CCEH investigators have been highly successful, publishing many collaborative papers in a broad array of high-quality journals (more than 80 at last count), and receiving over $30 million in new grant support.

“Our investigators are clearly making critical contributions to our understanding of autism,” says Pessah.
The mission of the M.I.N.D. Institute is to understand the biological features of autism and other neurodevelopmental disorders in order to develop more effective preventions, treatments and cures. The founding families admonished the scientists and clinicians at the M.I.N.D. Institute to determine the major roadblocks in this effort and then systematically eliminate them through research. For autism, a major roadblock is the incredible heterogeneity of the signs and symptoms of autism and its associated disorders. For example, some young children with autism have heads that are larger than is typical, whereas others have heads that are smaller. About 30 percent of children on the autism spectrum have epilepsy, whereas most do not. Many children with autism have gastrointestinal and immune problems, but others do not. More than simply a bewildering array of signs and symptoms, this heterogeneity seems to indicate that autism has multiple forms, or subtypes, with multiple causes and courses. If this is true, it is likely that each cause may have different preventative measures, best treatments, and, ultimately, cures. But, how can we tell one form of autism from another?

The Autism Phenome Project, or APP for short (phenome is just another name for type), seeks to address this question. This collaborative study, which involves 12 M.I.N.D. Institute faculty and 55 students and staff, is designed to identify subgroups of children with various biological similarities from within a large group of young children with autism. The guiding principle of the APP is that if enough biological and behavioral data are collected on a large number of children with autism, then clusters of children with similar patterns of signs and symptoms will emerge. By working with these clusters, the causes, best treatments and potential cures for each type can be more productively explored.
Children with autism enter the APP between 2 and 3 1/2 years of age, at a time that is as close as possible to initial diagnosis. For comparison, the APP also studies age-matched typically developing children. Each child’s diagnosis is confirmed and additional behavioral testing is carried out. Each child also has a thorough medical examination and copies of their previous medical records are obtained. In subsequent visits, the child receives a magnetic resonance imaging (MRI) scan of their brain and an EEG analysis of how their brain processes auditory stimuli. A blood sample is drawn from each child and from their parents and siblings for immunological and genetic studies. Each family is invited back annually so that the development of the child’s brain can be monitored with an MRI and additional behavioral measures can be acquired.

Currently, 280 families have enrolled in the APP. Of these, 200 have children with autism and 80 have children who are typically developing. One unusual facet of this project is that both boys and girls with autism are being studied. Generally, because there are more boys with autism than girls, the girls are often overlooked in research projects. Not in the APP.

It is anyone’s guess how many autism subtypes there may actually be. So, a large number of participants will be needed. But, data from the APP are already showing patterns that allow subgrouping of the children with autism.

Behavioral analyses show that the developmental quotient of children in the APP is very broad, ranging from a low of 30 (a child who is severely developmentally delayed) to 150 (a gifted child). In a paper recently submitted for publication with colleagues from the National Institute of Mental Health, data from the APP confirmed that there are at least four different patterns of autism onset: 35.3 percent have signs of autism very early in life, whereas 22.4 percent develop normally for 18 to 24 months and then lose social and/or language function to regress into autism. An additional 42.3 percent of children with autism either show early signs followed by regression or reach a plateau of development and then fall below the level of age-matched controls.

The MRI analyses are showing very striking differences in the way the brain of an individual with autism develops. The MRI team has focused on two...
“Tikkun olam,” or, “repairing the world,” is the Hebrew phrase that guides the philanthropic practices of Mort and Marcy Friedman. For the two of them, it really is a matter of giving back to a city they cherish.

“I feel a strong obligation to give back to a community that has been so kind to us and our family,” says Marcy. “We feel a sense of love for the place where we live.”

This commitment to their community is the reason the two were named “Sacramentan of the Year” by the Sacramento Metro Chamber of Commerce and “Philanthropist of the Year” by the National Society of Fundraising Executives.

Three years ago, the Friedmans extended their generosity to the M.I.N.D. Institute. Their pledge helped to sponsor the Distinguished Lecturer Series, a monthly series of free public presentations that focus on groundbreaking discoveries in the world of neurodevelopmental disorders. Marcy says it was a gesture to honor a beloved family member.

“We first decided to support the M.I.N.D. Institute for a personal reason. It was to honor my daughter-in-law.”

Their daughter-in-law, Marjorie Solomon-Friedman, is a professor in the Department of Psychiatry and Behavioral Sciences at UC Davis, and director of the M.I.N.D. Institute’s Social Skills Program, a program that has received praise for assisting children and teens who are struggling with autism to develop and strengthen their social skills.

But the Friedmans’ support is also rooted in an appreciation for health care and the need to educate the public.

“My family has an extensive background in medicine,” says Marcy, “so I have a great affinity for this field. The education component of the Distinguished Lecturer Series, in terms of enhancing outreach to the community, is right on target.”

The Friedmans’ annual support has enabled the Distinguished Lecturer Series to expand from a six- to a nine-month lecture series, spanning the entire academic school year. Guest speakers are many of the most brilliant and well-respected scientists in the field of neurodevelopmental disorder research. After witnessing the success and growth of the program, the Friedmans have now pledged to co-sponsor the event for another two years.

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“If our gift, in some small way, serves as a catalyst to stimulate others to give – it has served its purpose.”

– Marcy Friedman
Now in its ninth season, the M.I.N.D. Institute’s Distinguished Lecturer Series annually features nine presentations, October through June, by internationally recognized scientists known for their contributions to the understanding and treatment of neurodevelopmental disorders.

This year’s series, which is free and open to the public, is made possible by the generous support of Mort and Marcy Friedman. We thank them for their commitment to raising awareness of and providing education about neurodevelopmental disorders.

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and welcome not only scientists and researchers but the general public as well. In a time when autism is becoming more and more common, this issue is of vital interest,” says Marcy.

The Friedmans’ pledge of $20,000 each year will provide half the funds needed to support the Distinguished Lecturer Series, and they have given this amount for a reason. Private funding is becoming increasingly important to continue the research and outreach at the M.I.N.D. Institute. The Friedmans hope that their pledge will help inspire others to give.

“This should be a way to leverage giving,” says Marcy. “We want to offer other people an opportunity to give back to this wonderful program. The UC Davis Health System is the second-largest employer in Sacramento and the M.I.N.D. Institute itself is a groundbreak-
Thank You for Giving to the M.I.N.D. Institute  

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<td>$100,000-$500,000</td>
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brain regions: the amygdala, which is important for detecting dangers in the environment and may contribute to the anxiety that is common in autism, and the frontal lobe, which is important in the organization of social behavior and in planning future actions. In a paper submitted for publication, the MRI team has shown that 40 percent of children with autism have an amygdala that grows twice as fast as is typical, whereas the rest of the brain develops at a normal rate. Another 30 percent of the sample with autism have amygdalas that grow at a normal rate and 30 percent actually grow at a slower rate. Twenty percent of the children with autism have frontal lobes that are bigger than those of any of the control children. When this group is selected for further analysis, they are found to have the most prominent changes in connectivity. Moreover, there is a clear relationship between increased frontal lobe size and autism severity — the more abnormally large the frontal lobe in children with autism, the more severe is their disability.

As one final example, the EEG group has shown at least four patterns of how the brain processes auditory information in autism. Complex tones are presented to the children through earphones at four different volumes. In typically developing children, brain activity increases as the tones get louder. A similar response is seen in some children with autism. But, in another distinct group, the brain activity actually decreases as the sounds get louder. In a third group, brain activity is no different for soft and loud tones and, for the last group, brain activity appears to reverberate more than typical after a single stimulus.

Efforts are now under way to answer questions across disciplines. For example, are there any immune differences in the children with the large frontal lobes? What might be the genetic basis for the rapidly growing amygdala? The answers to these questions will help define autism subtypes and move us forward along the path toward discovering the causes of each.

The Autism Phenome Project continues to enroll families of children who have autism and who are between 2 and 3½ years of age. The project also recruits families to participate who have typically developing children in the same age range. Participating parents have said that the experience was very rewarding and they received much useful information. Interested families should contact Kateri Ross, APP Study Coordinator, 916-703-0410, kateri.ross@ucdmc.ucdavis.edu, or sign up directly on the M.I.N.D. Institute website at, www.ucdmc.ucdavis.edu/mindinstitute/research/clinicalstudies.html. For more information about the Autism Phenome Project, please go to our website at, www.ucdmc.ucdavis.edu/mindinstitute/research/app/index.html.

On behalf of all the faculty, staff, patients and research subjects at the UC Davis M.I.N.D. Institute, our Board of Directors would like to thank our generous donors for their support of groundbreaking research on the causes, preventions and treatments of neurodevelopmental disorders.

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Please accept our apology if we have made any errors or omissions. If your listing requires correction, contact An Nguyen, at (916) 703-0221 or an.nguyen@ucdmc.ucdavis.edu.
This issue of M.I.N.D. Matters includes progress reports from some of the earliest and largest research efforts associated with the M.I.N.D. Institute. Isaac Pessah provides an overview of the Children’s Center for Environmental Health (CCEH) which has led the way in investigating the potential role of environmental pollutants, such as mercury, pesticides and fire retardants, in the etiology of autism. It is fair to say that the researchers involved with CCEH have contributed in a major way to convincing scientists, as well as government and elected officials, that environmental factors must be taken seriously when one considers the causes of autism. A substantial portion of the data acquired by the CCEH has come as a result of the CHARGE study. As Irva Hertz-Picciotto describes, CHARGE is the largest, epidemiologically rigorous study of autism ever conducted and is providing compelling analyses of factors ranging from age of the parents to prenatal care to pesticides and how they influence the occurrence of autism. More than 1400 families have already participated in this study.

The final article is one that I wrote about the Autism Phenome Project (APP). The goal of this longitudinal study is to gather sufficient behavioral and biological information on children with autism to define more homogeneous subtypes. Over 300 families are currently participating in the APP.

All of these studies represent what the M.I.N.D. Institute was created to do – collaborative, interdisciplinary, state-of-the-art research to understand the causes of autism and other neurodevelopmental disorders. Studies such as these, however, are in jeopardy at the M.I.N.D. Institute. With current federal funding for the CCEH coming to an end in 2011, and for the CHARGE Study and APP ending in 2012, new sources of support will be needed to allow the work of these dedicated groups of scientists to move forward. In this time of belt-tightening among federal agencies, that both limit the type, timing, and levels of funding available, the next phase of these important projects will require both bridge funding and new sources of permanent funding. For this reason, the financial support of philanthropists, like Mort and Marcy Friedman, has become increasingly critical for the work of the M.I.N.D. Institute. I would encourage readers of this issue of M.I.N.D. Matters to consider making a financial contribution to support one of the projects highlighted here or one of the many other projects under way at the institute.

As the holidays approach, I would like to express my sincerest gratitude to all of the families that have participated in our research program. Through this partnership we are unraveling the mysteries of neurodevelopmental disorders. This new knowledge will lead to reduction of disability and an improved quality of life for our children and for our children's children. We couldn't do it without you!

Happy Holidays and Best Wishes for a Wonderful 2011.

– David G. Amaral, Ph.D., Director of Research
UC Davis M.I.N.D. Institute