MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
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Novel Treatments for Autistic Spectrum Disorders

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In no area of developmental pediatric practice is there more controversy regarding the choice of treatment than related to children with autistic spectrum disorders (ASD). Complementary and alternative medical therapies (CAM) are often elected because they are perceived as treating the cause of symptoms rather than the symptoms themselves. CAM used for autism can be divided by proposed mechanism: immune modulation, gastrointestinal, supplements that affect neurotransmitter function, and nonbiologic intervention. Secretin as a therapy for autism is discussed as an example of how a clinical observation rapidly grew to a widespread treatment before well-designed studies demonstrated absence of effect. The plausibility for behavioral effect was not substantiated by clinical studies. CAM used for treatment of autism is examined in terms of rationale, evidence of efficacy, side effects, and additional commentary. Families and clinicians need access to well-designed clinical evidence to assist them in choice of therapies.
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In no area of developmental pediatric practice is there more controversy regarding the choice of treatment than related to children with autistic spectrum disorders (ASD). There are several explanations that may account for this phenomenon. The natural history of the disorder involves regression of social and language skills in up to one-third of children [Tuchman and Rapin, 1997]. Families hope that an external toxic exposure or event could be reversed to allow the child to return to a typical rate of development. There are many anecdotal descriptions of children who once fit diagnostic criteria for autism who have matured or responded to treatment so that they appear to no longer meet diagnostic criteria [Seroussi, 2000; Michelloti et al., 2002]. The phenotypic and developmental profile of children with ASD may vary. Children with ASD may not have characteristic congenital anomalies recognized as dysmorphic or abnormalities on clinical neuroimaging and may have areas of preserved skills. This may be seen as evidence for absence of underlying neurological dysfunction or insult. The lack of identification of a specific biomedical cause accepted by the scientific and medical establishment allows for proliferation of multiple hypotheses that may not be compatible with current scientific understanding of neuroscience. Lastly, conventionally prescribed treatments for ASD address the symptoms of autism, not the underlying causes. Complementary and alternative therapies purport to address eradication of the cause.

Conventional therapies focus on educational or developmental interventions designed to address skill acquisition associated with core deficits of ASD, including communication, social interaction, and play [National Research Council, 2001]. Few of the treatments prescribed in conventional practice have been evaluated using randomized placebo-controlled trials, with adequate sample size to determine effect. Although the literature supports behaviorally based educational interventions [Lovaas, 1987; McEachin et al., 1993], the original case series has been questioned on the basis of the randomization strategy and the validity of the outcome measures at school age [Gresham and MacMillan, 1997]. Reports in the peer-reviewed literature regarding the efficacy of conventional medications and treatments include open label studies in heterogeneous populations using poorly validated or subjective outcome measures. There are few well-designed studies that are adequately powered to support conclusions of efficacy. An example is the Research Units in Pediatric Psychopharmacology (RUPP) trial demonstrating the efficacy of risperidone for treatment of irritability and aggression [McCracken et al., 2002].

"BIOLOGICAL TREATMENTS"

The term "biological treatments" for ASD may be confusing to traditional health care providers. "Biological treatments" or "biomedical treatments" seek to alter physiology or change the underlying processes that result in the symptoms of autism. They are administered by oral, parenteral (injection or intravenous), or topical routes. In common usage this term typically excludes treatment with conventional prescription medications used for symptomatic treatment of behavior or concurrent medical disorders such as seizures. Many comple-

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mentary and alternative medical (CAM) therapies are not "biological" but invoke alterations in physiological processes based on touch, movement, manipulation, and other sensory experiences. A series of treatments has been proposed by a group of practitioners who have joined together as Defeat Autism Now! (DAN!™). This program is described in the website http://www.autismwebsite.com/ari/index.htm. The Autism Research Institute is a nonprofit organization of parents and professionals that supports dissemination of information about causes and treatment of ASD. It has sponsored workshops and conferences and developed a manual that discusses the approaches and provides a listing of practitioners who subscribe to the DAN!™ approach. Some of the interventions suggested by DAN!™ practitioners include nutritional supplements, special diets, avoidance of allergenic foods, treatment of intestinal bacterial/yeast overgrowth, and detoxification of heavy metals. Much of the support for proposed treatments is predicated on subjective data from practitioners. The consensus endorsement includes some treatment strategies that are not currently supported by data published in peer-reviewed literature. This review article will discuss the evidence that supports or refutes these and other CAM treatments.

WHAT WE "KNOW" ABOUT THE ETIOLOGY OF AUTISM

For the purposes of this article, we are including in ASD the diagnoses of Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder–Not Otherwise Specified. Since Rett's Disorder has an identifiable etiology, the mutations at the MECP2 locus [Weaving et al., 2005], and Childhood Disintegrative Disorder is likely to have a different etiology and course, we are not including them in this review. Current conventional science has not identified either the genetic or neurobiologic basis of all of the symptoms of autism.

Research to date indicates that there is a multifactorial genetic component to the disorder [Muhle et al., 2004]. Linkage studies have identified regions on several chromosomes that are likely to contain genes associated with ASD, but no specific region is highly associated with ASD across all studies. Similarly, abnormalities in candidate genes associated with early brain development or neurotransmitter function are not uniformly replicated, which reflects the heterogeneity of the disorder. It is possible that the genetic predisposition alone is not sufficient to result in the symptoms of autism and that one or more environmental factors must be in place for symptoms to be evident. Some of the environmental factors that have been investigated include environmental contaminants [Bertrand et al., 2001] and maternal exposures during gestation [Arndt et al., 2005]. Immune bases for neurological insults leading to autism have been proposed [Krause et al., 2002]. It is plausible that some symptoms of autism may be amenable to interventions that address these areas on a pharmacological or physiological level.

This review will be organized by proposed mechanisms of action including immune modulation, gastrointestinal tract functions, neurotransmitter regulation, and nonbiological treatments. Each section will include a discussion of proposed mechanisms for complementary and alternative therapies for ASD, the evidence supporting each treatment, known or potential side effects, and a commentary. We will start with a discussion of secretin, which is an excellent allegory for careful study of a proposed treatment of autism.

SECRETIN

It is ironic that the intervention for treatment of children with Autistic Spectrum Disorders that has been most carefully studied is an alternative, off-label treatment that gained popularity prior to adequate scientific scrutiny [Volkmar; 1999]. Secretin as a treatment for ASD came into demand after the lay television and print media publicized results of a case series by Horvath et al. [1998]. The report describes three children with autism who underwent diagnostic endoscopy with intravenous secretin infusion. Subsequent resolution of symptoms of autism was reported. Following the publicity, thousands of children with autism received intravenous secretin treatments, resulting in a secretin shortage.

Secretin is a gastrointestinal hormone, which is a member of the family of brain–gut peptides including vasoactive intestinal peptide (VIP), glucagon, growth hormone–releasing hormone, pituitary adenlyate cyclase–activating polypeptide (PACAP), and others [Schutt, 1998]. Its local actions in the gastrointestinal tract have been well described, and, until 1998, it was primarily administered by gastroenterologists for diagnostic purposes during endoscopy to examine pancreatic secretion.

The case report of changes in behavioral or developmental symptoms following secretin administration [Horvath et al., 1998] led to a search for physiological mechanisms of effect. In the ideal situation, the reverse process would be desirable—-understanding the pathophysiologic cause(s) of the core symptoms of autism, and then developing appropriate treatments.

The original case report [Horvath et al., 1998] appeared at the same time as a growing appreciation of the brain–gut interaction, with gut-derived hormones signaling receptors or centers in the brain. Since secretin is a member of the family of brain–gut peptides, perhaps it also acts as a neuropeptide, signaling centers in the brain [Ng et al., 2002; Kern et al., 2004]. A landmark study by Nelson and colleagues [2001] demonstrated differences in levels of VIP, a regulatory molecule in brain development, in neonatal blood of children with autism. However, they did not find similar elevations in PACAP, which is in the same family of hormones. No difference in secretin receptor genes has been identified in people with ASD [Martin et al., 2000].

Studies have shown that, not only is secretin located peripherally (in the gastrointestinal tract), but secretin and secretin receptors are also located centrally [Charlton et al., 1983; Yung et al., 2001; Koves et al., 2002; Nozaki et al., 2002; Welch et al., 2003; Kern et al., 2004; Welch et al., 2004; Yang et al., 2004]. Kern described secretin's potential role as a neuropeptide, with stimulation of receptors in the amygdala. Kern further described secretin as a brain–gut stress regulatory hormone, with impact on GABA levels. Several studies have investigated the location of action of secretin in the central nervous system (CNS). Several studies in rats [Welch et al., 2003; Koves et al., 2004; Kuntz et al., 2004] have described activation and immunoreactivity of multiple areas of the brain with intraventricular secretin injection. Areas of activation included Purkinje cells, central cerebellar nuclei, hippocampus, and amygdala. In addition, Kuntz et al. [2004] and Yung et al. [2001] have described increases in GABA levels upon secretion injection, which supports the hypothesis that secretin acts as a neuropeptide.

An important question would be whether the action of secretin in the brain impacts behaviors related to ASDs or whether the gut-related secretin can cross the blood–brain barrier and have an effect in that manner. Several studies have demonstrated that secretin can cross the blood–brain barrier (in rats) and have uptake in the hypothalamus [Banks et al., 2002] and expression in the central

Table 1. Peer-Reviewed Secretin Studies

Author	Secretin	*N*	Outcome
Owley et al., 1999	P	20	NS
Sandler et al., 1999	HSS	60	NS
Chez et al., 2000	P	25	NS
Dunn-Geier et al., 2000	P	95	NS
Coniglio et al., 2001	P	60	NS
Roberts et al., 2001	P[a]	64	NS
Corbett et al., 2001	P	12	NS
Unis et al., 2002	P or HSS	85	NS
Molloy et al., 2002	HSS	42	NS
Sponheim et al., 2002	HSS[a]	6	NS
Carey et al., 2002	HSS	8	NS
Kern et al., 2002	P	14	NS[b]
		5	#
Honomichl et al., 2002	P	14	NS[c]
	HSS	6	NS[c]
Levy et al., 2003[b]	HSS	61	NS
Repligen, 2004	HSS[a]	132	NS
Total		709	

All studies double blind/placebo controlled. P, porcine secretin; HSS, human synthetic secretin. All doses at 2 CU/kg
[a]multiple dose
[b]Positive response (decreased maladaptive behavior) in subgroup ($N = 5$) with diarrhea
[c]Sleep worse with secretin.

amygdala and area postrema [Yang et al., 2004].

The identification of secretin and secretin receptors in the brain may not be relevant to treatment of symptoms of autism, however. More than a dozen well-designed studies, published in peer-reviewed journals, involving over 700 children, have failed to confirm the treatment effect [Esch and Carr, 2004; Sturmey, 2005] that was initially reported [Horvath et al., 1998]; (Table 1). These studies paid close attention to study design, including standardized methods of diagnosis, well-established and valid outcome measures (e.g., symptoms of autism related to language, attention, maladaptive behaviors, and physiological responses), homogenous populations, and prospective randomized trials with placebo controls; and adequate numbers of patients for statistical analysis. Phase III drug trials by the pharmaceutical company Repligen have also failed to confirm the remediation of symptoms of autism [Repligen, 2004]. When studies did not confirm a therapeutic effect for intravenous secretin, a market was developed for other routes of administration that could be done over the counter without a doctor's assistance. There is a single case report of sublingual administration of secretin [Lamson and Plaza, 2001]. No evidence in the peer-reviewed literature confirms absorption by this route.

Several reports have described the impact of the placebo response among children with autism treated with secretin [Sandler and Bodfish, 2000; Coplan et al., 2003]. Sandler and Bodfish [2000] observed that families chose to continue secretin even after they were notified that their child did not have a treatment response in the blinded study. They note that the effect of attention on reinforcing communication and positive behaviors after an anticipated intervention like secretin infusion may have an independent effect on children's behavior. They discuss the power of positive language and the potential utility of placebo in modern practice. Families participating in a double-blind placebo, crossover trial of human synthetic secretin were unable to accurately guess the sequence of treatment [Coplan et al., 2003] despite significant changes in function in a few children in each group. Further research into how families make decisions regarding treatment choices, how they analyze information available to them, and their reasons and specific expectations of CAM will be important to guide clinicians and researchers in the care of children and families with ASD.

Reports of frequency of gastrointestinal symptoms in children with ASD vary from 18% to 52% [Kuddo and Nelson, 2003], with the most common reported symptoms including diarrhea, gastroesophageal reflux, and food selectivity. A beneficial side effect of secretin in some children appears to be an increase in formed stool. It is unclear what the long-term side effects or allergic response of the body to repeated administration of a foreign substance such as porcine secretin would be.

This treatment has been subjected to be one of the largest series of controlled trials of interventions for any disorder in childhood. The attention paid to determining whether secretin can "cure" autism is unparalleled. The clinical studies were adequately powered, well designed, and did not demonstrate efficacy. Despite this, interest and demand still occurs. On the other hand—-it is appropriate to continue to study the contribution of neuropeptides to the pathophysiology and evolution of the symptoms of autism. We need to move away from looking at secretin as a treatment and continue to investigate neuropeptides as a piece of the puzzle of autism. Other popular but unproven interventions need to be studied with the same scrutiny.

CAM AND THE IMMUNE SYSTEM IN AUTISM

It is possible that immune factors are associated with some cases of autism. This hypothesis is the core of several popular CAM approaches. These approaches are based on the supposition that the symptoms of autism are due to brain damage secondary to immunologic response to infections or autoimmunity, primary immune deficiency, or secondary immune deficiency.

Evidence for Neuroimmune Insult in ASD

Although histological examination of the brains of people with autism do

not typically have evidence of early infection, chronic inflammation, or autoimmune disorders [Bailey et al., 1998], antibodies directed toward endothelial cells, neurofilaments, and myelin basic protein have been reported in children with autism [Pliopys et al., 1989; Singh et al., 1993, 1998; Connolly et al., 1999; Singh et al., 2002; Singh and Jensen, 2003]. Viral infection, or the immune response to viral infection, has been proposed to result in antibody production to neurotransmitter receptors such as serotonin binding sites [Todd and Ciaranello, 1985; Singh et al., 1997]. The possibility of immunoreactivity at serotonin binding sites is controversial [Yuwiler et al., 1992; Cook et al., 1993]. Prenatal exposures that might alter brain development by immunologic mechanisms have also been proposed. Both prenatal and neonatal exposure to novel viruses that do not result in an inflammatory response [Hornig and Lipkin, 2001] and maternal immune response to viral infection *in utero* have been demonstrated to alter brain development in mouse models with resultant behaviors related to social interaction [Shi et al., 2003].

Evidence for General Immune Dysfunction or Autoimmune Dysfunction in ASD

Primary immune deficiencies in children with ASD have been suggested because of reports of increased frequency of otitis media [Konstantareas and Homatidis, 1987], allergies, and gastrointestinal problems. However, Fombonne et al. [2001] did not identify an increased rate of ear infections in children with PDD. Many families report food intolerances and allergies, but it has not been determined whether children with autism have a greater prevalence of true allergic responses using standard testing and definitions [Renzoni et al., 1995; Fombonne et al., 2001]. Antibodies to milk protein have been identified in some children with autism [Vojdani et al., 2002]. Families of children with autism report an increased rate of family members with autoimmune disorders [Sweeten et al., 2003]. This supports Comi et al. [1999], who reported that 46% of the families of children with autism in their study had two or more family members with autoimmune disorders. Micali et al. [2004] could not confirm an association of autism with family members with autoimmune disorders in another sample. The accuracy of parent report and relation to immune disorders in the children with autism will require additional study.

No uniform pattern of laboratory measures of peripheral immune function is consistently reported in children with autism. Reported findings include decreased natural killer cell cytotoxicity [Warren et al., 1987]; alteration in CD +4:CD +8 [Warren et al., 1986; Plioplys et al., 1994]; lower levels of Th1 cells and resultant lower levels of IL2, IFN-gamma, and natural killer cell activity [Gupta et al., 1998]; and decreased tissue necrosis factor alpha [Torres et al., 2001]. Altered immune function might impair the immune response to viral infection. Genetic predisposition to immune dysfunction in people with autism related to expression of *CD4+* remains controversial [Warren et al., 1996; Rogers et al., 1999].

Environmental exposures that alter immune function have also been proposed including (1) immune response directed toward a vaccine that cross reacts with host antigens, (2) host response to a vaccine that would result in production of cytokines and subsequent autoimmune reaction, or (3) components of a vaccine that would be directly toxic to the immune or nervous system. Regarding this last hypothesis, the preservative thimerosal, which was previously present in some multidose vaccines, has been the focus of scrutiny.

Although the evidence for a primary immune deficit in children with autism is not consistent or well developed at this time, several popular CAM therapies implicate immune mechanisms to justify their use and explain potential treatments, which we will describe below.

Dietary Restriction of Known Allergens

If documented food allergy is present, behavioral response to symptoms of discomfort might be related behavioral symptoms of irritability, food refusal, and sleep disturbance. These symptoms may be perceived as negative behaviors. Lucarelli et al. [1995] found one-third of 36 children with autism to have food allergies documented by skin tests. A general behavioral rating scale monitored dietary restriction of the identified food in addition to milk for 8 weeks. Double-blind food challenges after 8 weeks of restriction resulted in behavioral deterioration as measured on a rating scale.

Dietary treatment of symptoms of ASD is not typically based on conventional understanding of food allergy or intolerance, but on the hypothesis of altered neuropeptide availability in the CNS [Shattock et al., 1990; Reichelt et al., 1991].

Intravenous Immunoglobulins (IVIG)

Pooled human immunoglobin has been administered to children with ASD to address generalized and specific immune deficits as noted above. IVIG is the recommended treatment for many immune-mediated disorders and the application to autism was an extension from the success seen with neurological disorders of autoimmune origin such as myasthenia gravis and Guillain Barre Syndrome. Three case series have been published reporting on the experience of IVIG in children with autism. Gupta et al. [1996] published an open trial including 10 children who demonstrated subjective improvement with worsening after discontinuation of infusions. A second case series by Pliopys [1998] included 10 children with autism of whom 5 did not improve and 4 had mild improvement of attention. No parents elected to continue the infusions. The third group to study IVIG did not see improvement in their 7 subjects over 6 months [Del Guidice et al., 1999]. As a derivative of human plasma, IVIG carries a very small but present risk for blood-borne infection. Although rare, side effects include renal tubular acidosis, thromboembolic events, aseptic meningitis, and rash. IVIG has been in short supply and most institutions request that practitioners use this product only for treatment of diseases in which there has been documented benefit [Dalakas, 2004].

Antiviral Agents

Treatment strategies have arisen to target viruses that are suggested causes of autism, chronic fatigue syndrome, Attention Deficit/Hyperactivity Disorder (ADHD), and other chronic disorders. Proponents of the neuroimmune treatment approach acknowledge that the research literature has not yet identified the mechanism or the specific viruses that might be responsible for the neurological symptoms but suggest that clinical practice supports treatment with antiviral agents. No peer-reviewed publications addressing safety or efficacy of treatment of children with ASD with long-term valacyclovir or other antiviral agents were identified. A major concern regarding chronic administration of antiviral agents is bone marrow suppression. Other side effects of these agents include nausea, headache, dizziness, abdominal pain, and depression. Concern has been raised that antibodies to myelin basic pro-

tein may be a nonspecific response to infection and may not reflect specific neural damage related to autism. The safety of antiviral agents used over time has not been established.

Chelation: DMSA, Lipoic Acid, Clay Baths, and Natural Chelating Agents

Since up to one-third of children with autism may present with regression in milestones in the second year of life, families and professionals might suggest association of symptoms of autism with environmental events that are temporally related. With the increase in reported prevalence of ASD over the past 15 years [Barbaresi et al., 2005], associations with environmental exposures that have systematically changed have been proposed. One such association is with thimerosal, which is an ethylmercury derivative used to stabilize killed virus vaccinations packaged in multidose vials. It is reported that mercury exposure shifts cytokine production from Th1 to Th2, which may decrease T cell and natural killer cell activity. Some strains of mice have enhanced genetic susceptibility to the effects of mercury [Hornig et al., 2004]. Live virus vaccines like the trivalent measles–mumps–rubella vaccine do not contain thimerosal. Thimerosal is no longer present in childhood vaccines except for DT and influenza vaccine.

Several studies have examined the relationship of thimerosal-containing vaccines and ASD. Thimerosal was removed from childhood vaccines in Denmark in 1992. This allowed Madsen et al. [2003] to examine the rate of reported autism before and after this change in practice. The rate of diagnosis of autism increased prior to the removal of thimerosal and continued at that trajectory after its removal. Verstraeten et al. [2004] used the Vaccine Safety Datalink to investigate any relationship of thimerosal exposure based on number of immunizations and body weight with developmental disabilities. No consistent associations were identified. Causality could not be implied. Geier and Geier [2002] reported an analysis of the Vaccine Adverse Events Reporting System database set that suggested an increased rate of reported speech delay, mental retardation, and autism after thimerosal-containing vaccine. This type of study does not determine causality. The Institute of Medicine review in 2001 [Stratton et al., 2001] did not endorse an association of thimerosal and autism based on the evidence available. There is genetic variation in the capacity to detoxify mercury as evidenced by data from different strains of mice [Hornig et al., 2004].

Dimercaptosuccinic acid (DMSA) is a commonly used agent in clinical practice for chelation of lead and other heavy metals. Although effective at removing lead from the bloodstream and periphery, follow up studies do not demonstrate resolution of neurodevelopmental sequelae [Dietrich et al., 2004]. By extension, chelating agents like DSMA are used in an attempt to remove mercury that is believed to be sequestered in the tissue after early childhood vaccination in children with autism. There are no peer-reviewed publications regarding efficacy of chelation agents for the treatment of autism that have yet come to press. Natural chelation using mud baths or dietary fiber supplements and augmentation of chelation with antioxidants have not been evaluated in the peer-reviewed literature.

Renal and hepatic toxicity must be monitored with DMSA chelation. In the absence of documented elevation of heavy metal burden, there is no rationale for chelation therapy outside of controlled clinical trials. By extrapolation from the data related to lead poisoning, neurological damage should not be affected by chelation at a later date [Dietrich et al., 2004].

GASTROINTESTINAL TREATMENTS

It is plausible that some children with autism have increased frequency of symptoms related to the gastrointestinal tract, such as diarrhea, constipation, and gastroesophageal reflux (and discomfort) for which the families will seek medical attention. Despite reports of a higher frequency of associated gastrointestinal symptoms [Horvath et al., 1999; Horvath and Perman, 2002], epidemiological data does not support this claim [Black et al., 2002; Kuddo and Nelson, 2003]. Differences in reported frequency may be related to referral bias [Molloy et al., 2002]. Of children seen in tertiary care clinic for ASD, 24% had a history of at least one chronic gastrointestinal symptom.

Potential explanations for gastrointestinal symptoms in children with autism could be related to genetic, embryologic, neurological, or immunologic factors. Early developmental genes implicated in some cases of autism are expressed in both brain and intestine [Ingram et al., 2000]. Increased levels of plasma serotonin are one of the most consistent biological findings in people with autism and their relatives. The source of this serotonin is likely to be platelets, but serotonin is the primary neurotransmitter functioning in the enteric nervous system [Goyal and Hirano, 1996]. Neural control of intestinal transit via the vagal nerve also provides input centrally in a bidirectional fashion [Goyal and Hirano, 1996]. After Wakefield et al. [1998] reported an increased prevalence of lymphonodular hyperplasia in a referral population of children with previously diagnosed pervasive developmental disorder; it was suggested that viral exposure might lead to immune response in the colon, which could alter permeability and produce symptoms of a "leaky gut." D'Eufemia and colleagues [1996] described evidence of gut mucosal damage through abnormal results of an intestinal permeability test compared to controls.

A case series of endoscopic evaluations of children with autism and gastrointestinal symptoms described an increased rate of ileal lymphoid nodular hyperplasia and evidence of colitis [Wakefield, 2002; Ashwood et al., 2003], gastroesophageal reflux, and decreased disaccharidase in the brush border of the small intestine [Horvath et al., 1999]. These observations and the question of lymphonodular hyperplasia have yet to be replicated in other populations with data on dietary and medical history and compared to appropriate controls for described symptoms such as constipation.

Given the observations that relate to gastrointestinal functions and the focus on nutrition and colonic function of many complementary belief systems, as would be expected, many CAM therapies involve diet and methods of altering intestinal function.

Digestive Enzymes

With the assumption of underlying gastrointestinal dysfunction, including malabsorption and incomplete breakdown of ingested proteins (see gluten-free/casein-free diet below), digestive enzymes are used to assist with the digestive process and remove toxic compounds ("exorphins") from the gastrointestinal tract. Brudnak et al. [2002] reports an open clinical trial with a formulated combination of enzymes (EnzymAid™) and probiotic agent (acidophilus) in which 29 of 46 subjects completed the trial. Personal issues, lack of palatability of the preparation, and behavioral or medical side effects ($n = 6$) were cited as reasons for leaving the study. Of note, 40% of the subjects were already consuming a gluten-free/casein-free diet. Outcome measures were ratings by observers who were not blinded to the treatment condition. The authors report

a positive trend for all parameters. Despite the lack of supportive evidence, enzyme aids or digestive enzymes appear to be in frequent use. As noted above, little objective data is available regarding efficacy, and close to 15% of subjects experienced undesired side effects.

Yeast Overgrowth: Probiotics, Antifungal Agents, "Yeast-free Diet"

A hypothesis of cause of symptoms of autism was suggested by Crook [1986] that overgrowth of candida in the intestine might occur secondary to antibiotic use, underlying immune alteration, or secondary to ingestion of processed sugars and other foods that enhance yeast growth. While it is true that antibiotic use may alter intestinal bacterial flora and can lead to diaper area or vaginal infection, there is no evidence that typical antibiotic use leads to intestinal candida infection in individuals with normal immune systems. Candidal overgrowth in the intestines has not been documented [Wakefield et al., 1998; Horvath et al., 1999; Wakefield et al., 2000] by endoscopy. Two brothers with regression of milestones, intermittent ataxia, and symptoms of autism were reported by Shaw et al. [1995]. Possible interpretations included a toxic effect of yeast metabolites, an effect of the yeast on the intestinal membrane causing abnormal absorption of other substances, or an epiphenomenon. No further studies or cases are available in the peer-reviewed literature.

Treatments to minimize yeast overgrowth in the colon include conventional systemic antifungal agents, probiotic agents such as acidophilus and lactobacillus to alter the bacterial flora of the intestine [Garvey, 2002], and dietary modifications to decrease the substrate for yeast overgrowth. No clinical trials to date have been published in the peer-reviewed literature examining these treatments for ASD, although they remain popular. Minimizing processed sugars in the diet is not likely to alter colonic yeast. Chronic use of antifungal agents such as fluconazole requires monitoring for liver toxicity and exfoliative dermatitis. Nystatin is not systemically absorbed but may result in diarrhea. This diarrhea is sometimes interpreted as a "die off' reaction with elimination of yeast from the colon. No known negative side effects of probiotic agents or a "yeast-free" diet are reported. The presence of Krebs cycle intermediates of potentially fungal origin in the urine of some children with autism needs further investigation.

Gluten-free/Casein-free Diet

The gluten-free/casein-free diet is currently one the most commonly used noneducationally or developmentally based treatments for symptoms of autism [Adams et al., 2004]. The popularity of this intervention may be based on the presumption it is a healthy; noninvasive approach and is presented in an optimistic fashion describing the likelihood of rapid response. The rationale for the gluten-free/casein-free diet is based upon the assumption that children with ASD have a "leaky gut" associated with inability to completely break down selected proteins (e.g., gluten and casein), with the resultant systemic absorption of peptide fragments. These gliadinomorphins (from barley, rye, oats, and wheat) and casomorphins (from all dairy products) then act centrally as endogenous opioids. The comparison to an opioid effect with symptoms of autism remain speculative [Reichelt et al., 1990; Shattock et al., 1990; Reichelt et al., 1991; Gilberg, 1995; Shattock and Whitely, 2004] Despite this, the implementation of a diet excluding gluten and casein proteins is widespread, and reports of success are common in the nonmedical literature [Lewis, 1998; Serousi, 2000]. The significance of elevated urinary peptides related to gluten and casein remains controversial [Reichelt et al., 1990; Shattock et al., 1990; Williams and Marshall, 1992; Hunter et al., 2003]. Micali et al. [2004] completed a review of randomized control trials of gluten and/or casein elimination diets. Only one trial met their criteria for review so a metaanalysis could not be completed. This case series [Knivsberg et al., 1995] reported reduction in autistic traits over a 1-year period compared to the prior year. Double-blind placebo-controlled challenge studies are now in progress. In a population in which food selectivity is common, additional dietary restriction may negatively impact nutritional status. Milk is a major source of vitamin D, calcium, and protein in children in the United States, so attention to nutritional status is important. The cost and stress related to maintaining the diet must be considered by families electing this intervention. This treatment may have value in selected populations, for selected symptoms. Existing literature neither supports nor refutes the anecdotal reports in the lay press. In the near future more data will be available to allow for informed decisions regarding implementation of the diet.

Specific Carbohydrate Diet™ (SCD)

This diet is predicated on the assumption that the gastrointestinal dysfunction (abnormal permeability and dysbiosis) experienced by children with ASD (and outlined above for gluten-free/casein-free diet) can be countered by administering a diet that includes carbohydrates of smaller molecular size so that they do not need to be broken down [Gottschall, 2004]. This diet was initially developed for people with celiac disease. In practice, disaccharides and polysaccharides are avoided in preference for monsaccharides. There are no published studies of efficacy for this diet other than the anecdotal reports. Attention to the nutritional sufficiency of this diet is necessary. As in other specialized diets for children with developmental disability or autism, it places additional pressure on families to implement the diet and provides higher expectations and an additional source of guilt if changes are not seen. As with any intervention, families who report improvement with dietary treatments may counter that families might feel guilt if they did not try an intervention that might have symptomatic improvement. This reinforces the need for evidence on which to base treatment decisions.

Antibiotic Therapy

Anecdotal reports of the recognition of symptoms of ASD after antibiotic use led Sandler et al. [2000] to suggest that an alteration in intestinal flora may have precipitated symptoms of autism. When the stools of children with autism were compared to children without autism, colonization with clostridium species were different [Finegold et al., 2002; Song et al., 2004]. The relationship of altered colonic flora and neurological symptoms on the basis of toxins and/or alteration of the integrity of the intestinal lining is suggested.

Oral vancomycin [Sandler et al., 2000] was given in an open label study to 11 children with ASD who had a history of behavioral regression and diarrhea. Outcome parameters included blinded videotape evaluations and nonblinded behavior and communication assessments. Eight of 10 children had significant improvement. Stool samples prior to treatment had fewer *Peptostroptoccal* species than adult controls. Vancomycin provides broad coverage for anaerobic bacteria. Colitis is a known side effect. Widespread use of vancomycin is dis-

couraged to prevent the emergence of resistant strains of bacteria.

SUPPLEMENTS: MODULATION OF CENTRAL NEUROTRANSMITTERS AND NEUROPEPTIDES

The Autism Research Institute surveys parents who contact them regarding their therapeutic choices and impressions. Parent ratings from this questionnaire describe that the most commonly used vitamins are vitamin B6 and magnesium, DMG, (dimethylglycine), and vitamin C [Adams et al., 2004]. This section will concentrate on the theory behind and scientific evidence to support administration of nutritional supplements as a treatment for autism.

Nutritional supplements include vitamins, minerals, and other substances considered to be "natural" and available without a prescription. The proposed basis for improvement of function using vitamins and supplements is the enhancement of neurotransmitter function by increasing availability of substrate or cofactors [Hyman and Levy, 2000] and/or to compensate for presumed biochemical deficits that may cause autism [Pfeiffer et al., 1995]. Evidence for deficits in the body of various endogenous vitamins has been circumstantial and has been extrapolated from fetal abnormalities associated with prenatal deficiencies in the context of genetic predisposition, such as folic acid and neural tube defects [Cabrera et al., 2005]. Certainly, children with autism and selective diets may have dietary insufficiency, but no correlation with etiology has been established [Arnold et al., 2003]. The suggested doses of supplements typically suggested are above the recommended daily allowance and with limited data on long- or short-term side effects. The supplements we shall discuss include those related to neurotransmitter production (vitamin C, folic acid, B6, and magnesium, B12, DMG or dimethylglycine, D-cycloserine, tyrosine, and tryptophan supplementation, L-carnosine, and cyproheptadine), neuropeptides (oxytocin), and immune mediation by second messengers (essential fatty acids).

Vitamin C

Vitamin C has a number of important functions, including as a cofactor in the conversion of tyrosine to dopamine, tryptophan to 5-HT, as an antioxidant, and in regulation of cellular immune function. Vitamin C has limited popularity as a CAM treatment for symptoms of ASD despite a study by Dolske et al. [1993] describing positive results decreasing stereotyped behavior in a 30-week double-blind/ placebo-controlled trial in 18 children. This study has not been replicated. Few side effects are described, except in high doses where there might be gastrointestinal upset (including diarrhea) or potential of kidney stones.

Folic Acid

Folate supplementation typically occurs in the context of a multivitamin. The potential mechanism to address symptoms of autism would include provision of additional substrate as a cofactor in methylation reactions in catecholamine synthesis and metabolism [Fernstrom, 2000]. No clinical studies were available examining efficacy or side effects in children with autism.

B6 and Magnesium

The combination of B6 (pyridoxine) and magnesium was identified as the most commonly used supplement for treatment of autism in a survey of parents contacting the Autism Research Institute [Adams et al., 2004]. Pyridoxine functions as a cofactor in the conversion of dopamine to norepinephrine, and tryptophan to serotonin, thus raising serotonin levels [Bernstein, 1990]. It also plays a role in synthesis of other neurotransmitters, including biogenic amines (dopamine, serotonin, histamine, norepinephrine, and epinephrine) and GABA [Lerner et al., 2002].

A number of clinical trials have been conducted. Unfortunately they have not been at the level of sophistication of the secretin studies. Many of the reports are either surveys or open-label studies [Rimland, 1978; Lelord et al., 1981; Martineau et al., 1981; Lelord et al., 1982; Rimland, 1988] that do not eliminate the possibility of placebo effect. Double-blinded clinical trials of low dose [Tolbert et al., 1993] and high dose B6 [Findling, 1997] did not demonstrate efficacy in improving symptoms of autism in small samples. Pfeiffer et al. [1995] and Nye and Brice [2002] reviewed the literature and concluded that, due to methodological deficits and small sample sizes, no recommendations could be made for this treatment. Although not clinically reported in any of the studies, untoward side effects of pyridoxine excess include peripheral neuropathy. No data are available for a tolerable upper limit of dosage in children (safe doses in adults appear to be under 100–150 mg/day).

B12

It has been suggested that increased oxidative stress is present secondary to metabolic abnormalities in children with autism. Lower plasma concentrations of methionine, *S*-adenosylmethionine, homocysteine, cystathionine, cysteine, and total glutathione were found in 20 children with autism diagnosed on clinical grounds compared to 33 controls without autism. Significantly higher concentrations of adnosine, oxidized glutathione, and *S*-adenosylhomocysteine were identified in the children with autism [James et al., 2004]. The authors suggest that a mechanism for neurodevelopmental harm might be through impaired antioxidant defense that predisposes children with autism to be less able to detoxify mercury and other environmental contaminants.

Based on the possible impairment in capacity for methylation and oxidative stress, James et al. [2004] went on to treat a subset of children with autism with oral folinic acid and subcutaneous B12. They report that this treatment normalizes the laboratory measures drawn at baseline and subjectively improves behaviors associated with autism.

It is unknown whether excess folinic acid has clinical sequelae. Intramuscular B12 is conventionally used to treat people with deficits in intrinsic factor. It is found in animal protein and may need to be supplemented in vegans and people with celiac disease. Symptoms of excess B12 are unknown.

The laboratory findings reported by James et al. [2004] are unlikely to be related to dietary peculiarities, although one of the major sources of methionine in young children is milk. No dietary or medical history is provided on the subjects or controls. Replication and additional clinical trials data are indicated prior to acceptance into widespread practice.

DMG

The next most commonly used supplement as reported by the Autism Research Institute survey was DMG (dimethylgycine). DMG is not technically a vitamin but is sold as a nutritional supplement. It is metabolized in the liver ultimately to glycine, an excitatory neurotransmitter. Additional action as an immune enhancer is suggested, although not confirmed. Two double-blind, placebo-controlled studies [Bolman and Richmond, 1999; Kern et al., 2001] have not demonstrated differences between DMG and placebo. Bolman and Richmond studied 10 males (7 children and 3 adults) and used clinical rating scales without documentation of clinical improvement. Kern and colleagues studied

37 children and noted improvement in behavior in both groups. Few side effects are reported in these studies. One participant exhibited symptoms of hyperactivity, leading to discontinuation of this supplement. Despite the absence of evidence for either safety or efficacy, DMG remains a popular intervention. There are no studies in the peer-reviewed literature related to treatment with the related compound, trimethylglycine.

Tryptophan and Tyrosine Supplementation

The amino acid tryptophan is a precursor of serotonin (5-hydroxytryptophan). Multiple studies have documented differences in serotonin metabolism related to ASD, including abnormal peripheral levels of serotonin [Anderson et al., 1987], serotonergic abnormalities in brain [Chugani, 2004;], serotonin dysregulation in animal models of ASD [Whitaker-Azmitia; 2005], and abnormalities of Serotonin 5-HT_{2A} Receptor or transporter genes [Anderson et al., 2002; Betancur et al., 2002; Veenstra-VanderWeele et al., 2002]. The rationale for dietary treatment implies that supplementation with a natural amino acid would be safer than administering a drug that enhances serotonin release or reuptake inhibition. Depletion of tryptophan has been reported to cause significant deterioration in patients with autism [McDougle et al., 1993; Cook and Leventhal, 1996].

Recently, Croonenberghs and colleagues [2005] described differences in peripheral metabolism of 5-hydroxytryptophan after an oral challenge in 18 adolescent subjects with autism and 20 controls. This study did not examine clinical effects. While this study is intriguing, it is not without concerns about safety. In the past, contamination of commercial tryptophan supplements led to *Eosinophilia myalgia syndrome*, necessitating its recall [Fernstrom, 2000].

Similarly the rationale for tyrosine supplementation is its status as a precursor for catecholamines (dopamine, norepinephrine, and epinephrine). No studies are available to evaluate nutritional manipulation of tyrosine.

Cyproheptadine

Cyproheptadine (Periactin™) is an antihistamine that is a 5-HT2 receptor antagonist with reported antipsychotic activity [Akhondzadeh et al., 2004]. Studies have described elevated blood levels of 5-HT [Ritvo et al., 1970], which is now determined to be associated with increased levels of serotonin in platelets [Mulder et al., 2004; Spivak et al., 2004]. As in other therapeutic innovations of treatment in autism, information obtained from trials of adults with schizophrenia paved the way for trials in autism. Several open clinical trials of ritansin, a selective 5-HT2/1C antagonist; showed promising results in reduction of symptoms [Akhondzadeh, 2004]. A double-blind, placebo-controlled 8-week trial of oral cyproheptadine compared to haloperidol and placebo in 40 children between 3 and 11 years of age with severely disruptive behavioral symptoms was completed. Children who received cyproheptadine and haldol had better outcomes as measured by the Aberrant Behavior Checklist—-Community and the Childhood Autism Rating Scale (CARS). The authors suggested confirmation with a larger population. Side effects noted included sleepiness and increased appetite (which might not be a problem in subsets of children with autism).

This represents an off-label use of an approved medication, taking advantage of actions (e.g., 5-HT antagonism) other than the primary one as an antihistamine. It is possible that the combination of cyproheptadine with an atypical neuroleptic rather than haloperidol might be more effective.

D-Cycloserine

D-cycloserine, an antibiotic that is a partial agonist at the glycine binding site of *N*-methyl-D-aspartate (NMDA) glutamate receptor, has been proposed as a treatment for autism. Several reports have related GABA receptor genes [Martin et al., 2000; Buxbaum et al., 2002] and the GABA system to pathophysiology of autism [Carlsson, 1998; Dhossche et al., 2002]. Earlier studies of adults with schizophrenia [Golf, 1999] demonstrated a decrease in disruptive symptoms with D-cycloserine in combination with a neuroleptic. Posey et al. [2004] published a 2-week single-blind placebo lead-in phase to treatment with three different doses of D-cycloserine. Subjects ($n = 10$) were aged 5–27 years. Outcome measures included the Clinical Global Impression scale and Aberrant Behavior Checklist. On the highest dose, subjects had statistically significant improvement in social withdrawal. Adverse effects reported included motor tics and increased echolalia in two subjects. The authors acknowledge the wide age range, lack of clinician blinding, absence of a control group, and small number of subjects. The order of treatments was not randomized. This is an intriguing idea that might deserve further pursuit, pending documentation of an association between glutaminergic neurotransmission and autism.

Carnosine Supplementation

Supplementation with carnosine, a dipeptide (histadine and alanine), is presumed to act on GABA receptors in the frontal lobe [Chez et al., 2002]. GABA is an inhibitory neurotransmitter in the cerebral cortex. Petroff and colleagues [2001] correlated GABA levels and homocarnosine levels using magnetic resonance imaging. Homocarnosine levels (when GABA and carnosine bind together) were higher in the frontal lobe.

Chez et al. [2002] completed an 8-week open trial of oral supplementation with 800 mg L-carnosine in 31 children. Most subjects either had an abnormal EEG or were also treated with valproate. Outcome measures included parent impression (Clinical Global Impression Scale) and observation or assessment instruments by clinicians. The authors report improvement on a measure of socialization and receptive vocabulary. Improvement in receptive language could have been due to maturation, educational interventions, placebo effect, or improvement in seizure management among other potential confounds that were not addressed in the study design.

Oxytocin Infusion

Oxytocin is a member of a family of neuropeptides (9 amino acids) released from the posterior pituitary gland. The central pathways and actions of oxytocin and vasopressin are well described [Insel, 1999] with important cognitive, behavioral, and social effects. Since oxytocin does not cross the blood–brain barrier, studies of the central effects are based on pharmacological studies of agonists and antagonists. Winslow and Insel [2002] report that mice with a null mutation of the oxytocin gene show social deficits that resolve after administration of oxytocin directly into the amygdala. Increased stereotyped behavior following intracerbroventricular oxytocin administration has also been demonstrated in an animal model [Hollander et al., 2003]. Children with autism have both lower plasma oxytocin levels and atypical oxytocin [Modahl et al. 1998; Green et al., 2001].

Hollander et al. [2003] studied 15 adults with autism, administering parenteral synthetic oxytocin and placebo, with each subject serving as his own control. Outcome measures included a rating scale sensitive to repetitive behaviors. The authors noted a reduction in number and type of repetitive behaviors following oxytocin. This study cannot currently

be generalized to care of children with autism spectrum disorders. It does, however, suggest the need for additional research into mechanisms of core behaviors of autism and the permeability of the blood–brain barrier to exogenous peptides.

Omega-3 Fatty Acids or Polyunsaturated Fatty Acid (PUFA)

Oral supplementation of dietary intake with essential fatty acids has gained popularity for children with a range of developmental differences, including ADHD [Stevens et al., 2003]. The mechanism of action to support supplementation is often unclear; except for presumption of deficiency states. In theory, fatty acids or PUFA have important roles as precursors of second messengers such as prostaglandins, prostacyclins, and leukotrienes [Fernstrom, 2000] and constituents of structural lipids in cellular membranes.

There is little clinical or research evidence to support this practice. Several case reports describe profiles of essential fatty acids in children with autism. A child with autism and abnormal acyl-carnitine levels possibly consistent with LCAD (long-chain acyl-CoA dehydrogenase) deficiency is described [Clark-Taylor and Clark-Taylor, 2004]. The plasma acyl-carnitine levels improved with supplemental carnitine. Johnson and Hollander [2003] describe an 11-year-old boy with autism whose severe behavior difficulties improved following addition of fish oil supplements to his pharmacotherapy. These are all interesting observations of unclear clinical significance at this time.

NONBIOLOGICAL INTERVENTIONS

It certainly is possible to change behaviors and responses through nonbiological means. Early experiences may actually change the underlying neural architecture in the brain. The nonbiological CAM therapies typically cannot be explained by current understanding of brain functions.

Auditory Integration Training (AIT)

Language disorders in children with autism are often complicated by difficulties with auditory perception. Hyperacusis or sound sensitivity is a common symptom in children with ASD and may cause agitation. Auditory Integration Training uses repeat exposure to altered sounds by earphone to "retrain" the ear and central listening mechanism. Because of confounding factors of other varying individual interventions, it has been complicated to assess clinical effect [Rimland and Edelson, 1998]. Studies that include a sham listening procedure to control for the social support aspect have not been able to detect a benefit from AIT in core features of autism or general behavior [Sinha et al., 2004]. It is unknown whether the procedure might have an effect on hyperacusis on behavioral principles or might have benefit on some aspects of behavior in a defined subgroup. The American Academy of Pediatrics does not endorse this therapy at this time [AAP, 1998].

Behavioral Optometry

Many individuals with autism have stereotyped behaviors relative to visual scrutiny or inspection at the periphery of their visual field. Subjective improvement has been reported in the behavior of children with autism using prism lenses [Kaplan et al., 1998]. In the absence of data in the peer-reviewed literature, the American Academy of Pediatrics does not recommend optometric exercises for children with developmental disabilities [American Academy of Pediatrics, 1998].

Craniosacral Manipulation

Therapeutic touch and manipulation has been associated with behavioral improvement anecdotally. It is often used as part of an overall sensory program in academic settings. Craniosacral manipulation purports to be able to sense the fluid waves of spinal fluid by touch and to be able to manipulate them. Objective measurement indicates that it is highly unlikely that human senses could detect changes in pressure at the skin surface [Moran and Gibbons, 2001]. Although the mechanism is unlikely to be correct, it may be that the touch and circumstances around the therapy might result in behavioral effect.

Facilitated Communication

Facilitated communication should not be confused with augmentative communication. Many people with autism are nonverbal but can communicate through independent use of picture cards, computerized devices, or sign. Facilitated communication refers to a specific intervention where a facilitator physically guides the hand of a nonverbal person to use a computerized or other device to spell. Although initially heralded as a breakthrough in permitting communication, objective analyses demonstrated that, if the facilitator guides the individual without the individual learning independent use of the device, communication is very likely to be subconscious direction from the adult partner [Mostert, 2001].

CONCLUSIONS

Many of these novel therapies have emerged by serendipitous observations. Hypotheses of causation may be based on coincidence or association. The search for an explanatory pathophysiology may follow. As a hypothetical treatment evolves in the marketplace, the mode of delivery may change such that conventional understanding of physiological properties cannot be applied. We have evidence of abnormal distribution, action, and genetic predisposition to atypical neurotransmitter and neuropeptide metabolism in ASD. It is conventionally accepted that vitamins have important physiological actions in the CNS, but there is currently no evidence to support use of supratherapeutic doses of dietary supplements. The safety of supratherapeutic doses has not been evaluated, especially in special populations such as young children and pregnant women.

Families with young children with autism often feel pressure to act immediately, and not to wait for confirmatory scientific studies. For that reason, clinicians need to be aware of the interventions that families use in order to be able to assist in supporting the family and monitoring the child for side effects. Clinical and basic researchers need to subject all interventions that have popular support to scientific study and scrutiny. Collaboration of basic scientists with clinical investigators to assure rigorous study design requirements is critically important if future studies are to reach valid conclusions regarding treatment for ASD. In addition, the publication of both positive and negative studies in the peer literature can help guide practice. It is important that evidence and not the marketplace be the source of information for families and clinicians as they determine treatment for children with autism. ■

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