

# Autism, An Extreme Challenge to Integrative Medicine. Part II: Medical Management

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## Abstract

Autism and allied autistic spectrum disorders (ASD) present myriad behavioral, clinical, and biochemical abnormalities. Parental participation, advanced testing protocols, and eclectic treatment strategies have driven progress toward cure. Behavioral modification and structured education are beneficial but insufficient. Dietary restrictions, including removal of milk and other casein dairy products, wheat and other gluten sources, sugar, chocolate, preservatives, and food coloring are beneficial and prerequisite to benefit from other interventions. Individualized IgG or IgE testing can identify other troublesome foods but not non-immune mediated food sensitivities. Gastrointestinal improvement rests on controlling *Candida* and other parasites, and using probiotic bacteria and nutrients to correct dysbiosis and decrease gut permeability. Detoxification of mercury and other heavy metals by DMSA/DMPS chelation can have marked benefit. Documented sulfoxidation-sulfation inadequacies call for sulfur-sulphydryl repletion and other liver p450 support. Many nutrient supplements are beneficial and well tolerated, including dimethylglycine (DMG) and a combination of pyridoxine (vitamin B6) and magnesium, both of which benefit roughly half of ASD cases. Vitamins A, B3, C, and folic acid; the minerals calcium and zinc; cod liver oil; and digestive enzymes, all offer benefit. Secretin, a triggering factor for digestion, is presently under investigation. Immune therapies (pentoxifyllin, intravenous immunoglobulin, transfer factor, and colostrum) benefit selected

cases. Long-chain omega-3 fatty acids offer great promise. Current pharmaceuticals fail to benefit the primary symptoms and can have marked adverse effects. Individualized, in-depth clinical and laboratory assessments and integrative parent-physician-scientist cooperation are the keys to successful ASD management.

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## Introduction

The first part of this two-part series documented myriad abnormalities typical of autism and autistic spectrum disorder (ASD).<sup>1</sup> Despite their bewildering array, most of these abnormalities are amenable to medical intervention.<sup>2</sup> In part II of the series the medical management of autism is reviewed.

Conventional medicine has largely failed autistic individuals and their families. Autism went through a long period during which institutions hesitated and parents struggled to find any means to help their children. Some of these parents were scientists and physicians. They carefully observed their children and built cooperative networks to share experiences. They implemented various interventions such as diet, vitamins, behavioral modification, and specialized education. As a result, autism has emerged as a model of successful integrative medicine.

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Integrative autism management was first driven by the efforts of Rimland<sup>3</sup> and the Autism Research Institute,<sup>4</sup> then by its offshoot DAN! (Defeat Autism Now!),<sup>5</sup> a collaborative network founded in 1995 by Rimland and 29 other scientists, parents, and physicians – many additionally motivated by being parents of autistic individuals. DAN! has generated an extensive collection of conference reports, practitioner referral services, assessment tools, and intervention protocols with the objective of transforming the autistic child into a productive adult.<sup>5</sup> DAN! supports the current research consensus that autism is primarily organic in origin, while understanding that many of its features respond to psychological interventions.<sup>6</sup> Brevity dictates that behavioral interventions and special education not be reviewed herein, except to state their utility for the autistic child is well established.<sup>7</sup>

In part I of this review,<sup>1</sup> it was documented that every ASD child has some combination of clinical and laboratory abnormalities (Table 1). Clinical improvement is difficult to achieve without individualized assessment of these abnormalities.<sup>1,2,6</sup>

### Getting Started: Recruiting the Parent

While complex medical assessments are in progress, a parent can do (or learn to do) many things to help the child. Parents can be pacesetters in helping the child become productive and happy, and can begin by keeping a day-to-day record of the child's life.

**Table 1. Clinical and Laboratory Findings in Autism<sup>1</sup>**

Congenital: inborn errors of metabolism; prenatal susceptibilities; differing genetic load interacting with combinations of these factors
Biochemical peculiarities: impaired sulfoxidation capacity; multiple nutritional deficits
Central Nervous System (CNS): altered sensitivity to, and abnormal processing of, sensory and expressive information; neurotransmitter imbalances, sometimes with abnormal transmitters such as exorphin peptides
Gastrointestinal tract (GI): impaired digestion, bowel flora alterations, food intolerances, "leaky gut" – increased permeability to poorly digested food particles, peptides, microbial toxins, and other antigenic and metabolically active substances
Liver: impaired detoxification capacity, often with low cysteine, taurine, or glutathione levels
Immune system: abnormal hypersensitivity; abnormal antibody- and cell-mediated processes; pro-inflammatory cytokines; autoimmune antibody imbalance

Many parents have learned the value of detailed record keeping. Sidney Baker, MD, advises, "Do not depend on medical professionals to keep a clear record. Doctors generally keep lousy records."<sup>2</sup> He suggests organizing copies of lab results, consultation reports, and flow sheets of treatments and symptom progress. His published protocol provides blanks of a symptom flow sheet and a treatment list.<sup>2</sup> The Autism Brain Tissue Program circulates a set of "Quick Tips" to parents for keeping track of medical records.<sup>8</sup> Suitably equipped, parents can be the physician's eyes and ears. Taking daily notes on the child's personal habits, diet, sleep patterns, and any changes, however miniscule, will help the physician more closely monitor the child's status. One essential early step is to change the child's diet.

## Dietary Revision, the First Phase

Among practitioners familiar with autism, there is strong consensus that modifying the diet and the gastrointestinal system sets the stage for the success of other treatments, and therefore should come first.<sup>2</sup> Parents have found that, by closely regulating their child's diet, they can observe improvement, and that when dietary constraints are relaxed, the child often worsens. The recognition in recent years of a gut-immune-system-brain axis of pathology further supports this priority.<sup>9</sup>

## Food Additives, Colorings, Sweeteners, Preservatives

Food additives can be a particular problem for autistic subjects. Although many of the worst offenders have been banned, others remain in the food supply. Two organizations, critical of irresponsible food additives, that publish useful information in this area are the Center for Science in the Public Interest<sup>10</sup> and the Feingold Association.<sup>11</sup>

Artificial coloring agents can have carcinogenic or mutagenic effects. Simple sugars and artificial sweeteners have adverse behavioral effects in some children. Lab tests (urine organic acids<sup>6</sup>) reveal abnormal carbohydrate chemistry in most autistic children. Baker urges the parent to test the sugar-avoidance diet by tapering off slowly over three weeks (to avoid withdrawal symptoms), then reintroducing sugar for five days, watching the results.<sup>2</sup> Whether or not the child has a strong adverse reaction to sugar reintroduction, Baker advises sugar in the diet be decreased because it is food for many potentially harmful intestinal dwellers.

For ASD children unusually food sensitive, the Feingold Diet is likely to be highly beneficial<sup>11</sup> by systematically excluding additives, colorings, salicylates, and preservatives. This and other more restrictive diets for integrative management of ADHD (attention deficit hyperactivity disorder) were previously reviewed.<sup>12</sup> Baker has published a list of additives least likely to affect ASD subjects.<sup>2</sup>

## Removing Casein and Gluten Foods from the Diet

There is a great deal of evidence that foods containing casein or gluten contribute significantly to ASD and should be eliminated from the diet. In well-conducted studies, as many as 80 percent of ASD subjects improved following strict dietary exclusion of these proteins.<sup>13,14</sup> Implementation of a strict casein- and gluten-free (CFGF) diet almost always leads to symptomatic improvement, and lays the foundation for a diet that can markedly benefit the condition.

It has been suggested that the adverse brain effects associated with dietary casein and gluten are likely due to opioid-acting peptides (small amino acid polymers, also called exorphins) metabolically generated from these proteins.<sup>15</sup> In their Sunderland Protocol for autism, Shattock and Whiteley note that clinical improvement often occurs on the CFGF diet even when laboratory tests fail to detect such peptides in the urine.<sup>14</sup> They suggest autistic subjects could be biochemically processing casein and/or gluten into other bioactive derivatives not being detected; or, while urinary levels measure normal, the quantities reaching the CNS could be high, perhaps due to abnormal permeability of the blood-brain barrier. Yet another possibility they suggest is children subjected to oxygen deprivation or other perinatal brain insults may have heightened vulnerability to even "normal" levels of the offending peptides.

Reichelt et al studied 15 ASD subjects (5 girls and 10 boys, age 3-17 years) for one year after implementing casein and gluten restriction.<sup>16</sup> They reported that 13 of 15 showed some degree of behavioral improvement and none got worse, as judged from parent-teacher consensus. Seizure activity was decreased in 3 of 4 subjects; gross motor behavior improved in 13 of 15; social contact increased in 10 of 15; eye contact improved in 9 of 15; ritualistic behavior decreased in 8 of 11; language improved in 10 of 13; and sleep patterns normalized in 9 of 11. These investigators concluded that incomplete digestion of casein or gluten-gliadin by digestive peptidase enzymes could be a biochemical cause of autistic syndromes.

Since abrupt simultaneous removal of casein and gluten from the diet can cause withdrawal symptoms, a two-step phased withdrawal is appropriate. The first phase is removal of casein via removal of milk and other dairy products. From a 1995 trial, Lucarelli et al reported 66 percent of subjects showed benefits from this intervention.<sup>17</sup> Benefits can manifest quickly – usually within 2-3 days in young children or 10-14 days in adults. However, a much longer period is required for casein to be fully cleared from the body.

Shattock and Whiteley documented the known metabolic dangers to children from consuming cow's milk.<sup>14</sup> Milk consumption is linked to increased autism incidence among the immigrant population in Sweden as compared to the indigenous population.<sup>18</sup> Some children are clearly addicted to cow's milk and will drink large quantities. Symptoms linked to casein intake 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. Shattock and Whiteley report that casein withdrawal symptoms can be severe, especially in young children.<sup>14</sup>

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.<sup>19</sup> Gluten exclusion requires the removal of several common cereals from the diet, wheat, barley, rye, and oats, in particular; but many other foods contain hidden gluten.<sup>19-21</sup> The elimination process usually takes a minimum of 3-4 weeks, and a trial period of three months is appropriate. 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.

Full clearance of dietary casein-gluten symptoms is a long-term process. Withdrawal can be evident for three months or longer.<sup>16</sup> Whiteley's group<sup>19</sup> found a mere 26-percent reduction in urinary levels of gluten after a five-month exclusion diet. In some cases dramatic improvement

emerged a full 7-9 months after initiating the diet, but maximal improvement can require up to two years of rigid dietary exclusion. Shattock and Whiteley advise against adding these foods back into the diet, since severe opioid symptoms could result.<sup>14</sup>

### *Sensitivities to Other Foods*

Whereas children with neurodevelopmental disorders frequently have sensitivities to common foods, ASD children seemingly have extreme sensitivity to a wide range of foods. These sensitivities may contribute to the perceptual and processing difficulties that typify autism, yet are difficult to objectify. The classic allergy symptoms such as stuffiness, eczema, wheezing, and itching may be absent, yet cognition and behavior remain affected.<sup>2</sup>

Once the main sources of food intolerance – casein, gluten, and gliadin – are removed from the diet, other foods may emerge as sources of symptoms. Parents, particularly those who keep food diaries, can often associate the child's consumption of a particular food with deterioration in behavior, sleep patterns, or performance. Beef, pork, rice, and potatoes are only occasionally implicated; whereas, foods that consistently cause problems are eggs, tomatoes, eggplant, avocados, red peppers, soy, and corn. Seroussi<sup>21</sup> described how corn was revealed as a problem food only after strict removal of gluten and casein from the diet. If a particular food is suspected, it should be removed from the diet for a trial period of at least three weeks and any improvements noted. On being reintroduced into the diet, it will likely trigger an exacerbation of symptoms.

Even immune-mediated food allergy diagnosis can be challenging.<sup>6</sup> Hospital-based laboratories often test for food allergy by measuring antibody levels, in particular IgE antibodies. But the food allergies seen in autism usually are not of the IgE-mediated, immediate hypersensitivity type that typically feature hives or sudden symptom onset. Rather, they tend to 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) testing by reliable laboratories. Both trials demonstrated significantly better symptom reduction in subjects avoiding IgG-reactive foods versus IgG-nonreactive foods.<sup>2,6</sup>

Food intolerances and sensitivities – a wide spectrum of reactions to foods or food constituents, sometimes highly nonspecific and not necessarily immune-mediated – are sometimes erroneously equated with food allergies, which by definition are immune mediated. While screening for serum antibodies can be a useful means to screen for suspected food allergens, it is unlikely to detect the full range of food sensitivities. For example, in the study mentioned above, Reichelt and collaborators<sup>16</sup> examined 15 ASD subjects for serum antibodies to dietary proteins by ELISA (IgA and IgG) and for abnormal protein-peptide complexes in the urine. Just one-third of the subjects (5 of 15) scored abnormally high at baseline for antibodies to casein, gluten, or gliadin. They implemented dietary restriction of casein and gluten foods, and after six months urinary levels of protein-peptide complexes were down in every subject. After one year, 13 of 15 subjects were improved in at least some of 14 symptom categories. Although not double-blind, this study supports two other studies on casein and gluten restriction in which up to 80 percent of subjects improved.<sup>13,14</sup>

While food allergy testing is confined to immune-mediated mechanisms, and can miss a much broader spectrum of food intolerances and other sensitivities, the basic approach to food allergy management closely resembles that for food intolerance; i.e., eliminate the food from the diet as completely and as early in life as possible. Thus, for the treating clinician, systematic dietary elimination of suspect foods is likely to have more clinical value than painstaking laboratory assessments for food allergy.

Perhaps due to wide-ranging difficulties with foods, children with autism are typically “picky” eaters who will often accept only a restricted range of foods. Further dietary restrictions

and removal of staple elements of the diet are likely to result in reduced intakes of vitamins, minerals, and other essential nutrients. Therefore, a nutrient supplementation regimen is always appropriate.

## Nutrients Most Likely to Benefit Autism

A variety of nutrients have been reported as deficient or imbalanced in autistic children, with wide variability from child to child. Relatively little controlled research has been conducted on the benefits of dietary supplementation for the disorder. However, since 1967, the Autism Research Institute (ARI) has collected and periodically publishes semi-quantitative ratings of various nutrients.<sup>22</sup>

The ARI developed the Treatment Effectiveness Survey questionnaire and provides them to parents, asking for a rating of each nutrient, drug, dietary modification, or other biomedical intervention. These are now available online.<sup>23</sup> Parents are asked to score “made better,” “made worse,” or “no effect.” Periodically the ratings are tabulated, and a “Better:Worse” ratio (B:W ratio) derived for the number of children parents judged got better versus worse. The cumulative nutrient data from 21,500 parents were summarized in April 2002.<sup>24</sup> This section covers those nutrients that, from clinical trials and/or the ARI’s B:W ratios, seem to offer the best benefit:risk ratio.

## Multiple Vitamin-Mineral Supplements

Individuals with autism typically have poor nutritional status. They often have poor digestion (approximately 25 percent have chronic diarrhea; 25 percent have constipation).<sup>25</sup> Many have intestinal inflammatory conditions that limit nutrient absorption.<sup>26</sup> Often beneficial bacteria in the intestines are depleted, so fewer vitamins are produced by these friendly symbionts (vitamin B12, biotin, and vitamin K, in particular).<sup>1</sup> Rimland asserts that adults and half of ASD children benefit from multivitamin supplementation.<sup>22</sup>

In 2000, Vogelaar reported on the nutrient status of 20 autistic children.<sup>27</sup> Over 50 percent of subjects had low levels of vitamins A, B1, B3, and B5, and biotin; minerals selenium, zinc, and magnesium; essential amino acids; and two essential fatty acids (omega-3 eicosapentaenoic acid (EPA) and the omega-6 dihomo-gamma-linolenic acid (DGLA)). Other clinicians report frequent deficiencies of vitamins B6 and B12 and folate. In 2002, Adams reported on a double-blind, placebo-controlled trial supplementing a multivitamin-mineral complex to 16 autistic children for three months.<sup>25</sup> Blood levels of vitamins B6 and C were significantly increased, and sleep and bowel patterns (parents' scores) were significantly improved. Multivitamin-mineral supplements for ASD children should not be supplemented with copper because it is one mineral they often have in excess.<sup>28</sup>

### ***Vitamin B6 and Magnesium***

Vitamin B6, in its active form of pyridoxal-5-phosphate (P5P), is an essential cofactor for a majority of metabolic pathways of neurotransmitters, including serotonin, gamma-amino-butyric acid (GABA), dopamine, epinephrine, and norepinephrine. Magnesium is an essential macromineral required for a wide range of enzyme-catalyzed metabolic pathways. Rimland recently reviewed 18 autism studies conducted with vitamin B6, especially in combination with magnesium,<sup>22</sup> and concluded that all provided positive results with no significant adverse effects. While no cures of autism by vitamin B6 are known, many cases of remarkable improvement have been documented.

A 1988 paper by Rimland provided an in-depth review of the history of vitamin B6 for autism.<sup>29</sup> In 1966, Heeley and Roberts reported vitamin B6 corrected abnormal tryptophan metabolism in 11 of 19 autistic children.<sup>30</sup> In 1968, Bonisch (cited in Rimland, 1988<sup>29</sup>) reported vitamin B6 (100-600 mg per day) improved behavior in 12 of 16 autistic children. According to Rimland, three of Bonisch's subjects spoke for the first time while participating in this open trial.

After conducting an exploratory, non-controlled study in the early 1970s,<sup>31</sup> in 1978 Rimland published the findings from a small double-blind trial that involved 15 children with autistic symptoms.<sup>32</sup> In this trial only half the children involved qualified as ASD by current criteria.<sup>32</sup> In this crossover trial, each child received vitamin B6 at a dose of 2.5-25.1 mg/kg body weight/day (75-800 mg per day) or a placebo. Following a complex, five-phase protocol, each child continued taking whatever vitamins, minerals, or drugs they had been receiving prior to the study and the duration of B6 dosing was individualized. Rimland stated they also received "several hundred" mg per day of magnesium and a B-complex vitamin to guard against overdosing with B6.<sup>22</sup> Statistically significant benefits emerged from this trial, including better eye contact, less self-stimulatory behavior, more interest in surroundings, fewer tantrums, and better speech.<sup>32</sup> Rimland began to suspect for many children autistic symptomatology might be a type of vitamin B6 dependency syndrome.<sup>29</sup>

Following these promising findings, LeLord and colleagues were persuaded to further the research on vitamin B6 and magnesium for autism.<sup>29</sup> By 1981, after completing a number of studies, these researchers concluded vitamin B6 used with magnesium was a breakthrough autism intervention for about half the cases they studied.<sup>33,34</sup> Urinary homovanillic acid (HVA) levels fell, an indication of improved metabolism of dopamine; and average evoked potentials (AEP), a measure of sensory processing ability, also were improved.<sup>34</sup>

Rimland recently reviewed 18 studies on high-dose vitamin B6 for autism,<sup>22</sup> with positive outcomes. Eleven were double-blind, placebo-controlled trials. One small study with negative outcome was criticized by Rimland for "obvious bias."<sup>35,36</sup> Conducted by Findling et al, its sample size was 10 children.<sup>35</sup> Its design was double-blind, and included a crossover but no washout period was allowed between the B6 and placebo phases. Rimland<sup>36</sup> pointed out that the full outcome data were not provided. The authors admitted this study could not rule out benefit for vitamin B6 and magnesium in autism.

Taken together, the studies seem to establish that vitamin B6 can benefit as much as half of children and adults with autism, and that its efficacy and safety are improved when combined with magnesium. None of these studies reported any significant adverse effects, even though the vitamin B6 doses ranged as high as 1,000 mg per day. Rimland emphasized that thousands of autistic people have been taking large daily doses of vitamin B6 (as much as 1,000 mg) for decades without experiencing problems. One publication reported on seven cases of peripheral neuropathy from daily intakes of more than 2,000 mg vitamin B6.<sup>37</sup> These patients were not taking magnesium or other B vitamins, as usually recommended when taking large vitamin B6 doses; nor were they taking the active form – P5P – that has not been associated with toxicity. In a later study, doses of 30 mg/kg/day of B6 as pyridoxine hydrochloride (equivalent to as much as 2,100 mg for a 70 kg adult) were administered with 10 mg/kg/day of magnesium lactate to 11 autistic children for eight weeks; behavior significantly improved and no adverse effects were evident.<sup>38</sup> The latest ARI parent ratings in 2002<sup>24</sup> 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.

Cases of hereditary impairment of pyridoxine metabolism have been described, sometimes manifesting as seizure disorder and autism symptomatology.<sup>39</sup> Conversion of vitamin B6 to its active form P5P by the liver can be compromised in some autistic children. For these cases P5P supplementation may work more effectively, although hyperactivity is a possible adverse effect.<sup>40</sup> An intake threshold for achieving benefit may be approximately 200 mg vitamin B6 (as pyridoxine) and 100 mg magnesium per day for the 70 kg individual.<sup>41</sup> In any case, the cumulative results from the double-blind trials and numerous other studies and case history reports are consistent with impressive efficacy of the combination of vitamin B6 and magnesium for autism, superior to either nutrient alone.<sup>38,42-44</sup>

### *Dimethylglycine*

Dimethylglycine (DMG) is an orthomolecule present in small amounts in foods, and is an important methyl donor with antioxidant character. Early feedback from parents promoted interest in DMG for autism; however, to date only three small autism studies with DMG are available.

Kun administered DMG to 39 autistic children (age 3-7 years) for three months;<sup>22</sup> benefits were reported for 31 (80%). Kern and collaborators conducted a four-week, double-blind, placebo-controlled trial on 37 children age 3-11 years.<sup>45</sup> Both the DMG and placebo groups improved but with no significant difference between the two groups. The short period of this trial may have been insufficient for the full DMG benefits to emerge. Similarly, Bolman and Richmond<sup>46</sup> conducted a small, double-blind, short-term trial with low-dose DMG (125-375 mg/day) and found no significant results. The parent B:W ratio for DMG is currently 5.9:1, from 4,547 questionnaires.<sup>24</sup>

The nutrient TMG (trimethylglycine; betaine) has a third methyl group, and some experts believe it could prove more clinically effective than DMG. To date the B:W ratio is less favorable for TMG, at 3.1:1 (182 questionnaires). It may be that DMG does more for the autistic subject than merely supporting methylation. Both these nutrients may best be 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. DMG usually begins to show benefit after 1-4 weeks and, in an occasional case, has had dramatic results within the first 24 hours. Although speech is the most consistent benefit, behavior might also improve. Seizures have been ameliorated by DMG, an important benefit since an estimated one-third of ASD subjects have seizures by adulthood.<sup>47</sup> Occasionally an ASD child will experience transient hyperactivity; administering folic acid and vitamin B12 with DMG lessens the likelihood of this effect.<sup>48</sup>

### *Folic Acid*

Folic acid is essential to numerous metabolic pathways. Its current B:W ratio is 11:1, from 1,100 questionnaires. Several researchers report folic acid has favorable effects on patients with autism associated with fragile X syndrome. LeJeune pioneered folic acid treatment of fragile X and, according to Rimland,<sup>29</sup> obtained favorable results on several non-fragile X autistic children by giving relatively large doses of folic acid (0.5-0.7 mg/kg/day).

### *Calcium*

Bradstreet and Kartzinel report calcium and magnesium deficiency is common in autistic children.<sup>14</sup> Landgrebe and Landgrebe found 22 percent of an autistic children sample had low 24-hour urinary calcium excretion.<sup>49</sup> ARI parents gave calcium a B:W ratio of 14:1 (988 questionnaires).

### *Vitamin B3 (Niacin/Niacinamide)*

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

### *Vitamin C*

Vitamin C has a reputation for its involvement in a plethora of metabolic, antioxidant, and bio-synthetic pathways, and as a cofactor for certain enzymes necessary for neurotransmitter synthesis. In a double-blind trial for 30 weeks, vitamin C (8 g/70 kg body weight/day) improved total symptom severity and sensory motor scores.<sup>50</sup> Its current parent B:W ratio is an excellent 16:1, from 1,306 questionnaires.

### *Zinc*

Among its many functions, zinc is needed for the development and maintenance of the brain, adrenal glands, GI tract, and immune system. Serotonin synthesis relies on zinc-activated enzymes; and zinc is also essential for antioxidant enzyme activity and other proteins important for growth and homeostasis. Breeding experiments with rodents indicate a zinc deficiency in the mother can

be passed on to the offspring and negatively influence immunity and brain development.<sup>51</sup> Zinc currently has a very favorable B:W ratio, 17:1 from 835 questionnaires.

Zinc operates in a relationship with copper, i.e., when zinc levels go down, copper levels often go up. Bradstreet and Kartzinel assert zinc is deficient in 90 percent of ASD cases and copper in excess in 90 percent of cases.<sup>14</sup> Walsh analyzed copper and zinc in the blood of 318 ASD subjects and reported finding abnormally elevated copper:zinc ratios in 85 percent.<sup>52</sup> A smaller sampling of 22 subjects had 100-percent incidence of abnormally high, unbuffered copper (unbound to ceruloplasmin proteins) – about four times normal. Walsh's findings corroborate recommendations by Adams<sup>25</sup> and others that autistics should exclude copper from their multiple vitamins.

### *Essential Fatty Acids*

Essential fatty acids (EFAs) function as homeostatic constituents of cell membranes, helping to relay signal information from outside the cell to the cell interior and are precursors to eicosanoids that influence other cells, similar to hormones. The longer-chain, 20- and 22-carbon species are crucially important for prenatal and postnatal brain development.<sup>53</sup>

Biologically, the 18-carbon EFAs linoleic acid (omega-6) and alpha-linolenic acid (omega-3) qualify as vitamins since deficiency states are known. Some adults can generate the longer-chain EFA from the shorter-chain fatty acids, but infants are highly limited in this capacity.<sup>54</sup> 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 (around 4:1 omega-6 to omega-3). This confirms a major role for EFAs in postnatal development.

Essential fatty acids, particularly the omega-3s, are deficient in other neurodevelopmental disorders, including ADHD, dyslexia, and dyspraxia. These conditions have a striking degree of symptomatic, familial, etiopathological, and other biological overlap with the autistic spectrum.<sup>55</sup> Recently, in a unique workshop held at Inverness, Scotland, it was proposed

that abnormalities of fatty acid and phospholipid metabolism could help account for many features common to these conditions and to other neuropsychiatric disorders such as schizophrenia, bipolar disorder, and depression.<sup>56</sup>

Studies on EFA deficiency in autism are few, but with consistent results. Bradstreet and Kartzinel found omega-3 fatty acids are deficient in nearly 100 percent of ASD cases.<sup>14</sup> Vancassel and collaborators reported DHA 23-percent reduced, total omega-3s 20-percent reduced, and omega-6s unchanged in plasma phospholipids.<sup>57</sup> Hardy and Hardy studied 50 children with the more inclusive diagnosis Pervasive Developmental Disorder (PDD), and reported almost 90 percent omega-3 deficient via red cell analysis.<sup>58</sup>

Controlled trials testing EFAs for their role in autism are clearly overdue. Stoll has outlined a research agenda that might be appropriate.<sup>59</sup> Still, physicians report autistic patients benefit from omega-3 supplementation. Fatty acid supplements (nature unspecified) currently have a B:W ratio of 12:1. Megson reported cod liver oil (CLO), rich in omega-3 EFAs and vitamins A and D, provided substantial benefit for autism.<sup>60</sup>

### 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 children to whom natural vitamin A from CLO was administered for three months or longer.<sup>60</sup> Some cases exhibited marked improvement within days; core autism symptoms, such as language, eye contact, ability to socialize, and sleep patterns, were consistently improved. Megson noted that the natural vitamin A found in CLO is mostly in the “trans” form but about 12-percent is in the “cis” configuration, which is entirely lacking in synthetic vitamin A. Megson hypothesizes the cis-vitamin A of CLO is unblocking central retinoid receptors in the brain and G-alpha signal transduction proteins to which they are attached.

Although cod liver oil is unlikely to provide a sufficiently high content of omega-3 fatty acids to correct the extent of deficiency extant in

developmentally impaired children, and the possibility of vitamin A toxicity limits its upper dosing level, it still has good clinical value. It is important to avoid CLO contaminated with mercury and other heavy metals. The B:W ratio for CLO is 14:1, and for vitamin A (probably mostly the synthetic form) 22:1.<sup>24</sup> To the extent that the parent feedback ratings have meaning, a comparison of these specific ratios might cast doubt on the importance of natural as opposed to synthetic vitamin A.

### Other Nutrients with Possible Autism Benefit

Bradstreet and Kartzinel claim poor diet results in vitamin, antioxidant, and fiber deficiencies in close to 100 percent of children with autism.<sup>14</sup> Supplementation with vitamins as well as conditionally-essential nutrients such as taurine, coenzyme Q10, and carnitine may provide benefit.

Carnitine is an amino acid indispensable for energy generation. Although it is produced in the body, it may require supplementation. Valproate, a drug prescribed for seizures, is known to deplete carnitine.<sup>61</sup> In one open-label study carnitine benefited patients with Rett Syndrome, a developmental disorder that shares features with autism.<sup>62</sup> Constipation and self-abuse decreased while mood improved. A small, double-blind trial with 35 Rett Syndrome patients demonstrated clear improvement in well-being.<sup>63</sup>

The pterin substances, biopterin and its precursor neopterin, are nutrient orthomolecules found naturally in body fluids, including urine. During periods of immune activation (as with autoimmune exacerbation) their levels in urine are increased.<sup>64</sup> Biopterin, in its reduced form (5,6,7,8-tetrahydrobiopterin, R-BH4), is a limiting factor for the biosyntheses of dopamine, epinephrine, and serotonin. Autistic children, particularly those six years or younger, can have relatively low R-BH4 in their cerebrospinal fluid (CSF) and abnormally high urine R-BH4, indicating increased loss from the body. Also, the enzyme (dihydropteridine reductase) that recycles biopterin into its biologically active reduced form, R-BH4, is lower in au-

tistic children younger than 12 years. In a pilot study, six autistic children, age 3-5 years, were treated with R-BH4 for three months.<sup>65</sup> All parents reported improvement in language, eye contact, and sociability. The CSF levels of R-BH4 were significantly increased. Positron emission tomographic (PET) findings were equivocal. The investigators suggested further investigation of R-BH4 therapy in autism.

Inositol is a precursor for the synthesis of phosphatidylinositol (PI), a phospholipid that is part of a complex cellular transmission pathway that facilitates serotonin receptor function. In double-blind trials it has been found safe and beneficial for depression, panic disorder, and obsessive-compulsive disorder. In a small, double-blind trial with nine autistic children, no significant benefits emerged.<sup>66</sup> The investigators conceded their efficacy measures were crude and suggested inositol be re-investigated.

Magnesium sulfate (Epsom salts) can 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.<sup>67</sup> Other parents who used the treatment soon reported improvements in speech, mood, cooperation, and motor development.

## Second Phase: The Medical Workup

Autism is not a condition that can be managed by frequent visits to a routine medical practice. Finding a physician experienced with ASD can be challenging, but is aided by the Autism Research Institute's referral service.<sup>4</sup> Veteran DAN! practitioners Baker and Pangborn<sup>6</sup>

**Table 2. Recommended Laboratory Evaluation of Autistics<sup>6,68</sup>**

- Blood chemistry screen, including thyroid tests
- Complete blood count
- Urinalysis
- Serum ferritin and iron
- Amino acid screen (urine)
- Organic acid screen for inborn errors of metabolism (urine)
- PKU screen, routine in the United States but not in some other countries
- Chromosome studies—Fragile X, Rett, Lesch-Nyhan (when indicated)
- MRI, CAT scan, or X-rays (when indicated)
- Electroencephalogram (when indicated)
- Landau-Kleffner screening (when indicated)

recommend a series of tests be undertaken promptly following diagnosis (Table 2).

## Ruling Out Genetic and Metabolic Predispositions

The issue of genetic predisposition to autism has great clinical relevance and was reviewed in depth in part I. Autism undoubtedly has a strong heritability component, and sophisticated, noninvasive genotyping on siblings and other relatives will sometimes yield fruitful leads concerning the ASD subject's symptom patterns.<sup>20</sup>

A number of congenital enzymatic weaknesses (inborn errors of metabolism) can mimic or contribute to ASD symptomatology (Table 3). Amino acid analysis can often give clues to their presence. Altogether, these abnormalities amount to compromised formation and balance of purines and pyrimidines that provide the bases of RNA and DNA.<sup>68</sup> Page discussed the sometimes-successful use of metabolites to override the metabolic weakness and improve autistic-like symptoms.<sup>69</sup>

**Table 3. Inborn Errors of Metabolism that Mimic or Contribute to Autism or ASD. From Pangborn<sup>6,68</sup> and others<sup>69</sup>**

- PKU variants
- 5-Phosphoribosylpyrophosphate deficiency
- Fragile X
- Inosine 5-phosphate dehydrogenase weakness
- Histidinemia/Histidinuria
- Lesch-Nyhan disease
- Adenosine deaminase (ADA) weakness
- Adenylosuccinate lyase deficiency
- ADA binding protein weakness
- 5'-Nucleotidase superactivity
- Dihydropyrimidine dehydrogenase deficiency

### Amino Acid Abnormalities

At least two-thirds of autistics have abnormal amino acid levels, as measured in 24-hour urine or fasting blood plasma. High phenylalanine is rarely seen (one per several thousand autistics) but can occur without overt phenylketonuria (PKU), which may be observed in children from countries that do not test for PKU at birth. High histidine (histidinuria and usually concurrent histidinemia) is seen in one per 250-500 autistics, and also can mimic autism. High urine levels of several amino acids (generalized hyperaminoaciduria) almost always indicate toxic chemical exposure and consequent liver damage. Such is also attributable to heavy metal contamination and Wilson's disease, Fanconi syndrome, cystinosis, fructose intolerance, galactosemia, and several other hereditary disorders.<sup>6</sup>

Low urine threonine suggests malabsorption. In maldigestion, anserine and carnosine are high, while the essential amino acids are low. Anserine and carnosine may also be high due to zinc insufficiency. When citrulline, methionine, ethanolamine, and phosphoethanolamine are elevated, functional magnesium deficiency is likely. Elevated sarcosine indicates toxic exposures and/or folate deficiency. And,

when detoxification capacity is limited, the cysteine/cystine ratio, and methionine, taurine, and glycine levels tend to be abnormal.

The essential sulfur amino acid methionine is occasionally found to be low, more frequently in subjects age four years or younger. Cysteine, another sulfur amino acid important for the formation of glutathione and taurine, is often low in young autistics and high in those older than five years. Since glutathione (GSH) is often low in ASD, a flaw in cysteine's incorporation into GSH could be involved. Cysteine abnormalities also would be consistent with the impaired sulfation and metallothionein synthesis often found in ASD.<sup>1</sup> Overall, the evidence suggests frequent impairment(s) in the pathway:

**Methionine ⇒ S-adenosylmethionine ⇒ S-adenosylhomocysteine ⇒ cystathionine ⇒ cysteine ⇒ taurine**

Pangborn found taurine deficiency is common in autistic children, reaching a 62-percent frequency on 24-hour urine analysis.<sup>70</sup> When taurine is low bile function is low, which can cause maldigestion and impaired liver detoxification capacity. Taurine is also a potent antioxidant, osmotic buffer in the brain and elsewhere, a pro-homeostatic neurotransmitter, and an immunoprotectant.

Glutamine is an energy source for enterocytes of the small intestine, helps form nicotinamide for energy transfers and glucosamine for connective tissue, and contributes to purine and pyrimidine nucleotides. Glutamine is also a building block for GSH. Glutamine is low in some autistics, particularly in those with an aversion to meat or poultry.

Autistic subjects who poorly metabolize tryptophan can carry its potentially toxic metabolite indoylacrylic acid (IAA) in their blood. IAA would normally be detoxified by combining it with glycine to make indoylacryloylglycine (IAG). Organophosphate pesticide contamination may shunt tryptophan down the IAG pathway.<sup>6</sup>

Tryptamine, found in tomatoes and all types of bananas, may also raise IAG levels. Certain citrus fruits also may contain tryptamine-like substances. Assays for IAG are not routinely available and are easily contaminated.

Clostridium bacteria that can produce neurotoxins in the intestines can also elevate IAG. A minimally absorbable antibiotic such as vancomycin can be useful,<sup>71</sup> especially if given concomitantly with a high-potency probiotic re inoculation.<sup>72</sup>

The DAN! assessment manual lists the laboratories best qualified to perform assays, and the pharmacies that custom-blend formulations for correcting measured abnormalities. They also list cautions to be observed when prescribing amino acid mixtures.

### **Peptide Abnormalities<sup>6</sup>**

Peptides (small polymers of amino acids) act as regulatory or signal molecules, affecting a variety of neurotransmitter systems that regulate behavior. Certain peptides can be abnormally elevated in the urine of ASD subjects.<sup>73</sup> For example, as previously mentioned, high urinary levels of the dipeptides anserine and carnosine generally indicate poor digestive function.

Certain food-derived peptides have endorphin-like effects on the dopamine neurotransmitter system, and to differing extents also the cholinergic, serotonergic, noradrenergic, and GABAergic systems. In 1979, Panksepp suggested incompletely digested peptides with opioid activity could be causative in autism.<sup>74</sup> Thus began the “opioid excess” theory of autism alluded to in part I of this review. In 1981, Reichelt and colleagues reported abnormal peptides with opioid activity in the urine of 22 of 25 autistics studied.<sup>73</sup> Gillberg later found excessive levels of endorphin-like substances, later coined exorphins, in the CSF of autistics.<sup>75</sup>

Dietary exorphins are peptides produced from incomplete digestion of casein or gluten foods – casomorphins, gluteomorphins, and gliadomorphins<sup>4</sup> – all with powerful endorphin-opiate activity in the brain. Effective digestive

breakdown of these substances normally relies on only one, highly specialized peptidase enzyme called dipeptidyl-peptidase IV (DPPIV). Congenital weakness in DPPIV function was linked to autism by Stubbs in 1982.<sup>76</sup> The DPPIV enzyme is also highly sensitive to mercury and organophosphate xenobiotics.<sup>6</sup> This metabolic weakness may be a cause of ASD by enhancing absorption of exorphins, leading to adverse reactions in the brain and to immune dysregulation.<sup>68</sup>

In 1990 Shattock et al reviewed the various mechanisms by which opioid peptides may initiate perceptual impairment, stereotypic behaviors, self injury, and other autistic behavior.<sup>77</sup> They discussed how the blockade of dopamine receptors by opioids can result in spillage of dopamine into the CSF, or into the urine predominantly as homovanillic acid. High CSF and/or urine HVA is a frequent finding in subgroups of ASD children, and is an indicator of possible CNS insufficiency of dopamine.<sup>77</sup>

To decrease the possibility of abnormal peptide production from foods, protein digestion can be improved by supplementing with digestive enzymes and betaine hydrochloride (HCl).<sup>48</sup> Since enzyme supplementation does not guarantee inhibition of exorphin production from casein and gluten foods, a strict casein- and gluten-free diet should still be considered.

### **Correcting Gastrointestinal Abnormalities**

Many ASD individuals have GI abnormalities (see part I of this review). Maldigestion and malabsorption are common and combine with dysbiosis that commonly results from repeated antibiotic treatment. Chronic inflammation of the GI tract afflicts at least half of ASD subjects sampled, whether or not symptoms manifest.<sup>78</sup> Melmed et al reported that a study of 385 autistic people found 46 percent had chronic diarrhea, constipation, or other GI symptoms.<sup>79</sup> Horvath et al reported on 36 ASD children with chronic diarrhea, gas, abdominal discomfort and distension.<sup>80</sup> More than two-thirds had GI inflammation, associated with impaired digestive enzyme activity.

In 2002, Wakefield's group published a provocative overview of a pattern designated autistic enterocolitis,<sup>26</sup> featuring motility disorder combined with inflammation. They reported impressive improvement from the use of 5-aminosalicylates and a limited diet, including casein and gluten elimination, to decrease inflammation. The dysmotility could be due to exorphin actions directly on the GI tract. They discussed a scenario in which exorphins, such as gluteomorphin or gliadomorphin from wheat and beta-casomorphin from milk, escape digestion by the DPPIV enzyme due to gut damage. These substances can either be absorbed, reach the bloodstream, and travel to the CNS; or act locally to directly impair the intestinal wall motility.

Integrative practitioners have worked closely with laboratories to develop comprehensive assessments of GI abnormalities.<sup>20,68</sup> One result of this effort is the comprehensive digestive and stool analysis (CDSA) that includes tests for digestive function (undigested food, for example), metabolic function (particularly short-chain fatty acids that reflect probiotic activity), microbiology (from bacterial culture), mycology (presence and types of yeasts and other fungi), and parasitology. The Biomedical Assessment manual from DAN! lists laboratories that offer CDSAs.<sup>20</sup>

Frequent findings in autism are discussed below, together with some of the corrective approaches suggested by Baker and Pangborn in the DAN! assessment manual.<sup>6</sup> For a more comprehensive list of options this manual should be consulted directly.

Bolte<sup>81</sup> suggested the possibility of a subacute, chronic tetanus infection of the gut as an underlying cause of autism in some individuals. *Clostridium tetani* is a ubiquitous anaerobic bacterium that is opportunistic in the gut and produces a potent neurotoxin. This toxin can move from the intestine to the brain via the vagus nerve. Antibiotic treatment should be accompanied by high-potency probiotic replacement.

### ***Correction of Intestinal Hyperpermeability (Leaky Gut)***

The luminal-facing surface of the intestinal wall is only a few cell layers thick, yet it must function to efficiently absorb nutrients while acting as a barrier to prevent other intestinal contents from entering the bloodstream. A variety of insults can increase the permeability of this layer. A 1996 study by D'Eufemia<sup>78</sup> found that 43 percent of a sample of autistic children had increased intestinal permeability or "leaky gut" syndrome.

Inflammation commonly causes increased intestinal permeability.<sup>26</sup> Nutritional deficiencies; localized food intolerance or allergic responses; infection, *Candida* overgrowth, parasites; oxidant or inflammatory xenobiotic toxins; and drugs such as aspirin that can damage the protective mucus all may contribute to leaky gut. Integrity of the gut should be corrected before other modalities can optimally benefit autism.

The test for permeability is based on the differential absorption of two inert (non-metabolized) substances. Mannitol, a sugar alcohol, has low molecular weight and routinely passes across the healthy intestinal epithelium, later to be excreted in the urine. The lactulose molecule is larger and normally is not absorbed but passes with the feces. A urine-based test can detect signs of potential intestinal hyperpermeability from the amount of each of these two substances that reaches the urine.

Measures to correct intestinal hyperpermeability include correcting other intestinal abnormalities such as pancreatic insufficiency, dysbiosis, *Candida* or other fungal overgrowth, parasites, and so on. The diet should be redesigned to increase protein and fiber intake and lower digestible carbohydrates,<sup>2</sup> and 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. The amino acid L-glutamine can be supplemented, as a direct source of energy for the damaged enterocytes. To ensure the most efficient food digestion to minimize allergenicity, digestive enzymes with defined protease, amylase, and lipase activities can be comprehensively

supplemented. Betaine HCl supplementation may be useful and secretin therapy could be an option.

### *Effect of Secretin in Autism*

Secretin is a small protein substance (27-amino acid polypeptide), a neuropeptide hormone normally secreted by cells of the upper intestinal tract. It is secreted in response to a bolus of food entering the stomach and stimulates the pancreas to release bicarbonate, which raises the pH of the intestinal environment so that the digestive enzymes later secreted by the pancreas can work optimally. It also stimulates release of bile from the liver and pepsin from the stomach. With GI disturbances reported in two-thirds of autistic children,<sup>80</sup> use of secretin supplementation seems rational. In laboratory rats, receptors for secretin were found throughout the brain, and secretin injected into the brain was demonstrated to activate the amygdala.<sup>82</sup>

A “secretin craze” began in 1998, when reports circulated from an uncontrolled trial with just three autistic children.<sup>83</sup> Its findings indicated secretin therapy might dramatically improve socialization and communication abilities along with GI symptoms. Several controlled clinical trials of secretin since completed yielded mixed results. Single or double intravenous doses were not consistently beneficial under double-blind or other controlled conditions, but investigators were unable to rule out the possibility a subgroup of children may benefit. A meta-analysis conducted in 2000 left open the possibility of a response rate to secretin of one child in 10.<sup>84</sup>

Drawing on an unpublished secretin study, Bradstreet and others have asserted that severely autistic children respond better to secretin than those only mildly autistic.<sup>13</sup> Improvements were claimed for behavior, eye contact, and spontaneous communication. But in a double-blind, placebo-controlled, phase II, multi-dose trial conducted by the manufacturer,<sup>85</sup> parent ratings of significant improvement were not corroborated by professional raters. In Japan secretin is used intramuscularly (i.m.) as ulcer therapy. Shaw referred to a Japanese double-blind trial, using i.m. secretin, that claimed benefit of core symptoms

in 75 percent of a sample of autistic children.<sup>86</sup> This product was less purified, and Shaw suggested other enzymes in the preparation may have conferred additional benefits beyond those of secretin alone.<sup>86</sup>

Herlihy<sup>85</sup> and Shaw<sup>86</sup> recently summarized the current information on secretin. Despite the lack of clear benefit found in controlled trials to date, case histories continue to suggest it may have utility for special cases. Secretin can be administered by oral, intravenous, intramuscular, or transdermal routes. Transdermal application is a highly convenient means of delivery and may be effective.<sup>87</sup> Secretin is safe and adverse effects are usually minor.<sup>84</sup> It is currently in phase III trial assessment.

Another hormone from the small intestine, cholecystokinin (CCK), works similarly to secretin. But sulfation deficits as seen in many autistics can compromise CCK’s activity.<sup>88</sup> CCK was reported by parents to be efficacious when taken by mouth. However, Shaw states that CCK can cause harm if handled inappropriately; the dosing and timing of its administration are critical and it should only be used under a physician’s supervision.<sup>86</sup>

### **Heavy Metal Detoxification**

The biochemical profile of autism frequently features heavy metal overload, complicating impaired detoxification, as documented in part I of this review.<sup>1</sup> The affected detoxification pathways are sufficiently understood that rational intervention with nutrients can effect clinical improvement. The heavy metal burden can be reduced by oral chelation. But for these interventions to have lasting benefit, ongoing exposure to heavy metals and other toxins must be lowered to as near zero as possible.

With toxin overload and intolerance to chemicals so common in ASD individuals, a “zero tolerance” stance is essential to medical progress.<sup>89</sup> Home, school, and other locales frequented by the ASD individual should be purged of toxic materials.<sup>90</sup>

### *Mercury Chelation*

Heavy metals contaminate the everyday environment and could contribute to ASD. While lead, cadmium, arsenic, and aluminum are suspects, the evidence for mercury as a causative factor is somewhat stronger.<sup>1,91</sup> The visual disturbances, motor/coordination defects, and immune dysfunctions of autism are reminiscent of mercury poisoning.<sup>28,91</sup> Young children have been exposed to mercury through vaccination at levels that exceed the U.S. Environmental Protection Agency's (EPA) safe limit.<sup>92</sup> The mercury-based preservative thimerosal is widely used in medical solutions (e.g., RhoGam injection for Rh-sensitive mothers) and still contaminates some vaccines.<sup>92</sup> Seafood intake or dental amalgams can load the pregnant woman with mercury, some of which may be transferred to the developing fetus. A number of practitioners report virtually all their autism cases show improvement following oral chelation for heavy metal removal.<sup>28,93</sup>

Mercury continues to permeate the environment; air, water, and foods (especially marine fish) are contaminated, and mercury vapor from dental amalgams is a major emission source.<sup>28</sup> Mercury is toxic via many mechanisms. It depletes glutathione and other antioxidants, destroying antioxidant defenses; it impairs enzyme and receptor function; it poisons mitochondria, robbing the cells of energy; and it causes three-dimensional changes in proteins and other biomolecules, sometimes transforming them to autoantigens that promote autoimmunity. Mercury as thimerosal must be considered extremely toxic, inhibiting biological enzymes at very low concentrations. It likely has synergistic toxicity with aluminum, copper, and other heavy metals also present in the medical preparation.

In autistics, body mercury load is not directly reflected in results from hair analysis. For reasons still not understood, many ASD subjects exhibit lower hair mercury than the non-ASD population.<sup>28</sup> Some other, more esoteric tests for mercury intoxication are detailed by Cathcart<sup>94</sup> and by Laidler for the ARI's Mercury Detoxification Consensus Group.<sup>28</sup> Mercury appears to bind so tightly to proteins and other biomolecules that it is hard to dislodge, particularly in the tissues of

individuals afflicted with detoxification abnormalities. Following exposure, some mercury may be loosely bound and possibly detectable in the urine for a few weeks to months. After that the mercury becomes tightly bound to enzymes and other proteins, and is distributed to the liver, kidney, brain, and other organs with little remaining in the blood, hair, or urine. The best option for detection is a provoked urine excretion challenge, using a chelating agent that clears mercury via the urine.

Clearance of mercury from the tissues is a prerequisite for "fixing" homeostatic balance, detoxification capacity, and overall health status of the ASD subject. The best mercury chelators are DMSA (2,3-dimercaptosuccinic acid; succimer) and DMPS (2,3-dimercapto-1-propanesulfonic acid). DMSA is approved by the U.S. Food and Drug Administration (FDA) to treat lead poisoning in children, and is regarded as safer and better proven for this population. However, DMPS may work better for some subjects, including those who do not yield urine mercury with DMSA.<sup>95</sup> Lead, cadmium, arsenic, antimony, and other metals are also chelated by these agents and cleared via the urine; therefore, the urine analysis may show a number of toxic metals.<sup>28</sup> Some practitioners also monitor stool mercury levels during detoxification treatment.

To be conducted safely and effectively, 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. For the subject to be considered for detoxification most physicians require:<sup>48</sup>

- ◆ **Normal creatinine clearance**
- ◆ **No allergic reaction to a small sample of chelating agent**
- ◆ **Discontinuation of vaccines containing thimerosal**
- ◆ **Removal of mercury-containing amalgams (more of a concern with DMPS than DMSA)**
- ◆ **Vitamin, mineral, fatty acid deficiencies corrected**
- ◆ **Intestinal/GI health assessed and restored**

- ◆ **Seafood consumption cut (some sources may be allowed)**
- ◆ **Casein- and gluten-free diet**

The active detoxification process begins with the choice of chelating agent. Most often the first choice will be DMSA, due to more ample clinical experience with its use. Prior to starting the patient on DMSA, CBC and liver transaminase enzyme tests should be performed to obtain a baseline in the unlikely event the patient has an adverse reaction.<sup>28</sup> Blood urea nitrogen (BUN), creatinine, and creatinine clearance help establish normal renal function. As DMSA begins binding mercury, levels of this and other heavy metals should appear in the urine.<sup>96</sup> The schedule involves “on and off” cycles, in which the chelator is applied for a few days, then a rest period is taken for a longer period to allow for replenishing of essential trace minerals lost in the chelating process. The most common cycle is three days on and eleven days off the chelators (3/11); but 3/4, 5/9, or even alternating-days cycles have been used. The recommended dose is generally 10 mg/kg/day (total) in three divided doses between meals; higher doses may be used if the patient is monitored and accompanied by colonics.<sup>28,48,92</sup> If adverse effects manifest, the dose can be lowered and given more frequently.

Cathcart, who uses a modification of the Holmes protocol,<sup>92</sup> advocates that DMSA blood levels should be kept elevated throughout the day for best results.<sup>94</sup> He recommends DMSA at 6 mg/lb/day, in a time-release form prepared by compounding pharmacies. Serious adverse effects of DMSA are rare (for details consult the ARI Mercury Detoxification Consensus Group<sup>28</sup>). Toxic epidermal necrolysis and Stevens-Johnson syndrome are absolute contraindications to DMSA therapy.

After the DMSA on/off cycle has been repeated several times, the urine should be tested for the progress of mercury clearance. Cathcart recommends this be done once per month.<sup>96</sup> He observes after 3-5 months the urine mercury usually falls to zero. This should mark the end of the body compartment clearance. Then comes a second phase, clearing mercury from the brain.

Since DMSA crosses the blood-brain barrier but does not readily extract tightly bound mercury from brain tissues, the Holmes and Cathcart protocols rely on DMSA to clear the body mercury first, then concentrate on the less accessible brain mercury by adding alpha-lipoic acid (ALA) to the DMSA. ALA is a potent glutathione repletor that readily enters cells and easily crosses the blood-brain barrier. A slow-release DMSA-ALA can be used.<sup>96</sup> During this phase urine mercury measurements and chelation are continued until mercury levels fall to zero. This protocol can be used to remove other heavy metals, including lead, cadmium, arsenic, and bismuth.<sup>94</sup>

In 2001, Holmes reported at a DAN! conference on 152 ASD children, ages 1-18 years, treated with a detoxification protocol.<sup>92</sup> She documented improvement in 83 percent of the total sample (126/152), but with a strong age gradient. Ninety-one percent of subjects ages 1-5 years demonstrated improvement; whereas, only 28 percent of those age 18 and above showed improvement. No one experienced marked improvement. Holmes noted that behavior sometimes worsened before improvement was noted. In some cases CNS autoantibodies and IgE-mediated allergies cleared following mercury clearance. Most common side effects of the chelation process were diarrhea and fatigue. Less common side effects included abnormal blood counts, liver enzyme elevation, and mineral abnormalities. The most rapid responders were younger children and those with a history of normal development followed by regression to autism.

### *Nutrient Support During Chelation*

The DMSA chelation process can be very taxing on the patient because minerals other than toxic heavy metals are invariably chelated and require replacement by supplementation. Further, some minerals and vitamins actually assist the detoxification process. ALA not only may help chelate heavy metals but is important for replenishing GSH levels. Other nutrients to supplement during chelation are outlined in Table 4.<sup>28</sup> Aluminum apparently is not chelated by DMSA.

**Table 4. Nutrient Supplementation for Heavy Metal Detoxification in Autistic Individuals<sup>28</sup>**

- A hypoallergenic multiple vitamin daily, during both chelation and non-chelation phases
- A hypoallergenic multiple mineral, during the chelation off days (should exclude copper)
- Alpha-Lipoic acid (ALA), preferably in combination with chelator<sup>96</sup>
- Zinc – 2 mg/kg body weight/day, maximum 50 mg/day, only during chelation off days
- Selenium – 1-4 mcg/kg/day, preferably as L-selenomethionine
- Vitamin C – 4,000 mg/day up to bowel tolerance<sup>94</sup>
- Vitamin E – 6 IU/kg/day, as mixed tocopherols. Soy sensitivity is possible
- Coenzyme Q10 – 100 mg/day
- Vitamin B6 – up to 500 mg/day, or P5P – up to 100 mg/day
- B complex, including generous folate and B12
- Glycine – 150-250 mg/day
- Melatonin – up to 0.1 mg/kg at bedtime, as a sleep aid when indicated

Brudnak makes a strong case that probiotics Lactobacilli and Bifidobacteria can assist with mercury detoxification.<sup>97</sup> The hypothesis is probiotics take up organic mercury from their surroundings, then convert highly toxic Hg<sup>2+</sup> to Hg(0) via a redox reaction. Hg(0) is hydrophobic and volatile, allowing it to escape the bacterial cell into the intestinal lumen.

Clinical signs that can improve following mercury chelation include dilated pupils, increased heart rate, a mercury rash, excessive sweating, knee jerks, hand flapping, and others. Laboratory results that can indicate improvement include pyruvic acid (blood or urine), porphyrins (urine), glutathione (red cells), blood immune system markers (IgE, IgG, NK cells), and plasma sulfate levels. Some children improve while on DMSA, then regress whenever they discontinue it, even during the “off days” of the predetermined dosing cycle. The full significance of this pattern is not yet understood.<sup>28</sup>

The ARI Consensus Group recommends that the supplements cysteine/cystine, N-acetylcysteine (NAC), and chlorella and other algae not be supplied during mercury detoxification.<sup>28</sup> They also caution that full benefits from mercury detoxification are unlikely if GI symptoms and especially dysbiosis were not previously corrected.

### ***Liver Detoxification Support Following Mercury Clearance***

In addition to mercury overload, the autistic population is documented to have higher xenobiotic pollutant load.<sup>1</sup> Edelson has reviewed a substantial body of evidence indicating environmental toxic exposure plays a role in the etiology of autism. He reports some patients have regained near-normal function after meticulous detoxification.<sup>98</sup>

The cytochrome p450 system of detoxification is vulnerable to mercury poisoning. With mercury no longer present, the liver can restore its pathways of detoxification. GSH is the single most important resource for the p450 pathways<sup>99</sup> and is often found deficient in ASD individuals. This nutrient is absorbed into the cells of the intestinal mucosa, but does not enter the liver intact.<sup>99</sup> Since it does enter the intestinal mucosal cells intact, it may be useful for individuals with inflammatory intestinal symptoms. To best replete liver GSH, its precursors can be given, including glutamine, N-acetylcysteine, alpha-lipoic acid, and glycine. Phosphatidylcholine is also hepatoprotective as it is the primary phospholipid in hepatic cell membranes.<sup>100</sup>

For the majority of ASD subjects, impaired sulfur metabolism places further stress on the liver. Sulfation is one of four major means for p450 phase II conjugation of xenobiotics, along with glutathione, glucuronic acid, and glycine.<sup>101</sup> When sulfation fails these other pathways must take up the slack. Molybdenum, an essential trace mineral, is a cofactor for sulfite oxidase, the main sulfation enzyme, and magnesium also assists with sulfur metabolism. Methylsulfonylmethane (MSM) is a safe and effective sulfur source. Taurine, a sulfur-containing amino acid, is an antioxidant, bile salt constituent, and secondary p450 conjugant.

As previously established from non-autistic populations,<sup>102</sup> poor sulfation capacity is linked to poor metabolism of dietary phenols. Pangborn advises that ASD subjects be shielded from phenolic xenobiotics (e.g., “Lysol” cleaner) and that foods high in phenols, such as bananas, onions, and coffee should be considered suspect.<sup>68</sup>

### Define and Treat Immuno-Inflammatory Imbalances

Inflammatory and immune hyperactivity states have considerable mechanistic overlap, and evidence links inflammatory cytokine imbalance to autoimmunity, both of which appear to contribute to ASD.<sup>1,103,104</sup> In a recent review, Rimland and McGinnis conclude there is “clear-cut evidence of activation of the immune response system” in autism.<sup>104</sup> They further corroborate the argument that vaccines contribute to depressed immunity, autoimmunity, and inflammatory activation commonly seen in autism. Fortunately, from research on cardiovascular disease, arthritis, and other immuno-inflammatory diseases, nutritional interventions have emerged that show promise to help mitigate immuno-inflammatory imbalances in ASD populations.<sup>104,105</sup>

Proteolytic enzymes such as bromelain and papain are well-documented anti-inflammatories and may well contribute to dampening inflammatory cascades in autism. Used in combination with other digestive enzymes and cofactors, they contribute to improved digestive efficiency and the correction of malabsorption.<sup>40</sup>

Jyonouchi and colleagues<sup>103</sup> have documented inflammatory imbalance in ASD subjects by using measures of tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-6 (IL-6). The antioxidant vitamins C and E, and GSH may help lower these *in vivo*, but currently the most promising approach is generous dosing with long-chain, omega-3 fatty acids (LCFA-3),<sup>105</sup> in particular, EPA and DHA, appropriately screened for absence of mercury or other pollutants.

Ongoing work with clinical and animal models of inflammatory over-activation has established that inflammation can be inhibited by loading the cell membranes with LCFA-3. The omega-6 to omega-3 EFA balance in cell membranes helps determine the pro- to anti-inflammatory balance of eicosanoids the membranes can produce. Once produced, eicosanoids help regulate cytokine balance.<sup>104,105</sup> Given that many, if not most, autistic children appear to produce excessive amounts of TNF-alpha and other pro-inflammatory cytokines,<sup>103</sup> it is reasonable to expect the anti-inflammatory LCFA-3s should offer benefit.

The rationale for LCFA-3 benefits – resetting the balance of prostaglandins and cytokines – can be extended to the management of pro-inflammatory coagulation states.<sup>106</sup>

### Treating Coagulation Abnormalities

Several integrative practitioners have reported seeing coagulation abnormalities in autistic children.<sup>14,107,108</sup> ISAC (Immune System Activation of Coagulation) is the test panel most often used.<sup>109</sup> The rationale is that inflammation can trigger the conversion of circulating fibrinogen to fibrin deposits that then adhere to linings of the capillaries and other small vessels to occlude blood flow. The indicated treatment is usually heparin,<sup>109</sup> although LCFA-3 might prove efficacious in this situation as well, but may take months to demonstrate efficacy.<sup>104,105</sup>

Bradstreet and Kartzinel reported finding vasospasm in autistic patients, which they treated successfully with Nimotop, a calcium channel blocker.<sup>14</sup> This condition also might respond to long-term LCFA-3 dosing.

### *Immune-Based Treatments*

Immune-based treatments include transfer factor (TF), pentoxifyllin (PXF), intravenous immunoglobulin (IVIG), and colostrum. Transfer factor is a low-molecular weight mix of molecules produced by white cells. Fudenberg,<sup>110</sup> in an open-label study, treated autistic children ages 6-15 years with TF prepared from parents of children with autism. More than half of these children had autoantibodies to myelin basic protein (MBP), and half of them had depressed lymphocyte responsiveness to mitogens.<sup>1</sup> After TF administration a majority of this sample showed significant symptomatic improvement. Food sensitivities and symptoms associated with *Candida* overgrowth also decreased.

PXF is a drug approved in the United States for treatment of intermittent claudication, but also has immunomodulatory effects. Although it can affect many cytokines, it primarily suppresses TNF-alpha production.<sup>111</sup> TNF-alpha is one of the most pleiotropic and pluripotent cytokines known, and is consistently pro-inflammatory.<sup>112</sup> It is produced systemically, including by microglia and astrocytes of the brain, and is a suspected major contributor to inflammatory and/or autoimmune brain pathologies.<sup>113,114</sup> An agent that effectively modulates TNF-alpha has potential efficacy for diverse neurodegenerative diseases.

In addition to cytokine-modulating effects, PXF has a number of other potential benefits for ASD subjects. Its hemorheologic properties include vasodilation, reduced platelet aggregability, and enhanced blood flow. It enhances serotonergic nerve transmission and can enhance long-term potentiation of electrical stimulation, a mechanism associated with learning and memory. Gupta and collaborators reviewed PXF's clinical features and several preliminary uncontrolled trials in autism.<sup>112</sup> Of a total 115 autistic patients treated with PXF, one-third experienced benefit. The most consistent benefits were increased attention and speech, improved sociability and behavior, and amelioration of seizure activity. Adverse effects, in a few patients, included nausea, vomiting, low blood pressure, headache, and (rarely) transient excitation or sleep

disturbance. The researchers concluded pentoxifyllin warranted further investigation for autism under double-blind conditions.

Intravenous immune globulin (IVIG) is prepared plasma using a highly involved purification process, from plasma donated by a large pool of donors (2,000-10,000), and contains predominantly monomeric IgG. IVIG has been used to treat a variety of antibody deficiency and autoimmune disorders, including neurological conditions such as chronic inflammatory demyelinating neuropathy and Guillain-Barre syndrome. This latter condition, like autism, features anti-MBP autoantibodies.<sup>111</sup> Since this material is in short supply, priority is normally given to children who exhibit failure to thrive, have significant serum autoantibodies or immune dysfunction, exhibit seizure disorders, or fail to respond to heavy metal detoxification programs.<sup>14</sup>

IVIG may work by correcting antibody deficiency, inhibiting TNF-alpha and perhaps other pro-inflammatory cytokines, or blocking an autoimmune response. In autism there are several clues that molecular mimicry and other autoimmune processes are operative. Among these are elevated urinary neopterin and biopterin, most likely resulting from TNF-alpha stimulation of immune cells.<sup>115</sup> Serum autoantibodies to MBP were found in 58 percent (19/33) of autistic children.<sup>116</sup> In a related study anti-brain autoantibodies reached 27 percent for IgG-type and 36 percent for IgM-type.<sup>117</sup> Torrente et al reported finding autoantibodies bound to the surfaces of intestinal epithelial cells in children with regressive autism.<sup>118</sup> A shift of T-helper cells from T-helper 1 to T-helper 2 – often seen in autoimmune conditions – was also reported in 13 of 20 children in a small study, as reviewed by Gupta.<sup>111</sup>

Gupta's group conducted a small, six-month study with IVIG on 10 autistic children ages 3-12 years.<sup>119</sup> IVIG was well tolerated and symptoms improved in a majority of patients. Behavior became calmer, eye contact improved, and in a few patients expressive speech improved. Children under five years showed more improvement and faster response.

Colostrum, the fluid expressed by the nursing breast for the first few days following birth, is another immune support agent under active scrutiny for possible benefit to autism.<sup>120</sup> Colostrum contains a wide range of immunoglobulins that generally boost immunity; antibodies, and other less specific antiviral factors; glycoproteins that inhibit the attachment of unwanted bacteria to the intestinal mucosal lining; significant amounts of the cytokine interleukin-10 (IL-10), transforming growth factor-beta (TGF-beta), and other potent anti-inflammatory factors; and various growth factors that promote cell growth, lymph node and other immune organ maturation, intestinal IgG production, and tissue repair. Interest in colostrum may be justified by the report of low levels of insulin-like growth factor I (IGF-1) in the CSF of children with autism;<sup>121</sup> and by the presence of maternal autoantibodies in the neonatal infant.<sup>122</sup>

### Autism Pharmacotherapy

The autistic spectrum has been notoriously difficult to study in controlled fashion for numerous reasons, including extreme symptom heterogeneity, the need for long-term monitoring, and the complexities of doing research with children, particularly disabled children.<sup>123</sup> With the central problems of autism (lack of communication and social connection, for example) practically unresponsive to medications, pharmacological intervention has been restricted to efforts to manage symptoms such as aggression, self-injury, inattention, and stereotypical movements.<sup>124</sup> The ARI B:W ratings suggest most of these medications demonstrate poor performance.<sup>24</sup>

### Dopamine Antagonists

The dopamine receptor antagonists, or neuroleptics, are the class of drugs that have been most extensively applied to autism, haloperidol (Haldol) being the most studied.<sup>125</sup> With short-term use (four weeks), this drug was found consistently superior to placebo in decreasing motor stereotypy, hyperactivity, withdrawal, and negativism. Side effects included dystonic reactions, acute

dyskinesia, Parkinsonism, akathisia, and autonomic and cardiovascular symptoms. With long-term use (six months), haloperidol is effective in up to 70 percent of ASD children, but the adverse effects can be severe and include tardive or withdrawal dyskinesias in up to 29 percent of the children, anxiety and depression, sedation, restlessness, and lethargy. Weight gain that does not necessarily resolve when dosing is ceased can also occur. Haloperidol currently has a B:W ratio of 0.9:1.

Other dopamine receptor antagonists generally parallel haloperidol in their benefit-to-risk profiles.<sup>125</sup> The newer, "atypical neuroleptics" block both dopamine (D2) and serotonin (5-HT2) receptors and have more favorable side effect profiles. Clozapine initially looked promising; however, its B:W ratio is currently 0.4:1. Risperidone currently has the best benefit-to-risk profile, with a B:W ratio of 2.8:1.

A series of open-label clinical studies in children, adolescents, and adults has documented risperidone's promising clinical improvements.<sup>125</sup> In adults it was effective in reducing irritability, aggression, and repetitive and affective symptoms. The most prominent side effect reported was mild sedation. With children there was significant clinical improvement; however, up to 29 percent had adverse effects, including increased anger, aggression, and agitation; mild sedation; weight gain; restlessness; occasional liver damage; and dyskinesias.

In 2002 a placebo-controlled trial of risperidone involving 101 children was published in the *New England Journal of Medicine*.<sup>126</sup> Finding significant improvement of irritability and overall clinical impression in 69 percent of the drug group (12% for the placebo group), the investigators claimed the best degree of improvement ever seen for a medication to mitigate the behavioral symptoms of autism. Adverse effects included increased appetite and weight gain, averaging six pounds; fatigue and drowsiness; dizziness; and drooling.

### *Psychostimulants*

Methylphenidate (Ritalin®) is the archetype for this pharmacological class, being the first line of drug treatment for hyperactivity, inattentiveness, and impulsivity, as occurs in ADHD (Attention Deficit/Hyperactivity Disorder).<sup>12</sup> Subjects with autism sometimes experience symptoms of ADHD, such as hyperactivity and distractibility. Ritalin's severe adverse effect profile was reviewed;<sup>12</sup> its B:W ratio is 0.7:1.

### *Tricyclic Antidepressants*

Tricyclic antidepressants have mixed effects in autism. Clomipramine (Anafranil) reportedly improves stereotypic and self-injurious behaviors, anger and aggression, impulsivity, and social relatedness.<sup>125</sup> In controlled trials it proved superior to desipramine, a tricyclic noradrenergic reuptake inhibitor. But in a double-blind comparison trial with haloperidol, clomipramine was no more effective than placebo and subjects experienced severe adverse effects. Clomipramine can be cardiotoxic and exacerbate seizure disorders. Its current B:W ratio is 1:1, identical to that for desipramine.

### *NMDA Receptor Antagonists*

N-methyl-D-aspartate (NMDA) receptors are a subclass of glutamate receptor that likely play a role in organizing brain circuitry during early development. Toxic or other adverse influences on NMDA receptors during brain development could conceivably contribute to ASD. Amantadine is an NMDA-receptor antagonist that may be marginally effective for hyperactivity and speech improvement.<sup>127</sup> Adverse effects include insomnia, sleepiness, tremors, confusion, poor concentration, depression, orthostatic hypotension, and hallucination (only at high dosages). This drug has antiviral effects, including against viruses that can affect behavior.<sup>128</sup>

### *Serotonin Up-Regulators*

Serotonin receptor agonist drugs have offered little benefit in autism. Fenfluramine, a halogenated amphetamine that boosts serotonin levels and blocks dopamine receptors, showed initial promise; later it was found ineffective and neurotoxic and was removed from the market.<sup>123</sup>

Buspirone (Buspar), a serotonin 5T1 $\alpha$ -receptor agonist with anxiolytic and mildly antidepressant effects, has undergone only uncontrolled studies.<sup>125</sup> It can reduce affective lability, anxiety, and sleeping problems in disorganized and hyperaroused, autistic children. In developmentally disabled adults with autism, it can relieve anxiety, temper tantrums, aggression, and self-injurious behavior. Its B:W ratio is 1.2:1.

Fluvoxamine (Luvox) and fluoxetine (Prozac) are selective serotonin reuptake inhibitors (SSRIs), both of which may work better for autistic adults than children. Luvox may benefit repetitive behavior in adult subjects, but in children its benefits were insignificant and adverse effects quite severe.<sup>125</sup>

Prozac, a more potent and selective SSRI than Luvox, may benefit obsessiveness and anxiety in autistic adults, but probably not compulsive behavior.<sup>125</sup> Another SSRI, sertraline (Zoloft), may also benefit adults. Children are likely to exhibit restlessness, anxiety, agitation, and insomnia in response to SSRIs. Prozac currently has a 1.2:1 B:W ratio, Zoloft a 1.1:1 ratio.

### *Naltrexone, Opiate-Receptor Antagonist*

Autism has been consistently linked to opioid hyperactivation, whether from exogenous (food-derived peptides)<sup>19</sup> or endogenous sources.<sup>125</sup> Naltrexone blocks the binding of heroin, morphine, or other opiates to brain receptors, and has been used since the early 1970s for drug addicts. Initial trials looked encouraging; however, it lost its allure after double-blind trials.<sup>123</sup> It may minimally reduce overactivity, but can worsen stereotypic behavior and has a bitter taste that affects compliance. The B:W ratio is 1.5:1.

## *Drugs Affecting Noradrenergic Receptors*

Clonidine is a presynaptic alpha-2 adrenergic receptor agonist that up-regulates adrenergic transmission.<sup>123</sup> It may reduce hyperactivity, impulsivity, and irritability in the short term; but tolerance develops over time. Adverse effects include drowsiness, decreased activity, and hypotension. Its B:W ratio of 2.2:1 is better than most other autism drugs.

## *Miscellaneous Pharmacological Agents*

When an autistic child exhibits a cyclic pattern or a bipolar mood disorder is suspected, treatment with lithium can be helpful.<sup>125</sup> Lithium may also be helpful for aggressive and self-injurious behavior. Its B:W ratio is 1.1:1.

Epilepsy afflicts 20-30 percent of children with autistic disorder,<sup>125</sup> and the anticonvulsant carbamazepine (Tegretol) can be useful. For antiseizure activity it has a good B:W ratio of 4.5:1. For its effects on mood and aggressive, irritable, or explosive behavior in autistic children, the ratio falls to 1.3:1. Valproate (Depakene) similarly has a B:W rating of 4.6:1 for seizures and 1.3:1 for calming behavior.

Judging from the existing knowledge base for autism, drug treatment may be most useful when symptoms associated with autism such as hyperactivity and inattention, aggression and self-injury, stereotypical behavior, rigidity, and anxiety interfere with psychosocial functioning or with other treatment approaches.

## **Conclusion**

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 that only integrative medical practice can offer. Ethical integrative management supports parents' initiatives to explore options that offer negligible risk and any degree of benefit for the child. A ten-phase protocol for parent-physician collaboration for autism is presented in Table 5.

Nutrients predictably have broader effects and better benefit-to-risk profiles than drugs. The integrative practitioner, however, cannot always shun the use of drugs. As one example, many are forced to treat a substantial percentage of their patients with antifungal drugs if *Candida* overgrowth becomes intransigent. With a child's future at stake, it is appropriate to use the most effective therapies, within the acceptable limits for adverse effects. Integrative physicians usually give nutrients a chance before turning to drugs.

Evidence is accumulating that LCFA-3 status is deranged across a spectrum of neurodevelopmental disorders – from learning disorders and ADHD through the autistic spectrum. A newly published double-blind, placebo-controlled trial showed definitive, albeit incomplete, benefit from LCFA-3 for ADHD.<sup>129</sup> Since the LCFA-3s function as components of membrane phospholipids and preliminary evidence indicates the phospholipid phosphatidylserine (PS) benefits ADHD,<sup>107</sup> a trial of LCFA-3 and PS for autism is an attractive recommendation.

Autism remains a challenge to basic and clinical researchers. More in-depth studies are needed to clarify the relative contributions to ASD symptomatology from the perspective of: (1) genetic predispositions interacting with toxins or other etiologic triggers;<sup>1</sup> (2) maternal toxic burden, maternal antibodies against the child's antigens, and prenatal contribution to autism risk;<sup>122</sup> (3) interactions between immune or detoxification impairment and vaccinations;<sup>104</sup> (4) pro-inflammatory cytokine imbalances in relation to anti-inflammatory nutrient status;<sup>103</sup> (5) likelihood of co-synergy between the intestinal, CNS, and immune abnormalities;<sup>9,26</sup> and (6) contribution of autoimmune mechanisms to the overall condition<sup>122</sup> and prospects for controlling such mechanisms.<sup>105</sup>

In many difficult medical conditions treatment strategies can emerge that at first seem irrational but eventually may prove themselves. In autism one of these strategies may be bioresonance therapy, the use of frequency-customized sound waves to treat certain features of the disease. Careful and responsible investigation of this technique is currently underway.<sup>130</sup>

*Table 5. Ten-phase Integrative Protocol for Autism Management*

1. Establish diagnosis, taking in-depth history. Initiate partnership with caregivers to implement detailed home record keeping.
2. Explore behavioral modification in cooperation with school and caregivers.
3. Supervise casein- and gluten-free, additive-free dietary modifications, tracked with food diary. Begin supplementation with multivitamin-mineral, vitamins B6, B12, and folate; magnesium; DMG; and omega-3 fatty acids.
4. Educate parents and all caregivers on zero tolerance for toxins. Test for mercury, other metals, and organochlorine pollutants as indicated.
5. Implement mercury chelation removal and nutrient support for detoxification.
6. Assess GI abnormalities: malabsorption, dysbiosis, intestinal hyperpermeability. Assess for gastritis-duodenitis-colitis and IgG/IgE food allergy testing. Supplement digestive enzymes, high-potency probiotics, prebiotics, glutathione, other GI nutrients.
7. Once detoxification and gastrointestinal healing is complete, test for vitamins, minerals, amino acids, essential fatty acids, and supplement as appropriate.
8. Check liver detoxification function; replenish liver support nutrients.
9. Test for immune system abnormalities: low white blood cell counts, antibody deficiencies, decreased lymphocyte proliferative response, cytokines, autoimmunity. Consider using nutritional and specialized immune therapies.
10. Periodically retest laboratory values and adjust management as indicated.

The ASD population is making steady advances toward improved quality of life and increased prospects for productivity. The marked degrees of benefit experienced by ASD patients have become a model for other challenging medical conditions that defy understanding. Spurred

by parent activism, practitioner commitment, and innovative organizational support, progress in understanding and treating autism has come from the power inherent in the integrative model of medical management.

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