safeMinds
Sensible Action For Ending Mercury-Induced Neurological Disorders

Brief: Environment Vs. Genetics

Why The Autism Epidemic Demands a New Approach

Background, Supporting Research and Analysis of Current Research Funding

The current infrastructure for autism research is misallocating funds based on an outdated paradigm that autism is primarily a genetic disorder. In order for meaningful progress to be made towards prevention and treatment, we must identify and investigate the environmental factors which have been implicated throughout the history of autism. ***November, 2011.***

Background: Autism was first described in a paper by Dr. Leo Kanner in 1943, based on a case series of 11 children born in the 1930's. Kanner, the world's leading child psychiatrist at the time, described these individuals as *"so markedly and uniquely different from anything reported so far, that each case merits – and, I hope, will eventually receive – a detailed consideration of its fascinating peculiarities.*" Independently, Hans Asperger described a group of four boys with a similar profile in Germany in 1944. The fact that there were no reliable reports of autism in the literature before this time period is the initial support for environmental causation. Autism was considered extremely rare, with all of the early cases occuring "from birth." Kanner reported a few cases of "regressive" autism beginning in 1955.

During the following decades, autism came to be considered a psychiatric disorder caused by cold, unfeeling parents whose behavior caused their children to withdraw from the world. This belief was debunked in 1964 by Bernard Rimland, PhD who wrote a book, *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*, on the biological basis of autism. He included the observation that identical twins had a high concordance of autism and that, therefore, autism was not the result of bad parenting but must have a genetic component. Dr. Rimland also founded the Autism Research Institute which collected early data on autism cases. ARI made the observation (ARI publications, April 2004) that, prior to 1990, approximately two-thirds of children with autism were autistic from birth and one-third regressed sometime between 12 and 24 months of age. Since the mid-1980s, that trend reversed, and by the late 1990s, two-thirds of autism cases were regressive. A study by EPA researchers using a worldwide composite showed a changepoint year of autistic disorder cumulative incidence of 1988-1989 (McDonald and Paul, 2010). Both of these observations support environmental causation.

The small amount of research on autism causation over the years had revealed a few known environmental risk factors for autism that included congenital rubella syndrome (4.12-7.3% risk of autism, Hwang and Chen, 2010), fetal valproate syndrome (8.9% have autism, Rasalam et al.,2005) or thalidomide embryopathy (4% of cases met autism criteria, Stromland et al.,1994). It was also known that certain genetic disorders had higher rates of autism, such as untreated phenylketonuria (5.71% of cases met autism criteria, Baieli et al.,2003), Fragile X (67% of males and 23% of females with the full mutation met criteria for autism or ASD, Clifford et al.,2007) and tuberous sclerosis (43-86% meet criteria for a PDD, Bolton and Harrison,1997), though these disorders can only account for low single-digit percentages of autism cases.

In the 1980s , several small twin studies showed that the rate of concordance of autism was higher for monozygotic twins than for dizygotic twins (Ritvo et al.,1985, Steffenberg et al.,1989), though neither of them showed a 100% concordance for monozygotic twins. It became accepted that autism was a "highly heritable disorder." As a result, researchers have spent 30 years and millions of dollars looking for the "autism gene." Over the past decade, as no single candidate gene has explained a significant proportion of autism cases, researchers have expanded their scope and now over 30 candidate genes are under investigation. Combined, they may account for 10% of autism cases, but what is often not mentioned is that some of these genes are common in the general population without autism. All of this makes it increasingly likely that environmental factors are the key to autism causation. In fact, a new study published July 4, 2011 in the *Archives of General Psychiatry*, based on 192 twin pairs born in California, showed a much larger environmental component to autism than previously thought. Siblings of autistic children have a 3-14% chance of developing an ASD, but the study found that dizygotic twins (who share the same 50% of DNA as other siblings) had a 35% chance of concordance, which strongly implicates their shared environment. At the same time, the study found that only 70% of monozygotic twin pairs were concordant for autism, much lower than previous estimates and also supporting the importance of environment vs. genetic factors since these pairs shared 100% of their DNA.

While the genetic research has been disappointingly inconsistent, environmental factors which increase autism risk have been reported in multiple investigations. In a study of children of agricultural workers in California, Eskenazi (2007) found that, for every 10-fold increase in the levels of dialkylphosphate (DAP) metabolites, the rates of pervasive developmental disorder (PDD), a form of autism, doubled. Roberts (2007) reported similar findings that ASD risk increased with the poundage of organochlorine pesticides applied and decreased with distance from field sites. Rauh (2006) found that children with high levels of pesticides in their blood were six times more likely to have PDD than children with low levels. In Texas, Palmer and colleagues (2006, 2008) have shown an association with environmental mercury release and overall rates of special education and autism. In California, Windham (2006) found an association between autism and metal concentrations (mercury, cadmium, and nickel) trichloroethylene and possibly solvents (vinyl chloride).

Environmental factors may be pertinent not only to brain development but also to chronic systemic features of at least some subgroups of ASD. An Institute of Medicine (IOM) workshop held in 2007 summarized what is known and what is needed in this field (Forum on Neuroscience and Nervous System Disorders, Institute of Medicine, 2008). During the workshop, it was pointed out that exposure to various levels of environmental toxicants such as metals, solvents, and pesticides is almost universal. Such exposures are known to induce oxidative stress and deplete glutathione, which is a major intracellular antioxidant that plays an important role in elimination of environmental toxicants. Resistance to injury from environmental exposures depends largely on levels of intracellular glutathione (IOM, 2008). There is a growing body of research documenting that individuals with autism are under chronic oxidative stress and have depleted levels of intracellular glutathione making them more vulnerable to environmental toxicants at lower levels of exposure (James, 2009, Sajdel-Sulkowska, 2009, Mostafa, 2010). Such alterations in redox balance can create a perpetual cycle of oxidative stress and cellular damage, but also provides targets for medical interventions.

Finally, one cannot ignore the astronomical increase in autism prevalence in the past few decades. In the early 1980s, autism was estimated to affect between one and four in 10,000 children. Today, autistic spectrum disorders affect one in 110 children or 91 children in 10,000 in the United States. Similar increases have been documented around the world, and a recent study found a rate of one in 38 children with ASD in one Korean city (Kim et al., 2007). Solid epidemiology has shown that only a small percentage of this increase can be attributed to earlier diagnosis, changes in diagnostic criteria or inclusion of milder cases (Hertz-Picciotto and Delwiche, 2009). Since genetics cannot cause an epidemic, that leaves environmental factors as the smoking gun. It is long past time to put our research dollars where they are most likely to bear fruit in terms of prevention and treatment.

Analysis of the Current Autism Causation Research Portfolio

In 2008 and 2009, the Interagency Autism Coordinating Committee produced reports on how total autism research funding was being allocated both publicly and privately. SafeMinds did an analysis of funding allocations for each objective under "Question 3 – What caused this to happen and can it be prevented?". Purely genetic objectives are marked with a **G**, while purely environmental objectives are marked **E**. The other objectives combine genetic and environmental components and cannot be categorized. What is immediately obvious is that genetic research is grossly overfunded even compared to the IACC's own recommendations. It is also obvious that with the exception of two pregnancy studies, the environmental objectives are not being funded appropriately. Lastly, a significant percentage of causation research dollars are being spent each year on research that is not even identified as needed within the IACC objectives. Here are the dollar totals:

2008 – Purely Genetic Research $41,108,802 Purely Environmental Research $12,860,527

3.2 to 1 Genetic to Environmental Ratio

2009 - Purely Genetic Research $63,832,250 Purely Environmental Research $10,425,200

6.1 to 1 Genetic to Environmental Ratio

The newly published twin study suggests that environmental factors account for at least 58% of autism risk while genetics may account for no more than 38% of autism risk. SafeMinds feels strongly that it is imperative that these research funding ratios be reversed. If we ever hope to prevent new cases of autism and treat those already affected, we must spend the limited research dollars as efficiently and scientifically as possible.

2008 Funding - $82, 846,620 (37% of total autism research funding for all areas)
Question 3: What caused this to happen and can it be prevented?

IACC Strategic Plan Objectives	Average Needed $ Per Year	Actual Funding	Percentage of Need Actually Funded
3.1 Initiate studies on at least five environmental factors identified in the recommendations from the 2007 IOM report "Autism and the Environment: Challenges and Opportunities for Research" as potential causes of ASD by 2010. IACC Recommended Budget: $23,600,000 over 2 years.	$11,800,000	$7,600,673	64% **E**
3.2 Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. IACC Recommended Budget: $43,700,000 over 4 years.	$10,925,000	$4,065,392	37% **G**
3.3 Within the highest priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of environmental exposure in biospecimens by 2011.	$1,166,667	$713,227	61% **E**

IACC Recommended Budget: $3,500,000 over 3 years.			
3.4 Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene – environment research by 2011. IACC Recommended Budget: $27,800,000 over 5 years.	$5,560,000	$4,703,867	84%
3.5 Enhance existing case-control studies to enroll broad ethnically diverse populations affected by ASD by 2011. IACC Recommended Budget: $3,300,000 over 5 years.	$660,000	$84,628	12.8%
3.6 Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the pre-and early postnatal period of development by 2015. IACC Recommended Budget: $25,100,000 over 7 years.	$3,585,714	$1,803,628	50% **E**
3.7 Conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014. IACC Recommended Budget: $11,100,000 over 5 years.	$2,220,000	$2,742,999	124% **E**
3.8 Identify genetic risk factors in at least 50% of people with ASD by 2014. IACC Recommended Budget: $33,900,000 over 6 years.	$5,650,000	$37,043,410	656% **G**
3.9 Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including U.S. populations, to collect nested, case-control data on environmental factors during preconception, and during prenatal and early postnatal development, as well as genetic data, that could be pooled (as needed), to analyze targets for potential gene/environment interactions by 2015. IACC Recommended Budget: $44,400,000 over 5 years.	$8,880,000	$17,297,788	195%
Not specific to objectives		**$6,791,008 8.2%**	

2009 Funding – $100,043,216 (32% of total autism research funding for all areas)
Question 3: What caused this to happen and can it be prevented?

IACC Strategic Plan Objectives	Average Needed $ Per Year	Actual Funding	Percentage of Need Actually Funded
3.S.A Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. Studies should investigate factors contributing to phenotypic variation across individuals that share an identified genetic variant and stratify subjects according to behavioral, cognitive, and clinical features. IACC Recommended Budget: $43,700,000 over 4 years.	$10,925,000	$13,926,663	127% **G**
3.S.B Within the highest priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of	$1,166,667	$0	0% **E**

environmental exposure in biospecimens by 2011. IACC Recommended Budget: $3,500,000 over 3 years.			
3.S.C Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene – environment research by 2011. IACC Recommended Budget: $27,800,000 over 5 years.	$5,560,000	$8,033,454	144%
3.S.D Enhance existing case-control studies to enroll racially and ethnically diverse populations affected by ASD by 2011. IACC Recommended Budget: $3,300,000 over 5 years.	$660,000	$103,827	15%
3.S.E Support at least two studies to determine if there are subpopulations that are more susceptible to environmental exposures (e.g., immune challenges related to infections, vaccinations, or underlying autoimmune problems) by 2012. IACC Recommended Budget: $8,000,000 over 2 years.	$4,000,000	$1,739,200	43% **E**
3.S.F Initiate studies on at least 10 environmental factors identified in the recommendations from the 2007 IOM report "Autism and the Environment: Challenges and Opportunities for Research" as potential causes of ASD by 2012. Estimated cost $56,000,000 over 2 years.	$28,000,000	$2,952,960	10.5% **E**
3.L.A Conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014. IACC Recommended Budget: $11,100,000 over 5 years.	$2,220,000	$3,740,812	168% **E**
3.L.B Identify genetic risk factors in at least 50% of people with ASD by 2014. IACC Recommended Budget: $33,900,000 over 6 years.	$5,650,000	$49,905,587	883% **G**
3.L.C Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the pre- and early postnatal period of development by 2015. IACC Recommended Budget: $25,100,000 over 7 years.	$3,585,714	$1,992,228	56% **E**
3.L.D Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including U.S. populations, to collect data on environmental factors during preconception, and during prenatal and early postnatal development, as well as genetic data, that could be pooled (as needed), to analyze targets for potential gene/environment interactions by 2015. IACC Recommended Budget: $44,400,000 over 5 years.	$8,880,000	$9,135,505	102%
3.O Not specific for any objective		**$8,512,980 9%**	