Autism Research - An Unconventional Approach to a Complex Disorder

The school's Center for Children's Environmental Health is the first federally funded center to perform basic and translational science that investigates how exposure to toxic compounds may combine with genetic predisposition to alter brain development and lead to autism, a severe brain disorder. Partners in this novel effort include the U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences and the University of California, Davis, M.I.N.D. Institute.

Environmental aspects of autism –When the Department of Molecular Biosciences and colleagues began investigations a dozen years ago, health professionals rarely mentioned environmental aspects of autism. Today, because of seminal discoveries in veterinary science, the medical community acknowledges that genetics and environmental factors each play an essential part in our understanding of autism causes, prevention and treatment.

"Top Ten Accomplishments in Autism Research"–In 2011 and 2012, the Autism Speaks organization commended the school's research on the list of "top ten research accomplishments." In 2012, no fewer than six scientific papers from UC Davis faculty in the category of "Deeper Understanding of Link between Chemical Pollutants and Autism" were cited as major advances in autism research.

Exposures to flame retardant, antibacterial and related environmental chemicals–In what may be the first study to link genetics and epigenetics with exposure to brominated diphenyl ether (PBDE) flame retardants, school scientists found that mice genetically engineered to be susceptible to autism-like behaviors and exposed to a common flame retardant were less fertile. Mouse offspring were smaller, less sociable and markedly deficient in learning and long-term memory when compared with offspring of normal, unexposed mice. More extensive studies by SVM researchers have identified similar neurotoxic potential with chemically related polychlorinated biphenyls (PCBs) and the widely used antibacterial compound called triclosan.

Strong evidence–Laboratory researchers found that triclosan, commonly used in antibacterial products, can attach itself to "receptor" molecules, termed ryanodine receptors, which are found inside virtually every cell in the body thereby altering their ability to regulate calcium levels. Such dysregulation in calcium dynamics confuses cells and can lead to their abnormal development and function. Some people carry mutations in the genes that encode ryanodine receptors that are likely to make them more vulnerable to the adverse effects of triclosan exposure. The authors state that their findings provide "strong evidence that the chemical is of concern to both human and environmental health."

PCB exposure disrupts brain development –Neurobiologists working with Washington State University colleagues, discovered that exposure to polychlorinated biphenyls-PCBs-leads to an overabundance of dendrites, which disrupts normal neuronal connections in the brain during early brain development. The scientists also helped identify the specific trigger for this cellular chain of events as the ryanodine receptor calcium channel(RyR)-proving that RyR is a necessary component in the pathway that controls dendritic growth. The study suggests that PCB presence may increase the likelihood of autism in children genetically predisposed to the disease.

Mitochondrial defects more common in autistic children–Molecular biologists in the school found that children with autism are far more likely to have deficits in their ability to produce cellular energy, or mitochondrial DNA, than are typically developing children. The defects may influence both the onset and severity of autism. In the groundbreaking study, the researchers learned about multiple abnormalities in autistic individuals:

- Widespread reduced mitochondrial DNA function
- Elevated levels of pyruvate, the raw material that mitochondria transform into cellular energy, suggesting that the mitochondria of autistic children are unable to process pyruvate fast enough to keep up with the demand for energy
- Hydrogen peroxide levels double those of normal children, indicating that cells of autistic children were exposed to higher oxidative stress, which can account for symptoms of autism related to cell damage and delayed brain development
- Higher mitochondrial DNA copy numbers in lymphocytes of half of identified autistic children, suggesting that the mitochondria made extra copies of their own DNA to help assure the presence of some normal genes, even if others were damaged
- Two of the five autistic children had deletions in mitochondrial DNA genes; none of the control children showed deletions

Potential target for autism treatment–Veterinary scientists demonstrated in mice how a single defective gene can disrupt energy use in neurons and cause significant brain changes. The harmful changes can be coupled with the antisocial and prolonged repetitive behaviors of autism. The research offers a potential target for drugs to treat the condition.

The mercury question–Mercury-based vaccine preservatives have been a concern in unraveling the mystery of autism. In the most rigorous examination to date of blood-mercury levels in children with autism, investigators reported in 2009 that typically developing children and children with autism show similar levels of mercury from a variety of sources in their blood streams. The researchers cautioned that, while the study did not examine whether mercury plays a role in causing the disorder, other studies indicate that mercury adversely affects the developing nervous system.

Long-term, multidisciplinary studies–"Childhood Autism Risks from Genetics and the Environment" is a comprehensive epidemiologic study launched by the school in 2003 to identify clues to the origins of autism and early diagnosis. Participants include autistic children between 24 and 60 months of age, children with other developmental disorders, and typically developing individuals.

Extensive "biobank"–"Markers of Autism Risk in Babies-Learning Early Signs" is the first prospective study of pregnant women who have a biological child with autism spectrum disorder. The women undergo intensive evaluations during pregnancy, birth and nursing of their environmental exposures, genetics, immune systems and other risk factors. The new child's development is carefully monitored until age three. School of Veterinary Medicine faculty maintain the "biobank" of samples on which these complex studies are based.

276 collaborative studies–From 2005 through 2012, more than 20 members of the UC Davis veterinary School of Veterinary Medicine, School of Medicine, and College of Agricultural and Environmental Sciences published a remarkable 276 peer-reviewed scientific papers on autism in the top journals in their fields, including *Human Molecular Genetics, Environmental Health Perspectives, Proceedings of the National Academy of Sciences*, and *Journal of the American Medical Association*.

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