

Special Issue On AUTISM SPECTRUM DISORDERS

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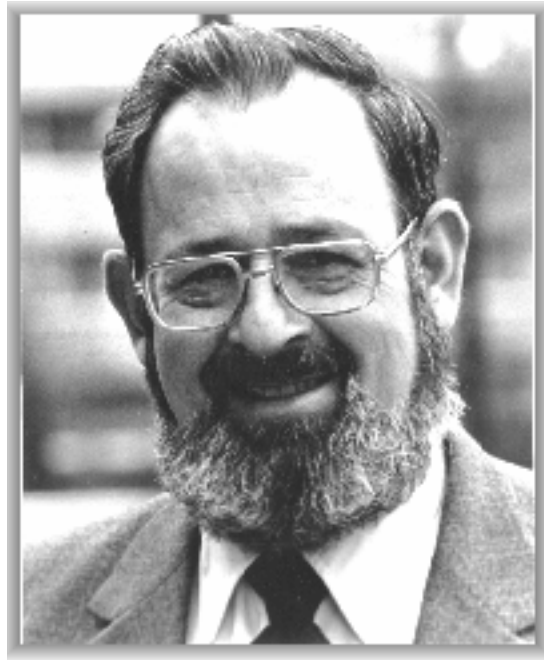
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DEDICATION



Dr. Bernard Rimland
1928-2006

This Special Issue on Autism Spectrum Disorders is dedicated to Dr. Bernard Rimland, who is considered the father of modern autism research. In his book entitled "*Infantile Autism: The Syndrome and its Implications for a Neural Theory of Behavior*" published in 1964, Dr. Rimland argued that autism is a biological disorder, and demolished the then general opinion that autism was the result of child's response to neglect by "refrigerator mothers." In 1965, he founded the National Society for Autistic Children, now known as the Autism Society of America, an organization for parents of children with autism. Dr. Rimland was also the Founder and Director of the Autism Research Institute.

EDITORIAL

Autism spectrum disorders (ASDs) are a group of behaviorally defined neurodevelopmental disorders characterized by deficits in social interaction, impairments in verbal and non-verbal communication, and restricted, stereotyped patterns of behaviors and interests. Recently, the Centers for Disease Control and Prevention have issued an “Autism Alarm” with an estimated prevalence of autism to be 1 in 150 children. Epidemiological studies suggest that more than 1.5 million people in the U.S. are affected with ASDs. Currently, there is no biochemical or genetic marker to support the behavioral diagnosis of autism. At the behavioral level, autism is classified under pervasive developmental disorders (PDDs). PDDs include autism, Asperger’s syndrome (a similar condition but not associated with language delay or general intellectual impairments), Rett’s disorder, childhood disintegrative disorder, and PDD-not otherwise specified (atypical or milder form). Within this autism spectrum, there are variations in the severity, level of cognitive functioning, the presence or absence of associated medical conditions such as seizures or other neurological disorders, and whether or not there is a history of regression from apparent normal development.

Autism is a heterogeneous disorder, both etiologically and phenotypically. While the cause of autism remains elusive, autism is considered a multifactorial disorder that is influenced by genetic, epigenetic and environmental factors as well as increased vulnerability to oxidative stress. Several reports suggest that inflammatory phenomena, immune dysregulation and certain autoimmune risk factors may also contribute to the development and pathogenesis of autism.

This Special Issue on Autism Spectrum Disorders contains 16 reports that include 11 original research articles and 5 review articles. These articles address a variety of topics on autism such as oxidative stress, mitochondrial dysfunction and inflammation in autism, involvement of neurodevelopmental genes in infectious etiology of autism, roles of environmental factors, genetic factors and metals in autism, abnormalities in the sulfur-containing amino acid metabolism in autism, neuropathological abnormalities, brain function and synaptic plasticity in autism, potential target sites for therapeutic intervention in autism, and animal models for autism.

Under normal conditions, a dynamic equilibrium exists between the production of reactive oxygen species (ROS) and the anti-oxidant capacity of the cell. These ROS are highly toxic, and if not removed or neutralized, they react with lipids, proteins and nucleic acids and damage membrane properties and cellular functions. Oxidative stress is known to be associated with premature aging of cells and can lead to inflammation, damaged cell membranes, autoimmunity and cell death. The brain is highly vulnerable to oxidative stress due to its limited antioxidant capacity, higher energy requirement and high amounts of unsaturated lipids and iron. We and other groups have previously reported increased oxidative stress in autism. In this issue on autism, several articles present evidence that supports the concept of oxidative stress in autism. Increased oxidative stress in autism may lead to membrane lipid abnormalities, altered cellular signal transduction, mitochondrial dysfunction, abnormal energy metabolism, excitotoxicity, inflammation and immune dysregulation in autism. These abnormalities may then contribute to abnormal brain development and function resulting in a spectrum of clinical manifestations in autism.

In three independent studies presented in this issue, the authors report increased oxidative damage in brain tissues from autistic subjects. Evans et al. observed increased levels of lipid-derived oxidative protein modifications, i.e., carboxyethylpyrrole and iso[4]levuglandin E₂ – protein adducts, and heme-oxygenase-1 (an inducible antioxidant enzyme) in the autistic brain,

primarily in the white matter. Sajdel-Sulkowska et al. observed elevated levels of 3-nitrotyrosine (a specific marker for oxidative damage to proteins) in the cerebella of subjects with autism. In another study, Lopez-Hurtado and Prieto observed greater density of glial cells, lesser density of neurons and a greater number of lipofuscin (a matrix of oxidized lipid and cross-linked protein)-containing brain cells in language-related cortical areas 22, 39 and 44 in autistic brain, which suggest accelerated neuronal death in association with gliosis and oxidative stress in autism.

Three articles in this issue focus on the role of metals in autism. Metals are important in the biological redox system. Selenium is an essential component of glutathione peroxidase (an antioxidant enzyme) that metabolizes hydrogen peroxide. Copper catalyzes the propagation sequence of lipid peroxidation, and is also an important component of the antioxidant enzyme superoxide dismutase. Lead and mercury can induce oxidative stress by depleting glutathione, the most important antioxidant for detoxification and elimination of environmental toxins. The article by Jory and McGinnis suggests decreased concentration of selenium in red blood cells from autistic subjects, which may lead to increased lipid peroxidation in autism. We have previously reported decreased levels of ceruloplasmin (a copper –transport antioxidant protein) in the serum and of phosphatidylethanolamine (PE) in the erythrocyte membrane from children with autism. In this issue, we report that copper can oxidize and reduce membrane PE levels, and copper-mediated oxidation of PE is higher in lymphoblasts from individuals with autism than those from control subjects. It is suggested that decreased ceruloplasmin levels and abnormal copper metabolism in autism may then contribute to oxidative stress and membrane abnormalities. In another study, Rose et al. examined the frequency of polymorphisms affecting lead and mercury toxicity in children with autism. They report increased frequency of the delta aminolevulinic acid dehydratase (ALAD2) variant gene in autism, which may increase vulnerability to lead toxicity in these children.

Reactive oxygen and nitrogen species (free radicals) are generated endogenously during oxidative metabolism and energy production by mitochondria in the body. Damaged mitochondria may not only produce more oxidants, but mitochondria are also vulnerable to oxidative stress. Certain environmental toxins may act as triggers to damage the structure of mitochondria or impair its functional activity by increasing free radical generation and oxidative stress in autism. Two review articles presented in this Special Issue on Autism suggest mild mitochondrial dysfunction and energy deficiency in a cohort of autistic subjects. Gargus and Imtiaz discuss mild mitochondrial dysfunction and secondary carnitine deficiency in the subset of autistic patients with an inverted duplication of chromosome 15q11-q13. They also describe these abnormalities in rare cases of familial autism associated with sudden infant death syndrome (SIDS) or with abnormalities in cellular calcium homeostasis, such as malignant hyperthermia or cardiac arrhythmia. In another article, Rossignol and Bradstreet review evidence of classical mitochondrial disease or mild mitochondrial dysfunction without the classic features of mitochondrial disease in some individuals with autism. They suggest that treatment of oxidative stress with antioxidants or other nutritional supplements, and hyperbaric oxygen therapy for increasing oxygen delivery to mitochondria may improve mitochondrial function in these autistic subjects.

These and previous reports strongly indicate increased oxidative stress in autism. The oxidative stress and intracellular redox imbalance can be induced or triggered in autism by prenatal or postnatal exposure to certain environmental factors such as heavy metals, viruses, bacterial infections, air pollutants, toxins, valproic acid, thalidomide, terbutaline, retinoic acid or ethanol. Genetic factors can also modulate the threshold for vulnerability to oxidative stress in autism. In this issue, Lathe reviews evidence that the limbic brain (hippocampus, amygdala and functionally related regions) is especially vulnerable to toxic insult. He has argued that early

environmental toxic challenges in combination with genetic susceptibility may explain the rise in prevalence rates of ASD. In another review article, Anderson, Hooker and Herbert provide an overview of the interrelationship of environmental and genetic factors, oxidative stress, immune activation, neuroinflammation, and neuronal dysfunction, leading to behavior deficits in autism.

Increased oxidative damage and/or mitochondrial dysfunction can also lead to inflammation because oxidative stress serves as a major upstream component in the signaling cascade involved in activation of redox-sensitive transcription factors and pro-inflammatory gene expression resulting in an inflammatory response. Recent studies have demonstrated neuroglial and innate neuroimmune system activation in autism, as evidenced by neuroinflammation in brains, reactive astrogliosis, activated microglia and cytokine abnormalities. Furthermore, gastrointestinal symptoms and inflammatory mucosal pathology have been reported in a subset of children with autism. In this issue, Enstrom et al. report that plasma levels of interleukin-23 (IL-23) are decreased while levels of IL-17 are not affected in autism. IL-23 acts as a survival factor for Th-17 cells (T helper cells) that secrete IL-17, tumor necrosis factor- α , and IL-6. In another article, these authors report increased production of brain-derived neurotrophic factor (BDNF) in the plasma and peripheral blood leukocytes following mitogenic stimulation, particularly in early onset autism when compared with regressive autism and typically developing subjects. BDNF plays a critical role for neurodevelopment, neuronal differentiation and neuronal protection. The article by Suh et al. focuses on altered sulfur amino acid (SAA) metabolism in leukocytes from autistic children. SAA metabolism via the transmethylation, transsulfuration and glutathione synthesis pathways produces key metabolites that are essential for supporting immune cell functions and intracellular antioxidant defense. An interference with these pathways can affect proliferation of lymphocytes, synthesis of cytokines and intracellular redox homeostasis, leading to inflammation and oxidative stress.

In this Special Issue on Autism, three potential animal models of autism are described. MacFabe et al. present evidence of neuroinflammation, oxidative stress and behavioral changes in the propionic acid-treated rats. Ming et al. show that exposure of mice to either methylmercury or valproic acid caused behavioral deficits, which could be prevented by pretreatment of mice with antioxidant Vitamin E. These reports further emphasize the role of increased oxidative stress in autism. The article by Fatemi suggests a potential viral-induced autism model in mice. He has reviewed reports from his and other laboratories that viral infections during pregnancy in mice can cause deleterious effects on brain structure and function in the offspring of these mice. Fatemi describes several genes affected by prenatal viral infection in this mouse model that are also associated with autism in humans.

I would like to express my thanks to the Editorial Board Members of this Special Issue on Autism for their assistance in reviewing the manuscripts, and to the authors for contributing the articles. My sincere thanks also to Science Publications for their support in compiling and publishing this issue.

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