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Proceedings of the 2010 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

Cynthia J. M. Kane¹, Susan M. Smith², Rajesh C. Miranda³, and Julie Kable⁴

¹Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences

²Department of Nutritional Sciences, University of Wisconsin-Madison

³Department of Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center

⁴Department of Pediatrics, Emory University School of Medicine

Abstract

The annual meeting of the Fetal Alcohol Spectrum Disorders Study Group (FASDSG) was held on June 26, 2010 in San Antonio, TX, as a satellite of the Research Society on Alcoholism meeting. The FASDSG membership includes clinical, basic and social scientists who meet to discuss recent advances and issues in FASD research. The central theme of the meeting was “Glia and Neurons: Teamwork in Pathology and Therapy.” Alcohol disruption of neuron development and alcohol-induced neurodegeneration is central to the pathology and clinical expression of FASD. The active role of glia as perpetrator, victim, or bystander in neurotoxicology and neurodegenerative processes has emerged at the forefront of adult CNS disorders and therapy. Glia and neuron-glia interactions hold the potential to elucidate causes and offer treatment of FASD as well. Growing evidence indicates that neurons and glia are direct targets of alcohol, but may also be vulnerable to molecules produced in peripheral systems as a result of alcohol exposure. Diagnostics and therapies can take advantage of these processes and biomarkers, and these may be applicable to CNS pathology in FASD. Two keynote speakers, Howard E. Gendelman, M.D., and Ernest M. Graham, M.D., addressed the role of glia and neuroinflammation in brain development and neurodegeneration. The invited speakers and FASDSG members discussed new paradigms in CNS development and discuss new strategies for understanding and treating neurodegenerative disease. Members of the FASDSG provided updates on new findings through presentation of breaking research in the FASD Data Sessions. Representatives of national agencies provided updates on programs, activities, and funding priorities. The Henry Rosett Award was presented to R. Louise Floyd, R.N., D.S.N. for her career contributions to the field of fetal alcohol research. The Student and Postdoctoral Fellow Research Merit Award was presented to Shonagh O’Leary-Moore, Ph.D. for her contributions to the field as a young investigator.

The Fetal Alcohol Spectrum Disorders Study Group (FASDSG) held their annual meeting on June 26, 2010, in San Antonio, TX, as a satellite of the Research Society on Alcoholism

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Please send correspondence to: Cynthia J.M. Kane, Ph.D., Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, 4301 W. Markham St., #846, Little Rock, AR 72205, kanecynthiaj@uams.edu, Telephone: 501-626-9995.

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meeting. The 2009-2010 FASDSG officers, Cynthia J.M. Kane, Ph.D. (President), Susan M. Smith, Ph.D. (Vice-President), Rajesh C. Miranda, Ph.D. (Secretary), and Julie Kable, Ph.D. (Treasurer) organized the meeting. The FASDSG membership includes clinical, basic, and social scientists who meet to discuss recent advances and issues in FASD research. More than 150 individuals attended the study group, including 110 professionals and 46 students. Attendees were largely from the United States and included researchers from Canada, South Africa, Russia, and New Zealand.

Keynote Addresses

The principal theme of the meeting was “Glia and Neurons: Teamwork in Pathology and Therapy.” Regulation of neuroimmunity and the interaction between glia and neurons is pivotal to the functional integrity of the CNS. Emerging evidence, including presentations in the FASD Data Sessions, indicates that glia are direct targets of alcohol in the developing CNS and that microglial cell loss and activation occur in rodent models of FASD. Microglia are the primary immunocompetent cells in the parenchyma and astrocytes are important partners in a coordinated immunoresponsive milieu. Microglia and astrocytes secrete protective molecules in the undisturbed CNS. The pathology of neurodegenerative disease is typically characterized by an activated response of both microglia and astrocytes. Activation of each cell type is associated with specific functions including secretion of immune modulators such as cytokines and chemokines in addition to the potential to secrete neurotoxic molecules. Studies in non-alcohol neurodegenerative disease have elucidated several pharmacological therapies that can prevent microglial or astrocyte pathogenesis and prevent neuronal dysfunction and loss. The dynamic repertoire of these glia and mechanisms for controlling their activity opens an opportunity to prevent the neuropathology that is associated with fetal alcohol exposure.

The first keynote speaker was **Howard E. Gendelman, M.D.**, Professor and Chair of the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center. The title of the presentation was “*Neuroimmunity and Neuroprotection.*” Neuroimmune mechanisms that function daily in the CNS parenchyma promote neuronal survival and dendritic, axonal, and synaptic function, as well as systems communication. Dr. Gendelman’s research has focused on neuroimmune mechanisms of neurodegenerative disease including viral infection such as HIV, synucleinopathies such as Parkinson’s disease, and others. One of the most serious aspects of the neuropathology of these diseases is microglial and astrocyte activation. Neuronal loss ensues. This CNS pathology is particularly hard to treat because of the blood brain barrier and the vulnerability of neurons to traditional therapeutics.

This laboratory has pioneered research in the development and application of nanoformulations to treat CNS disease. A drug delivery system has been developed in which the therapeutic drug is bound to nanoparticles. The drug-labeled nanoparticles are injected into the bloodstream where they are internalized by circulating monocytic cells. Inflammation in the CNS parenchyma stimulates extravasation of the cells through the vascular component of the blood brain barrier. The effort required to develop this novel drug delivery system was clear and impressive. Establishing the parameters for nanoformulation included determination of particle size, morphology, ultrastructure, charge, and coating as well as drug incorporation. Atomic force microscopy and electron microscopy facilitated the necessary formulation challenges. In addition, extensive characterization was required to determine the pharmacokinetics, determine tissue distribution profiles consistent with delivery to sites of monocytes infiltration, and demonstrate distribution of the drug into the CNS.

A SPECT/CT scanner and two 7-Tesla MRI instruments for small animal bioimaging have provided quantitative data documenting cells and nanoparticle biodistribution into targeted regions of selected organs. Brain imaging profiles have been aligned in coregistration with histologically stained tissue sections for fine level resolution of cell type migration into brain subregions. Cells migrate into the CNS parenchyma within hours after nanoparticle injection and, once inside, release of the drug occurs within hours and is maintained for several weeks. Targeted release into the local microenvironment modulates the activity of the glia and neurons. Nanotherapy is a highly focused pharmaceutical approach that has the potential to deliver an array of antiviral, anti-inflammatory, or neuroprotective drugs directly to neurons or glia.

Dr. Gendelman discussed the importance of humanized mice as a next generation model of the human immune system. Transplantation of human CD34-positive hematopoietic stem cells into the bone marrow has been performed with strong results that permit study over months rather than limited studies of days or weeks. The cells repopulate secondary immune tissue including the thymus, spleen, and lymphatic tissue. The cells retain a naïve immunocyte phenotype and T lymphocyte receptor repertoire. The respond to immunological stimuli and elicit immunologic memory. It is particularly intriguing that HIV infection of the humanized mice leads to localization of human-derived immune cells positive for CD14, CD163, and HLA-DR in the meninges and perivascular spaces in the brain and CD4 and CD8 positive T lymphocytes in the peripheral blood. Humanized mice are a key resource for translational study of the human immune system, including neuroinflammatory processes, in rodent models. Using this model, this laboratory has demonstrated efficacy of nanotherapy targeted drug delivery against HIV infection.

Synucleinopathies are a group of neurodegenerative disorders characterized by fibrillary aggregates of α -synuclein protein in the cytoplasm of selective populations of neurons and glia. Deposition of synuclein aggregates in both neurons and glia suggests a common pathogenic mechanism. Although Parkinson's disease is the best characterized synucleinopathy others include dementia with Lewy bodies, pure autonomic failure, and multiple system atrophy. They are characterized by chronic and progressive decline in motor, cognitive, behavioral, and autonomic functions, which depend on distribution of lesions within the CNS. The primary lesion in Parkinson's disease is degeneration of dopaminergic neurons in the midbrain substantia nigra pars compacta and their termini in the striatal caudate putamen. The disease can be confirmed only by postmortem identification of cytoplasmic Lewy bodies. Initiation of the disease has been recently understood to involve inflammatory responses of glial cells in the parenchyma. The best rodent model of Parkinson's is 1-methyl -4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment of mice, which inhibits the mitochondrial electron transport system and ATP synthesis. Microglial activation in the substantia nigra is prominent within two days of MPTP treatment and dopaminergic neuron loss in this region is extensive within seven days. A secondary inflammatory response is characterized by both microglial and astrocyte activation. Glial activation may be responsible for up to 90% of the total neuronal loss as suggested by significant attenuation of neuron death by treatment with the anti-inflammatory agents minocycline or cyclooxygenase-2 inhibitors. In addition, neuron death is blocked in mice that have knockout of the inducible nitric oxide synthase (iNOS), cyclooxygenase-2, or nicotinamide adenine dinucleotide phosphate gene.

Emerging evidence suggests that peripheral immune processes can regulate CNS inflammation as well as initiation of inflammation through changes inherent to neurons or glia. Dr. Gendelman has investigated the role of T-effector and T-regulatory types of T lymphocytes on neuroinflammation in the MPTP mouse model. Interestingly, introduction of T-regulatory cells significantly attenuates microglial activation with reduced expression

of iNOS and the cytokine TNF- α . Even more important, loss of dopaminergic neurons does not occur in MPTP treated mice that receive donor T-regulatory cells. T-effector cells do not block neuroinflammation or neuronal loss when substituted for T-regulatory cells; in fact, Th17 effector T cells amplify neurodegeneration. Thus, protection against inflammation and neuron death was mediated specifically by T-regulatory cells. Characterization of the activity of the cells that mediates protection is underway including analyses of pro-oxidative molecules, cytokines, chemokines, immunomodulators, and other immune signals.

Research by this laboratory has also demonstrated that treatment with glatiramer acetate (copaxone) is effectively delivered by nanotherapy in the MPTP mouse model where it is neuroprotective against dopaminergic neuronal loss as demonstrated by the previously described imaging technologies and pathological analysis. Copaxone is FDA approved for treatment of multiple sclerosis, which increases excitement and potential for targeted therapeutic intervention with nanoformulated copaxone in Parkinsons' disease. Continuing studies are also examining the potential for therapy of synucleinopathies with vaccine against α -synuclein and positive results are emerging. Together, these studies reveal the complexity of both initiation and maintenance of neuroinflammatory processes. Investigation of similar mechanisms in the pathogenesis of FASD will provide new understanding of alcohol effects on the developing brain. Even more important, the studies presented by Dr. Gendelman illustrate multiple approaches to regulate both pro- and anti-inflammatory mechanisms and prevent neuronal death.

The second keynote speaker was **Ernest M. Graham, M.D.**, Professor in the Department of Gynecology and Obstetrics at Johns Hopkins University School of Medicine. The title of the presentation was "*Identification of Diagnostic and Prognostic Biomarkers for Perinatal Brain Injury.*" Discovery and development of diagnostic and prognostic biomarkers will provide an alternative and direct indicator of CNS damage when clinical and radiological assessments are still silent. Detection of injury or disease within the first few hours after birth would be particularly valuable for diagnosis and therapy. Effective biomarkers would provide a quantitative indicator of the extent of developmental brain lesions. In ideal circumstances, a tissue biomarker would be able to determine an underlying etiology such as inflammation, acute or chronic ischemia, etc. Importantly, they can serve as indicators to provide useful information on the effectiveness of therapeutic strategies performed. Without the use of biomarkers, the timing, duration, and effectiveness of therapeutic interventions are ascertained in a relatively blind fashion because the determination of the effect of a therapy may be years from its causation and institution.

To maximize its effective utilization, a biomarker must be a simple assay that performs measurements with good reproducibility, sensitivity, and specificity. Examples in use or under research for a variety of neurological diseases include lactate, interleukin (IL)-1 β , IL-6, IL-8, non-protein-bound iron, CD14 cell NK-kappa B, ionized calcium, neuron specific enolase, tumor necrosis factor (TNF)- α , adrenomedullin, S100 β , activin A, and glial fibrillary acid protein (GFAP). Optimally, a biomarker would permit measurement in different, biological fluids in order to avoid newborn stress due to invasive sampling modalities. In addition, samples should be easy for staff to obtain, store, and transport in a pediatric hospital or clinical setting. Examples include urine, cord blood, neonatal serum, cerebrospinal fluid, and saliva. Acquisition of samples and the biological assay itself should be low cost. Parameters of a good biomarker should also permit its utilization in longitudinal monitoring of disease. Finally and most importantly, it should be well established and validated as an early and quantitative marker of brain lesions or brain damage. Validation requires extensive preclinical and clinical research before a biological biomarker can be implemented in the patient setting.

Hypoxic ischemic injury in the perinatal developing brain produces a range of serious neurological consequences including in some cases seizures or hypotonia. As demonstrated by Dr. Graham in the neonates, low cord blood pH, high base deficit, and hypoglycemia are aid in diagnosis of perinatal brain injury. Bioimaging with MRI that he has performed in his patients reveals hypoxic ischemic encephalopathy (HIE) associated with the injury. Significant differences are quantified in the normal brain volume, the presence of edema, intracranial hemorrhages, infarct, and changes in the structure of the thalamus and basal ganglia.

Compared to conventional MRI, anisotropic imaging clearly delineates white matter anatomy that is not otherwise visualized or quantified. Distinctions in development of white matter tracts between brains of normal control children and those who suffered perinatal brain injury emerge. Three dimensional reconstructions in the 19 week fetus, newborns, and children at 5 years of age allows detailed structural comparison of cortex, brainstem, cerebellum, hippocampus, thalamus, ganglionic eminence, caudate nucleus, basal ganglia, and ventricles between normal control and injured brains. Imaging and reconstruction of projection fiber tracts was presented at fine levels of detail. For example, imaging of normal control, a patient with dystonia and normal IQ, and a patient with developmental delay demonstrated that corticospinal tract and fibers penetrating the posterior limb of the internal capsule were well preserved. Analysis demonstrated severe defects in the posterior thalamic radiation, which is sensory and connects the thalamus with the parietal and occipital lobes.

Fluid biomarkers for developmental brain disorders with neurodegeneration require identification of disease-relevant molecules, in particular, glial and neuronal proteins that reflect meaningful features of the neuropathology. Measurement of serum levels of relevant glial and neuronal proteins can add a new dimension to the clinical assessment of the primary damage and prediction of outcome after developmental insult. Much can be learned from research into other types of brain injury that have begun to discover biomarkers that meet the necessary criteria outlined above. Traumatic brain injury is one example in which glial and neuronal proteins including GFAP, S100 β , and neuron specific enolase have been detected in serum. In one study, elevation of these markers 2-20 fold correlated with injury severity score, CT imaging measurements, and poor neurological outcome at 6 months post-injury. In two other reported studies, the serum level of GFAP up to 48 hr post traumatic brain injury or cardiac arrest correlated with either diagnostic CT imaging, mortality rate, or 6-month neurological outcome. Particularly meaningful for its relevance to developmental brain injury, he discussed that S100 β was reported to be increased more than 2-fold in the urine of asphyxiated neonates up to 72 hr after birth using an immunoluminometric assay.

These studies led Dr. Graham to develop the glial marker GFAP as a biomarker of intrapartum HIE and other neurological injuries in neonates. An electrochemiluminescent sandwich immunoassay was used to quantify the concentration of GFAP in serum collected at delivery up to 7 days after birth. Compared to a control group of infants, those with neurological injury demonstrated marked, significant increase in serum GFAP. Most striking, elevated GFAP persisted in children ages 4-16 years old following neonatal neurological injury. Elevated levels of GFAP, greater than 0.08 ng/ml, within 1 day of birth was an excellent predictor of neurological injury. Treatment with hypothermia and improved neurological outcome correlated with reduced levels of GFAP in longitudinal analysis from birth to 7 days. Thus, diagnosis, prognosis, and therapeutic outcome were effectively determined using serum GFAP concentration as a robust biomarker of neurological injury in the developing brain. It is yet to be determined whether these or other biomarkers of an inflammatory or glial response in the CNS can be developed as diagnostic, prognostic, or therapeutic endpoints for FASD.

FASt Data Session

From abstracts submitted by FASDSG members, fourteen were selected to provide brief presentations on new research findings. Research from both students and established investigators was selected for these one-slide, 5 minute presentations. Eight of these presentations were by students and postdoctoral researchers, representing a strong opportunity for junior investigators. Three sessions focused on 1) *Pathogenic Mechanisms: New Horizons*, 2) *Clinical and Translational Science* and 3) *Therapeutic Research and Development*.

FASt Data Presentations I – *Pathogenic Mechanisms: New Horizons*

Wendy L. Comeau, Joanna H. Sliwowska, Linda Ellis and Joanne Weinberg (University of British Columbia) studied the influence of prenatal alcohol exposure (PAE) on the medial prefrontal cortex. When examined in early adulthood, the PAE rats had significant changes in the prelimbic thickness at P45 but not at P65 whereas other regions were unaffected. After experiencing a mild chronic stressor at adolescence, the PAE animals in adulthood had increased difficulty in learning a T-maze task, suggesting that the PAE-stressor combination may worsen cognitive function.

Helen Anni, R. Vadigepalli and J. Ogony (Thomas Jefferson University) used computational analysis to investigate ethanol's impact upon neuronal differentiation, using mouse embryonic stem cells stimulated to differentiate by retinoic acid. They found that ethanol altered the differentiation progression of these cells. Ethanol treatment significantly reduced the expression of several key, early transcriptional factors (Nanog, Sox2), suggesting that ethanol had accelerated the cells into abnormal developmental outcomes.

Paul Drew, Kevin D. Phelan, and Cynthia J.M. Kane (University of Arkansas for Medical Sciences) reported their recent findings on the role of toll-like receptor signaling in ethanol induced neurodegeneration. Ethanol was demonstrated to enhance lipopolysaccharide induced microglial activation and phagocytosis. Co-treatment with an agonist of liver X receptor (LXR), a member of the nuclear receptor family, counteracted the proinflammatory actions of ethanol. These studies suggest that LXR agonists may be effective in suppressing ethanol induced neuroinflammation and associated neurodegeneration.

Pamela Roque, Lucio G.Costa, G. Giordano, and Marina Guizzetti (University of Washington) examined the effect of ethanol-treated astrocytes upon hippocampal neuron synaptogenesis. Because ethanol inhibits muscarinic signaling-induced release of astrocytic factors that promote neurodevelopment, they predicted that ethanol would attenuate the pro-synaptogenic actions of the cholinergic agonist carbachol. Instead, they found that ethanol alone enhanced synapse formation and with no further stimulation by carbachol. One possibility is that ethanol might accelerate synapse stabilization, an interpretation supported by recent findings elsewhere.

Megan Brady, Andrea M. Allan, and Kevin K. Caldwell (University of New Mexico) looked at the long term effects of moderate PAE upon NMDA receptors within the hippocampal dentate gyrus. In this mouse model, they found that moderate PAE led to elevated NR2A subunit levels. Subcellular fractionation revealed that a rise in the extrasynaptic NR2A compartment accounted for this increase, and suggests a possible mechanism for the reduced NMDAR activation reported previously for alcohol-exposed neurons.

FASt Data Presentations II – *Clinical and Translational Science*

Janine Hutson, B. Stade, Denis C. Lehotay, and B.M. Kapur (University of Toronto) examined the nutrient composition of maternal and cord blood sampled at delivery from alcohol-abusing mothers and controls; many in the alcohol group were also drug abusers. They found that women consuming >8 drinks/wk had significantly lower folate in cord blood but not in maternal blood, a reduced fetal:maternal serum folate ratio, and no correlation between maternal and cord folate levels. Their data suggest that alcohol and drug abuse may impair placental folate transport.

Shameena Bake, Joseph Tingling and Rajesh C. Miranda (Texas A&M Health Science Center) used Doppler ultrasonography in a second-trimester mouse model to investigate the consequences of acute ethanol exposure upon fetal blood flow. Maternal exposure to 3.0 g/kg ethanol selectively and significantly reduced fetal blood flow in the heart and carotid arteries. In contrast, maternal heart rate and respiration were unaltered by ethanol. This suggests that acute ethanol exposure may cause significant hypoxia and nutrient loss in the developing fetal brain.

Leana Olivier, M. Urban, M. Chersich, and D. Viljoen (Foundation for Alcohol Related Research, South Africa) reported that holistic interventions were successful at reducing the prevalence of FASD in the Northern Cape Province of South Africa. They found that the implementation of educational activities aimed at altering community norms (intense intervention, theatre shows, support groups) significantly reduced FASD prevalence and dysmorphology scores in the study population's offspring as compared with pre-intervention rates.

Rebecca Titman, D.P. Munoz and James N. Reynolds (Queen's University) spoke about methods they have developed to measure planned motor responses in children with FASD. Saccadic eye movements were monitored as the children were asked to perform a delayed memory-guided sequential task and a predictive task. In the sequential task children with FASD had difficulty in completing correct trials and had increased rates of false starts, sequence errors and timing errors. They had increased variability in saccade timing in the predictive task. Both techniques may be useful to reveal deficits in response inhibition and sensory-motor integration in children with FASD.

Jeff Wozniak (University of Minnesota) used resting-state functional MRI connectivity methods (fcMRI) to investigate potential network disturbances in children with FASD. Network efficiency was evaluated using a graph theory mathematical approach. In their resting-state, children with FASD showed significantly lower global efficiency and higher clustering than controls, suggesting the presence of a more fragmented and less efficient functional network. These data offer insights into the nature of the processing deficits seen in FASD.

FASt Data Presentations III – *Therapeutic Research and Development*

There is substantial interest in therapeutics and interventions that may attenuate alcohol's neurotoxic effects upon the developing brain. Several FASt data speakers presented findings on these potential interventions.

Arco Paul and Alexandre Medina (Virginia Commonwealth University) used a ferret PAE model to investigate how PAE alters the capacity for neural plasticity in the eye. They previously found that PAE blunts the normal ocular response to monocular deprivation, in which the unused ocular columns of the visual cortex are reduced and that of the experienced eye is expanded. Here they showed that forced expression of serum response

factor (SRF), using Sindbis viral vector, restored ocular dominance plasticity in the PAE animals. Interestingly their data suggested that the transfected cell population that was responsible for this action were astrocytes rather than neurons. Pomegranate juice is a rich source of plant polyphenols that have multiple cellular actions including potent antioxidant potential. **Bradley Monk** and Jennifer Thomas (San Diego State University) used a third trimester-equivalent rat model of binge alcohol exposure to show that oral administration of a pomegranate juice extract mitigated cerebellar Purkinje cell losses when given during neonatal alcohol exposure period. Similar doses also normalized the animals' motor functions and these data suggest that compounds in these extracts may be neuroprotective against alcohol exposure.

George Henderson (Texas Tech University Health Science Center) investigated the neuroprotective effects of the γ -glutamyl cycle and its synthesis of the antioxidant glutathione. GSH synthesis is driven by the transcriptional factor Nrf2 and its interaction with the antioxidant response element. GSH synthesis is normally quite low during early cerebral cortical development, and he reported that forced expression of Nrf2 enhanced GSH synthesis and blocked the pro-apoptotic effects of ethanol upon neurons.

Bahri Karacay, Jo Mahoney, and Daniel J. Bonthius (University of Iowa) previously demonstrated that stimulation of the cAMP-Protein Kinase A-CREB intracellular signaling pathway protects immature neurons against alcohol toxicity. Here they reported that rolipram, a phosphodiesterase inhibitor that elevates intracellular cAMP levels, protected cerebellar granule neurons against alcohol-induced death in a dose-dependent manner. Rolipram is approved for human use in Europe and might offer pharmacologic protection against alcohol's neurotoxicity.

Agency Updates

Representatives from governmental agencies provided highlights of news related to progress on FASD programs.

Dale Hereld, M.D., Ph.D., from the National Institute on Alcohol Abuse and Alcoholism (NIAAA; <http://www.niaaa.nih.gov>), National Institutes of Health, overviewed new programs and priorities of the Institute. The strategic plan of the NIAAA is to understand the impact of alcohol across the lifespan, from fetal life into the senior years. Key perspectives will be gained by investigating the interplay of genes and environment beginning in the fetus with FASD development, to childhood with an alcoholic family environment, to adolescence with binge drinking consequences, to young adulthood with development of alcohol dependence, to middle age with cumulative organ damage, and into the senior years with interactions between alcohol and medications. The challenges for FASD include development of effective strategies for preventing prenatal alcohol exposure and for recognizing and intervening in at-risk pregnancies, understanding FASD etiology, application of new technologies for early diagnosis of FASD including detection of FAS facial dysmorphism, improved case recognition for FASD including alcohol related neurodevelopmental disorder (ARND) through discovery of biomarkers and refinement of a childhood neurobehavioral phenotype, development of preventive measures as well as clinical and educational interventions based on understanding of a neurobehavioral phenotype, and development of preventive measures by changing social norms. He emphasized the necessity to identify mechanisms underlying FASD and that development of preventive measures is crucial.

The NIAAA budget and grant funding in support of FASD research goals were illustrated, with research funding focused on prevention of drinking during pregnancy, etiology, diagnosis, and therapeutic intervention. The American Recovery and Reinvestment Act

provided additional funding to NIAAA and approximately \$8 million dollars was provided to study FASD in the form of peer-reviewed research awards. Recent Requests for Funding Announcements for FASD research included those with a focus on mechanisms of alcohol-induced organ damage, novel interventions for neurodevelopmental disorders, and case ascertainment to estimate the U.S. prevalence of FASD. Ongoing, funded research initiatives include the Collaborative Initiative on FASD (CIFASD) and the Prenatal Alcohol in Sudden Death Infant Syndrome and Still Birth (PASS) Network, and the University of New Mexico NIAAA Alcohol Research Center focused on FASD etiology, diagnosis, and intervention. Publications by NIAAA related to FASD were highlighted, including an exciting new issue of *Alcohol Research & Health* on FASD.

Sally M. Anderson, Ph.D., Coordinator and Executive Secretary for the Interagency Coordinating Committee on FASD (ICCFASD) at the NIAAA, National Institutes of Health, began with an overview of the goals and programs of the ICCFASD (<http://www.niaaa.nih.gov/AboutNIAAA/Interagency>). This is an interagency committee supported and funded by NIAAA whose purpose is to increase communication, cooperation, and collaboration among the many disciplines and federal agencies with programs focused on FASD or a special interest in FASD. The individuals include researchers, educators, medical professionals, legal professionals, parents and advocates. She discussed groups central to ICCFASD, including the NIAAA, the National Institute on Child Health and Development (NICHD), Health Resources Services Administration, Agency for Health Care Research and Quality, Indian Health Services, Department of Education, Department of Justice, Centers for Disease Control and Prevention, and the Substance Abuse Mental Health Services Administration.

The power of these coordinated efforts and programs were described for selected activities including, among others, funding announcements from the Agency for Healthcare Research and Quality on prevention and care management, health information technology, and effectiveness research. The Office of Special Education Programs has developed web based information dissemination for special education teachers and a shared program for technical assistance. The Health Resources Services Administration continues to increase annual training for maternal screening and treatment referral for alcohol use disorders, and childhood screening for diagnostic FASD criteria. The National Children's Study, a nationwide prospective study that will recruit and collect outcomes data on a large child cohort, spanning the period from prenatally to 20 years of age is a major coordinated study through the Department of Health and Human Services including the National Institutes of Health and the Centers for Disease Control and Prevention, and the Environmental Protection Agency (<http://NationalChildrensStudy.gov>).

The National Institute on Child Health and Human Development collaborates with the National Institute on Alcohol Abuse and Alcoholism to sponsor the FASDSG meeting, is sponsoring a prospective study in Chile on the effects of heavy alcohol exposure on the fetus, and sponsors research on risky behavior in adolescents as well as developmental brain defects and therapies. The Indian Health Service has an enhanced electronic health record system with a prenatal module for screening for alcohol use and a well-child module for documentation of all pediatric encounters from two days to nineteen years of age. The Office of Juvenile Justice and Delinquency Prevention, Department of Justice, is updating and revising the MOFAS Resource Guide for Working with Youth in the Justice System, translating Substance Abuse Mental Health Service Administration *Tools for Success Curriculum* for online training of justice system partners. In addition, an FASD awareness program is being developed for presentation at the 2011 meeting of the National Association of State Judicial Educators. She also elaborated further on additional funding announcements and conferences.

Louise Floyd, R.N. D.S.N., from the National Center on Birth Defects and Developmental Disabilities of the Centers for Disease Control and Prevention (<http://www.cdc.gov/fasd>), began with highlights of the formative research on alcohol use in pregnancy that has been contracted with RTI International. New funding is integrating Project CHOICES into sexually transmitted disease clinics, community clinics, and American Indian communities. Training curriculum for public health providers to deliver the Project CHOICES intervention is being translated from efficacy studies into publication and dissemination of counselor manuals, client workbooks, assessment tools, training curriculum and videos, and online tutorials. Strategic intervention for children, youth and young adults with FASD is progressing.

The Interventions for Children with FASD Research Consortium has completed phase I and II and is developing materials as well as dissemination strategies. New research projects are focusing on prevention of substance misuse in individuals with prenatal alcohol exposure and behavioral modification in individuals with FASD. In addition to a wealth of continuing projects at the CDC, a cooperative partnership has been implemented with the American Academy of Pediatrics to improve prevention, diagnosis, and treatment of FASD through a comprehensive education and dissemination program for pediatricians.

Dan Dubovsky, M.S.W., from the FASD Center for Excellence of the Substance Abuse and Mental Health Services Administration (SAMHSA; <http://www.fasdcenter.samhsa.gov>), presented a multidisciplinary overview of the strategy at SAMHSA for addressing FASD. The Center has generated tremendous progress in FASD through the Building FASD State Systems program. This vital national-level approach facilitates training of professionals in federal, state, and local public health programs, clinical settings, and court systems. In addition, it provides technical expertise and assistance, produces and disseminates educational materials, sponsors an annual conference to bring together state programs from across the nation, and promotes translation of evidence-based approaches for FASD prevention and diagnosis into practice. As an example, the Center conducted over 50 training and technical assistance events to more than 1600 participants in 12 states in the preceding year. Targeted intervention in the Native American community is a complex issue that is a major focus of the Center with significant ongoing progress. A new website for the Center has been immensely successful with over 17,500 unique visitors in a recent month and an average of 1-2 million page views per month. The site is fully translated into Spanish. In addition, the online searchable database contains nearly 13,000 FASD-related print and multimedia materials.

One mechanism of SAMHSA outreach is through subcontractor activities. The past year saw almost two dozen state, local, and juvenile court subcontracts, with each of these groups completing full electronic data collection and outcomes reporting. Subcontracts at 15 sites screen women for alcohol use in which more than 13,000 women were screened, almost 3200 screened positive for alcohol consumption, and over 80% entered into intervention. Further, FASD diagnosis is conducted at 8 sites, with over 3000 individuals screened for possible referral, over 250 diagnostic evaluations, and almost 125 FASD diagnoses. Subcontract has also launched the Medical and Psychological Diagnostic Learning Community whose imminent purpose is to build consensus on the FASD diagnostic process separate and apart from consideration of diagnostic criteria.

Award presentations

This year, seven young investigators were presented with travel awards to attend the meeting. The **2010 Merit Award** for Outstanding FASD Research by a graduate student or postdoctoral fellow was presented to **Dr. Shonagh O'Leary-Moore** of the Bowles Center

for Alcohol Studies at the University of North Carolina at Chapel Hill. Her mentor was Dr. Kathleen K. Sulik. Dr. O'Leary-Moore's talk was titled "Functional and neuroanatomical consequences of prenatal alcohol exposure (PAE) in early gestation," and it was authored by S.K. O'Leary-Moore, S.E. Parnell, S. Pecevich, E.A. Godin, G.A. Johnson, M. Styner, I. Oguz, F. Budin, Y. Jiang, D.B. Dehart, and K.K. Sulik.

In an elegant series of studies, Dr. O'Leary-Moore showed that an isolated alcohol exposure at the equivalent of the human third week of pregnancy was sufficient to cause substantial neuroanatomical, physiological, and behavioral changes in the offspring. Following acute ethanol exposure (2.9 g/kg given twice i.p.) at gestational day 7 (neurulation / early somitogenesis), C57Bl/6J mice had substantial brain dysmorphologies that affected regions including the corpus callosum, hippocampal commissure, and lateral ventricles, as imaged using diffusion tensor imaging. As young adults (P45) the PAE mice had a blunted hypothermic response to acute ethanol challenge as compared with controls. Although ethanol challenge impaired the rotarod performance of both groups, the PAE animals had a longer latency time to fall from the apparatus. Her research showed that a single acute alcohol exposure, even at a time quite early in development, can have lasting consequences to brain morphology and response to ethanol challenge. Her findings have clinical significance because women often do not recognize their pregnancy at this early time point.

The highlight of the 2010 FASDSG program was the presentation of the **Henry Rosett Award**, the highly prestigious award for recognition of major career contributions to the field of fetal alcohol research, to **R. Louise Floyd, R.N., D.S.N.** Dr. Floyd was presented this award for her preeminent work to develop programs in FASD research, prevention, and intervention. She is the Leader of the FAS Prevention Team of the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention. When Dr. Floyd joined the National Center on Birth Defects and Developmental Disabilities, she led the development of the FAS Prevention Team. Under her leadership the team began and continues to implement research and provide technical assistance in research and program services development to a variety of entities including state health departments, universities, the Indian Health Service, and non-profit organizations.

In acceptance of the award, she gave an exciting presentation on "Key Challenges to Building Public Health Programs for FASD Prevention and Intervention". Dr. Floyd summarized data on the incidence and prevalence of FASD in the U.S., which mandates an investment in research and programs to prevent prenatal alcohol exposure as well as therapeutic intervention for individuals born with these disorders. Despite attempts to prevent drinking during pregnancy the percentage of pregnant women who report alcohol consumption, including distinction of binge drinking, is relatively unchanged in 1991-2005. The strategy of the CDC for prevention of FAS leads from the recommendations of the Institute of Medicine model for FAS prevention. This strategy is based on a Core Research paradigm with a spectrum of approaches spanning universal and selective prevention of maternal alcohol abuse, case identification of maternal alcohol abuse, brief intervention, formal treatment, and compliance monitoring of identified cases, followed by after-care of at-risk individuals.

Project CHOICES, whose progress was described by Dr. Floyd in the agency update above, is the premier national program for prevention of FASD and is a multi-site collaboration of the CDC and academic institutions in Florida, Texas, Virginia, and Georgia. The goals of the project are to identify settings with high proportions of women at high risk for an alcohol exposed pregnancy in the preconception period, design and implement a brief intervention aimed at risk reduction and prevention of an alcohol exposed pregnancy, and test the efficacy of the brief intervention using a randomized controlled design. Interventions

include informational literature, counseling sessions, motivational interviewing, and family planning consultation and services visit. The results and programs derived from FASD research performed within Project CHOICES are multilevel and, thus, have provided key information to guide the work of researchers, program leaders, and clinicians.

Marketing and disseminating the evidence based interventions involves significant challenges. Approaches include (1) partnering with Project Choices primary investigators, SAMHSA, Indian Health Service and other health and social services providers to expand access to Project CHOICES for women at-risk for an alcohol exposed pregnancy, (2) developing a CHOICES curriculum based on the protocols and material used in the original efficacious intervention trial, (3) developing a CHOICES training plan including targeted stakeholders and health providers who will implement the intervention in health care settings, (4) providing capacity-building resources including booster training, technical assistance in developing adaptations, and recommendations for evaluation of intervention implementation, (5) evaluating implementation results and determining next steps based on lessons learned.

There are major ongoing challenges. The key challenges highlighted in the presentation include the (1) high proportion of women of childbearing age who engage in hazardous drinking, (2) high rates of other co-occurring risk factors and conditions among drinkers that can affect reproductive health outcomes, (3) lack of population-based, national estimates of the proportion of women at risk for an alcohol exposed pregnancy, (4) social norms supporting hazardous alcohol use among young women of childbearing age, (5) stigma surrounding alcohol abuse and alcoholism in women, (6) push back from women and physicians regarding the federal policy of “zero tolerance” for alcohol use during pregnancy, (7) prevailing concerns that clinical interventions are too costly, contribute less than other interventions, and are unsustainable, (8) need for better models and mechanisms for bringing successful evidence-based intervention to scale in targeted populations, (9) lack of a national FASD surveillance and monitoring system using uniform diagnostic criteria to capture cases of FAS, partial FAS, and ARND, (10) need for consensus defining diagnostic criteria for ARND. The dedication and complex work of Dr. Floyd to face the plethora of challenges has made real and lasting impact to prevention and intervention in FASD, as recognized by this career achievement award.

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