Department of Health and Human Services
Interagency Autism Coordinating Committee
Meeting Highlights
May 16, 2005
National Institute of Health
Bethesda, Maryland

IACC Members in attendance: Tom Insel, M.D. (Chair), Susan Swedo, M.D., Ann Wagner, Ph.D. (Executive Secretary), Alice Kau, Ph.D., Duane Alexander, M.D. (represented by James Hanson, M.D.), Deborah Hirtz, M.D., James Battey, M.D., Ph.D., Judith Cooper, Ph.D., Barry Gordon, M.D., Ph.D., Gail Houle, Ph.D., Jose Cordero, Ph.D., MPH, Jonathon Shestack, Elizabeth Duke, Ph.D. (represented by Merle McPherson, M.D.), Lee Grossman, Lester Crawford, D.V.M, Ph.D. (represented by Kathryn Carbone, M.D.), Carolyn Clancy, M.D. (represented by Steven Fox, M.D., M.P.H.), David Schwartz, Ph.D. (represented by Cindy Lawler, Ph.D.), Story Landis, M.D. (represented by Audrey Penn, M.D.), Patricia Morrissey, Ph.D. (represented by Margaret Schaefer, M.A.), Lucille Zeph, Ed.D.

Member agencies not represented: Agency for Toxic Substances and Disease Registry; Centers for Medicare and Medicaid Services; Substance Abuse and Mental Health Services Administration.

Introductions & Matrix Related Activities

Dr. Thomas Insel, Director of National Institute of Mental Health (NIMH) and chair of the Interagency Autism Coordinating Committee (IACC) called the meeting to order. He welcomed the IACC committee and asked the members to introduce themselves. Following the introductions, Dr. Insel provided an overview of the autism research matrix that was designed to serve as a strategic plan for autism research. He highlighted several current initiatives that have helped to address the targets outlined for the first three years. Specifically, he described two ongoing studies within the National Institute for Environmental Health Sciences (NIEHS) centers that focus on illuminating peripheral biomarkers for autism. He described another study within the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute that is examining a proteomics approach to identify proteins that may differentiate autistic children from controls. In addition, Dr. Insel discussed the multi-site citalopram study that is underway within the Studies to Advance Autism Research and Treatment (STAART) centers and a gluten-free, casein-free diet placebo-controlled study that is taking place within the Rochester STAART center. With respect to genetics, Dr. Insel reported on a request for applications (RFA) that was released a few months ago, focusing on the fine mapping of current repository resources. He also mentioned that the M.I.N.D. Institute recently launched a phenome project that will be paralleled on the east coast within the intramural autism program at NIH. In terms of extramural happenings, Dr. Insel discussed a new RFA that will be released announcing the Autism Centers of Excellence (ACE). The ACEs are designed to merge the current two independent centers, the STAARTs and the Collaborative Programs of Excellence in Autism (CPEA), into one entity.

Discussion:
Mr. Shestack asked about the dollar amount that is being set aside for the intramural effort, and he asked for further clarification about the folding of the STAART and CPEA centers into one program. Dr. Insel responded that the budget for the centers will be roughly $22 million, which is the current funding level of both the STAART and CPEA centers. He further described the new Autism Centers of Excellence that would include both the classic center program and networks, which would involve multiple sites working on a particular scientific problem.

Dr. Swedo responded to the question about intramural funding by indicating that it is not possible to come up with an exact figure for intramural research, as intramural research works differently than research conducted in the extramural program. However, she reported that twelve staff members are dedicated to the intramural effort and that the staff is in the process of launching two major characterization studies. The first study will be a phenome pilot study similar to the study being conducted at the M.I.N.D Institute at UC-Davis. The second characterization study will focus on examining regressive autism to determine if there are any immune deficiencies associated with the disorder. Dr. Swedo also noted that three treatment trials would take place within the intramural program over the next six months. These trials will examine glutamate antagonist riluzole, immunophenotyping associated with riluzole, and a subtype of children with autism that suffer from a severe anxiety disorder.

Mr. Grossman asked Dr. Insel how he would rate the progress of the matrix given that we are currently half way through the first three years of it. Dr. Insel suggested that this question would be better answered by the committee or the individuals on the forefront of the research. He noted that the treatment network and phenome projects are moving more slowly than he would like. However, Dr. Insel pointed out that the most progress has been made in the area of early intervention. For example, the tools that allow for early detection have been established.

Dr. Gordon stated that as a parent, he was upset about the lack of progress in translating known treatment modalities into actual application for children and young adults who need them. Dr. Insel responded that during this early phase of the matrix, a lot of what is required is establishing the infrastructure necessary to make progress. Initiatives such as the database, which will serve as this infrastructure, are still being developed.

Autism Treatment Network (ATN)
Presented by Richard Fade & James Perrin, M.D.

Mr. Fade talked with the committee about the development and vision of the ATN. He described the overarching goal of the ATN as the establishment of a national nonprofit organization designed to create a network of hospitals and physicians whose focus will be on the study and advancement of treating individuals with autism. He noted that the creation of the ATN grew out of a desire to accelerate advances in the treatment of autism, as the treatment component of autism research has moved rather slowly.

Mr. Fade further described the design of the ATN as a collaborative approach that would span across several existing centers that already see patients with autism. Currently, there are six

centers in the network in which the focus of collaboration between the centers is on treatment, sharing of information on outcomes, and the discussion of better ways to capture data regarding health issues of individuals with autism. Mr. Fade described the visions for the ATN as being able to publish treatment articles, define treatment guidelines, and serve as a credible "good science, good medicine" entity that parents and primary care physicians can reference when looking for treatment options for their loved ones.

The concept of the ATN was inspired by the models of the Cystic Fibrosis Foundation and the Children's Cancer Network. Essentially, each of these models provided a vehicle or framework in which to establish a set of tools, support, and leadership to unite a group of institutions to share information regarding treatment outcome. Mr. Fade suggested that this vehicle is missing from the autism field. Therefore, the goal of the ATN is to serve as this vehicle by establishing a framework for the exchange of information among institutions.

For the initial three years of the ATN, the plan is to add new practices, bring in specialists, and establish more standardized and stringent medical review and diagnosis to the current six centers. Mr. Fade reported that it will take a minimum of $10 million to do this across three years. Cure Autism Now is contributing a significant proportion to the funding of this initiative.

Mr. Fade ended by reporting on the current activities of the ATN, which includes the establishment of a group of 20 to 25 physicians that have met every 3 months for the last 18 months. This group has focused on the development of a common multi-disciplinary practice to be used across all six centers by the end of the calendar year.

Dr. Perrin further elaborated on accomplishments of the ATN thus far. He noted that agreements have been established among six institutions and that the ATN is working in collaboration with a leading data epidemiology group to establish a research database protocol. Dr. Perrin also mentioned that the six institutions are working on providing standardized assessment protocols for three conditions associated with autism including: gastrointestinal manifestations, metabolic conditions, and issues relating to sleep. In September, the ATN will hold a physician conference entitled "Emerging Practices in the Care of Children and Youth with Autism." The focus of the meeting will be on sharing clinical experience with medical issues found in children with autism.

Mr. Fade provided closing remarks stating that in starting the ATN there was an understanding of the complexity of the matter, but that this complexity often falls on the shoulders of parents who have limited resources to address these complexities. He suggested that the time has come to establish the ATN as this model has been used successfully with other diseases. Furthermore, Mr. Fade exclaimed that the desire to be a credible resource of physician knowledge and just sharing this information can have a large impact on the field of autism research.

Discussion:
Dr. Gordon commented that the concept behind ATN was fantastic. He asked if the plan was to use the ATN as an add-on to current clinical efforts or to have the ATN be a stand alone research program that would require a separate consent process. Dr. Perrin responded by saying that the ultimate goal of the ATN is to have every child that meets criteria entered into research

protocols. However, he also stated that he recognizes the difficulties that come along with this goal.

Dr. Cordero also applauded ATN for its efforts and asked if there was any plan to address early recognition. Mr. Fade mentioned that they will rely more on the work that is already being done in the agencies, rather than have early recognition as one of their own initiatives. Mr. Fade continued to state that the ATN's time will be devoted to examining the most effective ways to treat children with autism once they are in the clinic.

Dr. Zeph stated that the ATN complements what the IACC has been doing with respect to early identification. She further commented that she hopes that the ATN will at least attend to introducing the concept of early identification into the medical community by spreading the word. Dr. Zeph posed a question as to why there was no mention of neuroimaging. Dr. Perrin stated that the ATN discussed the point of routine neuroimaging among all children with autism spectrum disorders, but decided not to include routine neuroimaging given current evidence. The ATN may consider developing stronger evidence for when neuroimaging would be appropriate.

Dr. Insel asked if another institution posed interest, would there be room for additional centers. Mr. Fade responded that the vision of ATN is to become much broader than the six centers that are currently in the network.

Autism Speaks
Presented by Gary Goldstein, M.D.

Dr. Goldstein introduced Alison Singer as the CEO of Autism Speaks and then provided a brief background on the development of Autism Speaks. He discussed that Autism Speaks was only 11 weeks old and therefore there was a degree of uncertainty as to how it would fit into the roadmap. Dr. Goldstein mentioned that while the advances thus far within the field of autism are tantalizing, there appears to be a financial limitation to what can be done. In addition, he stated that he agreed with ATN's focus on moving beyond supporting one single program in one city to the creation of networks. However, Dr. Goldstein pointed out that in order to do this, more resources would be necessary and that these resources could come from funds raised from the public. He claimed that the idea to raise public funds came from an NBC Gallup Poll in which 20 percent of the 1,000 callers indicated that they would make a donation to autism research. Dr. Goldstein stated that the mission of Autism Speaks is to serve as a foundation that could raise money from the public in comparable amounts to other disease-focused childhood foundations.

Report from the IACC Services Subcommittee: Implementation of the Autism Services Roadmap
Presented by Merle McPherson, M.D.

Dr. McPherson began by stating that the charge of the services subcommittee was to address the need for services for individuals with ASD. The IACC had previously seen a presentation from the Expert Working Group (EWG) on services, which was convened by the subcommittee. She explained that the focus of her presentation at this meeting was to discuss the implementation

plan based on those recommendations. Furthermore, Dr. McPherson explained that the EWG and the services roadmap were based on the President's New Freedom Initiative, and that within this initiative, six performance measures for community systems of services were identified. The six performance measures include: (1) strong family-professional partnerships, (2) early and continuous developmental and medical screening, (3) availability of all needed health, education, and social services, (4) easy access to community-based coordinated service systems, (5) effective youth transition to adult services, work, and independence, and (6) access to adequate public insurance, private insurance, or other financing mechanisms.

On March 22, 2005 the services subcommittee met with the EWG to discuss their recommendations. Dr. McPherson reported that from that meeting two major implementation recommendations were outlined: (1) to obtain ongoing involvement of high-level federal agency officials to address the development of infrastructure and coordination, and (2) that there was a need to secure resources to contract with an organization that would convene key public, private, and voluntary stakeholders in the development of a strategic services plan. In addition, Dr. McPherson pointed out that the implementation plan of these recommendations is a short-term response that is limited by current resources. However, before outlining the implementation plan, she highlighted the current activities that were already taking place within the agencies that address the recommendations. For example, Dr. McPherson noted that significant activity is taking place with respect to achieving family-professional partnerships and early and continuous developmental and medical screening.

Activities toward implementing the services roadmap were presented, outlining immediate actions that are within the authority of the federal agencies represented on the subcommittee. Dr. McPherson acknowledged however, that there was recognition by the services subcommittee that state and community involvement is crucial to the implementation of services. Using the guide of the six short-term actions, Dr. McPherson outlined the agencies that have agreed to take the lead in implementing the EWG recommendations. The recommendations and agency leads are:

1) Improving access to comprehensive information about autism spectrum disorders (ASD) services and providers – the Agency for Healthcare Research and Quality will take the lead on coordinating existing federal disability and ASD websites to establish a comprehensive clearinghouse of information about federal resources for ASD.
2) Support screening subcommittee efforts to increase public awareness and routine screening – the Center for Disease Control and Prevention (CDC) is currently taking the lead on coordinating efforts with other agencies to increase current screening and diagnostic efforts.
3) Develop and promulgate professional guidelines for ASD service providers – the Health Services and Resources Administration (HRSA) will be responsible for involving key public and private stakeholders in the development of a multi-disciplinary approach to developing professional guidelines.
4) Identify Medicaid waivers covering individuals across the lifespan with ASD – the Centers for Medicare and Medicaid Services (CMS) will carry out the plan to develop and publish a monograph of promising practices of waivers that have been approved by CMS/Medicaid for ASD.
5) Convene an interagency task force to address the gap in services for adults with ASD –

the Administration on Developmental Disabilities within the Administration of Children and Families will engage federal staff in the compilation of information regarding the gaps in services for adults with ASD.

6) Develop strategies for technical assistance to states and communities on the organization of community-based services – the Office of Special Education and Rehabilitative Services will recommend mechanisms to link ASD/IDEA service providers with experts on best community-based models to develop technical assistance strategies. (Note: ASD/IDEA service providers are those who work within the authorization of the Individuals with Disabilities Education Act.)

Discussion:
Dr. Gordon mentioned that he was excited about the plan to move ahead with the services roadmap; however he questioned the effectiveness of federal involvement when it appeared as though the implementation of services is better carried out on the state and local levels. Dr. McPherson responded by agreeing with Dr. Gordon that these efforts at the federal level were intended to facilitate and support the implementation of universal, equitable, and sustained service systems at the state and local levels. The EWG recommendations felt that leadership activities from the federal level were key to moving implementation forward. She noted that HRSA awarded a grant to James Perrin, M.D. to establish the evidence base for service systems for the broad population of children with special health care needs. This evidence base should serve as a template in addressing the unique needs of persons with autism.

Mr. Grossman further added that the expert working group identified a comprehensive set of many recommendations, but that all of these could not be addressed today. He mentioned that what was presented today was what the federal agencies were willing to commit to in order to move the process forward and that this did not take away from the important fact of involving state and local workers in providing these services.

A National Data Sharing Resource for Autism Research
Presented by Alex Rosenthal and Don Preuss

Mr. Rosenthal, the director of the Division of Enterprise and Custom Applications within the NIH Center for Information Technology (CIT), began the presentation by providing background for the autism database. He discussed that the inspiration for a national database for autism research was the research advances in childhood leukemia via an effective and sustained collaboration effort. Furthermore he indicated that CIT had been charged with examining the feasibility of a national autism database. The CIT team reviewed six systems that currently collect and analyze data, interviewed more than forty-five people, and examined hundreds of documents to establish the feasibility, requirements, and architecture for a national system.

Mr. Preuss, a consultant expert from the CIT team, reported on the findings from the feasibility study. He described the vision of the National Database for Autism Research (NDAR) as a vehicle that would promote data sharing, establish standards, use proven cutting-edge technology, provide broad access to knowledge across domains, and use global sources and powerful analytic tools. The goal of NDAR is to support collaboration within autism research and clinical practice to ultimately shorten the time for discovery of causes and treatments for

autism. Mr. Preuss explained how NDAR would include different types of data, including behavioral, genomic, neuroimaging, video, dysmorphology, and clinical-trial research data, as well as access to tools to help interpret that data.

NDAR would be a federated database. The Biomedical Informatics Research Network (BIRN), supported by the National Center for Research Resources (NCRR), will provide basic technologic infrastructure. Other resources, including the Cancer Bioinformatics Grid (caBIG) and the Internet System for Assessing Autistic Children (ISAAC) will serve as references for components of the solutions. The goal is to use existing common standards or to develop new standards to promote data sharing among research entities. These entities include NIH-funded autism centers, the CDC, Autism Speaks, the ATN, and the Brain Bank. The aim is to provide the autism research community with a cohesive, Web-based tool for the purpose of data gathering, analysis, and review.

Mr. Preuss demonstrated how NDAR could work using an example of Alzheimer's research based on a BIRN model. A researcher could log in to a Web resource to access global data via a grid of distributed computers. Mr. Preuss described how the Web makes the data accessible from multiple sites, and can leverage different technologies and databases.

Governance, both technical and scientific, is a critical factor in reaching NDAR's goals. Mr. Preuss suggested that NIH establish a steering committee that involves technical and scientific workgroups to manage standards and processes. He also suggested that the establishment of an NDAR consortium office to oversee coordination, logistics, and project management.

Mr. Preuss discussed the metadata that gives researchers important information about how the data was collected, which protocols were used, and what data elements were included. NDAR would include a resource library of protocols and standards that can be used for data collection, providing a framework for collaboration among the community of autism researchers.

Discussion:
Dr. Swedo referred again to the pediatric leukemia example as a success story that shows how quickly treatment research can advance when an effective infrastructure is in place. Dr. Insel added that by developing NDAR now, the system can take full advantage of technology development in related fields.

Mr. Shestack, the discussant for this presentation, said that not sharing data or using a common database was a tremendous problem in autism research. He commended the group for presenting such a "visionary" concept and agreed with Drs. Insel and Swedo on the importance of establishing NDAR. Mr. Shestack asked how NDAR would be financed, when the project would start, and how the "culture" would be changed to provide incentives for investigators to participate. He also asked if there were plans to include historical data and whether imaging data would be included in NDAR.

Dr. Swedo said that NDAR will be designed to incorporate historical data without necessarily having complete commonality, because for some data, the cost of standardization would be more than the cost of re-collection. Dr. Swedo said the plan for NDAR was to allow all researchers,

even junior investigators, to use the database to answer quick research questions and to look for patterns. She said some data will be available to all, while access to other data may be limited. Dr. Swedo said that NIH and investigators on the STAART and CPEA imaging committees are already discussing standards for imaging. She said NIH will have to demonstrate that being involved with NDAR is a benefit to every individual researcher, perhaps by establishing policies that will increase data sharing.

Dr. Battey asked if there would be a standardized, controlled vocabulary used for the database. Mr. Rosenthal described the development of a full end-to-end analytical ontology. He said that the only way to come up with over-arching standards is to provide a controlled dictionary.

Mr. Shestack asked where NDAR would be hosted, and Mr. Rosenthal responded that it would be hosted at NIH, possibly by CIT, or hosted by other locations under the NIH scientific community's leadership. Mr. Shestack also asked how genetics data from the genetics repository would be included. Dr. Swedo answered that standards were already in place for incorporating genetics data and that it will be a core component of NDAR.

Dr. Gordon asked about the inclusion of non-standardized data in NDAR, saying that some of the most cutting edge work will not necessarily conform to the standards that are developed. Mr. Preuss said that NDAR would include non-standardized data, because this data may be important for autism research in the long term. Mr. Rosenthal added that at some point, scientists may wish to structure such data to be able to better link it to other structured data.

Mr. Fade complimented the group's efforts in designing NDAR and said there was a further need for a government-sponsored office that would help with the scientific processes (e.g., IRB issues, etc.). He said governance and common standards would help the public and private organizations coordinate with the database.

Ms. Lajonchere, the director of the Autism Genetics Resource Exchange program, said there is a deficit within the field of autism research with respect to a normal control population and asked if there would be any efforts to include normal control data in NDAR. Mr. Preuss responded that normal control data would be available, citing as an example the data being collected from the Pediatric MRI Study of Normal Children.

Research on Environmental Influences in Autism

Presented by Cindy Lawler, Ph.D.

Dr. Lawler introduced NIEHS as a fairly new entity within autism research. She stated that NIEHS has been part of the IACC for five years. With respect to progress, Dr. Lawler reported that the scientific field is still looking primarily toward genetics in autism, but that there is a growing movement toward examining the role that environmental influences may play. Furthermore, she indicated that part of the reason why there is a bias toward genetic influences involved with autism is that there is more genetic data available than environmental data. For example, there is data available from twin studies, family studies, and gene association studies. In addition, Dr. Lawler described how studies examining environmental factors are less developed than genetic studies of autism. However, she pointed out that the field of children's

environmental health is a mature field from which autism environmental studies can draw. For instance, using the knowledge gained from children's environmental health studies, we now know more about low-dose effects, critical time periods of exposure, sources of susceptibility, and how genes interact with the environment to produce dysfunction.

Dr. Lawler briefly reported on some of the public concerns that raised attention to environmental influences in autism. The dramatic increase in the number of autism cases has sparked more attention on environmental influences. She asked the question regarding what we know about this increase. In response, Dr. Lawler mentioned that we know that the increase is widespread both geographically and demographically and that there have been administrative and diagnostic changes over time that could account for some of the increase. But she reported that we do not know how much of the increase in autism rates can be attributed to diagnostic and administrative factors.

Dr. Lawler noted that another public concern that has received attention is the increased rate of autism and the relationship to vaccinations. The Institute of Medicine (IOM) conducted a thorough review on this issue and produced the final report in May 2004, stating that the committee did not find a link between thimerosal and autism. Dr. Lawler further added that while this finding is not universally accepted, we do know that some of the most methodologically rigorous epidemiological studies support the idea that vaccinations did not lend to the increase in the autism diagnosis. However, she pointed out that there is uncertainty regarding the relationship between autism and total mercury exposure. Also, it is unknown whether a small percentage of children with autism could be more susceptible to increased levels of a toxicant.

Dr. Lawler explained that we do know that some environmental influences can increase autism. For example, she highlighted Patty Rodier's work on thalidomide exposure and increased autism risk. Dr. Rodier is a principal investigator funded through the CPEA and STAART centers. In addition, Dr. Lawler described that if we accept the idea that there is a genetic component to autism, then the most reasonable approach to the study of autism is to look at how environmental exposures exert effects through their interaction with autism susceptibility genes. Essentially, the best studies would examine the gene-environment interactions rather than examining the two factors separately. An example of this kind of gene-environment study was published last year by Mady Horning. She indirectly looked at gene-environment interactions by choosing mouse strains that were known to have different responses to mercury-induced autoimmunity. The results from the study suggested that the difference in susceptibility was linked to genetics. In addition to this study, Mady Horning has measured the effects of thimerosal on behavior and brain morphology in these mouse strains and has identified that the effects of the thimerosal were only observed in the autoimmune sensitive strains. The NIEHS plans to replicate this study.

Dr. Lawler identified some key resources that are under development at NIEHS with respect to examining the environmental influences on autism, including the Environmental Genome Project and the Center for Rodent Genetics. She also mentioned that there are a number of newly-initiated population-based studies that are examining the risk factors associated with autism, and animal models of autism are being developed. The Environmental Genome Project was launched several years ago, focused on resequencing DNA to identify common polymorphisms

in environmental response genes. The Center for Rodent Genetics issued a two-year contract to Perlegen to sequence fifteen commonly used mouse strains. The data will be made publicly available as the sequencing proceeds.

In conclusion, Dr. Lawler noted that there are some environmental studies in place, but that more needs to be done. Furthermore, there does not appear to be enough research within the mainstream autism community to examine environmental influences. Part of the reason for this dearth is due to conflicting opinions surrounding the idea that autism is mostly of genetic origin and that while intriguing results are being identified, these results are often plagued by methodological issues. In looking forward, several population-based studies have been initiated to examine the potential role of environmental factors in autism, and these studies are well controlled and have a significant number of individuals.

Discussion:
Mr. Grossman thanked Dr. Lawler for presenting, and he indicated that the scientists supported by NIEHS are amazing and probably ahead of the curve. Mr. Grossman asked if there were plans for NIEHS to expand the centers. Dr. Lawler replied that there is most likely room to expand the centers, especially within the context of the merged CPEA and STAART networks. She also mentioned that with the next recompetition, there will be discussion about what components and types of research to include.

Dr. Zeph asked if any thought has been given to creating a standardized family intake on environmental exposures. Dr. Lawler indicated that this was a good idea, but that currently it is not feasible until classes of exposure have been narrowed. Dr. Insel followed up by stating that examining these potential environmental influences should be a priority for the IACC and that it could also serve as a framework for further collaboration with private partnerships. For example, he suggested that there could be web-based collection that might involve Autism Speaks or another group that is interested in this area of research.

Ms. Chase, a mother of an eight-year-old autistic child and a Maryland representative for Unlocking Autism asked why environmental studies could not look into past data for answers. She described how her doctor's son has been collecting information on heavy metal screens that he has been doing for years and that examining these types of data would be useful. Ms. Chase added that she was wondering if studies would be done to address the issue of metal exposure. Dr. Lawler discussed how the UC-Davis Childhood Autism Risks from Genetics and the Environment (CHARGE) center is currently conducting an analysis of various metals. In addition, Dr. Lawler agreed that there was a huge amount of data collected by clinicians, but that these data are best used for deriving hypotheses for future study. She noted that it would be difficult to use this data for other means because of a lack of appropriate control and selection procedures.

Science Update

NIEHS Center for Children's Environmental Health and Disease Prevention Research

Presented by Isaac Pessah, Ph.D.

Dr. Pessah reported on the progress that is being made in the Center for Children's Environmental Health (CCEH). Specifically, through collaborations with the M.I.N.D Institute, the Center of Excellence and the Superfund Basic Research Program, recruitment of families is underway. The focus of CCEH is on the development of animal models and the examination of gene-environment interactions that might be relevant to autism. The center is conducted under the belief that there is a genetic component to autism, but that genes alone cannot fully account for the cause of autism. Environmental factors may serve as promoters that not only affect genetic factors, but can exacerbate genetic weaknesses.

The CHARGE study that is being conducted at CCEH is a case-control study that aims to examine the childhood risk from genes and the environment in the development of autism. Recruitment for this study began in late 2001, before the M.I.N.D. Institute was established; however currently there are 667 families that have been included in the study. For purposes of analysis, children enrolled in this study are divided into three groups, (1) children with autism, (2) children with developmental delays without autism, and (3) typically developing children. A significant amount of biological tissue has been collected, yet much of it still needs to be analyzed. A midway point analysis of the data revealed that children with autism exhibit a sensitivity to environment at bedtime, which has been shown to be correlated with cognitive impairments. Further study in this area is necessary, as it is unclear whether autism exacerbates sleep problems or if sleep problems makes autism symptoms worse.

Another aim of the CHARGE study is to examine the blood samples for immunology and the plasma/serum samples for antibody-specific immunoglobulin testing. There will be an examination of 30,000 genes to see if it is possible to subcategorize the children in the CHARGE study. In order to do this, serum will be generated for genomic profiling and lipid profiling. Whole blood samples will be used for metal analysis, and hair analyses will also be conducted. The hair analysis is an innovative approach to examining mercury exposure in the sample. Specifically, examining hair will provide a temporal time line of exposure, versus the snapshot that is provided by examining the blood.

Dr. Pessah briefly discussed how there has been a lot of discussion around the cellular toxicity of thimerosal and the development of autism. He pointed out that vaccines are not the only place where thimerosal is present and that further investigation should be given to other environmental factors such as food. Dr. Pessah also reported on a set of data from the CHARGE study that was analyzed by Judy Van de Water. In examining how children with autism respond to bacterial toxins, results indicated that the children respond poorly to toxins such as diphtheria and tetanus, implicating immune problems in autism.

Updates on Federal Activities

Collaborative Programs of Excellence in Autism (CPEA)

Presented by Alice Kau, Ph.D.

Dr. Kau provided updates on two ongoing activities within the CPEA. First, she reported on the CPEA girls network project, which is using available common measures data to examine social behavior differences in girls with autism in comparison to boys with autism. The study aims to

address the hypothesis that in comparison to boys with autism of similar age and IQ, girls with autism will display milder autistic symptoms. The study is currently in the process of gathering data from all CPEA sites.

Dr. Kau also reported on the progress of the Baby Siblings Research Consortium, which is a consortium that includes the National Alliance of Autism Research (NAAR) and the National Institute of Child Health and Human Development (NICHD). The annual meeting took place on April 1, 2005 in Washington, DC and focused primarily on ethical issues related to conducting baby siblings research. Dr. Kau noted that there are currently ten research groups across the United States and Canada that are following cohorts of infant siblings of children with autism.

Studies to Advance Autism Research and Treatment (STAART) Centers
Presented by Deborah Hirtz, M.D.

Dr. Hirtz reminded the IACC that at her last talk she described in detail the intervention projects in the STAART centers. For her talk today she outlined two projects on early intervention, one project on dietary intervention, and two pharmacologic studies that are all in progress and recruiting successfully. She added that the projects are all periodically reviewed by the data and safety monitoring board (DSMB) and to date, there have been no reports of problems with children who are enrolled or any serious adverse events. Dr. Hirtz provided further detail on the two pharmacologic studies indicating that the first study of citalopram for children with high levels of repetitive behaviors is moving along well and has recruited almost half of its subjects. For the second pharmacologic trial, fluoxetine for young children, the protocol was approved by the DSMB and work is being done to finish the pilot protocol and consent forms. Dr. Hirtz anticipates that the pilot trial will be underway in a few months. Dr. Hirtz ended the STAART centers update by highlighting a meeting that took place in April 2005 in Atlanta, GA. She discussed how the meeting was a good avenue for junior and senior investigators within the STAART centers to come together and discuss common science interest. A joint STAART/CPEA meeting will take place in November 2005.

CDC Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE); Other CDC Activities
Presented by Jose Cordero, M.D., M.P.H.

Dr. Cordero provided updates on two CDC initiatives, the results of the autism listening sessions and the progress on the "Learn the Signs. Act Early" campaign. He briefly mentioned that surveillance activity within the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) is going well, but that more detailed information would be provided at the next meeting as more important data will be available then.

Dr. Cordero described four listening sessions that took place in Florida, California, Indiana, and New York under the direction of the CDC in conjunction with the Autism Society of America (ASA), Cure Autism Now (CAN), NAAR, and the M.I.N.D. Institute. Dr. Cordero noted that there were several cross-cutting themes including (1) parents concerned that they were not being heard by healthcare professionals, educational, research, and governmental sectors, (2) parents concerned about wanting a uniform definition of autism that would be used for state, federal, and

education agencies, (3) concern regarding the evaluation of the safety of the immunization schedule and the removal of thimerosal from the vaccines, (4) problems associated with insurance coverage, and (5) the lack of services for adults and adolescents transitioning to adulthood. A summary report from the sessions will be prepared and distributed to the IACC at a later date.

Dr. Cordero reported on the progress that has been made on the "Learn the Signs. Act Early" campaign. The campaign was launched on February 21, 2005 in coordination with Autism Speaks and NBC during the week-long series of programs on autism. Currently, the campaign has had tremendous success with respect to outreach. For example, 20,000 parent kits have been distributed and over 120,000 visitors have visited the website www.cdc.gov/ActEarly.

Discussion:
Mr. Shestack asked how the congressional appropriation of the "Learn the Signs. Act Early" campaign was actually spent. Dr. Cordero replied that he did not have the dollar amounts with him, but would be happy to share the information with Mr. Shestack at a later point.
A member from the audience asked when the Vaccine Safety Data Link Project would be accessible to independent investigators. Dr. Cordero did not have the answer, but stated that he would follow up with the individuals involved with vaccine program.

Margaret Dunkle, an audience member who works in Los Angeles with an organization focused on early identification and intervention for children with disabilities and delays, discussed the importance of developing a high quality developmental screening. She also mentioned that by using a broader developmental screen that encompasses several developmental delays, disabilities, and learning issues that they have been able to catch children with autism earlier than doing autism-specific screening.

Heterogeneity in Autism, Implications for Clinical Trials
Presented by Glenn Mannheim, M.D.

Dr. Mannheim described his perspective as a medical reviewer at the Food and Drug Administration (FDA). Specifically, he reported that his role is to determine whether a drug is both safe and effective for use in the intended population before it can go to market. He discussed how this process is difficult with autism because of the complexity of the disorder. For example, multiple neurotransmitters have been implicated in autism, therefore making it likely that any drug that is developed for use with autism will have to be closely monitored. In addition, there are environmental factors to be considered that might suggest that autism may not be amendable to pharmacotherapy.

The Food, Drug, and Cosmetic Act of 1938 requires that there is substantial evidence of effectiveness of a drug from adequately controlled investigations. At a minimum, a trial to test for the effectiveness of a drug designed for autism would have to be a randomized, double-blind, and concurrent-placebo controlled study. In addition, safety information would have to be gathered to show that the drug is safe. The next step for gaining approval of a new drug requires clearly identifying the clinical entity by distinguishing it from other clinical entities. This is a

difficult task for autism as the causes of autism are not yet clear, and there remains a rather heterogeneous population.

Regulatory Approaches to Behavioral Disease Treatment
Presented by Paul Andreason, M.D.

Dr. Andreason described the approval process that takes place within the FDA. The FDA has the authority to regulate the investigational exposure of drugs to human subjects prior to their marketing. In addition, the FDA is responsible for the initial approval of the safety and effectiveness of new chemicals and for the approval for expansion of drug indications once the drugs have been placed on the market. The authority for the FDA regulations comes from the Food, Drug, and Cosmetic Act of 1938, which was amended to include regulation of both safety and efficacy. However, the FDA does not regulate the practice of medicine, including the off-label use of drugs, psychotherapy, and rehabilitative medicine.

Dr. Andreason discussed the trends in psychiatric drug development over the past ten years, which includes a decrease in the number of applications for new chemicals, but an increase in the number of applications for supplemental indications or new marketing claims. In part this trend is due to the fact that there are few psychiatric symptoms that are unique to any one disorder. Furthermore, when the FDA approves drugs for the treatment of mental disorders, the approval is based on the symptom relief within the context of the disorder. Specifically, the examination of symptom relief is based within the context of a DSM-IV diagnosis and then the measure of symptom reduction is assessed using a validated rating scale.

There are several regulatory pitfalls in the approval of medications for mental illness, including those associated with applications looking to approve already-marketed drugs for use in treating autism. For example, Dr. Andreason discussed the problem of pseudospecificity whereby an artificial focus is placed on a general symptom as if the symptom was specific to a disorder. He used insomnia and autism as an example of this, in that insomnia is often a symptom associated with many other disorders such as depression and gastroesophageal reflux disorder. He also pointed out that once a drug has been established to have an acceptable risk to benefit ratio in one patient population that it does not necessarily mean it will be safe to use in another population. One patient group may be more susceptible to drug-related adverse events than another.

After providing the background on the FDA regulation process, Dr. Andreason posed several questions to the IACC regarding what the autism community would like to see happen with respect to drug development and autism. Would approval of already-marketed drugs for the relief of isolated symptoms associated with ASD be of interest? Is there an interest to know more about already-approved drugs that are being used off-label? What is considered a valid target symptom for drug approval? Dr. Andreason provided the example of how some selective serotonin reuptake inhibitors (SSRIs) are already being used to aid in the obsessive-compulsive behaviors that are often exhibited with autism.

Discussion:

Mr. Grossman thanked Drs. Mannheim and Andreason for their talks and stated that he was unsure of where drugs and autism are currently, as much more work needed to be done in terms of simply understanding the disorder. He mentioned that perhaps the FDA could address tests and labeling difficulties in the short run. For example, Mr. Grossman said that there are series of tests that can be applied and treatments used for gastrointestinal dysfunction issues associated with autism, but because of the autism diagnosis parents often cannot get reimbursed for these services. Dr. Andreason replied that there are situations when even approved drugs do not get reimbursed. Mr. Fade commented that the problem lies in not having a clear list of symptoms that make up autism. Dr. Insel suggested that the real key is to understand the pathophysiology of autism so that one can begin to identify the targets. He explained that without targets, there is nothing to take to the FDA with respect to drug development.

Open Session for Public Comments

Ms. Ruth Sullivan, a provider from the Autism Services Center (ASC) and a mother of an autistic child, thanked the IACC for the opportunity to be present at the meeting. She mentioned that several years ago, it would not have been possible for a parent to be able to speak in such a forum. Ms. Sullivan described the ASC as a 25 year-old organization that provides comprehensive services for those with developmental delays. Currently, the ASC serves 365 individuals, 100 of whom have autism. The center was originally developed due to the minimal services available for adults with disabilities. Specifically, the majority of adults with developmental disabilities are either at home or in inappropriate facilities. In 2001 a group of scientists organized the National Association of Residential Providers for Adults with autism, which is supported in part by a grant from the Administration on Developmental Disabilities. This organization created the Train-the-Trainer project, which involves three months of intensive training for individuals responsible for the direct care. The Train-the-Trainer Project has received good reception among the residential facilities, and parents are excited about the program.

Ms. Lynn Redwood, a representative from the Coalition of Safe Minds, voiced her concerns over the increasing rates of autism and the fact that an increase in the prenatal exposure to thimerosal has been overlooked. She indicated that there have been several stories where children with autism have been tested, and high levels of mercury have been found in their bodies. Ms. Redwood pointed out that families are reporting that their autistic children are improving with the use of nutritional supplementation and chelation therapy. Given the concerns and possible trends in improvement, Safe Minds has been sponsoring thimerosal autism research. She pointed out several examples of the research that has been conducted, including a study by Dr. Hornig that exposed autoimmune disease-sensitive mice versus control mice to vaccine levels of thimerosal. Ms. Redwood also discussed the preliminary work of Dr. Jill James on the levels of metabolites in autistic children. Ms. Redwood completed her statement by asking the NIH to refocus its efforts by moving away from genetic research and focusing more on the examination of what she believes is the root cause of the disorder.

Ms. Laura Bono, of the National Autism Association requested that the IACC change its funding perspective from examining children who are born with a defect to examining children who are born healthy and then regress to poor health. She also urged the IACC to stop funding genetic research and to focus more on environmental triggers.

Mr. Joe Pike, the Executive Director of the National Autism Association and parent of a seven year-old son with autism stated that he believes that mercury is the key to the problem. He explained how there are several replicated studies that show how the bodies of autistic children are overwhelmed with toxins. Mr. Pike asked that less emphasis be placed on attempting to find susceptibility genes and instead, to focus on toxicology, gastrointestinal factors, and environmental factors.

Ms. Kathy Young, President of the Virginia chapter of the National Autism Association, suggested that the IACC should concentrate on a list of studies that they have gathered – all from respected, peer-reviewed journals. She provided the list for the record.

Mr. Scott Bono has a son with autism and stated that as a parent, he is not looking for money, and he does not want to think about adult services for his soon to be adult son. He thanked the IACC for the current efforts, but stated that what he really wants is a cure to autism.

Ms. Jane Carlson, of the National Autism Center, described the development of this new agency. The National Autism Center is being supported by the May Institute and its focus is on promoting evidence-based practice for education and intervention. For example, one of the projects underway, the National Standards Project, is the creation of a practice manual for educators and clinical behavioral practitioners who serve children with autism.

Ms. Susan Moreno, a member of the Autism Society of America and the mother of a 33 year-old autistic daughter, described the difficulties that she has observed in adults with autism. She talked about how several of them are homeless or in the prison systems. Ms. Moreno urged the IACC to continue to provide ideas for services for children and adults.

Ms. Bernice Polinsky, a mother of an autistic adult son, described how wonderful her son's group home experience has been for him. The group home is being run by the Yai/National Center for Developmental Disabilities. She stated that her only concern with the facility is that many of the well-trained staff tend to leave because of poor funding.

Closing Comments and Future Agenda Items

Dr. Insel closed the IACC meeting by pointing out a theme that was expressed by both the presenters and the public – a continued focus on services. He encouraged the committee to further examine the Service Subcommittee roadmap report. Dr. Insel reminded the committee that there is a notice in the NIH Guide about an upcoming RFA for the Autism Centers for Excellence. He also discussed the need to move forward with the autism data-sharing effort, and he hoped that the database would be off the ground by the next IACC Meeting on November 18, 2005.