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# AN APPROACH TO THE NUTRITIONAL MANAGEMENT OF AUTISM

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**DESCRIPTION**

The cause of autism is not understood, and there is no cure for the disorder. However, certain therapies are associated with an improvement of autistic behaviors. This lesson is designed to discuss the hypothesis that nutritional management may help alleviate some of the behaviors associated with the disorder.

**TARGET AUDIENCE**

Healthcare providers who practice or who are interested in practicing nutritionally-oriented, integrative medicine.

**OBJECTIVES**

Upon completion of this article, participants will be able to do the following:

1. Identify three symptom sets that characterize autism
2. Discuss the principles of dietary revision for autistic patients
3. List 6 nutrients that are believed to be associated with improvement of autistic behavior.

In 1943 the psychologist Leo Kanner published case histories of a childhood developmental disorder he called autism. He defined three symptom patterns: (1) failure to use language for communication, (2) abnormal development of social reciprocity, and (3) desire for sameness, as seen in repetitive rituals or intense circumscribed interests.[1] These 3 symptoms, which were termed Kanner's triad, usually manifest by age 3. Autism is developmental, but need not involve mental retardation.[2]

Symptoms of autism may become evident as early as 4 months after birth. In a minority of cases, after developing normally a child regresses into autism. Clinically, neurological abnormalities usually dominate the symptomatology. Brain imaging has revealed zonal brain hypoperfusion and underresponsiveness, localized mainly in the fronto-temporal cortex (reviewed in Kidd[3]). Abnormalities in other organ systems add to the disorder's severity, and dictate a fully diversified approach to its medical management.[4]

Autistic children and their parents face great challenges. Autistics score consistently low on measures of adaptive or life skills.[3] As adults, their life outcomes range from complete dependence to (rarely) successful employment. People with autism also have abnormally short lifespans.[5] Death most often comes from seizures, nervous system dysfunction, drowning, or suffocation (rates more than 3 times the general population).[5] Epilepsy occurs in at least one-third of autistics,[3,6] and deaths due to epilepsy are approximately 24 times that of background.[5]

Autism has become epidemic in the industrialized societies[3] In the United States, autism was relatively rare through the mid 1980s, after which estimates indicate its prevalence increased by at least double,[7] and perhaps as much as 10 times.[7,8] Similar increases occurred in the United Kingdom and in Australia.[9,10] The gender ratio is around 3-5:1 boys to girls.

From the clinical-biological viewpoint, autism is a complex and multifaceted spectrum of disorders. Kanner's "classic" autism, termed autistic disorder or AD, is now included with the other autistic disorders into the category autistic spectrum disorder or (ASD), less commonly termed Pervasive Developmental Disorders (PDD).[3] It is not uncommon for more than one of these disorders to co-occur within the same family.

Autism is associated with various comorbid conditions, including, most often epilepsy, sensory impairment (blindness and/or deafness), tuberous sclerosis, and neurofibromatosis, all of which predominate in the most severely mentally retard-

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ed.[11-13] Blaylock has presented a hypothesis whereby endogenous, environmental, or food-derived excitotoxic factors interact with brain hypoperfusion, seizure tendencies, or an overactivated immune system, to produce ASD symptomatology.[6]

## FACTORS PREDISPOSING TO AUTISM: AN OVERVIEW

Autistic spectrum disorder is believed to be multifactorial.[3,14] Autism has been variously linked with inborn errors of metabolism; genetic abnormalities such as fragile X syndrome; rubella and other pathogens; thalidomide exposure; and many other factors.[3,15,16] There also is evidence for a coincidence of autism with modern intensified vaccination and the toxic mercury in many vaccines; a recent in-depth study may have confirmed this link.[17] Genetic predisposition, metabolic abnormalities, and abnormalities of the gastrointestinal, hepatic, and immune systems may also predispose autistics to vaccine sensitivity.[3,4,15]

### A Genetic Predisposition

Genetics plays a strong role in autism.[3,18] The degree of genetic determinism is strong, probably not sufficient to be classed as an inborn error, but more than sufficient to be a predisposing factor.[15] Classic twin studies indicate autism's heritability is high. The chance for co-occurrence among siblings is 50-100 times higher than the general population.[19] This degree of genetic conditioning is believed to exceed other known genetically-conditioned diseases such as Alzheimer's disease, asthma, diabetes, and schizophrenia.[3,15]

Findings from several genome-wide gene screening studies concur that ASD is multigenically determined, with as many as 10-20 genes involved.[3,20] Korvatska and collaborators[15] suggested the effectiveness of genetic analysis might be improved by dividing the ASD population into more strictly homogeneous phenotypic subgroups and conducting separate analyses on each of these.

A small proportion of autistic individuals (around 10-15%) have coexisting genetic conditions, including tuberous sclerosis, neurofibromatosis, X-linked gene mutations such as fragile X syndrome and the MECP2 of Rett's disorder; and other chromosomal abnormalities.[3] However, it is hypothesized that the majority of ASD cases may have suffered some non-genetic triggering event(s) that precipitated their symptomatology.[15]

### Developmental/Teratologic and Inborn Metabolic Contributions

Several lines of evidence implicate injury *in utero* as contributing to autism.[3,21,22] One example: minor physical anomalies of the ear are found in about 45%of autistic children. A chemical model for such teratologic insult is the drug thalidomide[22]: Exposure of human fetuses during neural tube closure (gestation days 20-24) caused some 30% to later develop autism symptoms, along with ear anomalies, hearing loss, facial paralysis, and poor eye abduction.[22]

Congenital enzymatic weaknesses (inborn errors of metabolism) may mimic or contribute to ASD symptomatology. The most prominent among these are phenylketonuria (PKU) variants, histidinemia, adenylosuccinate lyase deficiency, purine synthesis deficiencies, inosine phosphate dehydrogenase weakness, Lesch-Nyhan Disease, adenosine deaminase deficiency, and ADA binding protein weakness. Biochemical analysis[23] uncovers their presence, following which specific corrective metabolites can be administered.

### Serotonin and Other Transmitter Imbalances

Serotonin is a monoamine brain transmitter, one of the earliest to appear in the developing brain. It also plays a role in regulating brain development.[24] Elevated blood serotonin appears to be one of autism's most consistent abnormalities, perhaps with a genic connection (chromosome 6).[25] Up to 40% of ASD cases feature abnormally elevated blood serotonin, but some brain areas can have decreased concentrations while others are elevated, likely reflecting uneven development of brain networks.[24]

Dopaminergic imbalances are also frequent in ASD: High homovanillic acid in the CSF (cerebro-spinal fluid) and/or urine is a frequent finding, and indicates possible CNS insufficiency of dopamine.[3,26]

Variability in its onset, expression, symptom pervasiveness, and progression rank autism among the most perplexing disorders to manage. Yet within the past decade real progress has been made towards helping autistic people become fulfilled and productive members of society. This progress is partly attributable to nutrition-centered, nontoxic, integrative management.

### Nutrition-Centered Autism Management

Integrative autism management began with the efforts of Rimland[9] and the Autism Research Institute,[27] then also by DAN! (Defeat Autism Now!).[28] Founded in 1995 by Rimland and other scientists, parents, and physicians, DAN! now has an extensive collection of conference reports, practitioner referral services, assessment tools, and intervention protocols. DAN! continues to support the development of diagnostic and treatment protocols for autism.

Every ASD child has a unique combination of clinical and laboratory abnormalities, making individualized assessment a key requisite. Most often, detailed assessments begin with the parent. Sidney Baker, MD, worked with others in DAN! to generate parent protocols for keeping track of medical records.[29] According to Baker and colleagues, the first concrete therapeutic step is taken by the parent: to revise the child's diet.

### Dietary Revision,The First Phase

Among practitioners and parents familiar with autism, it is suspected that modifying the diet sets the stage for the success of other treatments and, therefore, dietary modification is recommended to come first.[30] Food additives can be a particular problem—though many of the worst have been banned,

others remain in the food supply. For ASD children unusually sensitive to foods, the Feingold Diet may offer benefits.[29]

Sugary foods are a target for dietary revision.[29,30] Anecdotal evidence from parents and practioners encountered in my practice suggests that sucrose and other simple sugars, even artificial sweeteners, appear to have adverse behavioral effects in some ASD children. Because urine testing frequently evidences abnormal carbohydrate metabolism, it is suspected that a sugar-avoidance diet may help the autistic child. Parents can test a sugar-avoidance diet by slowly removing sugary substances over 3 weeks (to avoid withdrawal symptoms), and then reintroducing sugar for up to 5 days and observing the results. Simple sugars in the intestine also support microorganisms (especially *Candida* fungus) that can produce toxins harmful to the lining and potentially also to other organs.[29]

Foods containing casein (dairy products) or glutens (wheat) are suspected to contribute to ASD.[29,30] In various controlled studies, as many as 80% of ASD subjects improved following strict dietary exclusion of these proteins (the casein-free and gluten-free [CFGF] diet).[30] In these studies, behavior improved, and seizure activity is decreased. Gross motor coordination, social contact, eye contact, ritualistic behavior, language all may improve; sleep patterns often normalize. This single dietary upgrade may be an essential prerequisite improvement in ASD; further, it is an essential prerequisite for implementing other dietary changes.

The CFGF diet requires gradual implementation. Since abrupt simultaneous removal of casein and glutens from the diet may cause withdrawal symptoms, a 2-step phased removal is appropriate.[30] First should come removal of the cow's milk and other dairy products, whose metabolic dangers are established.[31] The benefits can show within 2-3 days in young children or 10-14 days in adults, even though full clearance of casein from the body takes a much longer time.

Consumption of cow's milk was linked to increased autism incidence among immigrants to Sweden.[32] Symptoms of casein intolerance include projectile vomiting; eczema, particularly behind the knees and in the crook of the elbow; white bumps under the skin; ear discharges and infections; constipation, cramps, and/or diarrhea; and respiratory disorders resembling asthma.[32]

Some higher-functioning ASD children voluntarily cease casein intake, apparently sensing it is not good for them. Gluten products, on the other hand, stir strong cravings, and children are less likely to refuse them.[30] Gluten exclusion requires complete dietary exclusion of the common cereals wheat, barley, rye, and oats. Nonetheless, many other foods contain hidden glutens. Gluten elimination usually takes a minimum of 3-4 weeks, and 3 months is an appropriate trial period. The urinary gluten profile persists for much longer than does the casein profile, and correspondingly the withdrawal effects are usually milder in severity than casein's but typically more prolonged.

Gluten withdrawal symptoms can persist after 5 months on an exclusion diet.[30] In some cases improvement has been noted 7-9 months after initiating the diet, but maximal improvement can require up to two years of rigid dietary exclusion. Meanwhile, adding glutein and casein foods back into the diet can result in severe symptom resumption. Dietary casein and glutens very likely generate "excitotoxic" damage in the ASD brain,[31] but the CFGF diet often effects clinical improvement even when laboratory tests fail to detect such peptides via the urine.

**Sources of Possible Excitotoxic Damage**

Reichelt, Shattock and others observed clinical correlates between the symptoms of autism and impaired ability to digest proteins from dairy and wheat foods.[3,30,31] Incomplete protein digestion results in the accumulation of peptides (amino acid polymers) in place of the monomeric amino acids. Some of those derived from casein and gluten are dipeptides (two-amino acid molecules) or oligopeptides (a few amino acids), molecules small enough to be absorbed and access the brain. These can have endorphin-like, opioid effects on the brain's dopaminergic, cholinergic, serotonergic, noradrenergic, and GABAergic transmitter systems, so were dubbed exorphins.[33,34]

The "opioid excess" theory for autism arose around 1979, with Panksepp's suggestion that incompletely digested peptides with opioid activity could precipitate autism.[33] By 1981, Reichelt and colleagues detected such peptides in the urine of 22 of 25 autistics they studied;[31] later Gillberg found excessive levels in the cerebro-spinal fluid.[34] Enhanced absorption of exorphins could contribute to autism by way of numerous mechanisms.[3,6,17,21,33-36]

In 2002, Wakefield's group reviewed "autistic enterocolitis," an intestinal motility disorder characterized by inflammation of the lining.[35] They concluded exorphins were involved, such as gluteomorphin and gliadomorphin from wheat and beta-casomorphin from milk. Their work offers further evidence that these GI symptomatologies, present to some degree in the majority of autistics, can be resolved only through near-total elimination of casein and gluten from the diet. Although, this is impossible to fully achieve through food choices, a recent advance in digestive enzyme supplementation and probiotic repletion brings this goal closer to attainment.

Digestive breakdown of the small peptides from casein and wheat mostly relies on one enzyme, the dipeptidyl-peptidase IV (DPPIV). Congenital weakness in DPPIV function is linked to autism,[3] and the enzyme is highly sensitive to mercury and organophosphate xenobiotics. Recently, Brudnak, Rimland, and collaborators designed a sophisticated digestive enzyme supplement aimed at supporting DPPIV activity. Their pilot study with 22 subjects documented wide-ranging symptom improvements of between 50-90%.[36] The supplement included galactose, as a food source for the "probiotic" bacteria of the intestinal tract. Probiotic symbionts such as lactobacilli and the bifidobacteria produce DPPIV and are able to fully digest exorphins. This innovation may hold particular clinical

promise since there are normally far more probiotic cells housed in the human intestines (over $10^{11}$) than there are cells in the intestinal lining.[36]

Brudnak and collaborators also presented a rationale for repleting probiotics in the intestines, using multiple species on a rotating or "pulsed" basis.[36] Altogether, a new 4-pronged GI approach has emerged, one that combines food restriction with potent enzyme supplementation, probiotic substrate support, and probiotic supplementation. This approach represents the current best effort to restore GI function and epithelial lining integrity, thereby to protect the brain against damage from food-derived molecules.

**Subtle Relationships of Foods with Symptoms**

It has been reported that once the main sources of food intolerances—sugars, artificial additives, casein, glutens—have been removed from the diet, other foods may emerge as sources of symptoms.[29,30] Parents can often associate the child's consumption of a particular food with deterioration in behavior, sleep patterns, or cognitive performance. These symptoms can occur in the absence of classic allergy symptoms such as stuffiness, eczema, wheezing, and itching. Beef, pork, rice, and potatoes are only occasionally implicated; eggs, tomatoes, eggplant, avocados, red peppers, soy, and corn are more often problematic.[29] To confirm a food intolerance, the suspect food should be removed from the diet for at least 3 weeks and any improvements noted. Subsequently, on being reintroduced into the diet it will likely trigger an exacerbation of symptoms.

Hospital-based laboratories often test for food allergy by measuring IgE antibody levels. But the dominant food allergies seen in autism usually are not the IgE-mediated, immediate hypersensitivity type.[29] Rather, they take hours or days to develop and often require cumulative exposure to the offending food. This suggests the allergy is mediated mainly by IgG rather than IgE antibodies. Baker and Pangborn conducted two double-blind, placebo-diet controlled studies using IgG-ELISA (Enzyme-Linked Immunosorbent Assay). Both trials demonstrated significantly better symptom reduction in subjects avoiding IgG-reactive foods versus IgG-nonreactive foods.[37,38] Systematic dietary elimination of suspect foods is likely to have more clinical value than laboratory assessments for food allergy.

Perhaps due to wide-ranging difficulties with foods, children with autism are typically "picky" eaters.[29,30,39] Further dietary restrictions due to intolerances are likely to result in inadequate intakes of essential nutrients. For these reasons alone, it is my opinion that in autism a nutrient supplementation regimen is appropriate and indispensable.

**Specific Nutrient Supplements and Autism Management**

Controlled research on the benefits of nutrient supplementation for autism has been scant. However, since 1967, the Autism Research Institute (ARI) has collected and periodically published semi-quantitative ratings of various nutrients.[27]

The ARI Treatment Effectiveness Survey questionnaire solicits from parents a rating of each nutrient, drug, dietary modification, or other biomedical intervention used on their child. Periodically the ratings are tabulated, and a "Better to Worse" score (B:W ratio) derived. Because of the difficulty in controlling for length of time on the nutrient, dosage, and social, behavioral, and environmental factors, attributing a change in symptoms to one specific nutrient is not possible. However, the B:W ratio serves as an indicator. Most recently, cumulative nutrient data from 21,500 parents were summarized in April 2002 (available from ARI[27]). Orthomolecular nutrients—vitamins, essential minerals, and other substances that naturally participate in the body's metabolic pathways—consistently receive better ratings than do herbals.[27]

**Multiple Vitamin-Mineral Supplements**

Individuals with autism typically exhibit these deficiencies of many nutrients. Many have poor digestion; approximately 25% have chronic diarrhea; 25% have constipation. Still others have more subtle inflammatory conditions that limit absorption.[22] Often the probiotic (beneficial) bacteria in the intestines are depleted from antibiotic treatment for food-allergy related ear infections, and fewer vitamins are being produced by these populations (vitamin B12, biotin, and vitamin K, in particular). Thus, perhaps many autistic children may benefit from a multivitamin—mineral supplement, with one caveat: copper is one mineral they often have in relative excess.[40]

In 2000, Vogelaar reported on the nutrient status of 20 autistic children.[41] More than half were abnormally low in vitamins A, B1, B3, and B5, and biotin; essential minerals selenium, zinc, and magnesium; essential amino acids; and essential fatty acids. In a double-blind, placebo-controlled trial, a multivitamin-mineral complex was given to 16 autistic children for three months.[42] Blood levels of vitamins B6 and C significantly increased, and sleep and bowel patterns (parents' scores) were significantly improved.

**Vitamin B6 and Magnesium[4,43-45]**

This nutrient combination is the archetype for nutritional ASD management: many cases of remarkable improvement have been documented.[43-46] Vitamin B6 is an essential cofactor for a majority of neurotransmitter systems, including serotonin, gamma-amino-butyric acid (GABA), dopamine, epinephrine, and norepinephrine. Rimland, a pioneer in this area, notes that in 1968 Bonisch reported vitamin B6 (100-600 mg per day) improved behavior in 12 of 16 autistic children; and supposedly three of Bonisch's subjects spoke for the first time while participating in this open trial.[44]

Magnesium is an essential macromineral for literally hundreds of enzyme-catalyzed metabolic reactions. When combined with vitamin B6 it further increases the B6 clinical benefit.[43-45]

In the 1970s, after conducting an exploratory, non-controlled study Rimland did a small double-blind, crossover trial on 15 children with autistic symptoms.[44] Each child received

either a placebo, or vitamin B6 at 2.5-25.1 mg/kg body weight/day (75-800 mg per day) and magnesium at "several hundred" mg per day. Statistically significant benefits included better eye contact, less self-stimulatory behavior, more interest in surroundings, fewer tantrums, and better speech.

In the early 1980s, LeLord and colleagues did further research and concluded that the combination vitamin B6 and magnesium was a breakthrough for autism.[45] Urinary homovanillic acid (HVA) levels fell, indicating dopamine metabolism was improved; and average evoked potentials, a measure of sensory processing ability, also were improved.

Rimland recently reviewed 18 studies on high-dose vitamin B6 for autism.[43] Eleven were double-blind, placebo-controlled trials. One small study with negative outcome was earlier dismissed for its "obvious bias," since its design included a crossover yet no washout period was allowed.

Taken together, the studies establish that vitamin B6 may benefit as many as half of children and adults with autism, also that combining B6 with magnesium further improves its efficacy and safety. None of these studies reported any significant adverse effects, even with vitamin B6 doses as high as 1,000 mg per day. Vitamin B6 intakes went as high as 30 mg/kg/day (equivalent to 2,100 mg for a 70 kg adult); these were administered with 10 mg/kg/day of magnesium lactate to 11 autistic children for eight weeks, with no evident adverse effects.[4,43] The latest ARI parent ratings in 2002 reported a B:W ratio for vitamin B6 used alone of 4.1:1, for magnesium alone 5.2:1, and for the combination of vitamin B6 plus magnesium, 11:1.[27]

Cases of hereditary impairment of pyridoxine metabolism have been described, sometimes manifesting as seizure disorder and autism symptomatology.[6] Enzymatic activation of vitamin B6 (pyridoxine) to the fully active pyridoxal –5 –phosphate (P5P) can be hereditarily impaired, and P5P supplementation may work for these cases although hyperactivity is a possible adverse effect. Nonetheless, the cumulative data are consistent with vitamin B6 and magnesium having impressive efficacy for autism, superior over either nutrient alone.[3,43-46]

**Dimethylglycine (DMG)**

DMG is a nutrient orthomolecule involved in methylation reactions and widely required in metabolism.[47] Having two methyl groups, it is an important methyl donor to support cell growth and renewal. It also has antioxidant character. Early feedback from parents promoted interest in DMG for autism; to date 3 small studies are available.[4]

Rimland[43] reported that Kun administered DMG to autistic children aged 3-7 years, for 3 months; 31 of 39 benefited (80%). Kern and collaborators did a 4-week, double-blind, placebo-controlled trial on 37 children aged 3-11 years.[47] The DMG and placebo groups both improved but were not significantly different. The trial period may have been too short. Similarly, Bolman and Richmond[48] conducted a small, double-blind, short-term trial with low-dose DMG (125-375 mg/day) and found no significant results. The ARI parent B:W ratio for DMG is currently 5.9:1, from 4,547 questionnaires.[27]

The nutrient TMG (trimethylglycine; betaine) has a third methyl group and could be a better methylator than DMG. To date its parent B:W ratio is less favorable, at 3.1:1 (182 questionnaires). Both DMG and TMG are best taken earlier in the day, to avoid the rare possibility of interference with sleep.

Rimland recommends children be started on DMG at a low intake (60 mg per day with breakfast), then titrated up to 500 mg per day.[43] He asserts that speech is most consistently benefited but behavior also may improve. DMG helps ameliorate seizures, an important consideration for the estimated one-third of ASD subjects who have epileptic involvement; Blaylock suggests this proportion could be higher.[6] Occasionally an ASD child will experience transient hyperactivity with DMG; administering it together with folic acid and vitamin B12 lessens this likelihood.[49]

**Folic Acid**

Folic acid is essential to numerous metabolic pathways. Frequently it is deficient when B6 and vitamin B12 are deficient.[50] Its current B:W ratio is 11:1, from 1,100 questionnaires.[27] Folic acid may benefit autism associated with Fragile X syndrome.[51] According to Rimland,[44] LeJeune obtained favorable results on non-fragile X autistic children using relatively large doses (0.5-0.7 mg/kg/day).

**Calcium**

Calcium and magnesium deficiency is common in autistic children, around 22% in one study.[49] ARI parents gave calcium a B:W ratio of 14:1 (988 questionnaires).[27]

**Vitamin B3 (Niacin/Niacinamide)**

As with vitamin B6 and folic acid, vitamin B3 supports numerous pathways that sustain and renew the body's tissues. The current B:W ratio is 9:1.[27]

**Vitamin C**

Vitamin C has a reputation for its involvement in a plethora of metabolic pathways, and is a cofactor for neurotransmitter synthesis. In a double-blind trial over 30 weeks, multigram intakes (8 g/70 kg body weight/day) improved total symptom severity and sensory motor scores.[52] Its current parent B:W ratio is an excellent 16:1, from 1,306 questionnaires.[27]

**Zinc**

Participating in numerous metabolic pathways, this essential mineral is crucial to organ development and maintenance. Serotonin synthesis relies on zinc-activated enzymes, and zinc is also central to antioxidant enzyme function.[53] Breeding experiments with rodents indicate maternal zinc deficiency can negatively influence immunity and brain development.[54] Zinc currently has a very favorable B:W ratio, 17:1 from 835 questionnaires.[27]

Zinc operates in a "yin-yang" relationship with copper, ie, often when zinc levels go down copper levels go up. Walsh reported abnormally elevated blood copper:zinc ratios in 85% of 318 ASD children[55]; a smaller sample of 22 subjects had 100% incidence of abnormally high, unbuffered blood copper (unbound to ceruloplasmin proteins)—about 4 times normal. Walsh's findings corroborate the recommendation that supplements for autistics should exclude copper. Zinc is a key nutrient in Walsh's protocol to support metallothioneins, circulating proteins which buffer heavy metals.[56]

**Essential Fatty Acids (EFAs)**

Essential fatty acids are pro-homeostatic constituents of cell membranes, helping to relay signal information from outside the cell to its interior.[57] EFA also are precursors for cell-to-cell messenger molecules (eicosanoids, "prostaglandins"). The longer-chain, 20- and 22-carbon species are crucial for brain development and maintenance.[58]

Some adults can generate longer-chain EFA from the shorter-chain fatty acids, with poor efficiency, but infants have limited conversion capacity. Significantly, the C22:6 omega-3 (docosahexaenoic acid, DHA) and the C20:4 omega-6 (arachidonic acid, AA) occur in ample quantities in breast milk and at a fixed ratio (around 4:1 omega-6 to omega-3). This strongly suggests dietary essentiality for long-chain EFAs in postnatal development.[58,59]

Essential fatty acids, particularly the omega-3s, are frequently deficient in ADHD, dyslexia, and dyspraxia.[58-60] Conceivably, these neurodevelopmental conditions have a striking degree of overlap with the autistic spectrum.[59] Abnormalities of fatty acid and phospholipid metabolism could help account for many features common to these conditions.

Studies on EFA deficiency in autism are few, but with consistent positive outcomes. Vancassel and collaborators reported DHA 23%- reduced, total omega-3s 20% reduced, and omega-6s unchanged in plasma phospholipids.[60] Hardy and Hardy studied 50 children with the more inclusive diagnosis Pervasive Developmental Disorder (PDD), and reported almost 90% omega-3 deficient via red cell analysis.[61]

Prospective trials to assess EFAs for their role in autism are sadly lacking. Still, physicians report autistic patients benefit from omega-3 supplementation. According to the ARI, "fatty acid supplements" (exact composition unspecified) currently have a parent B:W ratio of 12:1.13 The long-chain omega-3 fatty acids are potent anti-inflammatories, though sometimes months of dosing are required to fully attain efficacy. They hold promise for treating the coagulation abnormalities and vasospasm sometimes seen in autistic patients.

**Vitamin A**

Vitamin A is especially important for cell growth and differentiation, especially in epithelial tissues of the gut, brain, and elsewhere. Megson reported on 60 case histories of children to whom she administered cod liver oil (CLO) for 3 months or longer.[62] Some may have benefited within days; core autism symptoms, such as language, eye contact, ability to socialize, and sleep patterns, all supposedly improved. Megson noted that the natural vitamin A found in CLO is about 12% "cis", a molecular configuration absent from synthetic vitamin A (all "trans"). She hypothesized this cis-vitamin A may be "unblocking" brain retinoid receptors linked to cell membrane signal transduction.

Although CLO is unlikely to provide a sufficiently high intake of omega-3 fatty acids to correct the deficiency in these developmentally impaired children, and its high vitamin A content limits its upper dosing level, evidently it does still have clinical utility. CLO products must be screened for mercury and other pollutant content, and so also the fish oils. The B:W ratio for CLO is 14:1, and for vitamin A (probably mostly the synthetic form) 22:1.[27]

**Other Nutrients Offering Possible Autism Benefit**

Bradstreet and Kartzinel[63] have asserted that close to 100% of children with autism have vitamin, antioxidant, and fiber deficiencies. If so, this would suggest widespread metabolic compromise. Supplementation with conditionally-essential nutrient metabolites (orthomolecules) such as taurine, coenzyme Q10, and carnitine often provides benefit, on a case by case basis.[4]

Carnitine is central to energy generation. It can be synthesized in the healthy body but many individuals benefit from supplementation. Carnitine can ameliorate the toxicity of valproate, a drug prescribed for seizures. In one open-label study carnitine benefited patients with Rett Syndrome, a developmental disorder that shares features with autism; a small, double-blind trial with 35 Rett Syndrome patients demonstrated clear improvement in well-being.[64]

The pterin substances, biopterin and its precursor neopterin, are nutrient orthomolecules found naturally in body fluids. During periods of immune activation (as with inflammation or autoimmune exacerbation) their levels in urine are increased.[4] Biopterin in its reduced form (rBH4), is a limiting cofactor for biosynthesis of the transmitters dopamine, epinephrine, and serotonin. Autistic children can manifest relatively poor rBH4 status, perhaps because the enzyme that produces it is somehow compromised. In a pilot study, 6 autistic children were treated with rBH4 for 3 months—all showed improvement in language, eye contact, and sociability.[65]

Inositol is a precursor for phosphatidylinositol, a phospholipid that facilitates serotonin receptor function. In one small, double-blind trial no significant benefits emerged.[66] The investigators conceded their efficacy measures were crude and suggested inositol be re-investigated.

Anecdotal reports suggest that magnesium sulfate (Epsom salts) may benefit the autistic child through a novel route of delivery. A parent reported her child's oppositional behavior disappeared overnight after a bath in Epsom salts. Other par-

ents who used the treatment reported improved speech, mood, cooperation, and motor development in their children.[4,39]

### Correcting Amino Acid Abnormalities

Dr. Jon Pangborn has developed diagnostic and therapeutic protocols for normalizing amino acid status in ASD subjects.[27,38,67]

He reports at least two-thirds of autistics have abnormal amino acid levels, as measured in 24-hour urine or fasting blood plasma. High urine levels of several amino acids (generalized hyperaminoaciduria) almost always indicate toxic chemical exposure and consequent liver damage. Low urine amino acids often suggests malabsorption, as do high urine levels of peptides—incompletely digested proteins.

Sulfur amino acids are often abnormally low in autism, and this has direct implications for the proven impairments of detoxication in ASD. When detoxification capacity is limited, the cysteine/cystine ratio, and methionine, taurine, and glycine levels all tend to be abnormal. Cysteine, important for the formation of glutathione and taurine, often is measured low in young autistics but paradoxically high in those older than 5 years. Methionine levels are occasionally found low, and taurine was reported deficient in 62% of autistic children by urine analysis.[38]

Glutamine is an energy source for enterocytes of the small intestine, is a glutathione precursor, and contributes to numerous other pathways. Glutamine is low in some autistics, particularly in those with an aversion to meat or poultry. Therefore, according to Pangborn glutamine may be supplemented to autistics.

Certain cautions must be observed when prescribing amino acid mixtures. Pangborn has recommended laboratories best qualified to perform amino acid and other assays related to possible inborn metabolic errors, along with the pharmacies that custom-blend formulations.[38,67]

## CORRECTING GASTROINTESTINAL ABNORMALITIES

A majority of ASD individuals have gastrointestinal (GI) abnormalities.[3] Maldigestion and malabsorption are common, as is inflammation of the lining. Dysbiosis (depletion and imbalance of symbiotic bacteria, fungal and/or other parasitic overgrowth) also is common. One study of 385 subjects found 46% had chronic diarrhea, constipation, or other GI symptoms.[68] In a smaller study on 36 ASD children with chronic diarrhea, gas, abdominal discomfort and distension, more than two-thirds had GI inflammation and impaired digestive enzyme activity.[3]

Integrative practitioners worked closely with independent laboratories to develop the comprehensive digestive and stool analysis (CDSA).[69] This includes measures for digestive function, metabolic function, microbiology, mycology (yeasts and other fungi), and parasitology. The Biomedical Assessment manual from DAN! lists laboratories that offer CDSAs.[67]

Findings with the CDSA reinforce other evidence for intestinal hyperpermeability or "leaky gut" in ASD.[68,70]

### Nutritional Status and "Leaky Gut"

The intestinal lining is only a few cell layers thick, so that diverse insults can damage its integrity and increase its permeability. The premier test for GI permeability is based on the differential absorption of 2 inert (non-metabolized) substances, mannitol and lactulose. Using this approach, D'Eufemia[68] found that 43% of a sample of autistic children and none of the controls had "leaky gut." Many differing real-life factors contribute to intestinal permeability breakdown, including nutritional deficiencies; localized food intolerance or allergic responses; viral or bacterial infection, Candida overgrowth, parasites; oxidant or inflammatory xenobiotic toxins; nonsteroidal anti-inflammatory drugs, NSAIDs and other pharmaceuticals that damage the protective mucus. This reality makes it important that gut integrity be assessed prior to exploring oral modalities for autism.

To correct gut hyperpermeability requires first, taking a comprehensive patient history to detect all the agents that could promote damage to the lining. The diet should be redesigned to increase protein and fiber intake and to lower digestible carbohydrates.[4] Constipation should be treated. When diarrhea occurs, viral activity should be considered and treated if indicated, but often this improves as reactive foods are eliminated. Gram-level intakes of the amino acid L-glutamine can help the enterocyte cells proliferate to reseal gaps in the epithelium. To ensure the most efficient food digestion and so minimize food allergenicity, digestive enzyme preparations such as that of Brudnak and collaborators[36] can be orally supplemented. The effects of oral secretin therapy are not yet understood, but this hormone may offer a further option.[71]

### Secretin to Aid Digestion?

Secretin is a small neuropeptide hormone (27 amino acids), normally secreted by cells of the upper intestinal tract. Secretin helps regulate stomach, pancreatic and liver functions in normal digestion. Its status for autism was recently critiqued.[4] To date, several controlled clinical trials have yielded mixed results, though the possibility remains that 1 child in 10 could be a secretin responder.[28,29] Oral secretin is well tolerated and adverse effects are usually minor.[71]

## ORAL MERCURY DETOXIFICATION

The biochemical profile of autism frequently features heavy metal overload. Often this comes on top of an inherently impaired detoxification capacity.[3,4,8,72-74] The affected detoxification pathways are somewhat responsive to rational intervention with nutrients. Also, the heavy metal burden can be reduced by medically supervised oral chelation, supported by nutrient supplementation.[4,75,76] But the experience with mercury suggests that for detoxification to be effective it is essential that ongoing exposure to heavy metals and other toxins be lowered to as near zero as possible. It is the author's belief that a worldwide consensus to eliminate worldwide toxins is urgently indicated. Autistic children could be the "minor's canaries" of society as a whole."[73-76]

**The Mercury Threat**

Heavy metals continue to be major environmental contaminants. Lead, cadmium, arsenic, and aluminum are suspected to be related to autism; the evidence for mercury as a causative factor in autism is well established.[4,40] Until recently, vaccinations were exposing young children to mercury at levels that exceed the US Environmental Protection Agency's (EPA) safe limit by as much as 100 times.[4] The mercury-based preservative thimerosal still contaminates some vaccines[72] and other medical liquid preparations. In addition, seafood intake or dental amalgams can load the pregnant woman with mercury, some of which may be transferred to the developing fetus. Practitioners have reported that many autism cases show improvement following oral chelation for heavy metal removal.[40,72]

It is hypothesized that the clearance of mercury from the tissues is a prerequisite for repairing homeostatic balance, detoxification capacity, and overall health status in the ASD subject.[3,4] To be conducted safely and effectively, oral mercury chelation is best entrusted to a qualified practitioner. Serious adverse side effects are rare but can occur, so professional monitoring and assessment is essential.[40]

**INFLAMMATORY AND AUTOIMMUNE IMBALANCES**

There is a growing body of evidence that the immune system plays an important role in the pathogenesis of autism, as summarized in recent reviews.[4,35,70,77] As much as 35-45% of the autistic population may have pervasive problems with immunity.[70,77-79] Humoral immunity may be compromised by IgA deficiency, also known to predispose to autoimmunity. On the cell-mediated side, cell counts can be abnormal and cell activities subpar; among the pivotal CD4+ "helper" cells the TH1/TH2 balance can be abnormal, as reported by 2 separate groups.[3] Cytokine profiles also appears to be off-balance in autism.[78,79] More than 80% of ASD sample children aged 2-14 years could be overproducing proinflammatory cytokines.[57,58] Interestingly, more than one study suggests siblings may share this tendency yet not be clinically autistic.[3,79]

Autoimmune imbalance is consistently apparent in autism. Autoantibodies to brain have been reported, including antibodies directed against specific neural self-antigens. These include anti-MBP (myelin basic protein) and anti-NAFP (neuron-axon filament protein) in 50-70% of subjects.[80,81] Many different inflammation-related mechanisms can be triggered by autoantibodies, including outright demyelination of nerve cells.[82]

Another oral immune-based, orthomolecular treatments for ASD is transfer factor. This is a low-molecular weight preparation of molecules produced by white cells. Fudenberg,[83] in an open-label study, treated autistic children ages 6-15 years with TF prepared from parents of children with autism. Fully half of these children had depressed lymphocyte responsiveness to mitogens, and the majority had autoantibodies to myelin basic protein (MBP). Most showed significant symptomatic improvement; their food sensitivities and Candida- associated symptoms also decreased.

Certain nutrients that are not strictly immune-specific can potentially assist in immune rebalancing. Primary candidates include the long-chain omega-3 fatty acids, mushroom glycans, phytosterols, and nutrient flavonoids. Controlled studies are urgently needed to explore their potential.

**CONCLUDING REMARKS**

The cause of autism/ASD is not understood, and there is no known cure for the disorder. Autism continues to increase in prevalence, and remains an extreme challenge to medical management. Medically, autism's expression is so individualized that its management requires individualized care; integrative medical practices appear best suited to treat the disorder. Ethical integrative management supports parents' initiatives to explore options that offer negligible risk and a degree of benefit for the child.

As a general rule, nutrients have broader effects and better benefit-to-risk profiles than drugs. The ethical integrative practitioner, uses pharmacologic agents where indicated. It is conceivable that as the therapeutic power of nutrients becomes more evident, it may become more appropriate to support nutrients before considering treatment with drugs. Furthermore, there is a chance that rational application of nutrients may ameliorate the adverse effects of some drugs.

The current intensified pace of vaccination is circumstantially implicated in autism causation. Blaylock has analyzed the factors that may be interacting between live, attenuated vaccines that are given frequently and often in multiple combination to the young child. He has presented in-depth suggestions for reorganizing vaccination types and scheduling, as well as for building up the child's immunity via nutrition prior to imposing vaccination on the delicate immune system.[6] These seem worthy of consideration as a kind of vaccine prophylaxis protocol. Such a protocol could help avert autistic regression in a child who has genetic predisposition to autism and/or other impairments that increase susceptibility.

Autism also will continue to challenge basic and clinical researchers. From the nutritional—integrative perspective, research funding is urgently needed. More in-depth study is required for, especially: (1) vaccination and nutritional vaccination prophylaxis; (2) nutritional status of the mother and antenatal contribution to autism risk; and (3) nutritional correction of pro-inflammatory and autoimmune imbalance. Improved understanding in these areas would facilitate stemming the current epidemic and moving a greater percentage of established cases into remission.

Despite the inherent severity of their impairments, the ASD population is making steady advances in everyday performance and overall life quality. Much of this progress is attributable to the current integrative model for medical management. Nutritional and other nontoxic interventions remain at the core of the integrative medical management presented in this lesson.

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# CME TEST INSTRUCTIONS

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# CME TEST QUESTIONS

## AN APPROACH TO THE NUTRITIONAL MANAGEMENT OF AUTISM

***SelfAssessment Questions****

In the following questions, only one answer is correct.

1. Autism:
A. Is a well-defined single disorder
B. Is made up of two disorders
C. Is caused by genetic inheritance
D. Is caused by vaccines
E. Is most likely multifactorial

2. Which of the following is true about autism?
A. Autistics are mentally retarded
B. Autistics are smarter than the average human
C. Autistics die earlier on the average
D. The symptoms are readily cured using available drugs
E. Dietary changes and nutritional supplements make no real difference

3. Dietary changes that may benefit the autistic child include which of the following:
A. A. Sticking to the USDA food pyramid guidelines
B. Eliminating dairy and wheat products
C. Cutting fats to less than 10% of calories
D. Eliminating carbohydrates from the diet

4. Dietary supplementation of autistic individuals:
A. Can compensate for poor eating habits
B. Can compensate for exposures to toxic substances
C. Works together with good diet to provide symptom relief
D. All of the above

5. Vitamin B6:
A. Must be used by itself
B. Works best when given with magnesium
C. Provides little benefit in autism
D. Provides benefit, but is life-threatening

6. The gastrointestinal (GI) system:
A. A. Is symptomatic in more than 50% of autistics
B. Is symptomatic in less than 10% of autistics
C. Becomes symptomatic only when antibiotics are given
D. Is affected only when dairy and wheat are removed from the diet

7. Digestive enzyme supplementation:
A. May benefit some autistic symptoms
B. Is not helpful in autism
C. Should only include secretin
D. Clears exorphins but has no clinical benefit

8. Integrative management of autism:
A. Includes dietary changes
B. Includes dietary supplementation
C. Includes avoidance of harmful foods and toxins
D. None of the above
E. All of the above

**** See page B7 for SelfAssessment answers***