

*NIH Strategic Plan for Autism Research Annual Updates, 2010
Submitted to NIH, IACC by the Coalition for SafeMinds
July 30th, 2010*

*Comments solicited by the
National Institute of Health
Interagency Autism Coordinating Committee
regarding updates to the
Strategic Plan for Autism Research
RFI# NOT-MH-10-025*

Submitted by

SafeMinds

July 30th, 2010

Question-Specific Recommendations on the NIH Strategic Plan

Question # 1 - When should I be concerned

What has been learned about the issues covered in this chapter in the past year?

Several recent studies have identified clinical findings in children with ASD that have the potential to be useful as biomarkers for both risk and disease. Such findings include a specific urinary metabolic phenotype in children with autism compared to unaffected siblings and age matched controls indicating perturbations in sulfur and amino acid metabolism and possibly abnormalities in gut microflora (Yap, 2010). There have also been several studies that document clinical, biochemical, and neuropathological evidence of oxidative stress and mitochondrial dysfunction (James, 2009, Weissman, 2008, Shoffner, 2009, Sajdel-Sulkowski, 2009) along with immune system abnormalities (Li, 2009, Wills, 2009, Enstrom, 2009, Goines, 2010). Such findings may be useful as both potential biomarkers for diagnosis and for monitoring therapeutic interventions.

What are the remaining gaps in the subject area covered by this chapter?

It is imperative that such research findings be urgently replicated through the issuance of RFA's in an effort to fast track critical research findings. If these associations are validated then these findings should be immediately translated into screening tools in an effort identify those at risk for the development of an ASD. In addition, an initiative to develop effective therapeutic strategies and treatment protocols should be added to the short term objectives in an effort to prevent progression of the disorder.

Question # 2 - How can I understand what is happening?

What has been learned about the issues covered in this chapter in the past year?

The "What we know" section alludes to the possibility of a biological basis of ASD but goes on to say that little evidence exists for such a basis outside of a transient pattern of brain growth. Multiple studies have been published the past 2 years documenting metabolic, immune, and neurological abnormalities that offer additional support for biological underpinnings of the disorder. Zecavati and Spence (2009) review neurometabolic disorders and dysfunction found in ASD. Enstrom (2009) identifies altered innate immunity capable of initiating and perpetuating autoimmune responses. Li (2009) documents an elevated immune response in the brains of autistic patients. Wills (2009) reports on detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders. Sajdel-Sulkowska (2009) reports an increase in cerebellar neurotrophin-3 and oxidative stress markers in autistic cerebella. James (2009) continues to expand her finding of oxidative stress, documenting cellular and

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mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. Palmeieri (2010) provides additional support for mitochondrial dysfunction in autism along with Shoffner (2009), who links fever and mitochondrial dysfunction with the development of ASD. Weissman (2008) argues that defective mitochondrial oxidative phosphorylation is an additional pathogenetic basis for a subset of individuals with autism.

This section of the plan is in need of updates in an effort to focus research initiatives more specifically on these new novel findings since they also may provide insight into the development of effective therapeutic strategies and possible etiology of the disorder.

What are the remaining gaps in the subject area covered by this chapter?

Although there was an objective added last year that focuses on the prospective characterization of children with reported regression, it is imperative that this objective include intensive evaluations of infants and toddlers during the reported timeframe of regression. These evaluations must include detailed historical data, extensive physical exams, brain imaging, and laboratory parameters that elucidate the function of a wide range of metabolic, immunologic, and toxicologic parameters in an effort to understand the mechanisms and responsible agents driving these regressions. In addition, many parents have opted to bank cord blood. A secondary research opportunity is to compare cord-blood parameters to those obtained during regression in order to identify what has changed in the child over time, including genetic analysis of both samples in an effort to identify epigenetic alterations, de novo mutations, CNV aberrations, and potential environmental exposures.

Existing databases of phenotype characteristics (behaviors and core deficits) should be expanded to include a list of co-occurring medical differences including CNS, sensory/perceptual, metabolic, immunologic, and gastrointestinal variations found in people with ASD. Attention to metabolic alterations should address detoxification pathways, cell signaling, methylation, apoptosis, growth factors, and porphyrin profiles. There should be a determination of how these characteristics change over time.

Rigorous and independent studies on autism prevalence rates over time and across geographies are needed to determine the extent of the apparent autism epidemic, the role of changes in diagnostic practices, the extent to which environmental factors play a causal role in any increase, and what future services might be needed, given the true increase in autism rates.

Question # 3 - What caused this to happen and can this be prevented?

What has been learned about the issues covered in this chapter in the past year?

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For years parents have reported that their children regressed developmentally and physically after vaccination, and subsequently were given a diagnosis of autism. The Vaccine Injury Compensation Program has compensated 1322 cases on the basis of vaccine-induced brain damage, seizure disorder, acute disseminated encephalomyelitis, and encephalopathy. Many of these cases were also diagnosed with autism after suffering the vaccine injury. Vaccine adverse events temporally related to a diagnosis of autism deserve to be investigated to the fullest extent possible.

It is also concerning that influenza vaccine is now universally recommended for all pregnant women during any trimester. The event of immunization induces an immune response in the mother that can interfere with neuronal growth of the fetal brain. Prominent researchers have questioned this policy, reporting that even if a prenatal immune response occurs only 1% of the time, vaccinating an entire population of pregnant women can affect thousands of children. According to the CDC, pregnant women may receive multiple flu vaccines (due to the addition of the H1N1 vaccine) which contain thimerosal and adjuvants to increase immune response. Unfortunately, clinical trials in pregnant women do not include long-term monitoring of health status or of developmental outcomes in the infants.

A recent study by Hewitson (2010) in infant primates documented accelerated brain growth in those receiving the recommended vaccination schedule from 1999 compared to unvaccinated controls. The vaccinated primates also showed altered maturation of their brains' amygdalas. Both of these findings are documented to also occur in ASD.

Reports of environmental toxicant exposure associated with ASD include metals and chlorinated solvents (Windham, 2006), environmental mercury (Palmer, Adams, 2009 DeSoto & Hitlan, 2010) organophosphates (Eskenazi, 2007) and lead (Lidsky & Schneider 2005). There is also evidence that individuals with ASD respond differently to environmental exposures and may be more vulnerable. Woods (2010) recently documented altered porphyrin profiles associated with metal exposure in 20% of autistic children compared to controls and gene expression in blood was correlated with mercury levels in blood of 2- to 5-year-old boys (Stamova, 2009) and lead (Tian, 2009). A recent study in prairie voles adds support to these findings; low dose ingestion of mercury or cadmium resulted in two hallmark characteristics of autism: social avoidance and greater effects on males. (Curtis, 2010)

These environmental agents need to be added as categories of highest priority for investigation in the short-term objective B and F and long-term objective C. Post mortem brain tissue should be investigated for direct and indirect indications of environmental exposures.

What are the remaining gaps in the subject area covered by this chapter?

Evaluate neurodevelopmental and neuroimmunological outcomes, longitudinal structural and functional imaging of the CNS, and tissue pathology, including gene expression and proteomic profiling, in response to the combined early infant immunization schedule (including prenatal

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exposure to influenza vaccine) in non-human primates.

Additional funding for the National Children's Study is necessary in order to capture detailed medical histories of all infants enrolled for medication and vaccine exposures (both pre-natal and post-natal), including manufacturer and lot number; this should be added to the strategic plan. There should also be an effort to enroll families who choose an alternative vaccine schedule or who, for religious reasons, do not vaccinate in an effort to compare total health outcomes

There is a need to develop mechanism-based biomarkers, using cellular and animal models, in an effort to facilitate assessment of environmental exposures and symptom profiles associated with high-priority environmental pollutants: metals, chlorinated solvents and organophosphates.

The plan must build on promising immune and metabolic system findings in order to more clearly understand the role of immune alterations in ASD, and how these alterations might arise from environmental exposures, both chemical and viral.

The plan must create animal models based on single exposures, multiple exposures, and multiple pre- and postnatal exposures to substances and viruses that ASD children have been exposed to, reflecting the doses to which they were exposed. These animal models should be used to understand genetic susceptibility, pharmacokinetics, mechanisms (including effects at the cellular level and systems level such as GI, immune, and brain), retention and localization of body burden, and response to potential treatments.

Question # 4 - Which Treatments and interventions will help?

What has been learned about the issues covered in this chapter in the past year?

Since 1967 the Autism Research Institute has been collecting parents' ratings of the usefulness of treatments they have tried on their autistic children. Data has been collected from more than 27,000 parents. Parents are asked if the treatment made the child worse (ratings 1-2) had no effect (ratings 3-4) or made better (ratings 5-6). To review these reports please go to <http://www.autism.com/pdf/providers/ParentRatings2009.pdf>

To date, the five top-rated interventions in order of success have been identified as chelation therapy, supplemental methyl B-12, specific carbohydrate diet, food allergy treatment, and melatonin. These interventions should be subjected to intensive investigations to determine their utility in the treatment of ASD.

Clinicians who care for children with autism report a variety of co-occurring medical conditions, including metabolic abnormalities, oxidative stress, mitochondrial dysfunction, body burdens of heavy metals, gastrointestinal dysfunction and pathology (constipation, diarrhea, ulcerative colitis, esophagitis, and malabsorption), dietary allergies, and immune abnormalities as common in this population. They also report that appropriate identification and treatment of these

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underlying medical abnormalities often result in improved behavior and in some instances a loss of ASD diagnoses. Investigations into both the incidence of these co-occurring medical conditions and into best practices for effective treatment represent a critical unmet need and a great opportunity for improving overall health of those with ASD.

When designing clinical trials the tremendous amount of heterogeneity present in those diagnosed with ASD must be taken into consideration. Therefore it is essential not to apply treatments across the broad spectrum, which would tend to dilute results, but instead to identify sub-groups of those who have documented medical histories or laboratory data indicating they might respond favorably to a particular targeted treatment.

In addition, it will be necessary to develop multifaceted treatment modalities (as opposed to single-treatment designs) due to the complexity of the medical co-morbidities that can occur. Treatment of just one condition might not be as successful in improving behavior as the successful treatment of several co-occurring conditions. Clinical trial methodologies must be developed that can accurately assess effectiveness of multiple treatment regimens.

Recent research has documented low levels of cholesterol in a subset of children diagnosed with autism and a clinical trial is now underway regarding supplementation with cholesterol. It has been the experience of clinicians that those with ASD suffer with a wide range of nutritional deficiencies and metabolic abnormalities. Hypocholesterolemia is merely one of numerous metabolic abnormalities frequently found in ASD, and most likely arises from a more upstream pathology. Some clinicians postulate an inability to adequately digest as a consequence of mucosal inflammation and villous destruction resulting in deficiencies of the various enzyme populations residing in the brush border of the villi. Nutritional deficiencies should be fully evaluated in an effort to better understand the underlying pathology (verses symptom resolution) in an effort to determine the most effective treatment regime.

What are the remaining gaps in the subject area covered by this chapter?

Short term goal number two that addresses co-occurring medical conditions in ASD should target conditions arising from altered/impaired immune, metabolic, and gastrointestinal function in those with autism.

Short term goal C involving assessments of safety and efficacy of five widely used interventions should target those reported by parents as being most effective, such as chelation therapy (or therapy aimed at increasing glutathione and promoting detoxification pathways), supplemental methyl B-12, specific carbohydrate diet, food allergy treatment, and melatonin.

Clinical trials should take into consideration heterogeneity and sub-group those with autism based on historical or laboratory data indicating that the child may benefit from the proposed treatment or intervention. Clinical trial methodologies also need to be developed that can accurately assess effectiveness of multiple treatment regimens.

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