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#2918- Environmental Factors in Autism and Steps for Therapy and Recovery

While many aspects of autism remain mysterious, the link to environmental toxins is becoming more obvious and well described. Recent advances in laboratory sciences allow many of the effects of toxins to be measured with simple urine tests. These results help doctors create plans for intervention to improve immune function, deal with food allergies, reduce the burden of lead and mercury in the body, and alleviate oxidative stress. Various genetic vulnerabilities to these environmental agents are being better understood and will be reviewed.

Presenter: *Jeff Bradstreet, MD, FAAFP, ICDRC and Florida Hospital Celebration, Director* - Dr. Bradstreet is the founder of the ICDRC in Florida and serves as the Director of Clinical Programs. His son, Matthew was diagnosed with autism at age 3, but is now fully included in mainstream school. He is a visiting Professor of Pediatrics and Neurosciences Southwest College of Naturopathic Medicine, Phoenix, where he also practices. Dr. Bradstreet serves as an active collaborator on research projects at numerous medical schools and recent published a landmark case controlled study of the levels of mercury in children with autism spectrum disorders. He is a Fellow of the American Academy of Family Physicians.

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For parents and clinicians interested in caring for children with autism, the Defeat Autism Now! have served as an excellent understanding of the complex chemistry, toxicology and immunology of these disorders. Many of the ideas underlying the problems targeted by these interventions were reviewed in an excellent article by Janet Kern, and Anne Jones of the Department of Psychiatry, at the University of Texas Southwestern Medical Center in Dallas, Texas (Journal of Toxicology and Environmental Health, Part B, 9: 485–499, 2006). While autism presents a complex clinical problem for physicians it seems that the approach can now be streamlined for many children. This is possible as a result of advances in the research on biomarkers. And given the most recent data from the US and the UK which reflect 1-2 % of males under 12 may have autism & – a simplified approach is needed for broad application to make it reasonable for mainstream pediatricians and family practitioners. ICDRC has records on about 4000 autistic children which we have evaluated and

treated over the past decade. This provides an extensive clinical experience, and it is very much similar to other practitioners. Obviously this process does not replace a good history and physical and an individual doctor's clinical judgment – it is not medical advice – but a general framework of how I look at this disorder and decide on treatment. Autism disorders generally have abnormalities in these related and overlapping areas: 1) oxidative stress, 2) decreased methylation capacity and limited transsulfation, 3) increased toxic burden – primarily of heavy metals and especially of mercury, 4) immunological dysregulation with a unique inflammatory bowel disease and immune activation of glial cells in the brain, as well as 5) central nervous system hypoperfusion or abnormal regulation of blood supply to the brain. Most children I evaluate have ALL of these happening at the same time. All of these have broad negative influences on development and will impact all of the secondary features of autism: sensory abnormalities, coordination, cognition, mood, general health, sleep and gastrointestinal function. They connect like gears in the child's system and for that reason we need all of them turning in the right direction and properly connected. By necessity of brevity this discussion will only provide an overview of the evaluations and treatments. It is my general belief, that unless all of the underlying major biological disruptions are dealt with simultaneously, the cyclical negative impact of these problems on each other will perpetuate the autism symptoms and delay recovery. Classical thinking regarding autism defines it as a developmental disorder with abnormalities in language, socialization and stereotypical unusual behaviors. Autism spectrum disorders (ASD) are increasingly reported as being both common and linked to various triggers. Two recent studies on prevalence increases concerns over the expansion of this disease, with indications 1 to 2 % of boys may be affected. Both studies confirm previous observations that approximately 4 times as many males are affected as females. However a genetic link to the XY chromosome axis is lacking, implying a likely hormonal vulnerability to certain environmental triggers. Abnormally high levels of androgens have been an inconsistent finding in autism: however, several studies confirm that at least a subset of children can be documented to have elevated testosterone and/or dehydroepiandrosterone (DHEA) levels in some children with ASD. It is also widely recognized as having a degree of gene – environment interaction as recently reviewed by the CHARGE study. Recognition has been growing over the past 30 years that autism spectrum disorders are often associated with abnormal immune function. In 1976, Stubbs first noted the absence of a normal response to rubella vaccination in a group of children with autism. Then in 1977, Stubbs and Crawford went on to demonstrate suppressed responsiveness to in vitro phytohemagglutinin (PHA) stimulation of lymphocyte cultures. Then as early as 1982, Weizman and colleagues demonstrated abnormal cell-mediated immune response to brain tissue in ASD. The understanding of cell-mediated immune dysfunction was expanded by 1986 to including reduced responsiveness in lymphocyte blastogenesis, decreased numbers of T lymphocytes, and an altered ratio of helper to suppressor T cells. Warren next demonstrated reduced natural killer cell activity in ASD affected children. As further evidence regarding immune abnormalities mounted in the neuroimmunopsychiatry literature, Francesetti and colleagues advanced the hypothesis of the role of the immune

system in the pathogenesis of both schizophrenia and infantile autism. By the 1990's the science of immunology was rapidly expanding, being spurred on by the successes of AIDS-related research and large governmental grants. This permitted a more advanced investigation of the neuroimmune aspects of autism. Singh et al first reported in 1991 finding abnormal cytokine levels which indirectly indicated activation of a subpopulation of T cells in autism. The autoimmune aspect of autism was furthered by Warren et al describing abnormalities in T cells compatible with an autoimmune disorder. Scifo et al reported a favorable decrease in autism symptoms directly related to normalization of immune abnormalities following intervention with naltrexone . The treatment resulted in a significant increase of the T-helper-inducers (CD4+CD8-) and a substantial reduction of the T-cytotoxic-suppressor (CD4-CD8+) thereby normalizing the CD4/CD8 ratio. Singh reported increased levels of interferon gamma and interleukin 12 and interpreted these as a further indication of autoimmunity. This autoimmune theory of autism was again reinforced by the observations of increased levels of urinary neopterin and biopterin, which was compatible with cellular immune activation. Adding more weight to this argument were the observations of autoantibodies to brain endothelium by researchers at Washington University in St. Louis. Connolly and associates further defined the association of brain directed autoimmune markers in sera against brain derived neurotrophic factor (BDNF). Recently researchers at the University of Cincinnati found a blood cytokine profile consistent with increased activation of both the TH2 and TH1 arms of the adaptive immune response, with TH-2 predominance, but without the compensatory increase in the regulatory cytokine IL-10. Simultaneous to this backdrop of brain related immune investigations other researchers were studying the link between dietary proteins in autism. Jyonouchi et al observed that children with autism produced an excess of tumor necrosis factor alpha (TNF-alpha) in response to dietary proteins and the bacterial endotoxin lipopolysaccharide (LPS) & . Of further interest in related research, others detected likely cross-reactivity of the wheat derived protein, gliadin, and Purkinje cell peptides. In this the researchers noted an eight amino acid shared sequence which would be more than adequate to trigger immune cross-reactivity and hence autoimmunity. This research would still fall short of a direct mechanism of peripheral activation of the immune system triggering neurodevelopmental disruption, but the immune state was become clearer. As the immune disruptions in autism were being defined, another pathway of immune research reported observations of a distinct inflammatory bowel disease and other gastrointestinal disorders, including abnormal carbohydrate digestion and reflux esophagitis. While this remains an emotionally charged debate in medicine secondary to issues surrounding purported measles mumps and rubella vaccine reactions, the observations of panenteric bowel disease are now well recorded in the medical literature. The gastrointestinal inflammation features of autism are finding greater acceptance by diverse investigators. Descriptions of specific brain immune findings have been assisted by greater access to autism brain tissue banks. With this resource, researchers are looking at details of the immunological changes within the brain. In what appears to be a landmark study, Vargas (2005) observed neuroglial activation and evidence of inflammation in both

children and adults with autism. Their observations were of unquestioned importance and included: marked activation of microglia and astroglia as well as cytokine profiling indicated that macrophage chemoattractant protein (MCP)-1 and transforming growth factor-beta 1, derived from neuroglia, were the most prevalent cytokines in brain tissues. Further the cerebrospinal fluid (CSF) showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1 and interferon gamma. Intriguingly, researchers from the same institution were not able to reproduce similar findings in the CSF in a different population of children in a later study. The original study differed from the later by specifically looking at brain tissue levels of immune activators as well as documenting the histological changes in both microglia and astroglial cells. The first study also histologically documented perivascular neuroglial activation in the brain. This observation is consistent with either astrocytic defense of the blood-brain barrier or autoimmune activation and is concerning in light of the previously mentioned endovascular autoimmunity reported by Connolly (1999). According to the data collected from parents and clinicians on the ARI website (www.autism.com/ari) most of the successful biomedical interventions target the immune system, heavy metal detoxification, food allergies and the methylation transsulfation pathway. These are becoming more accepted and easier to administer to children. General protocols will be reviewed in the course of this presentation.