Chapter 25

A Whole-Body Systems Approach to ASD

Martha Herbert

AU: Please check?

This should be consistent with chapter 3 where i am listed as Martha R. Herbert

INTRODUCTION

Although autism is defined at the level of behavior, it is becoming clear that there is much more than behavior impairments to autism. For a long time, the focus of autism research has been on genetics and neurobiology. The high heritability factor has supported a strong interest in genetics, while the brain basis of behavior, combined with findings documenting brain differences in autism, has supported a neurobiological focus.

In recent years, a growing amount of attention has been devoted to a range of somatic features in autism. Prominent among these are disturbances in gastrointestinal, immune, and metabolic functioning. Understanding the role these features play in autism is complicated by the fact that they do not present in any one uniform fashion, nor are abnormalities in these domains measurable in every autistic individual. While somatic features have often been classified as "secondary" in comparison to the "core" features of autism, this classification is increasingly challenged by advances in peer-reviewed scientific research, and more generally, in our understanding of gut-brain and immune-brain relationships, and of metabolic influences on brain functioning.

Going forward, it will be important to develop awareness of these whole-body and systems issues in autism, in order both to include them in thorough appreciation and documentation of clinical history, and to more fully appreciate scientific and clinical advances in these autism-relevant domains.

EVIDENCE AND RATIONALE FOR LINKING SOMATIC AND SYSTEMIC FEATURES WITH AUTISM

Evidence for, and considerations relevant to, whole-body and systems features of autism will be organized around the following propositions:

1) Biomedical problems are present in many individuals with ASD.

2) Biomedical problems are often related to each other, and also to neurobehavioral problems in autism.
3) Common underlying mechanisms may be found in various behavioral and biomedical features of ASD.
4) Biomedical problems may begin early in development, and in many cases may even precede the onset of ASD behavioral features.

There is substantial growing support for the first three propositions, but the fourth, while supported by significant anecdotal evidence, has received only limited systematic investigation, which has generally been retrospective and therefore based on medical records and questionnaires, rather than direct and prospective measures. These propositions will be discussed more thoroughly below.

Proposition 1) Biomedical problems are present in many individuals with ASD

Evidence for the common presence of biomedical features in autism can be organized into a set of domains; areas to be highlighted here are gastrointestinal symptoms, disordered sleep, electrophysiological and seizure abnormalities, immune system abnormalities, and metabolic and other laboratory abnormalities.

Gastrointestinal System

Divergent recruitment and ascertainment methodologies employed to assess the prevalence of gastrointestinal problems in ASD have yielded a wide range of prevalence estimates. Several recent publications based on prospective data show that gastrointestinal (GI) problems are more common in autism than in the general population. D'Souza and colleagues (2006) report 80% of their autistic subjects (n=54) had GI complaints, versus 32% of the control group; Valicenti-McDermott and colleagues (2006) report that 70% of their autistic subjects (n=50) had GI complaints, versus 28% of controls. Melmed, Schneider, and Fabes (2000) and Levy et al. (2003) report in the range of 50%—a substantial proportion but somewhat lower than the prior two studies. All of these publications drew their subjects from a general population of autistic subjects, without prior selection for previous complaints of GI problems. These numbers conflict with several retrospective reports which place the incidence of GI problems in autism at a much lower level, of 9–18% (Black, Kaye, and Jick, 2002; Taylor et al., 2002). These lower numbers were the yield of retrospective reviews of the patients' histories as recorded by psychiatrists and general practitioners, who may not have pursued signs and symptoms of gastrointestinal illness as they may present themselves in nonverbal or communicationally impaired autistic individuals who may also have atypical sensory thresholds and pain processing; therefore, these reports are unlikely to be as reliable as prospectively collected data.

A range of gastrointestinal disturbances has been reported in ASD. Horvath et al. (1999) performed endoscopic evaluations of the upper GI tract of 36 autistic children referred to their clinic because of GI complaints. Evaluations included an EGD (esophagogastroduodenoscopy), measurement of small intestine and pancreatic enzymes, biopsy samples, and bacterial and fungal cultures. Reflux esophagitis was found in 69.4% of patients. Chronic stomach inflammation was found in 42%, and inflammation in the duodenum in 67%. Abnormal carbohydrate digestive enzyme activity was found in 58% of patients. (Horvath & Perman, 2002; Jass, 2005). D'Eufemia et al. (1996), using the lactulose-mannitol test, found abnormal intestinal permeability in 43% of their autistic cohort of 40 patients, versus 0% of controls. Horvath and Perman (2002) found abnormal permeability in 76% of their cohort of autistic children with GI symptoms. Abnormal intestinal microflora colonization has been found in several recent studies, including those by Parracho et al. (2005) and Finegold and colleagues (Finegold et al., 2002 Song, Liu, and Finegold, 2004).

80: add semicolon between 2002 and Song

Sleep

Sleep disorders are found in a large majority of children with ASD—up to 80% (Malow, 2004). Atypical sleep architecture is common in ASD, and may include longer sleep latency, more frequent nocturnal awakenings, lower sleep efficiency, increased duration of stage 1 sleep, decreased non-REM sleep and slow-wave sleep, fewer stage 2 EEG sleep spindles, and a lower number of rapid eye movements during REM sleep than in non-autistic individuals (Honomich, Goodlin-Jones, Burnham, Gaylor, and Anders, 2002; Limoges, Mottron, Bolduc, Berthiaume, Godbout, 2005).

Epilepsy

A common accompaniment of autism is epilepsy, developing in approximately one-third of individuals with autism. EEG abnormalities are quite common in ASD, even in individuals who do not have epilepsy, though the proportion of individuals in whom this may be documented has varied widely depending upon study design. Percentages of individuals with autistic disorder or ASD who have epilepsy have ranged from 7.4–46%; part of the variability may be related to the subtype (e.g. presence or absence of additional neurological disorder; Canitano 2007). The potential impact of interictal epileptiform abnormalities is emerging as an area of active research interest. Such non-epileptic EEG abnormalities are more likely to be focal than primarily generalized. Autism may follow infantile spasms, which occur mainly during the first year of life. Continuous spike-wave during slow-wave sleep, which can be associated with language regression, can also be associated with autism, as well as with cognitive decline. Seizures and epilepsy are more common among children with autistic spectrum disorder with language regression, especially those who experience language regression after the age of 2 years, and particularly in autistic children with mental retardation and motor abnormalities (Trevathan, 2004).

Abnormal sensory responsiveness

There is a high prevalence of abnormal sensory processing in autism (see Chapter 11). In one study, out of a sample of 281 children with ASD, 95% exhibited sensory processing dysfunction on the Short Sensory Profile (Tomchek & Dunn 2007). Abnormal sensory responsiveness seems to be pervasive in ASD, affecting all main sensory modalities though not equally in every individual, as well as multimodal sensory processing (Leekam, Nieto, Libby, Wing, Gould, 2007), with severity of sensory processing dysfunction being correlated with autism severity in children, though not in adolescents and adults (Kern et al., 2006).

Autonomic nervous system abnormalities

Autonomic nervous system (ANS) disorders have been documented in autism. Additional autonomic abnormalities that have been reported include abnormal skin conductance, blunted autonomic arousal to social stimuli, and increased tonic electrodermal activity (Zimmerman, Connors, & Pardo, 2006) The frequently encountered sleep disorders, as well as gastrointestinal symptoms such as chronic constipation or diarrhea, may have a major autonomic component. Atypical autonomic response to mental and physical tasks has been reported (Goodwin et al. 2006; Ming et al., 2004, 2005; Toichi & Kamio 2003). Autonomic hyperarousal appears to be a common feature of autism, although hypoarousal has also been seen (Hirstein, Iversen, & Ramachandran, 2001). Abnormal arousal is likely to be a significant exacerbating factor in ASD, with contributors to this problem from both physiological factors (e.g. neurologically based high or low sensitivity to sensory stimuli), and from anxiety responses to ineffective coping with stressors.

57 add space after period

Immune system

Reported immune abnormalities have included autoantibodies (particularly to central nervous system proteins; Ashwood & Van de Water, 2004b), and deficits in immune cell subsets, cytokine abnormalities, impaired responses to viral infections, and prolonged and recurrent infections (Ashwood & Van de Water 2004a), activation of the inflammatory response, (Croonenberghs, Bosmans, Deboutte, Kenis, & Maes, 2002), as well as vulnerability factors, including family history of autoimmune disease (Comi, Zimmerman, Frye, Law, Peeden, 1999; Sweeten, Bowyer, Posey, Halberstadt, McDougle, 2003) and genetic variants associated with autoimmunity (Ashwood & Van de Water, 2004b; Torres, Maciulis, & Odell 2001;). Immune activation has been demonstrated in brain tissue and CSF (Li et al. 2009; Vargas, Nascimbene, Krishnan, Zimmerman, Pardo, 2005), and brain-specific antibodies have been identified in the plasma of subjects with ASD (Cabanlit, Wills, Goines, Ashwood, Van de Water, 2007), and associated with parent report of behavioral regression (Braunschweig et al. 2008).

Metabolic abnormalities

Mitochondrial abnormalities

Features of mitochondrial abnormalities have been found in autism, including elevated lactic acid, (Chugani, Sundram, Behen, Lee, Moore, 1999;

Clark-Taylor & Clark-Taylor, 2004; Correia et al., 2006; Filipek et al. 2003; Filipek, Juranek, Nguyen, Cummings, Gargus, 2004; Oliveira et al., 2005) and reduced free and total carnitine (Filipek et al. 2004). Other features of autism, such as oxidative stress, can lead to mitochondrial damage and impair mitochondrial function (Cadenas & Davies, 2000). Children with diagnosed mitochondrial disorders frequently present with features of autism (Marin-Garcia, Ananthakrishnan, Goldenthal, Filiano, Sarnat, 1999). It is becoming appreciated that metabolic perturbations can be acquired and not only inherited (Filiano, Goldenthal, Mamourian, Hall, Marin-Garcia, 2002; Graf et al., 2000; Poling, Frye, Shoffner, Zimmerman 2006; Zecavati & Spence, 2009).

Inborn errors of metabolism

Autism is associated with a variety of inborn errors of metabolism, and moreover modulation of autism severity in some such settings by treatment has been reviewed (Page, 2000) and further documented. Autistic symptoms are reduced in PKU by a low phenylanlanine diet (Gillberg & Coleman 2000); in hyperuricosuric autism by a low-purine diet with or without allopurinol (Coleman,1989; Gillberg & Coleman, 2000; Page & Moseley, 2002); in patients with low CSF biopterin by biopterin supplementation (Fernell et al. 1997); in some hypocalcinuric autistic patients by calcium supplementation (Coleman, 1989); in some patients with lactic acidemia by thiamine and/or ketogenic diet (Coleman, 1989); in cerebral folate deficiency by folinic acid supplementation (Bauman, 2006; Moretti et al. 2005); and in Smith-Lemli-Opitz syndrome by cholesterol treatments (Aneja & Tierney, 2008; Natowicz 2004).

Proposition 2) Biomedical problems are often related to each other and also to neurobehavioral problems in autism

Interrelationships have been discussed, both in the autism literature and in the peer-reviewed scientific literature more broadly, in multiple combinations of the above domains.

Gastrointestinal-immune

Many of the reported gastrointestinal abnormalities are of an immune character, such as altered mucosal immunity (Ashwood et al. 2003; Ashwood, Anthony, Torrente,. Wakefield, 2004; Furlano et al. 2001; Torrente et al. 2002); atypical immune responses to certain dietary components have also been reported (Jyonouchi, Geng, Ruby, Reddy, Zimmerman-Bier, 2005a, 2005b; Jyonouchi, Sun, & Itokazu, 2002; Murch, 2005; Vojdani et al. 2002). The gastrointestinal tract contains gut-associated lympoid tissue (GALT), which constitutes about 70% of the body's immune system tissue.

CNS, GI and immune systems may all interrelate as well; for example, the neurotransmitter serotonin, which has been documented in various ways as abnormal in autism, is prominent in the intestine and may be modulated by immune factors (Ashwood & Van de Water, 2004a; Barkhudaryan & Dunn, 1999); this type of multisystem involvement can be described for other neurotransmitters as well. An animal model of gut-brain interaction showed that inflammatory bowel disease activates areas of the brain implicated in autism (Welch et al. 2005), and in a fashion consistent with an underlying inflammatory pathophysiology, such as has been documented in postmortem brains of individuals with autism (Vargas, Nascimbene, Krishnan, Zimmerman, Pardo, 2005).

CNS immune activation and systemic inflammation

Systemic inflammation may lead to exacerbation of central nervous system inflammation (Perry, Newman, & Cunningham 2003); in one study, induction of TNF-alpha was shown to peak in serum in one hour and return to normal levels in six hours, and to peak in the liver in nine hours, but to persist in the brain for ten months (Qin, et al. 2007). Increased intestinal permeability has been found even in autistic individuals without gastrointestinal symptoms (D'Eufemia et al. 1996); such permeability has been associated with endotoxemia, which may render the blood-brain barrier more permeable (Kowal et al. 2004), and facilitate the impact of systemic immune alterations on the CNS. The proinflammatory cytokine profiles reported in the CSF and the peripheral blood overlapped, in that both showed MCP-1, but much else did not overlap (Vargas et al., 2005); tumor necrosis factor-alpha has been found in cerebrospinal fluid (Chez, Dowling, Patel, Khanna, Kominsky, 2007).

Immune activation, cytokines and epilepsy

There is an extensive literature about the general role of immune activation, inflammation, and cytokines in modulating seizure thresholds (Vezzani & Granata, 2005; Vezzani, Moneta, Richichi, Perego, De Simoni, 2004;). However, literature linking immune findings with electrophysiological findings in autism is just emerging (Connolly et al., 2006).

Immune system, infection and sleep

Immune-brain and brain-immune signaling are well known to mediate and modulate sleep regulation (Lorton et al. 2006), with cytokines and endotoxins playing a significant role in this mediation. Although both immune dysregulation and disordered sleep are common in autism, their relationship has not been studied.

GI and sleep

Gastrointestinal conditions that may occur in ASD can be associated with pain which, in turn, disrupts sleep. The inflammatory component of GI conditions may contribute through immune modulation of sleep. This has received little systematic study.

GI and oxidative stress

Reports of low-antioxidant and anti-inflammatory nutrient levels in autistic children (Audhya, 2005; Jory, 2005; Yorbik, Sayal, Akay, Akbiyik, & Sohmen, 2005) suggest a potential self-amplifying feedback loop between (possibly inflammation-related) intestinal malabsorption, which exacerbates poor nutritional status, and low levels of nutrients, which exacerbate inflammation, oxidative stress, and gut disease. These problems may reduce systemic metabolic resiliency, which could make the manifestation of problems more likely in other organ systems.

Epilepsy and language impairment

Various epileptic encephalopathies, including Landau-Kleffner syndrome, are associated with autism (Tuchman, 2006). However, it does not appear that language problems in typical autism can be attributed to epilepsy or epileptiform changes (Deonna & Roulet, 2006).

GI and problem behaviors

Pain, poor intake, and malabsorption of nutrients such as essential fatty acids can be associated with behavioral dysregulation (Garland et al. 2007). Inflammatory bowel disease has also been associated with neurobehavioral symptomatology (Solmaz, Kavuk, & Sayar, 2003).

Sleep and neurobehavioral problems

As compared with good sleepers with ASD, poor sleepers with ASD also had higher scores related to affective problems on the Child Behavior Checklist, and more problems with reciprocal social interaction on the ADOS (Malow et al., 2006). Disordered or insufficient sleep can affect cognitive functioning, attention, and information consolidation (Femia & Hasselmo, 2002).

Autonomic disturbance, abnormal arousal, and problem behaviors

Literature suggests that many of the behaviors associated with ASD are related to arousal, as stressful events frequently precipitate the maladaptive behavior problems seen in this population, such as aggression, self-injury, tantrums, and destruction of property (Groden, Cautela, Prince, & Berryman, 1991). Stereotypic behaviors including echolalia, twirling, rocking, flicking, and hand-flapping are also found to increase when this population is exposed to events commonly defined as stressors in the typical population (Howlin, 1998; Hutt & Hutt, 1968).

Proposition 3) Common underlying mechanisms may underlie various behavioral and biomedical features of ASD

A growing body of empirical evidence, and a number of models of autism, identify common pathophysiological features which can result from various combinations of genetic and environmental interactions, and which can manifest in multiple organ systems (Chauhan, Chauhan, & Brown, 2009; Herbert, 2009).

Increased excitation/inhibition ratio

The idea that information-processing problems in autism may be related to an increased ratio of

excitation to inhibition in the central nervous system has been widely advanced (Levitt, 2005; Rubenstein & Merzenich, 2003). This model links diverse findings in autism, including sensory issues, arousal issues, and seizures. It can also result from many different candidate genes, as well as environmental toxins. Intriguingly, such mechanisms may not be restricted to brain. For example, peripheral GABA receptors are widely distributed in multiple systems, and the peripheral GABAergic system is implicated in cardiovascular disease, lung disease, and intestinal and endocrine disorders (Akinci & Schofield, 1999; Gladkevich, Korf, Hakobyan, & Melkonyan, 2006; Veenman & Gavish, 2006).

Disturbed connectivity

Coordination of brain activation appears to be suboptimal in autism (Just et al., 2004; see Chapter 21). Murias and colleagues (2007) have found robust contrasting patterns of over- and underconnectivity at distinct spatial and temporal scales in adult ASD subjects, in the eyes-closed resting state, when compared to controls. This altered pattern of information processing may underlie multiple seemingly distinct behavioral impairments, related to impairments of central coherence (Happé & Frith, 2006) or complex information processing (Williams, Goldstein, & Minshew, 2006). Systemic metabolic and immune dysregulation is plausibly pertinent to disordered synaptic and network functioning (Anderson, Hooker, & Herbert, 2008; Herbert & Anderson, 2008) and long-distance white-matter connectivity (Herbert, 2005).

Immune dysregulation

As discussed above, this may be systemically pervasive in distribution and impact. The intriguing report of transient improvement in core features of autism in the setting of fever (Curran et al., 2007) could be consistent with an immune linkage to behavioral dysregulation.

Methylation

Abnormal levels of metabolites in methionine transmethylation and transsulfuration pathways have been measured in autism (James et al. 2006; Suh, Walsh, McGinnis, Lewis, Ames, 2008). Methylation is critical for regulation of gene expression, neurotransmitter synthesis, and other vital processes. Methylation abnormalities have been implicated in numerous other neurological disorders as well (Mattson & Shea, 2003; Muntjewerff et al., 2003; Pogribna et al., 2001; Schulz, Lindenau, Seyfried, Dichgans, 2000; Serra et al. 2001).

Oxidative stress

A growing body of literature has documented oxidative stress in autism by a variety of measures (Chauhan & Chauhan, 2006; James et al., 2006). Oxidative stress is found in many other neurological and chronic conditions. Redox abnormalities are a final common pathway of myriad genetic and environmental stressors, e.g. methylmercury (Kaur, Aschner, & Syversen, 2006), tributyltin (Liu et al., 2006), cadmium (Yang et al., 2007), and paraquat (Castello, Drechsel, & Patel, 2007), to name just a few, and the cell does not appear to distinguish sharply between different toxicants in its molecular and cellular responses (Li et al., 2007).

Energy metabolism

Mitochondrial metabolism abnormalities and oxidative stress can contribute to altered energy metabolism in ASD, which has been documented (Chugani et al., 1999; Minshew et al., 1993). Network activity in the brain can be highly sensitive to mitochondrial function (Huchzermeyer et al., 2008)

All of the above metabolic abnormalities are consistent with the idea that the neurological disturbances in autism could be a manifestation of systemic metabolic dysregulation or disruption (Anderson, Hooker, & Herbert 2008; Herbert, 2009; Herbert & Anderson, 2008).

Proposition 4) Biomedical problems may begin early in development, may have developmental trajectories, and in many cases may even precede the onset of ASD behavioral features

This proposition has been investigated through medical record review and other retrospective methods in the some of the at-risk siblings studies performed to date. For example, increased frequency of ear infections, greater use of antibiotics, and more illness-related fevers have been documented (Niehus & Lord,

33 replace the first sentence with
Reduction in the regulatory cytokine transforming growth factor beta 1 has been associated with lower adaptive behaviors and worse behavioral symptoms (Ashwood et al., 2008).

2006), and there were more gastrointestinal symptoms in children with ASD and regression, than in children with ASD and no regression (Richler et al., 2006). Prospective measures of head circumference have demonstrated that rapid head growth during the first year of life decelerates in the second year, at the same time as symptoms worsen (Dawson et al., 2007), while one neuroimaging study supports an increased rate of head growth starting around 12 months of age (Hazlett et al. 2005).

The idea that the pathophysiological accompaniments of autism may themselves undergo development, and may interact significantly with the emergence of behavioral features, is only beginning to be investigated. Studies aimed at elucidating physiological development only become conceivable as a worthwhile endeavor once epigenetics and gene-environment interactions are more thoroughly considered as possible contributors to autism. Careful documentation of physiological and behavioral development in autistic cases may contribute significantly to generating new insights about development and vulnerability in autism.

OPEN QUESTIONS IN CONSIDERING WHOLE BODY AND SYSTEMS FEATURES IN AUTISM

There are a number of questions that will need to be addressed going forward to make sense of the relationship between core behavioral features and somatic or systemic features in autism (Bolton, 2009). These include: 1) determining whether somatic and systemic features are secondary or intrinsic to the autism; 2) investigating the relationship between somatic and systemic features of brain structure and function changes; 3) looking for covariations in somatic and behavioral phenotypic features; 4) assessing whether interventions in one domain or level have an impact at other levels—e.g., whether treating gastrointestinal disease can reduce aggression, or whether treating immune function can improve sleep, sensory processing, or epilepsy; and 5) developing animal models that embody not only brain and behavior but also somatic features (MacFabe et al. 2007; Shultz et al., 2008a, 2008b). Including somatic features in phenotyping may also contribute to identifying meaningful subgroups.

If active pathophysiological processes, such as immune dysregulation, turn out to be contributors to aspects of the behavioral phenotype in autism, this raises a particularly clinically relevant consideration: Are language, communication, and Theory of Mind impairments intrinsic static deficits, and a manifestations of psychologically based lack of motivation, or do they at least in part derive from a physiologically based inability to mobilize cellular activity that is strong or organized enough to drive these functional systems? Insofar as these behaviors may be influenced by somatic physiological status, this raises the possibility that the core "impairments" we see in autism may be the effects at the behavioral level of a pathophysiology based *obstruction* of a capacity that is potentially still at least partly present.

To the extent that somatic and systemic features in autism are recognized and considered as worthy of documentation, investigation, and reflection, ongoing research and clinical experience may yield interesting insights into the above questions, and hopefully also an expanded and more comprehensive set of interventions, which will take these dimensions of autism more systematically into account.

61 add comma at end and add the phrase rather than an intrinsic and irretrievable impairment

68 change ...these dimensions... to ...these whole-body dimensions...

References

Akinci, M. K., & Schofield, P. R. (1999). Widespread expression of GABA (A) receptor subunits in peripheral tissues. *Neurosci Res*, 35(2), 145–153.

Anderson, M. P., Hooker, B. S., & Herbert, M. R. (2008). Bridging from cells to cognition in autism pathophysiology: Biological pathways to defective brain function and plasticity. *American Journal of Biochemistry and Biotechnology*, *4*(2), 167–176.

Aneja, A., & Tierney, E. (2008). Cholesterol deficit in autism: Insights from Smith-Lemli-Opitz syndrome. In A. Zimmerman (Ed.), *Autism: Current theories and evidence* (pp. 69–79). Totowa, NJ: Humana Press.

Ashwood, P., Anthony, A. Pellicer, A., Torrente, F., Walker-Smith, J. A., & Wakefield, A. J. (2003). Intestinal lymphocyte populations in children with regressive autism: Evidence for extensive mucosal immunopathology. *J Clin Immunol*, 23(6), 504–517.

Ashwood, P., Anthony, A., Torrente, F., & Wakefield, A. J. (2004). Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: Mucosal immune activation and reduced counter regulatory interleukin-10. *J Clin Immunol*, *24*(6), 664–673.

Ashwood, P., & Van de Water, J. (2004a) A review of autism and the immune response. *Clin Dev Immunol*, *11*(2), 165–174.

Ashwood, P., & Van de Water, J. (2004b) Is autism an autoimmune disease? *Autoimmun Rev*, 3(7–8), 557–562.

Add the following citation to the references: Ashwood P, Enstrom A, Krakowiak P, Hertz-Picciotto I, Hansen RL, Croen LA, Ozonoff S, Pessah IN, and Van de Water J. 2008. Decreased transforming growth factor beta1 in autism: a potential link between immune dysregulation and impairment in clinical behavioral outcomes. *J Neuroimmunol.* 204, no. 1-2: 149-53.

5-6 delete the capitalized comment and put the word (abstract) in parentheses after 3 and before the period (with a space between the 3 and the opening parenthesis)

Audhya, T. (2005) Nutrients, toxins, enzymes and oxidative biomarkers in children with autism. *Oxidative stress in autism symposium, New York State Institute for BasicRresearch in Developmental Disabilities, Staten Island* NY, p 3. THIS IS AN ABSTRACT FROM A CONFERENCE.

Barkhudaryan, N., & Dunn, A. J. (1999). Molecular mechanisms of actions of interleukin-6 on the brain, with special reference to serotonin and the hypothalamo-pituitary-adrenocortical axis. *Neurochem Res*, *24*(9), 1169–1180.

Bauman, M. (2006). Beyond behavior—Biomedical diagnoses in autism spectrum disorders. *Autism Advocate*, *45*(5), 27–29.

Black, C., Kaye, J. A., & Jick, H. (2002). Relation of childhood gastrointestinal disorders to autism: Nested case-control study using data from the UK General Practice Research Database. *BMJ*, *325*(7361), 419–421.

Bolton, P. F. (2009). Medical conditions in autism spectrum disorders. *J Neurodevelop Disord*, *1*, 102–113.

Braunschweig, D., Ashwood, P., Krakowiak, P. Hertz-Picciotto, I., Hansen, R., Croen, L. A.,… Van de Water, J. (2008). Autism: Maternally derived antibodies specific for fetal brain proteins. *Neurotoxicology*, *29*(2), 226–231.

Cabanlit, M., Wills, S., Goines, P. Ashwood, P., & Van de Water, J. (2007). Brain-specific autoantibodies in the plasma of subjects with autistic spectrum disorder. *Ann N Y Acad Sci*, *1107*, 92–103.

Cadenas, E., & Davies, K. J. (2000). Mitochondrial free radical generation, oxidative stress, and aging. *Free Radic Biol Med*, *29*(3–4), 222–230.

Canitano, R. (2007). Epilepsy in autism spectrum disorders. *Eur Child Adolesc Psychiatry*, *16*(1), 61–66.

Castello, P. R., Drechsel, D. A., & Patel, M. (2007). Mitochondria are a major source of paraquat-induced reactive oxygen species production in the brain. *J Biol Chem*, 282(19), 14186–14193.

Chauhan, A., & Chauhan, V. (2006). Oxidative stress in autism. *Pathophysiology*, *13*(3), 171–181.

Chauhan, A., Chauhan, V. & Brown, T. (2009). *Autism: Oxidative stress, inflammation and immune abnormalities*. Boca Raton, FL: Taylor & Francis/CRC Press.

Chez, M. G., Dowling, T., Patel, P. B., Khanna, P., & Kominsky, M. (2007). Elevation of tumor necrosis factor-alpha in cerebrospinal fluid of autistic children. *Pediatr Neurol*, 36(6), 361–365.

Chugani, D. C., Sundram, B. S., Behen, M., Lee, M. L., & Moore, G. J. (1999). Evidence of altered energy metabolism in autistic children. *Prog Neuropsychopharmacol Biol Psychiatry*, *23*(4), 635–641.

Clark-Taylor, T., & Clark-Taylor, B. E. (2004). Is autism a disorder of fatty acid metabolism? Possible dysfunction of mitochondrial beta-oxidation by long chain acyl-CoA dehydrogenase. *Med Hypotheses*, 62(6), 970–975.

Coleman, N. (1989). Autism: Nondrug biological treatments. In C. Gillberg (Ed.), *Diagnosis and treatment of autism* (pp. 219–235). New York: Plenum Press.

Comi, A. M., Zimmerman, A. W., Frye, V. H., Law, P. A., & Peeden, J. N. (1999). Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *Journal of Child Neurology*, *14*(6), 388–394.

Connolly, A. M., Chez, M., Streif, E. M., Keeling, R. M., Golumbek, P. T., Kwon, J. M… . Deuel, R. M. (2006). Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. *Biol Psychiatry*, 59(4), 354–363.

Correia, C., Coutinho, A. M. Diogo, L., Grazina, M., Marques, C., Miguel, T… . Vicente, A. M. (2006). Brief report: High frequency of biochemical markers for mitochondrial dysfunction in autism: No association with the mitochondrial aspartate/glutamate carrier SLC25A12 gene. *J Autism Dev Disord*, *36*(8), 1137–1140.

Croonenberghs, J., Bosmans, E., Deboutte, D., Kenis, G., & Maes, M. (2002). Activation of the inflammatory response system in autism. *Neuropsychobiology*, *45*(1), 1–6.

Curran, L. K., Newschaffer, C. J., Lee, L. C., Crawford, S. O., Johnston, M. V., & Zimmerman, A. W. (2007). Behaviors associated with fever in children with autism spectrum disorders. *Pediatrics*, *120*(6), e1386–1392.

D'Eufemia, P., Celli, M., Finocchiaro, R., Pacifico, L. Viozzi, L., Zaccagnini, M., Cardi, E., & Giardini, O. (1996). Abnormal intestinal permeability in children with autism. *Acta Paediatr*, 85(9), 1076–1079.

D'Souza, Y., Fombonne, E., & Ward, B. J. (2006). No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder. *Pediatrics*, *118*(4), 1664–1675.

Dawson, G., Munson, J., Webb, S. J., Nalty, T., Abbott, R., & Toth, K. (2007). Rate of head growth decelerates and symptoms worsen in the second year of life in autism. *Biol Psychiatry*, *61*(4), 458–464.

Deonna, T., & Roulet, E. (2006). Autistic spectrum disorder: Evaluating a possible contributing or causal role of epilepsy. *Epilepsia*, *47*(Suppl 2), 79–82.

Femia, L. A., & Hasselmo, M. E. (2002). Is autism partly a consolidation disorder? *Behav Cogn Neurosci Rev*, *1*(4), 251–263.

Fernell, E., Watanabe, Y., Adolfsson, I., Tani, Y., Bergstrom, M., Hartvig, P… . Langstrom, B. (1997). Possible effects of tetrahydrobiopterin treatment in six children with autism—Clinical and positron emission tomography data: A pilot study. *Dev Med Child Neurol*, 39(5), 313–318.

Filiano, J. J., Goldenthal, M. J., Mamourian, A. C., Hall, C. C., & Marin-Garcia, J. (2002). Mitochondrial DNA depletion in Leigh syndrome. *Pediatr Neurol*, *26*(3), 239–242.

Filipek, P. A., Juranek, J., Nguyen, M. T., Cummings, C., & Gargus, J. J. (2004). Relative carnitine deficiency in autism. *J Autism Dev Disord*, *34*(6), 615–623.

Filipek, P. A., Juranek, J., Smith, M., Mays, L. Z., Ramos, E. R., Bocian, M… . Gargus, J. J.(2003). Mitochondrial dysfunction in autistic patients with 15q inverted duplication. *Ann Neurol*, *53*(6), 801–804.

Finegold, S. M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M. L., Bolte, E… . Kaul, A. (2002). Gastrointestinal microflora studies in late-onset autism. *Clin Infect Dis*, *35*(Suppl 1), S6–S16.

Furlano, R. I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M. A… .Murch, S. H. (2001). Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J Pediatr*, *138*(3), 366–372.

Garland, M. R., Hallahan, B., McNamara, M., Carney, P. A., Grimes, H., Hibbeln, J. R… . Conroy, R. M. (2007). Lipids and essential fatty acids in patients presenting with self-harm. *Br J Psychiatry*, *190*, 112–117.

Gillberg, C., & Coleman, M. (2000). *The biology of the autistic syndromes (Clinics in developmental medicine)*.Cambridge: Cambridge University Press.

Gladkevich, A., Korf, J., Hakobyan, V. P., & Melkonyan, K. V. (2006). The peripheral GABAergic system as a target in endocrine disorders. *Auton Neurosci*, *124*(1–2), 1–8.

Goodwin, M. S., Groden, J., Velicer, W. F., Lipsitt, L. P., Baron, M. G., Hofmann, S. G., & Groden, G. (2006). Cardiovascular arousal in individuals with autism. *Focus on Autism and Other Developmental Disabilities*, *21*(2), 100–123.

Graf, W. D., Marin-Garcia, J., Gao, H. G., Pizzo, S., Naviaux, R. K., Markusic, D… . Haas, R. H. (2000). Autism associated with the mitochondrial DNA G8363A transfer RNA (Lys) mutation. *J Child Neurol*, *15*(6), 357–361.

Groden, J., Cautela, J., Prince, S., & Berryman, J. (1991). The impact of stress and anxiety on individuals with autism and developmental disabilities. In E. Schopler & G. Mesibov (Eds.), *Behavioral issues in autism* (pp. 178–190). New York: Plenum Press.

Happé, F., & Frith, U. (2006). The weak coherence account, detail-focused cognitive style in autism spectrum disorders. *J Autism Dev Disord*, *36*(1), 5–25.

Hazlett, H. C., Poe, M., Gerig, G., Smith, R. G., Provenzale, J., Ross, A… . Piven, J. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. *Arch Gen Psychiatry*, *62*(12), 1366–1376.

Herbert, M. R. (2005). Large brains in autism: The challenge of pervasive abnormality. *Neuroscientist*, *11*(5), 417–440.

Herbert, M. R. (2009). Autism: The centrality of active pathophysiology and the shift from static to chronic dynamic encephalopathy. In A. Chauhan, V. Chauhan, & T. Brown (Eds.), *Autism, oxidative stress, inflammation and immune abnormalities* (pp. 343–387). Boca Raton, FL: Taylor & Francis/CRC Press.

Herbert, M. R., & Anderson, M. P. (2008). An expanding spectrum of autism models: From fixed developmental defects to reversible functional impairments. In A. Zimmerman (Ed.), *Autism: Current theories and evidence* (pp. 429–463). Totowa, NJ: Humana Press.

Hirstein, W., Iversen, P., & Ramachandran, V. S. (2001). Autonomic responses of autistic children to people and objects. *Proc R Soc Lond B Biol Sci*, *268*(1479), 1883–1888.

Honomich, R., Goodlin-Jones, B., Burnham, M., Gaylor, E., & Anders, T. (2002). Sleep patterns of children with pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 32, 553–561.

Horvath, K., Papadimitriou, J. C., Rabsztyn, A., Drachenberg, C., & Tildon, J. T. (1999). Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr*, *135*(5), 559–563.

Horvath, K., & Perman, J. A. (2002). Autistic disorder and gastrointestinal disease. *Curr Opin Pediatr*, *14*(5), 583–587.

Howlin, P. (1998). *Children with autism and Asperger syndrome: A guide for practitioners and carers*. Chichester, UK: Wiley.

Huchzermeyer, C., Albus, K., Gabriel, H. J., Otahal, J., Taubenberger, N., Heinemann, U… . Kann, O. (2008). Gamma oscillations and spontaneous network activity in the hippocampus are highly sensitive to decreases in pO2 and concomitant changes in mitochondrial redox state. *J Neurosci*, *28*(5), 1153–1162.

Hutt, S. J., & Hutt, C. (1968). Stereotypy, arousal and autism. *Hum Dev*, *11*(4), 277–286.

James, S. J., Melnyk, S., Jernigan, S., Cleves, M. A., Halsted, C. H., Wong, D. H… . Gaylor, D. W. (2006). Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. *Am J Med Genet B Neuropsychiatr Genet*, *141*(8), 947–956.

Jass, J. R. (2005). The intestinal lesion of autistic spectrum disorder. *Eur J Gastroenterol Hepatol*, *17*(8), 821–822.

Jory, J. (2005). Oxidative stress in autism, A role for zinc. *Oxidative Stress in Autism Symposium, New York State Institute for Basic Research in Developmental Disabilities*, Staten Island NY, p. 2. THIS IS AN ABSTRACT FROM A CONFERENCE.

Just, M. A., Cherkassky, V. L. Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain*, *127*(Pt. 8), 1811–1821.

112-113 delete the capitalized comment and put the word (abstract) in parentheses after 2 and before the period (with a space between the 2 and the opening parenthesis)

Jyonouchi, H., Geng, L., Ruby, A., Reddy, C., & Zimmerman-Bier, B. (2005a). Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. *J Pediatr*, *146*(5), 605–610.

Jyonouchi, H., Geng, L., Ruby, A., & Zimmerman-Bier, B. (2005b). Dysregulated innate immune responses in young children with autism spectrum disorders, their relationship to gastrointestinal symptoms and dietary intervention. *Neuropsychobiology*, *51*(2), 77–85.

Jyonouchi, H., Sun, S., & Itokazu, N. (2002). Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. *Neuropsychobiology*, *46*(2), 76–84.

Kaur, P., Aschner, M., & Syversen, T. (2006). Glutathione modulation influences methyl mercury induced neurotoxicity in primary cell cultures of neurons and astrocytes. *Neurotoxicology*, *27*(4), 492–500.

Kern, J. K., Trivedi, M. H., Garver, C. R., Grannemann, B. D., Andrews, A. A., Savla, J. S… . Schroeder, J. L. (2006). The pattern of sensory processing abnormalities in autism. *Autism*, *10*(5), 480–494.

Kowal, C., DeGiorgio, L. A., Nakaoka, T., Hetherington, H., Huerta, P. T., Diamond, B., & Volpe, B. T. (2004). Cognition and immunity: Antibody impairs memory. *Immunity*, *21*(2), 179–188.

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord*, *37*(5), 894–910.

Levitt, P. (2005). Disruption of interneuron development. *Epilepsia*, *46 Suppl 7*, 22–28.

Levy, S. E., Souders, M. C., Wray, J., Jawad, A. F., Gallagher, P. R., Coplan, J… . Mulberg, A. E. (2003). Children with autistic spectrum disorders. I, comparison of placebo and single dose of human synthetic secretin. *Arch Dis Child*, *88*(8), 731–736.

Li, X., Chauhan, A., Sheikh, A. M., Patil, S., Chauhan, V., Li, X. M… . Malik, M. (2009). Elevated immune response in the brain of autistic patients. *J Neuroimmunol*, *207*, 111–116.

Li, Z., Dong, T., Proschel, C., & Noble, M. (2007). Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function. *PLoS Biol*, *5*(2), e35.

Limoges, E., Mottron, L., Bolduc, C., Berthiaume, C., & Godbout, R. (2005). Atypical sleep architecture and the autism phenotype. *Brain*, *128*(Pt. 5), 1049–1061.

Liu, H. G., Wang, Y., Lian, L., & Xu, L. H. (2006). Tributyltin induces DNA damage as well as oxidative damage in rats. *Environ Toxicol*, *21*(2), 166–171.

Lorton, D., Lubahn, C. L., Estus, C., Millar, B. A., Carter, J. L., Wood, C. A., & . Bellinger, D. L. (2006). Bidirectional communication between the brain and the immune system: Implications for physiological sleep and disorders with disrupted sleep. *Neuroimmunomodulation*, *13*(5–6), 357–374.

MacFabe, D. F., Cain, D. P., Rodriguez-Capote, K., Franklin, A. E., Hoffman, J. E., Boon, F… . Ossenkopp, K. P. (2007). Neurobiological effects of intraventricular propionic acid in rats: Possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders. *Behav Brain Res*, *176*(1), 149–169.

Malow, B. A. (2004). Sleep disorders, epilepsy, and autism. *Ment Retard Dev Disabil Res Rev*, *10*(2), 122–125.

Malow, B. A., Marzec, M. L., McGrew, S. G., Wang, L., Henderson, L. M., & Stone, W. L. (2006). Characterizing sleep in children with autism spectrum disorders: A multidimensional approach. *Sleep* *29*(12), 1563–1571.

Marin-Garcia, J., Ananthakrishnan, R., Goldenthal, M. J., Filiano, J. J., & Sarnat, H. B. (1999). Skeletal muscle mitochondrial defects in nonspecific neurologic disorders. *Pediatr Neurol*, *21*(2), 538–542.

Mattson, M. P., & Shea, T. B. (2003). Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. *Trends Neurosci*, *26*(3), 137–146.

Melmed, R. D., Schneider, C. K., & Fabes, R. A. 2000. Metabolic markers and gastrointestinal symptoms in children with autism and related disorders. *J Pediatr Gastroenterol Nutr*, *88*, 731–736.

Ming, X., Julu, P. O., Brimacombe, M., Connor, S., & Daniels, M. L. (2005). Reduced cardiac parasympathetic activity in children with autism. *Brain Dev*, *27*(7), 509–516.

Ming, X., Julu, P. O., Wark, J., Apartopoulos, F., & Hansen, S. (2004). Discordant mental and physical efforts in an autistic patient. *Brain Dev*, *26*(8), 519–524.

Minshew, N. J., Goldstein, G., Dombrowski, S. M., Panchalingam, K., & Pettegrew, J. W. (1993). A preliminary 31P MRS study of autism: Evidence for undersynthesis and increased degradation of brain membranes. *Biological Psychiatry*, 33, 762–773.

Moretti, P., Sahoo, T., Hyland, K., Bottiglieri, T., Peters, S., del Gaudio, D… . Scaglia, F. (2005). Cerebral folate deficiency with developmental delay, autism, and response to folinic acid. *Neurology*, *64*(6), 1088–1090.

Muntjewerff, J. W., van der Put, N., Eskes, T., Ellenbroek, B., Steegers, E., Blom, H., & Zitman, F. (2003). Homocysteine metabolism and B-vitamins in schizophrenic patients: Low plasma folate as a possible independent risk factor for schizophrenia. *Psychiatry Res*, *121*(1), 1–9.

Murch, S. (2005). Diet, immunity, and autistic spectrum disorders. *J Pediatr*, *146*(5), 582–584.

Murias, M., Webb, S. J., Greenson, J., & Dawson, G. (2007). Resting state cortical connectivity reflected

in EEG coherence in individuals with autism. *Biol Psychiatry*, *62*(2), 270–273.
Natowicz, M. (2004). Personal communication.
Niehus, R., & Lord, C. (2006). Early medical history of children with autism spectrum disorders. *J Dev Behav Pediatr*, *27*(2 Suppl), S120–127.
Oliveira, G., Diogo, L., Grazina, M., Garcia, P., Ataide, A., Marques, C., Miguel, T., Borges, L., Vicente, A. M., & Oliveira, C. R. (2005). Mitochondrial dysfunction in autism spectrum disorders: A population-based study. *Dev Med Child Neurol*, *47*(3) 185–189.
Page, T. (2000). Metabolic approaches to the treatment of autism spectrum disorders. *J Autism Dev Disord*, *30*(5), 463–469.
Page, T., & Moseley, C. (2002). Metabolic treatment of hyperuricosuric autism. *Prog Neuropsychopharmacol Biol Psychiatry*, *26*(2), 397–400.
Parracho, H. M., Bingham, M. O., Gibson, G. R., & McCartney, A. L. (2005). Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *J Med Microbiol*, *54*(Pt 10), 987–991.
Perry, V. H., Newman, T. A., & Cunningham, C. (2003). The impact of systemic infection on the progression of neurodegenerative disease. *Nat Rev Neurosci*, *4*(2), 103–112.
Pogribna, M., Melnyk, S., Pogribny, I., Chango, A., Yi, P., & James, S. J. (2001). Homocysteine metabolism in children with Down syndrome, in vitro modulation. *Am J Hum Genet*, *69*(1), 88–95.
Poling, J. S., Frye, R. E., Shoffner, J., & Zimmerman, A. W. (2006). Developmental regression and mitochondrial dysfunction in a child with autism. *J Child Neurol*, *21*(2), 170–172.
Qin, L., Wu, X., Block, M. L., Liu, Y., Breese, G. R., Hong, J. S… . Crews, F. T. (2007). Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia*, *55*(5), 453–462.
Richler, J., Luyster, R., Risi, S., Hsu, W. L., Dawson, G., Bernier, R… . Lord, C. (2006). Is there a "regressive phenotype" of autism spectrum disorder associated with the measles-mumps-rubella vaccine? A CPEA study. *J Autism Dev Disord*, *36*, 299–316.
Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism, increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav*, *2*(5), 255–267.
Schulz, J. B., Lindenau, J., Seyfried, J., & Dichgans, J. (2000). Glutathione, oxidative stress and neurodegeneration. *Eur J Biochem*, *26*(16), 4904–4911.
Serra, J. A., Dominguez, R. O., de Lustig, E. S., Guareschi, E. M., Famulari, A. L., Bartolome, E. L., & Marschoff, E. R. (2001). Parkinson's disease is associated with oxidative stress: Comparison of peripheral antioxidant profiles in living Parkinson's, Alzheimer's and vascular dementia patients. *J Neural Transm*, *108*(10), 1135–1148.
Shultz, S. R., Macfabe, D. F., Martin, S., Jackson, J., Taylor, R., Boon, F… . Cain, D. P. (2008a). Intracerebroventricular injections of the enteric bacterial metabolic product propionic acid impair cognition and sensorimotor ability in the Long-Evans rat: Further development of a rodent model of autism. *Behav Brain Res*, *200*, 33–41.
Shultz, S. R., Macfabe, D. F., Ossenkopp, K. P., Scratch, S., Whelan, J., Taylor, R., & Cain, D. P. (2008b). Intracerebroventricular injection of propionic acid, an enteric bacterial metabolic end-product, impairs social behavior in the rat: Implications for an animal model of autism. *Neuropharmacology*, *54*(6), 901–911.
Solmaz, M., Kavuk, I., & Sayar, K. (2003). Psychological factors in the irritable bowel syndrome. *Eur J Med Res*, *8*(12), 549–556.
Song, Y., Liu, C., & Finegold, S. M. (2004). Real-time PCR quantitation of clostridia in feces of autistic children. *Appl Environ Microbiol*, *70*(11), 6459–6465.
Suh, J. H., Walsh, W. J., McGinnis, W. R.,Lewis, A., & Ames, B. N. (2008). Altered sulfur amino acid metabolism in immune cells of children diagnosed with autism. *American Journal of Biotechnology and Biochemistry*, *4*(2), 105–13.
Sweeten, T. L., Bowyer, S. L., Posey, D. J., Halberstadt, G. M., & McDougle., C. J. (2003). Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics*, *112*(5), e420.
Taylor, B., Miller, E., Lingam, R., Andrews, N., Simmons, A., & Stowe, J. (2002). Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: Population study. *BMJ*, *324*(7334), 393–396.
Toichi, M., & Kamio, Y. (2003). Paradoxical autonomic response to mental tasks in autism. *J Autism Dev Disord*, *33*(4), 417–426.
Tomchek, S. D., & Dunn, W. (2007). Sensory processing in children with and without autism: A comparative study using the short sensory profile. *Am J Occup Ther*, *61*(2), 190–200.
Torrente, F., Ashwood, P., Day, R., Machado, N., Furlano, R. I., Anthony, A… . Murch, S. H. (2002). Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Mol Psychiatry*, *7*(4), 375–82, 334.
Torres, A. R., Maciulis, A., & Odell, D. (2001). The association of MHC genes with autism. *Front Biosci*, *6*, D936–43.
Trevathan, E. (2004). Seizures and epilepsy among children with language regression and autistic spectrum disorders. *J Child Neurol*, *19 Suppl 1*, S49–57.
Tuchman, R. (2006). Autism and epilepsy: What has regression got to do with it? *Epilepsy Curr*, *6*(4), 107–11.
Valicenti-McDermott, M., McVicar, K., Rapin, I., Wershil, B. K., Cohen, H., & Shinnar, S. (2006). Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. *J Dev Behav Pediatr*, *27*(2 Suppl), S128–36.

Vargas, D. L., Nascimbene, C., Krishnan, C., Zimmerman, A. W., & Pardo, C. A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol*, 57(1), 67–81.

Veenman, L., & Gavish, M. (2006). The peripheral-type benzodiazepine receptor and the cardiovascular system. Implications for drug development. *Pharmacol Ther*, *110*(3), 503–24.

Vezzani, A., & Granata, T. (2005). Brain inflammation in epilepsy, experimental and clinical evidence. *Epilepsia*, *46*(11), 1724–43.

Vezzani, A., Moneta, D., Richichi, C., Perego, C., & De Simoni, M. G. (2004). Functional role of proinflammatory and anti-inflammatory cytokines in seizures. *Adv Exp Med Biol*, *548*, 123–33.

Vojdani, A., Campbell, A. W., Anyanwu, E., Kashanian, A., Bock, K., & Vojdani, E. (2002). Antibodies to neuron-specific antigens in children with autism: Possible cross-reaction with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus group A. *J Neuroimmunol*, *129*(1–2), 168–77.

Welch, M. G., Welch-Horan, T. B., Anwar, M., Anwar, N., Ludwig, R. J., & Ruggiero, D. A. (2005). Brain effects of chronic IBD in areas abnormal in autism and treatment by single neuropeptides secretin and oxytocin. *J Mol Neurosci*, 25(3), 259–274.

Williams, D. L., Goldstein, G., & Minshew, N. J. (2006). Neuropsychologic functioning in children with autism: Further evidence for disordered complex information-processing. *Child Neuropsychol*, *12*(4–5), 279–98.

Yang, Z., Yang, S., Qian, S. Y., Hong, J. S., Kadiiska, M. B., Tennant, R. W… . Liu, J. (2007). Cadmium-induced toxicity in rat primary mid-brain neuroglia cultures: Role of oxidative stress from microglia. *Toxicol Sci*, 98(2), 488–94.

Yorbik, O., Sayal, A., Akay, C., Akbiyik, D. I., & Sohmen, T. (2005). Investigation of antioxidant enzymes and trace element levels in children with autistic disorder. *Oxidative Stress in Autism Symposium, New York State Institute for Basic Research in Developmental Disabilities, Staten Island* NY, p. 10. THIS IS AN ABSTRACT FROM A CONFERENCE.

Zecavati, N., & Spence, S. J. (2009). Neurometabolic disorders and dysfunction in autism spectrum disorders. *Curr Neurol Neurosci Rep.*, 9(2), 129–36.

Zimmerman, A. W., Connors, S. L., & Pardo, C. A. (2006). Neuroimmunology and neurotransmitters in autism. In R. Tuchman & I. Rapin (Eds.), *Autism: A neurobiological disorder of early brain development* (pp. 141–59). London: Mac Keith Press.

45-46 delete the capitalized comment and put the word (abstract) in parentheses after 10 and before the period (with a space between the 10 and the opening parenthesis)